Handbook of Research on

Pathophysiology and Strategies for the Management of COVID-19

Omar El Hiba, Arumugam R Jayakumar, Tiziano Balzano, and Faical Isbaine

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Handbook of Research on Pathophysiology and Strategies for the Management of COVID-19

Omar El Hiba
Chouaib Doukkali University, Morocco

Jayakumar Radhakrishnan
Veterans Affairs Medical Center, USA

Tiziano Balzano
University Hospital HM Puerta del Sur, Spain

Faical Isbaine
Emory University, USA

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Dedication

To the memory of my father Ahmed
To my mother
To my wonderful and my soul mate; my wife Maryam
To my brother Mohammed
To all my family and friends
To the memory of those we loved and we lost in the pandemic
To the selfless first line fighters
To those dedicating their lives to improve our knowledge
To all those who contributed directly or indirectly to this work

Editorial Advisory Board

List of Contributors

Adli, Djallal Eddine Houari / *Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria* 176
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Abdelmohcine Aimrane, Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco
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Maryam Mountassir, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Ahmed Taoufik Hakkoum, Laboratory of Biochemistry, Arrazi Hospital University Mohammed VI, Morocco
Raymond Klevor, Arrazi Hospital, Mohammed VI University Medical Center, Marrakech, Morocco
Ansumana Mohammed Keita, Mohammed VI University Teaching Hospital, Morocco
Said El Hizazi, Ecole Supérieure de Technologie, Université Ibn Zohr, Morocco
Draoui Ahmed, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Nadia Zouhairi, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Abdelmohcine Aimrane, Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco
Abdelhafid Benksim, Higher Institute of Nursing Professions and Health Techniques, Morocco
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Yassin Zemrani, Arrazi Hospital University Mohammed VI, Morocco
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Maryam Mountassir, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Said El Hizazi, Ecole Supérieure de Technologie, Université Ibn Zohr, Morocco
Raymond Klevor, Mohammed VI University Medical Center, Marrakesh, Morocco
Ansumana Mohammed Keita, Arrazi Hospital, Mohammed VI University Teaching Hospital, Morocco
Mustapha Mouallif, Higher Institute of Health Sciences, Hassan First University of Settat, Morocco
Yassin Zemrani, Arrazi Hospital University Mohammed VI, Morocco
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Arumugam R. Jayakumar, University of Miami School of Medicine, USA & South Florida VA Foundation for Research and Education, USA
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Nadia zouhairi, Faculty of Sciences, Chouaib Doukkali University, Morocco
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Miloud Slimani, Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria
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Ahmed Draoui, Neuroscience, Pharmacology and Environment Unit (ENPE), Laboratory of Clinical and Experimental Neurology, Morocco
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Nadia Zouhairi, Faculty of Sciences, University Chouaib Doukkali, El Jadida, Morocco
Abdelmohcine Aimrane, Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco
Redouane Chatoui, FST Beni Mellal, Université Sultane Moulay Slimane, Morocco
Mohamed Echchakery, Higher Institute of Health Sciences, Hassan First University of Settat, Morocco

Since December 2019, a pneumonia outbreak with unknown etiology occurred in Wuhan, China. Later, the pathogen was identified as novel human coronavirus and named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was named corona virus disease 2019 (COVID-19) and caused a pandemic. As of 23 June 2020, the global COVID-19 pandemic has battered the world. More than 1.5 million people have died with over 80 million people confirmed infected. This outbreak is spreading in approximately 216 countries and regions as of 22 July 2020. Comparing the three human coronavirus, SARS and MERS have significantly higher case fatality rates than COVID-19, but COVID-19 is more infectious and spreads more easily among people. Therefore, in this chapter, the authors summarize the most fatal pandemic in recorded history. Also, they collected all information about the current knowledge about COVID-19 pandemic including similarity and differences with other human coronaviruses.

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Mostafa Bentahir, Université catholique de Louvain, Belgium
Fatiha Chigr, Sultan Moulay Slimane University, Morocco
Mohamed Najimi, Sultan Moulay Slimane University, Morocco
Jean-Luc Gala, Université catholique de Louvain, Belgium

The outbreak of SARS-Cov2 in China and its subsequent spread has caused a global pandemic. The authors conducted a simple susceptible-infected (SI) model of the spread of COVID-19 in Moroccan population. The model is based on combining the average contact rate (μmax) extracted from the early exponential phase of the outbreak with a logistic simulation over time. Interestingly, this modeling approach showed a perfect fit with a strong correlation between real confirmed and estimated cases when calibrated on the Chinese declining outbreak. Subsequently, the model was applied for studying the ongoing COVID-19 outbreak in Morocco to determine the needed time for reaching 10,000 confirmed cases whose 15% (1,500) are at risk of developing health complications requiring patient care in hospitals. The latter total capacity does not exceed 1,640 beds according to the authorities. Incorporating these parameters in the logistic model, they predicted that the Moroccan healthcare system will be at 27%, 50%, 76%, and 90% of saturation on April 11, 16, 23, and May 4, 2020, respectively.

Section 2
Symptomatology, Diagnosis, and Transmissibility Characteristics of COVID-19

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Souad El Mouahid, Higher Institute of Nursing Professions and Health Techniques, Morocco
Soraia El Baz, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Maryam Mountassir, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Ahmed Taoufik Hakkoum, Laboratory of Biochemistry, Arrazi Hospital University Mohammed VI, Morocco
Raymond Klevor, Arrazi Hospital, Mohammed VI University Medical Center, Marrakech, Morocco
Ansumana Mohammed Keita, Mohammed VI University Teaching Hospital, Morocco
Said El Hizazi, Ecole Supérieure de Technologie, Université Ibn Zohr, Morocco
Draoui Ahmed, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Nadia Zouhairi, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Abdelmohcine Aimrane, Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco
Abdelhafid Benksim, Higher Institute of Nursing Professions and Health Techniques, Morocco
Redouane Chatoui, Sciences and Technologies Faculty Beni Mellal, Sultan Moulay Slimane University, Morocco
Yassin Zemrani, Arrazi Hospital University Mohammed VI, Morocco
Asmae Lamrani Hanchi, Faculty of Medicine and Pharmacy of Marrakech, Morocco & Cadi Ayyad University, Morocco
Mohamed Alouani, Faculty of Applied Sciences, University Ibn Zohr, Morocco

Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which was identified at the end of December 2019 in China. Symptoms of COVID-19 can appear after an incubation phase of the virus of 2 to 14 days, the most common being fever, cough, and asthenia. Other specific symptoms may include shortness of breath or difficulty breathing, muscle pain, sore throat, chills, loss of smell or sensation, chest pain, headache, nausea, rash, diarrhea, and vomiting. The severity of these symptoms can be mild or even extreme causing serious damage to several organs, directly and indirectly, namely pulmonary, renal, hepatic, cardiac, digestive, neurological. Some people

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Samia Boussaa, Higher Institute of Nursing Professions and Health Techniques, Morocco
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Maryam Mountassir, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Said El Hizazi, Ecole Supérieure de Technologie, Université Ibn Zohr, Morocco
Raymond Klevor, Mohammed VI University Medical Center, Marrakesh, Morocco
Ansumana Mohammed Keita, Arrazi Hospital, Mohammed VI University Teaching Hospital, Morocco
Mustapha Mouallif, Higher Institute of Health Sciences, Hassan First University of Settat, Morocco
Yassin Zemrani, Arrazi Hospital University Mohammed VI, Morocco
Asmae Lamrani Hanchi, Faculty of Medicine and Pharmacy of Marrakech, Cadi Ayyad University, Morocco
Soraia El Baz, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Mohamed Alouani, Faculty of Sciences, University Ibn Zohr, Morocco

The coronavirus disease 2019 (COVID-19) which has become the pandemic par excellence of our time places pressure on various aspects of human endeavor and as such requires detailed study to better combat it. However, diagnostic tests were used to provide data on the incidence of COVID-19 and to assess the immune status of infected individuals. The objective of this chapter is to describe the diagnostic methods currently used to identify SARS-CoV-2 infection. Obtaining the first SARS-CoV-2 genome sequence was decisive for the development of molecular diagnostic assays that currently make it possible to diagnose and screen for the Sars-CoV-2 infection. Their uses depend on the target to be detected. Antigenic tests detect the presence of a virus antigen, which usually makes a proteinaceous part of the virus surface. The serology tests detect the presence of antibodies generated against SARS-CoV-2 and are also a relevant tool for epidemiological studies.

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Soraia El Baz, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Ahmed Draoui, Cadi Ayyad University, Morocco
Mohamed Echchakery, Higher Institute of Health Sciences, Hassan First University of Settat, Morocco
Natalia Lopez-Gonzalez del Rey, Centre for Integrative Neuroscience A.C., University Hospital Puerta del Sur, Spain
Karima Chgoura, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Morocco

The coronaviruses group can affect mammals, including humans, causing generally mild infectious disorders, sporadically leading to severe outbreak clusters, such as those generated by SARS-CoV in 2003 and by MERS-CoV in 2012 and in 2015. The current coronavirus outbreak started December 29th, 2019

in Wuhan (Republic of China) and has progressively expanded to various parts of the world. A human-to-human transmission of COVID-19 occurs directly through individuals showing symptoms. But, recent researches support the possibility of SARS-CoV-2 transmission from persons who are asymptomatic. Indirect transmission occurs via touching infected surfaces or through inhalation of small, exhaled virus in respiratory droplets. To effectively fight the spread of COVID-19, it is vital to understand the different factors that promote superspreading of COVID-19. So, the aim of this chapter is to describe the invasion of SARS-CoV-2 in the human body and the different modes of transmission (directly and indirectly).

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Ahmed Draoui, Cadi Ayyad University, Morocco
Hicham Chatoui, LBI, FST BM, University Sultan Moulay Slimane. Morocco & Private University of Marrakech (UPM), Morocco
Soraia El Baz, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Hanane Rais, Cadi Ayyad University, Morocco
Bilal El-Mansoury, Chouaib Doukkali University, Morocco
My Abdelmonaim EL Hidan, Ibn Zohr University, Agadir, Morocco
Abdelmohcine Aimrane, Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco
Nadia Zouhairi, Cadi Ayyad University, Morocco
Mohamed Echchakery, Hassan First University of Settat, Settat, Morocco
Abdelaati EL Khiat, Cadi Ayyad University, Morocco
Lahcen Tamegart, Cadi Ayyad University, Morocco
Radouane El Fari, Cadi Ayyad University, Morocco
Hind Benammi, Cadi Ayyad University, Morocco
Karima Lafhal, Cadi Ayyad University, Morocco
Miloud Hammoud, Cadi Ayyad University, Morocco
Halima Gamrani, Cadi Ayyad University, Morocco

SARS-CoV-2 infection is characterized by its high contagiousness and unusual potential lethality. Microscopically, diffuse alveolar damage is the main histologic lung injury dominated by alveolar destruction. At the early stage, the authors note non-specific lesions similar to lesions of diffuse alveolar damage. In particular, the alveoli dilated and filled with exudative fibromyxoid material, the thickening of the interalveolar partitions by edema and an essentially mononuclear inflammatory infiltrate with eosinophilic hyaline membranes covering the alveoli. Viral inclusions are not generally found, and at an advanced stage, the installation of pulmonary fibrosis is noted. The place of non-invasive and/or invasive ventilation is undetermined in hypoxemic respiratory failure secondary to SARS-Cov-2 pneumonia, whereas in the most severe cases of COVID-19, the use of oxygenation by extracorporeal membrane is immediate. The cytokine storm in the lungs prompted clinicians to administer immunomodulators, the results of which was a reduction in hospital mortality.

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Hicham Chatoui, Faculty of Sciences and Techniques (FST), University Sultan Moulay Slimane, Morocco & Private University of Marrakech, Morocco
Nadia Zouhairi, FSJ, University Chouaib Doukkali, Morocco
Lahoucine Bahi, Faculty of Sciences and Techniques (FST), University Sultan My Slimane, Morocco
Lhoussaine Ammouta, Faculty of Sciences and Techniques (FST), University Sultan My Slimane, Morocco
Tiziano Balzano, Centre for Integrative Neuroscience A.C., University Hospital HM Puerta del Sur, Spain
Moulay Abdelmonaim El Hidan, Faculty of Applied Sciences, Ibn Zohr University, Morocco
Faical Isbaine, Emory University, USA
Arumugam R. Jayakumar, University of Miami School of Medicine, USA & South Florida VA Foundation for Research and Education, USA
Michael D. Norenberg, Departments of Pathology, Biochemistry, and Molecular Biology, University of Miami, USA
Amira Zaky, Faculty of Sciences, Alexandria University, Alexandria, Egypt
Halima Gamrani, Faculty of Sciences, Cadi Ayyad University, Morocco

Since December 2019, the world has been shaken by the spread of a highly pathogen virus, causing severe acute respiratory syndrome (SARS-Cov2), which emerged in Wuhan, China. SARS-Cov2 is known to cause acute pneumonia: the cardinal feature of coronavirus disease 2019 (COVID-19). Clinical features of the disease include respiratory distress, loss of spontaneous breathing, and sometimes neurologic signs such as headache and nausea and anosmia, leading to suppose a possible involvement of the nervous system as a potential target of SARS-CoV2. The chapter will shed light on the recent clinical and experimental data sustaining the involvement of the nervous system in the pathophysiology of COVID-19, based on several case reports and experimental data reporting the possible transmission of SARS-CoV2 throughout the peripheral nerves to the brain cardiorespiratory centers. Thus, understanding the role of the nervous system in the course of clinical symptoms of COVID-19 is important in determining the appropriate therapeutic approach to combat the disease.

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Aaron Lelo Pambu, University of Kinshasa, DRC
Abdellah Zinedine, Faculty of Sciences, Chouaib Doukkali University, Morocco

The current outbreak of the novel coronavirus, SARS-CoV-2 (coronavirus disease 2019; previously 2019- nCoV), epi-centered in Hubei Province of the People's Republic of China, has spread to many other countries caused an extreme burden for healthcare systems globally. Coronaviruses are traditionally considered nonlethal pathogens to humans, mainly causing approximately 15% of common colds. In this century, we have encountered highly pathogenic human CoVs twice. In this chapter, the authors propose to focus the gastrointestinal physiopathology of the infection of SARS-Cov2. This chapter will develop subject like the gastrointestinal manifestations of the infection to SARS-Cov2. The second part of this chapter will develop the role of the gut microbiome in the SARS-Cov2 diseases susceptibilities. And then the authors will show the etiopathogenesis of SARS-Cov2 associated diarrhea. As reported by previous

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Natalia López-González del Rey, Centre for Integrative Neuroscience A.C., University Hospital HM Puerta del Sur, Madrid, Spain
Souad El Amine, Ecole Normale Supérieure (ENS), Cadi Ayyad University, Morocco
Kamal Smimih, Faculty of Sciences, University Chouaib Doukkali, Morocco

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) preferentially infects cells in the respiratory tract, but several studies have also demonstrated low levels of SARS-CoV-2 copies in the liver. The hypothesis that patients with COVID-19 may develop liver dysfunction is supported by findings showing abnormal liver test results in such patients, but the exact mechanisms by which SARS-CoV-2 induces liver damage remain unclear. Liver injury in COVID-19 patients has probably a multifactorial etiology including the rapid onset of a systemic pro-inflammatory state due to viral infection, the use of potentially hepatotoxic drugs, pneumonia-associated hypoxia, and the eventual direct injury of the liver by SARS-CoV-2. This chapter will discuss the potential pathophysiological mechanisms for SARS-CoV-2 hepatic tropism and an overview about the main biochemical and histopathological findings observed in liver from COVID-19 patients. Finally, the effects that this infection can produce in patients with chronic liver disease will be also discussed.

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Said Sabir, Faculty of Medicine and Pharmacy, Marrakech, Morocco
Soraia El Baz, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Nadia Zouhairi, Faculty of Sciences, Chouaib Doukkali University, Morocco
Mohamed Echchakery, Institut Supérieur des Science de la Santé, University Hassan I, Morocco
Ahmed Draoui, Faculty of Sciences Semlalia, University Cadi Ayyad, Marrakesh, Morocco
Chatoui Hicham, BEL, FST, Sultan Moulay Slimane University, Morocco & Private University of Marrakech (UPM), Morocco
Naima Fdil, Faculty of Medicine and Pharmacy, Marrakech, Morocco
Souad Sellami, Centre Hospitalo, Universitaire Mohammed VI, Marrakech, Morocco
Abdesslam Ferssiwi, Faculty of Science, University Chouaib Doukkali, Morocco
Abdelali Bitar, Faculty of Science, University Chouaib Doukkali, Morocco
Hanane Rais, Faculty of Medicine and Pharmacy, Marrakech, Morocco

The newly emerged pandemic of coronavirus-induced disease of the year 2019 (COVID-19) has become the utmost health concern worldwide. Patients with COVID-19 are highly susceptible to develop hypercoagulable state increasing the risk of causing venous and arterial thrombosis at both small and large vessels. Additionally, in patients showing co-morbidities, for instance patients with inborn errors of metabolism linked to heart failure, the complications and mortalities are even higher than in any other case. In such frail patients already showing health concerns, the COVID-19-induced pneumonia may cause acute or chronic cardiovascular complications. Indeed, several reports of thrombotic complications in association with other complications has been presented, such as large vessels storks, clotting of catheters, and myocardial injury. Nevertheless, knowledge on the COVID-19-associated cardiovascular diseases remains scarce. Thus, in this chapter, the authors represent an overview of the available data on the induced heart failure related to COVID-19.

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Khaled Kahloula, Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria
Djallal Eddine Houari Adli, Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria
Nadia zouhairi, Faculty of Sciences, Chouaib Doukkali University, Morocco
Kaddour Ziani, Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria
Miloud Slimani, Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria
Wafaa Arabi, Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria
Abdelmohcine Aimrane, Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco
Soraia El Baz, Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco
Ahmed Draoui, Cadi Ayyad University, Morocco
Mohamed Echchakery, Institut supérieur des Sciences de la santé (ISSS), University Hassan I, Morocco
Abdelali Bitar, Faculty of Sciences, Chouaib Doukkali University, Morocco

Coronavirus (SARS-COV2) caused several deaths worldwide. This virus infects the target cell by binding to angiotensin-converting enzymes 2 (ACE2) receptor through its receptor-binding domain (RBD) and replicates. Thus, a high level of ACE2 expression is detected in the testicular cells so that the testis is believed to count as a potential target for direct damage by COVID-19. Moreover, the possibility of testicular damage may be caused by either direct viral invasion through interaction with ACE2 receptors or because of inflammatory response. Similarly, in women, literature reported the distribution and function of ACE2 in the female reproductive system, which is widely expressed in the ovary, uterus, vagina, and placenta. It regulates follicular development and ovulation, modulates luteal angiogenesis and degeneration, and influences regular changes in endometrial tissue and embryo development. Taking these functions into account, COVID-19 may disturb the female reproductive functions through regulating ACE2, resulting in infertility, menstrual disorder, and fetal distress.

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Naima Fdil, Metabolic Platform, Faculty of Medicine, Cadi Ayyad University, Morocco & MoSEAR, Morocco
Es-Said Sabir, Metabolic Platform, Faculty of Medicine, Cadi Ayyad University, Morocco
Karima Lafhal, Metabolic Platform, Faculty of Medicine, Cadi Ayyad University, Morocco
Noureddine Rada, Mohammed VI Hospital University, Morocco
Redouane El Fezzazi, Faculty of Medicine, Cadi Ayyad University, Morocco
Mohamed Amine, Mohammed VI Hospital University, Morocco
Fadl Mrahib Rabou Maoulainine, Mohammed VI Hospital University, Morocco
Mohammed Bouskraoui, Mohammed VI Hospital University, Morocco

People with respiratory problems and people prone to decompensations are particularly vulnerable to COVID-19. These characteristics are often present in patients with inherited metabolic diseases (IMDs). It is therefore conceivable that patients with IMDs are at a greater risk of infection and may present a more serious form of COVID-19 disease. Currently available data about the impact of COVID-19 on patients suffering from IMDs are very scarce and no study has been able to confirm this hypothesis. In this chapter, the authors have tried to show that the severity of COVID-19 infection in patients with IMDs is specific to the group that the disease belongs. Indeed, lysosomal storage diseases caused by impaired degradation and accumulation of metabolites in lysosomes leads to dysfunction of lysosomal and possible impairment of the COVID-19 egress process. The fact that COVID-19 disease may be considered itself as an IMD was also discussed to highlight the interference which can exist between COVID-19 disease and IMDs in a patient.

Section 4
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Youssef Ait Hamdan, Interdisciplinary Laboratory in Bio-Resources, Environment, and Materials, Higher Normal School, Morocco
Lahcen Tamegart, Neuroscience, Pharmacology, and Environment Unit (ENPE), Laboratory of Clinical and Experimental Neurology, Morocco
Ahmed Draoui, Neuroscience, Pharmacology and Environment Unit (ENPE), Laboratory of Clinical and Experimental Neurology, Morocco
Abdessamad Aglagane, Laboratory of Biodiversity and Ecosystem Functioning, Faculty of Sciences, Ibn Zohr University, Morocco
Radouane El Fari, Higher Institute of Nursing Professions and Health Techniques, Dakhla, Morocco & Ministry of Health, Morocco
Halima Gamrani, Neuroscience, Pharmacology, and Environment Unit (ENPE), Laboratory of Clinical and Experimental Neurology, Morocco

Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCov-2) or COVID-19 is a pandemic that appeared in December 2019 in China and which is an RNA virus. It gave rise to a major health crisis at the start of 2020, with numerous hospitalizations. It was quickly important to understand the pathophysiology of this viral attack on the human body in order to be able to develop treatment. However, there is no vaccine or effective therapeutic agent against SARS-CoV-2. Most of the therapeutic strategies used to deal with this virus come from the work of previous epidemics of SARS, and other influenza viruses, such as antiviral therapies (chloroquine, hydroxychloroquine), adjuvant therapies by combining antivirals with drugs. Antibiotics or immunostimulants (vitamins C, Dm and Zinc, etc,) and several other therapies to be used depending on the region.

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Ranjit Barua, CHST, Indian Institute of Engineering Science And Technology, Shibpur, India
Sudipto Datta, Indian Institute of Engineering Science And Technology, Shibpur, India
Pallab Datta, National Institute of Pharmaceutical Education and Research, Kolkata, India
Amit Roy Chowdhury, Indian Institute of Engineering Science And Technology, Shibpur, India

SARS-CoV-2 is a novel virus communicable disease affected by serious acute respiratory condition coronavirus 2 (SARS-CoV-2) which goes to the family of coronavirus. December 2019, in Wuhan, China, the first case of novel coronavirus was reported, and this widespread virus globally became a pandemic. Various studies show that drug applicants are used as antivirals or immune modulators. Yet, the outcome of this examination reported the drug applicants were not ominously operative in contrast to the infection. In the interim, it's believed that taking herbal immune-modulators can avoid and/or resist COVID-19. Unluckily, definite clinical and preclinical trials to assess the special herbal immune regulators' effects have not been directed. Specific natural elements might be actual for treating COVID-19 built on universal thoughts from former tests. Though there are no exact anti-COVID-19 medicines as well as a drugs until now, the use of traditional medicine and epidemiology of novel coronavirus disease will be discussed for COVID-19 treatment.

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Simran Jeet Kaur, PCTE Group of Institutes, India

COVID-19 is a human-infectious virus. The respiratory system is the primary target of the coronavirus, but it can also harm cardiac tissues and gastrointestinal organs. Many frequent circumstances, such as the medication's or medicine's purpose, the dosage/potency of the drug, and the patient's condition, can place patients in grave danger. Several cures have been reported using a variety of therapy methods. Among the various treatments, natural and synthetic medicines are the most commonly documented. Some herbal medicines, such as Tribulusterrestris, Withaniasomnifera, Curcuma longa, Ocimum sanctum, and Phyllanthusemblica, have powerful antiviral (AntiCOV-19) properties against novel coronavirus, heralding the start of a new era in herbal therapy.

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Muhammad Haseeb Ahmad, Government College, University Faisalabad, Pakistan
Muhammad Faizan Afzal, Government College, University Faisalabad, Pakistan
Muhammad Imran, Government College, University Faisalabad, Pakistan
Muhammad Kamran Khan, Government College, University Faisalabad, Pakistan
Nazir Ahmad, Government College, University Faisalabad, Pakistan

Nutrition is a known aspect that plays a pivotal role in the strengthening of the immune system. Populations with poor eating habits have more risk of severe COVID-19. Micronutrients such as vitamins, including vitamins A, B complex, C, D, and E; minerals including, zinc, selenium, magnesium, and copper are mainly present in plant based foods like legumes, fruits, and vegetables to build different types of immune cells that are helpful in supporting the immune system and promote the host health. Insufficient consumption of these nutrients may result to reduce the resistance to infections as well as an increasing in disease load. Garlic, black pepper, and basel leaves are known as ancient herbs which is helpful to boost the immunity. Numerous studies observed that a powerful antioxidant bioflavonoid quercetin and a glutathione may prevent the risk of COVID-19. In conclusion, foods from plant source show a vigorous role to boost the immunity for all aged groups to control COVID-19.

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Preface

According to the WHO, coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus (SARS-Cov2), which may cause mild to moderate respiratory complications in most of infected people. Older people and those with chronic and/or acute illnesses may present serious complications. While underlying mechanisms of the cellular responses to the virus are not fully revealed. Therefore, understanding the pathophysiology of COVID-19 is of crucial importance which will provide efficient data to define the appropriate and affective therapeutic strategy to cure and to prevent COVID-19 associated complications.

The *Handbook of Research on Pathophysiology and Strategies for the Management of COVID-19* summarizes and assembles the published data on COVID-19 and provides an answer to the reader for the mystery of SARS-Cov2's impact on human health through a deep analysis of the current data available in the literature. This book addresses the epidemiology and infectious patterns of the disease and the recent pathophysiological mechanisms of the disease and relationships to the medical history of the patient along with the available therapeutic approaches for either preventing or curing the disease.

The book is organized into three different parts covering the most important sides of the disease including a fist part on COVID-19 epidemiology and infectious patterns includes two chapters: Chapter 1, "COVID-19: The Pandemic," and Chapter 2, "The Modeling of the Capacity of the Moroccan Healthcare System in the Context of COVID-19 in Case of Non-Compliance With Lockdown: The Relevance of the Logistic Approach." This part of the book addresses the epidemiological and infectious patterns of COVID-19 worldwide as well a simple Susceptible-Infected (SI) model of the spread of COVID-19 in the Moroccan population.

The second part, "Symptomatology, Diagnosis, and Transmissibility Characteristics of COVID-19," aims to provide recent and updated data on the clinical features and symptomatology of the disease based on a literature overview of the recent published data from several countries affected by the pandemic. Additionally, we provide here, the main modes of SARS-Cov2 transmission and its spread according to studies realized in the four corners of the world, and this through three chapters: Chapter 3, "Symptomatology and Clinical Features Of Human COVID-19," Chapter 4, "Laboratory Methods for the Diagnosis of SARS-Cov-2," and Chapter 5, "Spread of COVID-19 and Its Main Modes of Transmission."

The third part of this book sheds light on the recent pathophysiological mechanisms of the disease and the relationships to the medical history of the patient. This part includes seven chapters covering different sides of the disease in association to different impairments of physiological functions including the respiratory (Chapter 6, "COVID-19: Lungs Facing the Storm"), the nervous (Chapter 7, "COVID-19 Beyond the Lungs: How SARS-Cov2 Invades the Human Nervous System"), the gastrointestinal (Chapter 8, "Gastrointestinal Tract and COVID-19: Insights Into the Role of Gut Microbiome," and Chapter

9, “Liver Injury in COVID-19 Patients: An Overview of the Current Evidence”), the cardiovascular (Chapter 10, “SARS-Cov-2 and Associated Heart Failure: An Overview on the Possible Mechanisms”), the genital (Chapter 11, “Viral Infection of the Reproductive System in Times of COVID-19”), and the clinical manifestations of patients with inherited metabolic diseases (Chapter 12, “Insights Into the COVID-19 Infection Related to Inherited Metabolic Diseases”).

The fourth and the last part of our book, “Management and Therapeutic Strategies of COVID-19,” includes four chapters: Chapter 13, “Therapeutic Management of COVID-19 Patients: Pharmacological and Non-Pharmacological Approaches,” Chapter 14, “The Study of Traditional Medicine for the Treatment of COVID-19,” Chapter 15, “Herbal Products for Management of COVID-19,” and Chapter 16, “Nutrition: A Strategy for Curtailing the Impact of COVID-19 Through Immunity Booster Foods.” This section of the book is focusing on the available therapeutic approaches for the management of COVID-19 including the classical and non-classical therapies as well as a summary of literature data on the medicinal plants with anti-viral potential used in traditional medicine for curing the disease.

Section 1

COVID-19 Epidemiology and Infectious Patterns

Chapter 1
COVID-19:
The Pandemic

Soraia El Baz
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

My Abdelmonaim El Hidan
Faculty of Applied Sciences, Ibn Zohr University, Morocco

Nadia Zouhairi
Faculty of Sciences, University Chouaib Doukkali, El Jadida, Morocco

Abdelmohcine Aimrane
Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco

Redouane Chatoui
FST Beni Mellal, Université Sultane Moulay Slimane, Morocco

Mohamed Echchakery
Higher Institute of Health Sciences, Hassan First University of Settat, Morocco

ABSTRACT

Since December 2019, a pneumonia outbreak with unknown etiology occurred in Wuhan, China. Later, the pathogen was identified as novel human coronavirus and named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was named corona virus disease 2019 (COVID-19) and caused a pandemic. As of 23 June 2020, the global COVID-19 pandemic has battered the world. More than 1.5 million people have died with over 80 million people confirmed infected. This outbreak is spreading in approximately 216 countries and regions as of 22 July 2020. Comparing the three human coronavirus, SARS and MERS have significantly higher case fatality rates than COVID-19, but COVID-19 is more infectious and spreads more easily among people. Therefore, in this chapter, the authors summarize the most fatal pandemic in recorded history. Also, they collected all information about the current knowledge about COVID-19 pandemic including similarity and differences with other human coronaviruses.

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INTRODUCTION

Human population has suffered from many pandemics throughout history such as influenza, smallpox, H1N1 or the recent incidence of COVID-19. Therefore, they have created catastrophic damage in many different ways (human, economics...). Many controlled diseases are getting re-emerged and new emerging infectious diseases are evolving and creating challenge among the global public health (Samal, 2014). The most critical factors which determine the effect of an epidemic are (i) the transmissibility and (ii) the severity (Swerdlow & Finelli, 2020).

All pandemics start as local outbreaks, often invisible in their early phases, and later they grow into disease events of major historical (Green, 2015). The pandemics tend to occur in waves and it is difficult to predict why, how, and when waves will occur in different countries. In the past, pandemics spread across military passages or trade routes. Nowadays, the globalization has multiplied the dominant routes. Therefore, human and animal transmission vectors can move speedily and stimulate the expansion of infectious diseases (Saunders-Hastings & Krewski, 2016). Several human coronavirus (HCoV) were thought to infect not only animals but also humans. This is the case of severe acute respiratory syndrome (SARS) in 2003 (Wang etal., 2013), and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (Zhong et al., 2003). Also, for the current COVID-19 coronavirus pandemic which was first emerged at the end of December 2019 in Wuhan, china. Subsequently, it is spreading in approximately 216 countries and regions as of July 22, 2020 (Hu et al., 2020). This pandemic is causing more than 80 million reported case and 1.5 million deaths (until December 31, 2020). Most countries have closed their borders and decided to apply the lockdown in expect to limit the spread of COVID-19. Also, the implementation of social distancing measures helped to control the outbreak. So, an event of this magnitude would have enormous global economic consequences and also profound social impacts that any pandemic or epidemic has had in the modern history.

This rapid development of coronavirus pandemic requires comparisons with previous epidemic, to analyze infection trends and to find the right prevention as was done in the past for similar cases. So, the purpose of this chapter is to provide a brief summary of different pandemics have affected the human, as well as lessons learned. Also, to better understand this deadly coronavirus, we highlight in this chapter the similarity with other human coronavirus.

WHAT IS A PANDEMIC?

Definition

Between 16th and 17th, Pandemic was the first use of this word and referred to “a Pandemick, or Endemick” (Harvey, 1666). Later in 18th (precisely in 1828), the epidemiologist and lexicographer “Noah Webster” listed epidemic and pandemic in her first edition of Webster’s Dictionary, as synonymous terms (Webster, 1828). By the early 19th century, the term epidemic had become the accepted term for what we would call now both an epidemic and a pandemic (Morens, Folkers, & Fauci, 2009).

Epidemic is an outbreak of infectious diseases occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people” (S. S. Harris, 2000). The term “pandemic” is the form of a large epidemic that occur worldwide, or over a very wide area, crossing

international boundaries, through human population, and affecting a large number of people (Ghendon, 1994; S. S. Harris, 2000; Last, 2001; Muthu, 2014).

The classical definition, do not take into consideration several factors such as virology and disease severity. Given that seasonal epidemics spread and cross international boundaries by affecting a lot of people, so pandemics can be said to occur annually. However, seasonal epidemics and some diseases are not considered pandemics (Kelly, 2011). As like cancer, is a dangerous disease but is not considered a pandemic because is not infectious and it can kill few persons.

Use of the term "pandemic" by scientists and health agencies often seemed to be at odds for many reasons: i) some scientists supported that declaration of a pandemic need a level of explosive transmissibility, but ii) others experts supported that severity of infection should also be considered (Altman, 2009; Morens et al., 2009).

To understand this concept better, there are eight key features of a pandemic: wide geographic extension, disease movement, novelty, severity, high attack rates and explosiveness, minimal population immunity, infectiousness and contagiousness (Qiu, Rutherford, Mao, & Chu, 2017).

THE MOST LETHAL PANDEMICS IN HISTORY

Cholera

Cholera is a water borne disease (an acute intestinal infection) caused by the bacterium *Vibrio cholera*, responsible for inducing a massive and rapid loss of body fluids (Weill et al., 2017). The first cholera pandemic was documented in pre-1817 and was limited to India especially in its ancestral home Bengal (Pollitzer, Swaroop, Burrows, & WHO, ⁋1959; Samal, 2014). During the 19th and 20th centuries, there have been seven pandemics of cholera. The first six cholera pandemics (1817-1923) disseminated from southern Asia (Indian subcontinent) to other parts of the world including South East Asia, China, Middle East, Union of Soviet Socialist Republics (USSR), Europe and Africa, and were caused by the classical biotype of *V. cholera* (Guerrant & Thielman, 1994; Morris, 2011; Pollitzer et al., ⁋1959; Samal, 2014). The first started in 1817 and subsequent pandemics began in 1829, 1852, 1863, 1881, and 1889 (J. B. Harris, LaRocque, Qadri, Ryan, & Calderwood, 2012; Van Heyningen & Seal, 1983). However, cholera had disappeared from North and South America as an epidemic in 1900 (Dziejman et al., 2002).

The last seventh pandemic of cholera began in 1961 in Indonesia, by pathogenic El Tor biotype strains and persisting until the present. These strains rapidly spread to cause endemic cholera in South Asia (1963) and in Africa (1970) (Rebaudet, Sudre, Faucher, & Piarroux, 2013). By 1991, *V. cholerae* El Tor caused a massive epidemic in Latin America especially in Peru. Since then, cholera has spread to Caribbean (i.e., Haiti) (2010) and to all neighbouring countries and, as a result, is now endemic in much of Latin America (Faruque, Albert, & Mekalanos, 1998; Guerrant & Thielman, 1994; Weill et al., 2017). On the basis of phenotypic and genotypic characteristics, *V. cholerae* O1 is subdivided into two biotypes, classical which was the agent of the first six pandemics and El Tor lineage is the dominant strain in the current seventh pandemic (J. B. Harris et al., 2012).

Each year, an estimated 2 to 3 million cases of cholera occur, and more than a billion people are at risk of disease (Weil & Ryan, 2018). The global cholera burden between 2008 and 2012 was estimated at 1.4 to 4 million cases of cholera annually, with 21 000 to 143 000 deaths (Ali, Nelson, Lopez, & Sack, 2015; Deen, Mengel, & Clemens, 2020). In 2009, 221 226 cholera cases were reported from 45 countries

to WHO, with 4 946 deaths (for a case-fatality rate of 2.24%). During the same year, the disease spread across the world with 98% of cases reported were from Africa (Morris, 2011). Later, in September 2016, the first cholera case in several decades was detected in Yemen in the setting of ongoing war without functioning health services, and has grown to one of the largest epidemics of the 21st century with over 1 million cases (Camacho et al., 2018; Weil & Ryan, 2018). In 2017, WHO were reported 1.2 million cholera cases and 5 654 fatalities worldwide (Cholera, 2017).

Influenza

Influenza is an infectious disease of birds and mammals caused by RNA viruses of the family Orthomyxoviridae. The 2009 pandemic of H1N1 is a real scourge, with a death of 151 700 to 575 400 people in the world (80% deaths were in people younger than 65 years of age) (CDC, 2012). According to historical data there have been four several pandemics:

-Spanish Flu "strain H1N1" (1918-1919): The influenza pandemic of 1918 'Spanish influenza' (owing to its high incidence in Spain) was the largest in recent history. The first established cases in the history of this pandemic were reported among army recruits in military camps "Camp Fuston in Kansas" in USA in March 1918 (Wever & van Bergen, 2014). Few months later, the infection moved on to Europe, and widespread throughout the world within a short period after First World War. Unfortunately, this influenza has affected more than 500 million people (CDC, 2013) and causing more than 50 million deaths worldwide (Martini, Gazzaniga, Bragazzi, & Barberis, 2019). In USA only, the 1918 influenza pandemic affected one-third of Americans and killed 550 000 to 675 000 people (0.5% of the population) (Cheng & Leung, 2007; Ghendon, 1994).

-Asian Flu "strain H2N2" (1957-1958): Started in China (Hong Kong) and then spread to Singapore, Taiwan, and Japan (Fukumi, 1959) before spreading to other parts of the globe (20 countries) in 1957 (Dunn, 1958). The H2N2 Asian pandemic virus is responsible for 2 million deaths globally (maximum case fatality rate approximately 0.67%) (Saunders-Hastings & Krewski, 2016), and disappeared from the human population after 1968 (Pappas et al., 2010).

-Hong Kong Flu "strain H3N2" (1967-1969): First case was detected in Hong Kong and then disseminated to other parts of the globe and killed one million people worldwide (Samal, 2014). During this pandemic, the mortality in the USA alone was estimated at around 30 000 deaths (Kavet, 1972). In Europe the mortality was estimated at 30 000 deaths just in Britain (Ghendon, 1994).

-Swine flu "strain H1N1" (2009): Also known as "swine flu", "Mexican flu", "New flu", and A(H1N1) (Saunders-Hastings & Krewski, 2016). This pandemic was first detected in children in California in April 2009 (CDC, 2009). Within weeks, the outbreak had subsequently spread worldwide in 122 countries, with 134 000 confirmed cases and 800 deaths in 2009 (Henderson, Courtney, Inglesby, Toner, & Nuzzo, 2009). The World Health Organization (WHO) declared a global influenza pandemic in June 11, 2009 (Chan, 2009). By August 1, 2010, there were more than 214 countries had reported confirmed cases including over 18 449 deaths (WHO, 2010). In the same year (August 2010), the WHO declared the pandemic officially over (Amato-Gauci et al., 2011). After the pandemic, there were 151 700 to 575 400 people perished from world (CDC, 2012; Saunders-Hastings & Krewski, 2016).

Plague

Plague is one of the most important epidemic infectious diseases shaping the history of humanity. Plague is a zoonotic infection primarily affecting the rodents caused by the gram negative bacterium *Yersinia pestis*. Humans are incidental hosts that do not contribute to the natural cycle of the disease outside of epidemics (Butler, 2009). Epidemics or pandemics of plague could be disastrous, because few microbes have killed as many as a third of the whole population during a pandemic (Butler, 2009; Samal, 2014). From 1958 to 2008, more than 60 000 cases were reported in Madagascar (17 000), in Congo (13 000), in Tanzania (9 000), in Myanmar (5 500), in India (4 800), in Peru (4 091), in Brazil (3 693), in Vietnam (3 500), and in the United States (438) (Raoult, Mouffok, Bitam, Piarroux, & Drancourt, 2013). Besides, 90% of reported cases occurred Africa in the late 20th and early 21st Century (especially in Madagascar, Central Africa and Eastern Africa (Algeria and Libya) (Bertherat et al., 2007; Bitam et al., 2010).

Historical data allowed recognizing three plague pandemics: (i) the first confirmed plague pandemic "Justinian plague" or Bubonic Plague (starting in 541 to 750) affected mainly the periphery of the Mediterranean Sea (Harbeck et al., 2013). In Egypt and Constantinople, this first plague caused the death of 10 000 a day at its height, perhaps as much as 40% of the city's inhabitants (Cohn, 2008). Between 542 and 546, this epidemic claimed nearly 100 million victims in Asia, Africa and Europe (WHO, 1999); (ii) the second pandemic is called "Black Death" or "medieval plague" (starting in 1347 to 1350), which devastated Mediterranean region and Continental Europe (Drancourt & Raoult, 2016). This pandemic may have killed 30% of the population in Europe (Raoult et al., 2013), spreading as far as Moscow and Scandinavia, and more than 75 million people died Worldwide (Samal, 2014); (iii) finally, the last pandemic broke out in China (Hong Kong) in the 19th century (1894) and grabbed many continents (Africa and America). Unfortunately, this pandemic caused 13 million people in India (WHO, 1999).

Smallpox

Smallpox was one of the major killers of humankind. This disease is an acute, febrile, contagious disease caused by the Variola virus "Poxviridae family". Until the 1970s, smallpox had been a pandemic disease for more than 3 000 years, and was responsible for the death of one out of every five children below five years of age (Nishiyama, Matsukuma, Matsumura, Kanatani, & Saito, 2015). There were two principal form of smallpox disease: (i) variol major predominated throughout the world (with case-fatality rates of 30% in Asia), and (ii) variol minor (or alastrim) was detected in South Africa, Folrida and after that it spread to United States, Latin America and Europe (with case-fatality rates of 1%) (Henderson et al., 1999). The World Health Organization (WHO) declared smallpox is no more a public health problem and to be completely eradicated by the end of 1979 as the result of effective vaccine, easy clinical identification, rarity of second attack, and slow transmission which helps in containment (Gupta & Mahajan, 2003).

HIV/AIDS

AIDS (Acquired immunodeficiency syndrome) is caused by chronic infection by HIV-1 (Human Immunodeficiency Virus-1), and is one of the most devastating pandemics ever recorded in human history (Sharp & Hahn, 2011). The first case was published by the US Centers for Disease Control and Prevention in 1981, and named as global pandemic of HIV/AIDS (CDC, 2016). This disease has spread worldwide and infecting close to 80 million people (Becerra, Bildstein, & Gach, 2016). HIV was initially discov-

ered and established widely in heterosexual populations and people who injected drugs in the United States and Europe, and in large populations of men, women, and children in Africa (Friedland, 2016). The first decades of the AIDS pandemic were associated with increasing mortality and became one of the principal causes of death among young men and women worldwide (Friedland, 2016). New HIV infections have been reduced by 17% over the past eight years. The number of new HIV infections in 2008 is approximately 15% lower in sub-Saharan Africa, 25% declined in East Asia and 10% in South and South East Asia (WHO, 2009). Globally, an estimated 34 million people were living with HIV and AIDS worldwide at the end of 2011(Hirsch & Duval, 2013).

HUMAN CORONAVIRUS AND HOW IT WAS CONTAINED

Classification of Human Coronavirus

Coronaviruses (CoVs) belong to the family Coronaviridae within the order Nidovirales (Siddell et al., 2019). Typically, coronaviruses broadly infect vertebrates including livestock, companion animals (such as pigs, cows, chickens, cats and dogs) and other wild, bats, snakes and mice (Fehr & Perlman, 2015; Weiss & Leibowitz, 2011). This new genus of viruses was found by Tyrrell in the late 1960s (McIntosh, Becker, & Chanock, 1967), and was named coronavirus. The term corona denoted the crown like appearance of the surface in the morphological structure of viruses (McIntosh et al., 1967). The majority of coronaviruses pose no threat to humans, but some factors such as recombination events, natural selection and genetic drift permit virulent coronaviruses to jump to human hosts and to acquire the capacity for person to person spread (Jones et al., 2008). Coronaviruses (CoVs) consist of four genera: Alphacoronavirus (α), Betacoronavirus (β), Gammacoronavirus (γ) and Deltacoronavirus (δ). Among these genera, α and β only infect mammals, whereas γ and δ mainly infect birds. Betacoronaviruses are divided into four lineages: A, B, C and D (Hu et al., 2020).

Seven known human coronaviruses (HCoVs) have been identified (Table 1) (Caldaria et al., 2020; Liu, Kuo, & Shih, 2020; Zhu et al., 2020): i) four commonly detected HCoVs are 229E, OC43, NL6 and HKU1, and ii) the three other strains SARS-CoV (severe acute respiratory syndrome coronavirus), MERS-CoV (Middle East respiratory syndrome coronavirus), and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), have a different pathogenicity and lead to higher mortality rates in human populations (Y. Yang et al., 2020).

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)

The first major human coronavirus outbreak caused by the coronavirus SARS-CoV, called SARS (Severe acute respiratory syndrome), appeared in Guangdong Province (southern China) in November 2002 (Anderson et al., 2004; Drosten et al., 2003; Ksiazek et al., 2003). During the 2002–2003 epidemic, approximately more than 8 000 infected individuals were recorded, and around 774 SARS-related fatalities at a mortality rate of 9% (Jahangir, 2020; Kahn & McIntosh, 2005; Li et al., 2005). SARS-CoV spread throughout the world with quantifiable speed (to 32 different countries) between November 2002 and August 2003 (Y. Yang et al., 2020). Therefore, the SARS-CoV outbreak was controllable through quarantining, and it died out in June 2003 (Lundstrom, 2020).

Table 1. Main aspects of human coronavirus

Strain	Discovery	Natural host	Intermediate host	Respiratory symptom
HcoV-229E	1966	Bats	Camelids	Mild
HcoV-OC43	1967	Rodents	cattle	Mild
SARS-CoV	2003	Bats	Masked palm civets	Severe acute
HcoV-NL63	2004	Bats	unknown	Mild
HcoV-HKU1	2005	Rodents	Unknown	Mild
MERS-CoV	2012	Bats	Dromedary camels	Severe acute
SARS-CoV-2	2019	bats	Pangolin?	Severe acute

Middle East respiratory Syndrome Coronavirus (MERS-CoV)

After the SARS-CoV epidemic, the novel human MERS-CoV emerged in the Middle East in 2012 (Zaki, van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012). MERS-CoV was first identified from a male patient who died from acute pneumonia and renal failure in Saudi Arabia in June 2012 (Ramadan & Shaib, 2019; Zaki et al., 2012). In total, 2 494 cases of MERS-CoV have been reported to WHO, including 858 deaths due to the infection and related complications (case-fatality rate: 34.4%) in 27 countries (Middle East and North Africa region, Europe, East Asia and the United States)(WHO, 2019). Despite fears, the MERS-CoV outbreak did not accelerate in 2013, with 855 confirmed cases and 333 deaths (mortality rate: 40%) (Aleanizy, Mohmed, Alqahtani, & El Hadi Mohamed, 2017). But in May 2015, another outbreak outside the Arabian Peninsula was reported in South Korea, which ended in 2018 (Afshar et al., 2020; Oh et al., 2018).

The Current SARS-CoV-2 Infection (COVID-19)

Since December 2019, a new pneumonia outbreak has infected more than 73 230 people and caused 1 871 deaths (case-fatality rate: 2.6%) in China and has spread to 25 countries (updated as of February 17, 2020) (Y. Yang et al., 2020). As of this date, the disease has spread to 202 countries. The number of confirmed and suspected cases is still increasing (Table 2) (80 million infected, as of December 31, 2020) as is the number of deaths (approximately more than 1.5 million, as of December 31, 2020), although there is a significant increase in the number of recovered patients as well (WHO, 2020c).

Researchers suggested that this pneumonia outbreak was related to animal market and seafood, and that the Chinese chrysanthemum bat is the origin of SARS-CoV-2 (Fan, Zhao, Shi, & Zhou, 2019). Recently, researchers believed that the pangolin was the intermediate host (approximately 99% sequence homology between metagenomic samples from the pangolin species and SARS-CoV-2 (S. Yang et al., 2021).

Initially, the disease was called “Wuhan pneumonia” because of the area and pneumonia symptoms. According to Whole-genome sequencing, the causative agent of this outbreak is a novel coronavirus. This human virus infection is the seventh member of the coronavirus family that affects humans (Wu et al., 2020). On January 12, 2020, the WHO termed the new virus 2019 novel coronavirus (2019-nCoV). Later, WHO officially named this infectious disease coronavirus disease 2019 (COVID-19) on February 12, 2020. International Committee on Taxonomy of Viruses (ICTV) officially designated the virus as severe acute respiratory syndrome coronavirus 2 “SARS-CoV-2” based on phylogeny, taxonomy and

Table 2. Compared situation of confirmed cases during one year of COVID19 pandemic

	December 31, 2019	June 31, 2020	December 31, 2020
Americas	-	5 697 954	36 339 371
Europe	-	2 783 379	26 990 655
South-East Asia	-	918 591	12 051 014
EasternMediterranean	-	1 153 238	4 977 852
Africa	-	356 666	1 961 234
Western Pacific	1	223 915	1 112 723
Total	**1**	**11 133 743**	**83 432 849**

established practice (Gorbalenya et al., 2020). As of March 11, 2020, COVID-19 caused approximately 37 364 confirmed cases and 1 130 deaths in 113 other countries worldwide. The WHO is deeply preoccupied by the global spread and severity of this outbreak. Therefore, on March 11, 2020, WHO finally announced that COVID-19 can be characterized as a pandemic, following 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 Pandemic flu (H1N1) (Liu et al., 2020; WHO, 2020a).

Comparing the three human coronavirus, as shown in Table 3, SARS and MERS have significantly higher case fatality rates (10% and 34%, respectively) than COVID-19 (2.12%) which it seems to be less lethal than MERS and SARS (Hu et al., 2020; Nikolich-Zugich et al., 2020). But, COVID-19 is more infectious and spreads more easily among people, leading to greater case numbers. Also, despite the lower case fatality rate, the number of deaths from COVID-19 far outweighs that from SARS or MERS.

Table 3. A comparison among SARS-CoV-2, SARS-CoV and MERS-CoV

Mortality rate	Deaths	Laboratory-confirmed cases	Countries affected	
10	774	8096	32	SARS-1
34	866	2519	27 (dominantly in the Middle East)	MERS*
2,12	1,5 M	70,5 M	213	COVID-19**

*as of 31 January 2020; ** as of 13 December 2020

The outbreaks of human coronavirus such as SARS-CoV and MERS-CoV provide us with significant lessons, including the previous pandemics, on how to better fight the SARS-CoV-2 epidemic. Therefore, coronavirus pandemic has highlighted the importance of investing in health systems to prevent, detect and respond to infectious disease outbreaks. For this reason, the first ever International Day of Epidemic Preparedness was called for by the United Nations General Assembly on December 27, 2020 (UN, 2020; WHO, 2020b).

CONCLUSION

In conclusion, though the world has progressed substantially in mitigating many epidemics from time to time owing to the improved public health measures, but the recent COVID-19 pandemic is a wake up slap to the global public health realm and there is still much more to know about COVID-19. The lessons learned from previous epidemics demonstrate that prevention and control of pandemics involves many factors such as isolation, quarantine, personal protection, social distancing, diagnosis, treatment, disinfection, immunization, health education and international measures.

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Chapter 2
The Modeling of the Capacity of the Moroccan Healthcare System in the Context of COVID-19:
The Relevance of the Logistic Approach

Mohamed Merzouki
https://orcid.org/0000-0002-9837-4312
Sultan Moulay Slimane University, Morocco

Mostafa Bentahir
Université catholique de Louvain, Belgium

Fatiha Chigr
Sultan Moulay Slimane University, Morocco

Mohamed Najimi
Sultan Moulay Slimane University, Morocco

Jean-Luc Gala
Université catholique de Louvain, Belgium

ABSTRACT

The outbreak of SARS-Cov2 in China and its subsequent spread has caused a global pandemic. The authors conducted a simple susceptible-infected (SI) model of the spread of COVID-19 in Moroccan population. The model is based on combining the average contact rate (μmax) extracted from the early exponential phase of the outbreak with a logistic simulation over time. Interestingly, this modeling approach showed a perfect fit with a strong correlation between real confirmed and estimated cases when

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calibrated on the Chinese declining outbreak. Subsequently, the model was applied for studying the ongoing COVID-19 outbreak in Morocco to determine the needed time for reaching 10,000 confirmed cases whose 15% (1,500) are at risk of developing health complications requiring patient care in hospitals. The latter total capacity does not exceed 1,640 beds according to the authorities. Incorporating these parameters in the logistic model, they predicted that the Moroccan healthcare system will be at 27%, 50%, 76%, and 90% of saturation on April 11, 16, 23, and May 4, 2020, respectively.

INTRODUCTION

In mid-December 2019, an outbreak of a cluster of atypical pneumonia of unknown origin has broken out in Wuhan City, Hubei Province, and spread rapidly to the mainland in China. Subsequently, the causative viral agent had been identified as a novel coronavirus named SARS-CoV2 (Huang *et al*., 2020; World Health Organization, 2020). Since then, the outbreak has progressed like wildfire to many other countries what prompted the World Health Organization (WHO) Emergency Committee to declare COVID-19 illness a global health emergency by the end of January 2020. Currently the case detection rate is changing daily as it can be tracked in almost real time on the websites of WHO and national health ministries of these countries.

When the WHO has listed 13 top-priority African countries at risk of importing COVID-19due to their direct links to China or a high volume of travel to China (Velavan et Meyer, 2020), the Moroccan government decided to interrupt commercial flights to and from China as measure to mitigate the risk of importing the disease to Morocco. However, the outbreak of new clusters of COVID-19 illness in European countries notably Italy, France and Spain where thousands of Moroccans live and from which millions of European tourists travel frequently for spending their holidays in Morocco has prompt the Moroccan government to set up additional preventive measures. Indeed, as of 21 February 2020, the virus had spread rapidly within China but also to 28 other countries, including in the World Health Organization (WHO) European Region [World Health Organization Regional Office for Europe] (Spiteri *et al.,* 2020; WHO, 2020).

Consequently, Morocco has recorded the first case of COVID-19 on 2 March 2020. It wasan imported case by a Moroccan resident living in Italy (Moroccan Ministry of Health, 2020). Subsequently, the next COVID-19 cases were all exclusively imported cases (either by Moroccan residents living abroad or national European citizens visiting Morocco). These imported cases were the main cause of the virus spread in Morocco and the disease transmission within the local population. In a response to the increase of cases, the Moroccan authorities have first decided to suspend all flights from Morocco to these European countries and vice versa later. Additionally, the authorities extended gradually the containment policy measures by closing schools, shutting down unnecessary economical activities and declaring lastly the sanitary emergency in order to help reducing the spread of the virus and COVID-19 disease progression of in Morocco (Moroccan Ministry of health, 2020). In this study, we used data from Chinese outbreak to test and assess the validity of a novel modeling approach of COVID-19 illness. This choice is justified by the ability of China to control and stop the spread of the disease trough setting aggressive containment measures. We have next analyzed the main features of the COVID-19

outbreak initiation and evolution in Morocco using the data gathered during the two first weeks after the outbreak initiation. Finally, a logistical model was used to predict crucial time points leading to the gradual saturation of the Moroccan health care system.

METHODOLOGY

Study Scope

The main working hypothesis of this paper is considering that the logistic model equations and parameters are sufficient to describe and analyze the evolution of the coronavirus epidemic COVID-19 without additional requirements such as the virus incubation period, incidence rate, healing time and the basic reproduction number R0. Therefore, the mathematical modeling has been built on the initial COVID-19-infected population (N0), infection rate (μ), time and the limited growing capacity factor (K).

Data Collection

The total confirmed cases of COVID19 in China were retrieved from the Chinese Center for Disease Control and Prevention Weekly platform (CCDC Weekly) (China, 2020). This platform, under the authority of the Chinese National Health Commission, is managed by the Chinese Center for Disease Control and Prevention CCDC (China CDC) publishes daily situation reports of COVID-19 in China (China CDC, 2020).

For Morocco, data used in this study were obtained from statistics released by the Moroccan health minister's in the press on daily basis and from its official portal on the web publishing daily situation reports (http://www.covidmaroc.ma/pages/Accueil.aspx).

Mathematical Models

Exponential Model (Malthus, 1798)

The model assumes that the variation of the infected population as a function of time can be described by the following linear differential equation(Malthus, 2018):

$$\dot{N} = \mu N \tag{1}$$

Where N is the number of cases infected at the time (t) and μ is the infection rate.
The initial condition is as follows $N(0) = N_0$, the solution of the differential equation is:
Where N_0 is the number of confirmed cases at t=t_0.

$$N = N_0 e^{\mu t} \tag{2}$$

Logistic Model (Verhulst, 1838)

The logistic model was originally deposited by Verhulst in his pioneer work on limits to population growth, and is defined by the following differential equation(Verhulst, 1838):

$$\dot{N} = \mu_{\max}(1-\frac{N}{K})N \tag{3}$$

The logistic model estimates the number of confirmed cases at time (t+1) by multiplying N by $\mu(1–N/K)$, where K is a parameter that will be interpreted retrospectively from the stationary phase of the outbreak and μmax is the maximum infection rate to be reached in the exponential phase.

In the initial condition $N(0) = N$, the solution of the equation (1.4) is as follows:

$$N(t) = \frac{N_0 e^{\mu_{\max} t}}{1+\frac{N_0}{K}\left(e^{\mu_{\max} t}-1\right)} \tag{4}$$

STATISTICAL TESTS

During the exponential growth, the significance of the Spearman's coefficient ''ρ'' for exponential models is verified at an error of 0.05 using the Spearman test. Concerning the correlation between real cases and those simulated by the exponential model, we used the correlation coefficient of Pearson "r". The two tests were carried out using the R 3.6.3 software under Windows.

Strategies for Modeling

At first, we have studied the evolution of the spread of the COVID-19 coronavirus epidemic in the Chinese and Moroccan populations during from the first day of the outbreak (exponential stage) to determine the maximum infection rate ($\mu_{\max}$). This latter parameter was used in the logistic equation to model the evolution of the COVID-19 outbreak in both countries.

RESULTS

Model Development and Calibration

Initially, we have reported the number of confirmed COVID-19 cases in China over 60 days period. We have thus noticed that the dynamics of the virus spread and infection of new persons follows two stages revealing two different processes. The first stage followed an exponential growth while the second stage was following a logistic fit (figure 1A). The simulation of these two components of the curve trends are depicted figure 1B. Therefore, we have decided to model the first the exponential phase of COVID-19

epidemic in China during the first 12 days of the epidemic using Malthus exponential model (figure 1B). This first model allowed us to retrieve the μ_{max} parameter, calculated as the average of μ during these days and then we have simulated the evolution of the outbreak during this period. The calculated μ_{max} during the first 12 days was 0.27 ± 0.09 and both curve trends of cumulative real confirmed and simulated cases showed a perfect correlation with an exponential evolution (figure 1C).Moreover, this model showed a significant correlation (r= 0.98) between real confirmed and estimated cases.

Subsequently, the calculated μmax was integrated into the logistic equation (1, 4))to model the evolution of the outbreak spread over 60 days among the Chinese population. The *K* parameter was set at 81,887, which corresponds at the total confirmed cases recorder at the end of the outbreak. Our adjusted logistic model for the Chinese population showed a perfect match between the real confirmed and estimated cases (r=0.98) as shown in figure 1D.

Figure 1. Evolution of confirmed cases of coronavirus infection (COVID-19) in China

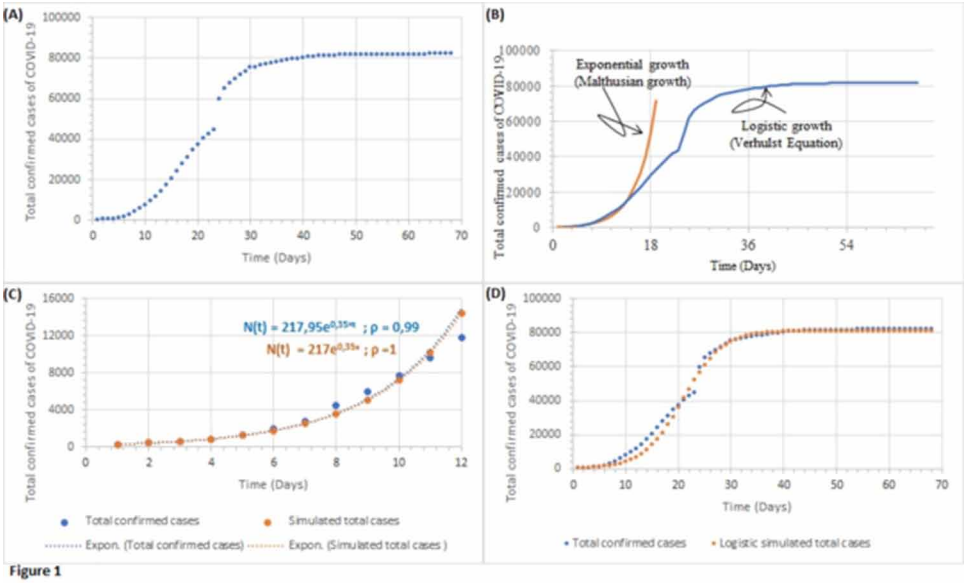

Figure 1

(A) and (B) show this evolution during the first 60 days without and according to the exponential and logistic models respectively. (C) report on the comparison of the evolution of growth in total confirmed cases of COVID-19 and the cases estimated by the adjusted exponential model during the first 12 days of the epidemic and (D) on evolution of real contaminated cases in and those simulated by the logistics model from January 21 to March 19, 2020 (60 days).

Application to Moroccan COVID-19 Outbreak

Similarly, we have estimated the infection rate ($\mu_{max} = 0.204 \pm 0.04$) from the exponential model during the first 28days of the outbreak using the cumulative confirmed case statistics of COVID-19. The exponential model showed a significant correlation over time and between real and estimated cases (figure

2A).Moreover, the real number of confirmed cases showed a clear deviation from the exponential growth starting from the 28th day of the outbreak onward (figure 2B).

Since the outbreak in Morocco is at the beginning phase, the value of *K* parameter is not known at this moment. The value of this parameter was set at 10.000 SARS-COV2 infected person taking into account that 15% (1500 cases) of infected persons will develop a severe disease outcome as stated by the Moroccan authorities. We assumed that this critical threshold number of cases would lead to the overwhelming of the Moroccan health care system capacity, which does not exceed 1640 beds in the intensive care units. We next used μ_{max} and *K* parameters determined above in the logistic model to estimate the number of expected cases (figure 2C and table 1). The data was then transformed into percentage as 15% of persons may develop severe outcome and over time to predict that the Moroccan health care system would be at 27, 50, 76 and 90% of saturation in April 11, 16, 23 and May 4, 2020, respectively (figure 2D).

Figure 2. Evolution of simulated cases of coronavirus infection (COVID-19) in Morocco after adjustment by exponential model (compared to confirmed cases) during the first 28 days of the epidemic (A), by the logistical and exponential models from March 2 to April 5, 2020 (35 days) (B) and in critical condition (15% of total confirmed cases) according to the logistic model (C) with evolution of saturation of health system in Morocco (D)

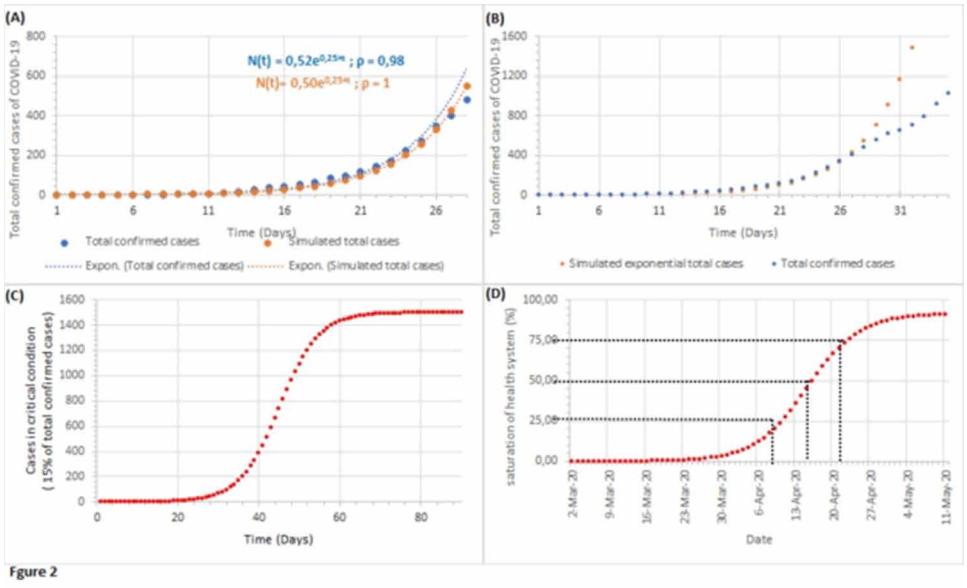

Figure 2

DISCUSSION

In the present investigation, we analyzed the evolution of the COVID-19 outbreak in Morocco and gave prediction and estimation of the speed of the disease spreading in relation the health care capacity saturation based on mathematical model. Indeed, our model has been used to predict the time-points when the Moroccan health care system will gradually be overwhelmed and even collapsed. Using the existing data and the mathematical model incorporating these data, we provide an estimation of the

Table 1. Simulated cases by logistic model in Morocco

Date	Days	Logistic Simulated total cases (K=10000, μ_{max} =0,204)	Date	Days	Logistic Simulated total cases (K=10000, μ_{max} =0,204)
2-Mar-20	1	1	13-Apr-20	43	3922
3-Mar-20	2	2	14-Apr-20	44	4417
4-Mar-20	3	2	15-Apr-20	45	4924
5-Mar-20	4	2	16-Apr-20	46	5433
6-Mar-20	5	3	17-Apr-20	47	5933
7-Mar-20	6	3	18-Apr-20	48	6415
8-Mar-20	7	4	19-Apr-20	49	6869
9-Mar-20	8	5	20-Apr-20	50	7290
10-Mar-20	9	6	21-Apr-20	51	7674
11-Mar-20	10	8	22-Apr-20	52	8018
12-Mar-20	11	9	23-Apr-20	53	8323
13-Mar-20	12	12	24-Apr-20	54	8588
14-Mar-20	13	14	25-Apr-20	55	8818
15-Mar-20	14	17	26-Apr-20	56	9015
16-Mar-20	15	21	27-Apr-20	57	9182
17-Mar-20	16	26	28-Apr-20	58	9322
18-Mar-20	17	32	29-Apr-20	59	9441
19-Mar-20	18	39	30-Apr-20	60	9539
20-Mar-20	19	48	1-May-20	61	9621
21-Mar-20	20	59	2-May-20	62	9689
22-Mar-20	21	72	3-May-20	63	9745
23-Mar-20	22	88	4-May-20	64	9791
24-Mar-20	23	108	5-May-20	65	9829
25-Mar-20	24	132	6-May-20	66	9860
26-Mar-20	25	161	7-May-20	67	9885
27-Mar-20	26	197	8-May-20	68	9906
28-Mar-20	27	241	9-May-20	69	9924
29-Mar-20	28	294	10-May-20	70	9938
30-Mar-20	29	358	11-May-20	71	9949
31-Mar-20	30	435	12-May-20	72	9958
1-Apr-20	31	528	13-May-20	73	9966
2-Apr-20	32	640	14-May-20	74	9972
3-Apr-20	33	774	15-May-20	75	9977
4-Apr-20	34	933	16-May-20	76	9982
5-Apr-20	35	1120	17-May-20	77	9985
6-Apr-20	36	1340	18-May-20	78	9988
7-Apr-20	37	1595	19-May-20	79	9990
8-Apr-20	38	1887	20-May-20	80	9992
9-Apr-20	39	2220	21-May-20	81	9993
10-Apr-20	40	2592	22-May-20	82	9995
11-Apr-20	41	3002	23-May-20	83	9996
12-Apr-20	42	3447	24-May-20	84	9996

spread trend of COVID-19 during the early stage. Moreover, the interesting data obtained in this study provides an expository account of the application of a mathematical model based on the integration of μmax parameter derived from the exponential stage into the logistic equation to allow a precise analysis of temporal trajectory of COVID-19 outbreak spread. The present model incorporating μmax and time factors, as a sole variable is therefore simpler compared to other models used recently to analyze the COVD-19 outbreak spread likeR_0 or SIR (susceptible-infected-recovered) epidemiological models. Importantly, in this model the working hypothesis considers that the logistic model is able to describe and analyze the evolution of the coronavirus epidemic COVID-19 without requiring specific knowledge about additional characteristics such as virus incubation period, incidence rate, healing time and basic reproduction number R_0 (Delamater *et al.,* 2019; Li *et al.,*2011). Furthermore, unlike the SIR model assuming that infection and recovery occur at constant rates (Chen *et al.,* 2020), the current logistical model only takes into account the rate of infection (susceptible-infected). It is noteworthy that this type of modeling of biological processes is widely used in various fields including bacterial growth or viral load (Arenas *et al.,* 2017; Peleg *et al.,* 2007) but to our knowledge, it is the first time that this approach is applied for simulating the evolution of a viral outbreak in an epidemiological context.

This work proposes the use of the logistic model to analyze and predict the spread of Coronavirus COVID-19 in China and Moroccan's populations. As a complement, we studied both early exponential phase of the outbreak and used logistic simulation to obtain a preliminary validation on the model based on the real data of China's population and then apply it to Moroccan's population. It is important to note that more COVID-19 epidemiological studies are now needed to assess the validity of the current model through rigorous statistical analysis as well as its capacity to simulate the evolution of the outbreak spreading in other locations of the world.

The Chinese episode has been extensively studied and many proposed models have been well characterized (Riou *et al.,* 2020; Yang *et al.,* 2020). Our model has firstly been applied for analyzing the epidemic evolution using the Chinese data (CCD, 2020) and showed a good fit between real confirmed and estimated. The graphical analysis of the evolution of infected cases in China showed that it follows a logistic growth model. We have divided this curve into two phases; an exponential one and another which is logistic. First, we determined the average maximum infection rate during exponential growth ($\mu_{max} = 0.27 \pm 0.09$) during the first 12 days of the epidemic. The correlation to an exponential growth was highly significant ($\rho = 0.99$). Next we integrated the infection into the logistic model by setting $k = 81000$ which corresponds to the cumulative number of the confirmed cases at the end of the outbreak. Interestingly, the comparison of the evolution of the curve found by the logistic model and that representing the real cases showed a strong resemblance. Furthermore, as for previous studies, our results showed a decrease of the infection rate over time that can be achieved by imposing quarantine, which results in a decrease of the average contamination rate coefficient μ that describes growth of the cumulative as well as the daily new cases in the exponential phase. Interestingly, when applied to the South Korean situation, we found that real and estimated cases do not fit perfectly which can be explained by the fact that South Korea did not apply strict containment measures but instead used a strategy based on the massive testing of its population (data not shown).

These interesting findings prompted us to apply the current modeling strategy in the Moroccan outbreak context. Similarly, the evolutionary trend of the cumulative cases recorded in Morocco showed an exponential trend in the early days. This trend allowed us calculating a maximum average infection rate in the Moroccan population ($\mu_{max} = 0.204 \pm 0.04$) during the first 28 days. According to official declarations from the authorities, almost 15% of COVID-19 confirmed patients require health care in

hospitals while the number of intensive care beds in intensive care units in Morocco is limited to 1640. All together these figures indicate that reaching a level of 10.000 patients or more should be considered as the critical threshold that may cause a total saturation of the Moroccan health care system capacity. Using our logistic April 11, 16, 23 and May 4, 2020, respectively. In our opinion, these dates should be taken as warning marks in the evolution of the outbreak in Morocco and need to be observed by decision-makers to assess the situation as the number of COVID-19 confirmed patients' increases progressively.

In that respect, unlike other European countries, the initial response in Morocco was rapid and proportionate and was increasingly highly judged by other countries. Indeed, authorities decided to apply a strict containment to avoid overwhelmed hospitals. They are meanwhile increasing their preparedness by increasing the capacity of testing, acquiring well-adapted personal protective equipment and ventilators (Jacobsen *et al.,* 2020). To what extent these responses and recommendations will attenuate the outbreak speed; this can only be verified in the next decisive weeks. In light of these data, Moroccan authorities are encouraged to go further in extending the duration of confinement and/or to apply it more drastic measures. As risk mitigation measures, authorities need to impose mask wearing for everyone (WHO, 2020) and increase drastically the rate of the population testing.

In conclusion, this investigation provides a new methodology for analyzing COVID-19 outbreak spread trends through using exponential and logistic models and applying it to the Moroccan situation. The model produced convincing results when applied to the local and well-studied outbreak in China and the ongoing epidemic in Morocco. The main advantage of the current model is its simplicity thanks to the use of conventional spreadsheets. The model presented here is deterministic, it is worth noting that such predictions are valid as long as the initial conditions remain valid, thus providing the possibility of at least a short-term forecast.

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Section 2

Symptomatology, Diagnosis, and Transmissibility Characteristics of COVID-19

Chapter 3
Symptomatology and Clinical Features of Human COVID-19

Mohamed Echchakery
Institut Supérieur des Sciences de la Santé, Université Hassan Premier Settat-Maroc, Morocco

Souad El Mouahid
Higher Institute of Nursing Professions and Health Techniques, Morocco

Soraia El Baz
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Maryam Mountassir
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Ahmed Taoufik Hakkoum
Laboratory of Biochemistry, Arrazi Hospital University Mohammed VI, Morocco

Raymond Klevor
Arrazi Hospital, Mohammed VI University Medical Center, Marrakech, Morocco

Ansumana Mohammed Keita
Mohammed VI University Teaching Hospital, Morocco

Said El Hizazi
Ecole Supérieure de Technologie, Université Ibn Zohr, Morocco

Draoui Ahmed
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Nadia Zouhairi
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Abdelmohcine Aimrane
Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco

Abdelhafid Benksim
Higher Institute of Nursing Professions and Health Techniques, Morocco

Redouane Chatoui
Sciences and Technologies Faculty Beni Mellal, Sultan Moulay Slimane University, Morocco

Yassin Zemrani
Arrazi Hospital University Mohammed VI, Morocco

Asmae Lamrani Hanchi
Faculty of Medicine and Pharmacy of Marrakech, Morocco & Cadi Ayyad University, Morocco

Mohamed Alouani
Faculty of Applied Sciences, University Ibn Zohr, Morocco

ABSTRACT

Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which was identified at the end of December 2019 in China. Symptoms of COVID-19 can appear after an incubation phase of the virus of 2 to 14 days, the most common being fever, cough,

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and asthenia. Other specific symptoms may include shortness of breath or difficulty breathing, muscle pain, sore throat, chills, loss of smell or sensation, chest pain, headache, nausea, rash, diarrhea, and vomiting. The severity of these symptoms can be mild or even extreme causing serious damage to several organs, directly and indirectly, namely pulmonary, renal, hepatic, cardiac, digestive, neurological. Some people have only mild symptoms, while others are asymptomatic. Seniors or those at risk for certain chronic diseases, such as massive obesity, diabetes, heart disease, lung disease, kidney disease, immune system abnormalities, and liver disease are more susceptible to COVID-19 and can develop more serious and fatal complications.

INTRODUCTION

In December 2019, an outbreak of severe pneumonia cases began in Wuhan City, Hubei Province, China in patients with severe unexplained lung disease (Zhu et al.,2019). In early January 2020, a new beta-coronavirus, later the World Health Organization (WHO)named severe acute respiratorysyndrome coronavirus 2 (SARS-CoV-2) as a new type of coronavirus, was isolated and identified from bronchoalveolar lavage fluid samples. SARS-CoV-2 causes an acute respiratory infection as in the case of SARS-CoV and MERS-CoV, with fever, cough and dyspnea; pneumonia is a serious manifestation that can rapidly progress to acute respiratory distress syndrome (ARDS) (WHO, 2020a), was declared a pandemic on March 11, 2020 (WHO, 2020a; WHO, 2020b).The impacts of this pandemic on health, both at the individual and global levels, as well as the impacts on other spheres of human endeavor are cumulatively being evaluated. While other human coronavirus outbreaks have occurred, the recent virus seems to have been favored by the peculiar political atmosphere, mass misinformation and global unpreparedness.

The human immune system is a perfect system that combines a variety of cells and mediators to provide protective immunity against infectious agents. Its intervention can be with early reactions, as in innate immunity and, later, in a set of cellular and humoral responses (adaptive immunity), both decisive in the defense against intracellular germs, such as SARS-CoV-2 (Shah et al., 2020).

Although the new SARS-CoV-2 coronavirus mainly affects the lungs, one of its main characteristics is the ability to infect many organs, and it shows a great clinical diversity of symptoms and manifestations. In other words, COVID-19 can show many faces and, when it is serious, evolve very differently. Different drugs are used and studied to treat it (N. Chen et al., 2020).From what is known to date, the incubation period of the disease is between 4 and 14 days after exposure to the virus, which is introduced into the body after inhaling microdroplets released by an infected person when breathing, talking, cough or sneeze. Once it enters the body through the inspired air, the virus can enter the epithelial cells of the nasal and pharyngeal mucosa via the angiotensin converting enzyme 2 receptor (ACE2) (Onder et al., 2020).During this time before symptoms appear, the virus actively multiplies and the person exhales microdroplets while speaking and coughing that spread the virus (Chan et al., 2020).The first symptoms of infection are usually fever, fatigue, dyspnea, anorexia, dry cough, sore throat, loss of taste and smell,

runny nose, general malaise, muscle pain and headache (Chan et al., 2020; N. Chen et al., 2020; Guan et al., 2020; Huang et al., 2020; Young et al., 2020). Infection with SARS-CoV-2, the causative agent of COVID-19, appears to have the lungs as the primary target, as pneumonia is the most common serious manifestation associated with this disease. If the immune system is not able to control the spread of the virus at this time, the virus may enter the lungs where the cells in the alveoli also express high levels of the ACE2 receptor, making them very susceptible to infection. When this happens, on the one hand, the alveoli cease to perform their gas exchange function efficiently, so that the patient can stop receiving oxygen at adequate levels. On the other hand, cells of the immune system initiate an inflammatory response in the lungs characterized by the release of large amounts of chemokines, the function of which is to recruit immune cells from other regions of the body (N. Chen et al., 2020). This causes inflammation, leading to the production of fluid and pus which contributes to the development of pneumonia and the decrease in oxygen levels in the blood. When this occurs, the patient should receive supplemental oxygen through nasal cannula or a mask, and if their condition worsens and progresses to Acute Respiratory Distress Syndrome (ARDS), they will need a mechanical ventilator. ARDS is a potentially fatal syndrome with inflammation and lung damage (Wu et al., 2020). If an x-ray or chest scan is done at this time, infiltrates can be seen scattered throughout both lungs which, when the autopsy is performed, indicate that they are made up of fluid made up of mucus and remnants of white blood cells and lung cells (N. Chen et al., 2020; H.Y.F.Wong et al., 2019; Zhao et al., 2019).However, in some patients, the lung is only the starting point for dissemination through other organs and tissues, causing a wide spectrum of manifestations such as diarrhea, renal failure, cardiomyopathy, liver failure, those derived from the predisposition to form blood clots, and overstimulation of the immune response which can lead to the failure of several organs (Chan et al., 2020; N. Chen et al., 2020).

In most cases, symptoms appear five days after exposure. The vast majority of patients (around 80%) do not have symptoms or show mild manifestations of the disease, and COVID-19 passes without major problems, sometimes even without knowing it (Wu et al., 2020). But in 20% of cases the disease worsens and its development can cause different clinical pictures.

If COVID-19 worsens, lung problems arise, which sometimes leads to a critical phase of the disease, with respiratory problems and damage to other organs. In a small percentage of cases (2-3%) the disease causes death. In the appearance and development of COVID-19 there are various factors that influence the risk of each person, such as age, gender, viral load, genetics, environment, previous diseases. Many symptoms of COVID-19 have been detected. Among them are fever, fatigue, shortness of breath, dry cough, sore throat, loss of taste and smell, muscle aches and headaches. These symptoms do not always appear at the same time or with the same intensity (Chan et al., 2020; N. Chen et al., 2020; Guan et al., 2020; Huang et al., 2020; Young et al., 2020).

Normally, the immune system is able to control the virus before it spreads through the body, preventing it from reaching the lungs. When the disease develops and reaches a severe phase, the following have been identified among the possible clinical manifestations (N. Chen et al., 2020; Jiehao et al., 2020).In addition to lung damage, the SARS-CoV-2 virus can cause these other manifestations:

- Infection in the lungs, with possible lack of oxygen and the appearance of pneumonia.
- Acute kidney failure, with loss of blood and protein in the urine, which may be due to both the virus's direct effect on kidney tissue and other effects on the body such as hypotension.
- Heart disease in the heart: arrhythmias, thrombi, heart attacks.
- Cardiovascular disorders such as arrhythmias, thrombi, endocarditis or myocardial infarction.

- Liver problems leading to an increase in blood transaminases.
- Alterations in the digestive system, with nausea, diarrhea, abdominal pain ...
- Appearance of blood clots.
- Neurological problems, from migraines and seizures to meningitis and stroke.
- Uncontrolled immune response that can lead to multi-organ failure.
- Loss of taste and smell due to damage to nerve cells in the nasopharyngeal area.
- Conjunctivitis.
- Dermatological involvement with skin rashes and hives, which appear more frequently in mild cases.

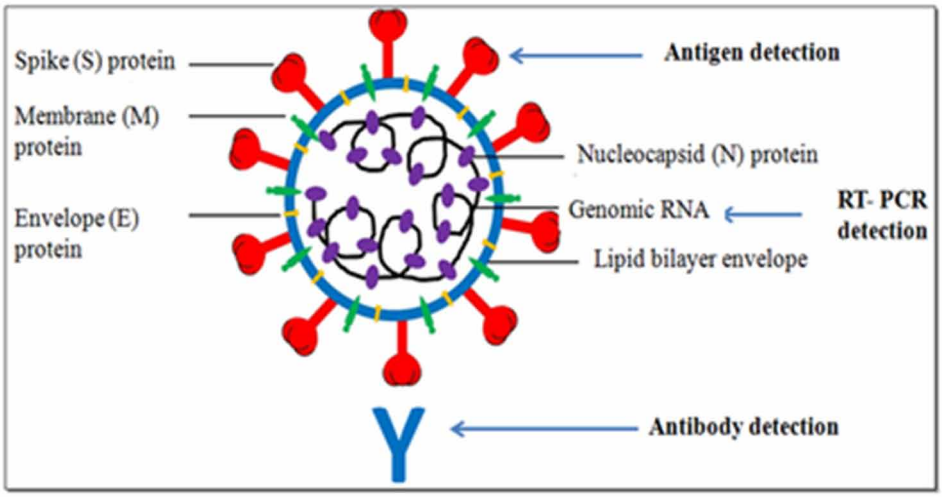
Without a doubt, the most serious condition is the exacerbated reaction of the immune system which gives rise to an acute syndrome called "cytokine storm", which is responsible for circulatory collapse,intravascular clot formation and catastrophic multi-organ failure resulting in death of the patient (Tang et al., 2020). One of the main concerns is to control the immune response that the body produces when the lung infection worsens. In most cases, the immune response controls the virus and slows down COVID-19. But sometimes this defensive response gets out of hand and causes inflammation, generating a process known as a cytokine storm which can cause multiple organ failure and death of the patient (Tang et al., 2020; Yazdanpanah et al., 2020). Certain laboratory values have been identified as markers making it possible to identify subjects who will present with more severe forms,such as a decrease in lymphocyte values or an increase in the concentration of different substances in the blood (lactate dehydrogenase, C-reactive protein, ferritin, D-dimer, troponin, creatine phosphokinase, transaminases), increased erythrocyte sedimentation rate or increased prothrombin time (Arentz et al., 2020 ; N. Chen et al., 2020; Qiu et al., 2020). Among these parameters most associated with a poor prognosis, the decrease in lymphocyte values and the increase in plasma D-dimer concentration have been defined as particularly relevant (Arentz et al., 2020 ; N. Chen et al., 2020 ; Qiu et al., 2020).

PATHOGEN

The SARS-CoV 2 is a novel strain of the family of coronaviruses. These are positive-sense, single-stranded RNA viruses and entail four genus: alpha, beta, gamma and delta coronaviruses. SARS-CoV-2 is a beta coronavirus. The lethality of coronaviruses is seen in the fact that outbreaks of other highly pathogenic strains of the family have been recorded in quite recent times. These are the severe acute respiratory syndrome–coronavirus 1 (SARS-CoV-1) and the Middle East respiratory syndrome–coronavirus (MERS-CoV) (Cui etal., 2019; Zaki et al., 2012; Zhong et al., 2003). SARS-CoV-2 is closest to the bat coronavirus with a genetic similarity of approximately 96%. Among the human coronaviruses, SARS-CoV-2 is closest to SARS-CoV-1 with approximately 79% genetic similarity (Wang et al., 2020).

The genome of SARS-CoV-2 codes for structural or non-structural proteins. Non-structural proteins include enzymes, the most relevant of which is the RNA-dependent RNA polymerase responsible for RNA replication. Structural proteins include the spike, envelope, membrane and nucleocapside, respectively, S, E, M and N proteins. Coronaviruses are named for the radiating crown of spike proteins constituting their outer covering (**Fig. 1**).

Figure 1. Illustration of SARS-CoV-2 showing structural proteins and viral RNA(Wang et al., 2020)



PATHOGENY

The interaction between the virus and the host is decisive because it depends on the health condition of the affected person.

SARS-CoV-2 Entry to the Host and Target Organs

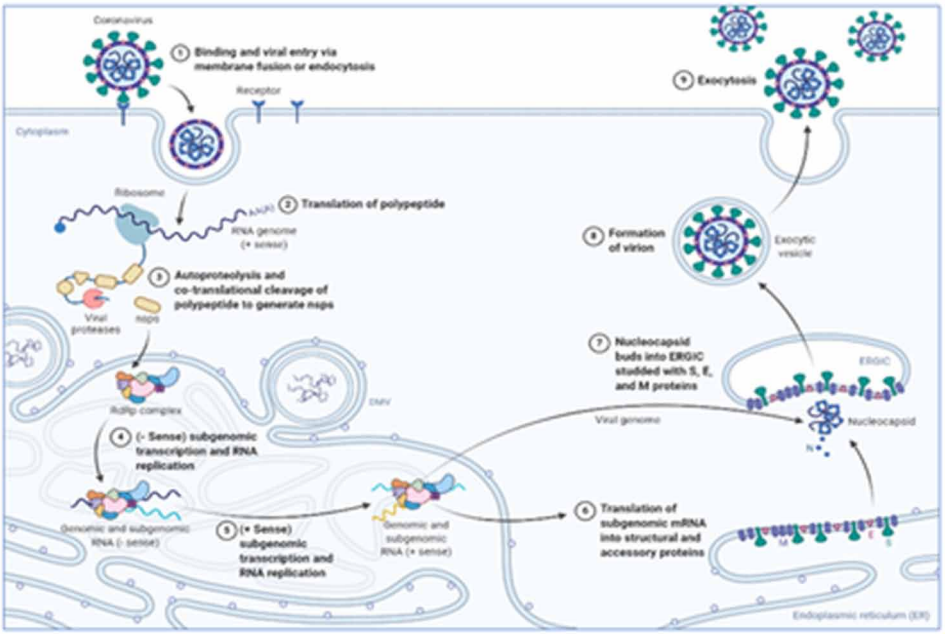
Once the inoculum reaches a potential host, the viral surface proteins come into play. The S protein is responsible for recognition and binding of the host cell (Mittal et al., 2020). The spike glycoprotein has two structural components, S1 and S2. The S1 component functions as the host ACE2 receptor ligand and as such is responsible for recognition of and adhesion to the host cell(Hoffmann et al., 2020; F. Zhou et al., 2020). The ACE2 receptor recognition explains the virus' tropism for the respiratory tract as there is a high expression of these receptors in the lung epithelial cells (P. Zhou et al., 2020). The S2 component is responsible for fusion of the virus with the host cell. This component has a transmembrane and a cytoplasmic domain which enable this function (Wegener& Campbell, 2008). Once attachment to the host cell has occurred, S protein priming follows with the involvement of the cellular serine, the transmembrane serine protease 2 (TMPRSS2) and cathepsin B and L which are endosomal cysteine proteases. S protein cleavage occurs at the S1/S2 site or within the S2 subunit activating S2 thereby allowing for fusion of the viral and cellular membranes (Hoffmann et al., 2020; Ou et al., 2020).

Following fusion of membranes, the viral RNA enzymes are released into the host cell and the viral replication cycle begins. Upon entry, a replicase-transcriptase complex is synthesized and drives the viral replication and transcription process. This intracellular phase requires the action of viral enzymes and the host cell machinery. Upon translation, viral proteins are inserted into the rough endoplasmic reticulum where they are carried along a secretory pathway to the site of assembly. Once assembled, the virus is exocytosed exposing adjacent host cells to infection (De Haan et al., 2005) (**Fig.2**).

The origin of all clinical abnormalities in patients with SARS-CoV-2 infection begins with the binding of glycoprotein S to the host cell receptor (Angiotensin-converting enzyme 2 [ACE2]), which is a critical step for virus entry (Zhang H.et al., 2020). ACE2 is found in the kidneys, cardiovascular system, liver and gastrointestinal tract, central nervous system, testes, and placenta (Soler et al., 2008). In adipose tissue, in addition to ACE2, the enzyme dipeptidyl peptidase 4 (DPP-4) is expressed, which has been identified as a MERS-CoV receptor and which is increased in diabetes and obesity; participates by promoting the inflammatory process by increasing the activity of T lymphocytes and the secretion of interleukins (Malavazos et al., 2020):

- Primary response to SARS-CoV-2 infection
- Role of antibodies in SARS-CoV-2 infection
- Cytokine release or storm syndrome in macrophage activation syndrome (SAM) secondary to SARS-CoV-2 infection
- Pulmonary pathology

Figure 2. Life Cycle of Coronavirus: contact, entry, synthesis and assembly of viral proteins, exocytosis of virus (Hartenian et al., 2020)



The Incubation Period, Symptomatology, Clinical Features, and Risk Factors Associated with Infection by SARS-CoV-2

According to the World Health Organization and the Centers for Disease Control and Prevention, the estimated range of incubation periods for SARS-CoV-2 was 1-14 days. The mean incubation period was estimated to be 5-6 days (CDC, 2020; WHO, 2020a).

After a median incubation period of about 5 days (range: 2 -14 days), a typical COVID-19 infection begins with a dry cough and mild fever (38.139 °C), often accompanied by a decrease in smell and taste. In most patients, COVID-19 remains mild or moderate and symptoms subside within a week, so patients generally recover at home (Qiu et al., 2020).About 10% of patients remain symptomatic until the second week (Verity et al., 2020). The longer the symptoms persist, the greater the risk of developing more severe COVID-19, which will require hospitalization, intensive care and invasive ventilation. The outcome of COVID-19 is often unpredictable, especially in older patients with comorbidities. The clinical picture ranges from completely asymptomatic to rapidly devastating pictures.

In the early stages of the pandemic, study analysis confirmed cases of COVID-19 (January 2020-February 2020) obtained in 50 provinces, regions, and countries outside of Wuhan, China (a total of 181 cases), estimated the average incubation period of SARS-CoV-2 to be 5.1 days (Backer et al., 2020; Q. Li et al., 2020). It is estimated that about 97.5% of patients with COVID-19 develop symptoms within 11.5 days of infection, and about 2.5% of patients develop symptoms within 2.2 days (Backer et al., 2020; Q. Li et al., 2020).

Regarding specific symptoms, the results of the study reveal that the average incubation period at the onset of fever is 5.7 days. The study also assumed that out of 10,000 confirmed cases, 101 will develop symptoms after 14 days of isolation (Q. Li et al., 2020).

The spectrum of diseases generated by coronavirus infection is mainly acute and chronic respiratory, enteric, hematologic and central nervous system (Qiang et al., 2020). The virus types β-Cov, SARS-Cov and MERS-Cov generate potentially serious infections of the respiratory system (Lai et al., 2020).

An important thing to remember is that the incubation period can vary from person to person. A study of 1,099 confirmed COVID-19 patients showed that the average incubation period is estimated to be 3 days, with an incubation period of 0 to 24 days (Guan et al., 2020). There is also some evidence that the incubation period can be extended up to 27 days (Shen&Woo, 2020). There is evidence regarding asymptomatic cases which claims that the incubation period of an asymptomatic patient is 19 days (Bai et al., 2020).

However, regarding an incubation period as long as 24 days, the World Health Organization mentioned in a press release that such a long incubation period is more likely due to a second infection than it is. in pursuit of the first infection.

The presentation of symptomatic and clinical pictures is very variable and, in most cases, they are mild manifestations (estimated at 80%) (Wu &McGoogan, 2020). Patients with symptoms may have the following clinical pictures, originally described by the China Center for Disease Prevention and Control (N. Chen et al., 2020; Verity et al., 2020; Wang et al., 2020; Wu &McGoogan, 2020):

- Patients with severe disease: they have a feeling of shortness of breath, poor blood oxygenation and pulmonary manifestations 24 to 48 hours after the onset of symptoms (14% of cases).
- Seriously ill patients: develop acute respiratory failure and multi-organ dysfunction (5% of cases).
- Patients with fatal illness and death (2.3%).

Among the main factors that influence the progression to a fatal form of the disease, we can cite the age and the presence of previous comorbidities, such as cardiovascular diseases, in particular hypertension, diabetes, pulmonary diseases, hepatic chronic, cancer, disease and obesity (Cao et al., 2020; N. Chen et al., 2020; Cheung et al., 2020; Goyal et al., 2020; Jiehao et al., 2020; Onder et al., 2020; Lighter et al., 2020; McMichael et al., 2020; Shi et al., 2020;Verity et al., 2020; C. Wu et al., 2020; Wu&McGoogan,

2020). Regarding age, COVID-19 has been described in all age groups (Wu et al., 2020). From what has been observed so far, children are generally asymptomatic (Qiu et al., 2020; Liu et al., 2020a), while people of middle age or older are usually the most and affected, and those over 80 are the patients who develop fatal forms of the disease (Verity et al., 2020; Onder et al., 2020; CDC COVID-19 Response Team, 2020; Goyal et al., 2020; Wu et al., 2020; McMichael et al., 2020; Chen N. et al., 2020).Other factors could also be linked to a greater predisposition to a more severe course of the disease, such as the male sex (N. Chen et al., 2020; Chan et al., 2020) or the black population, although this last was determined in the United States and may be more related to socio-economic factors (Webb Hooper et al., 2020; Holman et al., 2020; Liu et al., 2020a).

Figure 3. The most common symptoms of COVID-19 (Developed from the results of Lechien et al. (2020a))

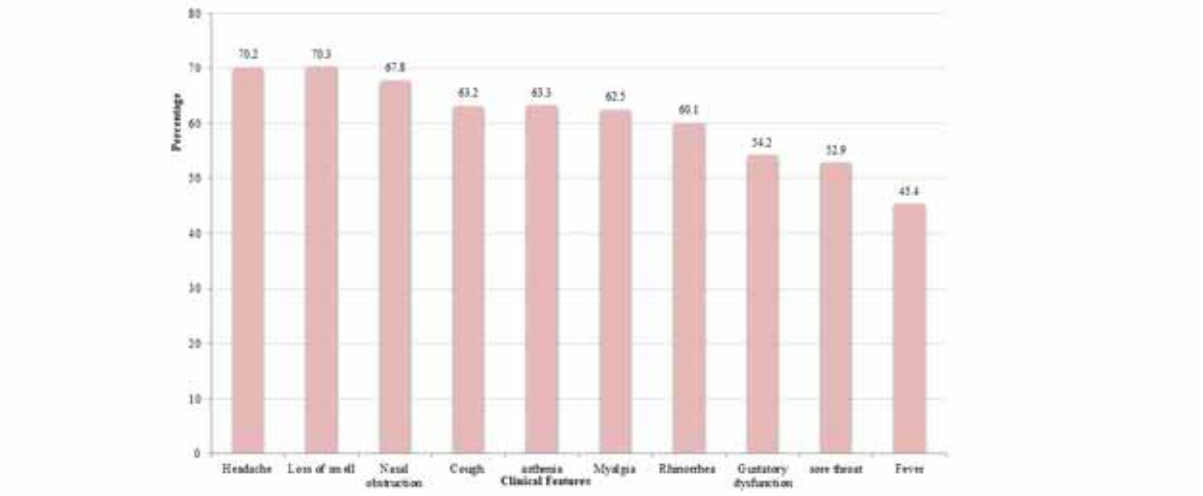
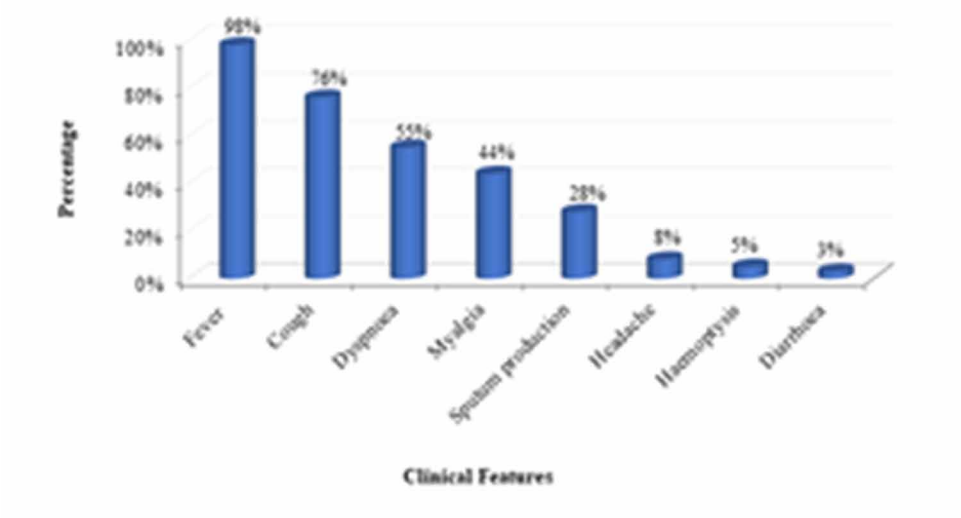


Figure 4. The most common symptoms of COVID-19 (Developed from the results of Huang et al. (2020)



A study carried out by Lechien et al. (2020a) on 1,420 patients including 962 women showed that the most common symptoms of COVID-19 are headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhea (60.1%), taste dysfunction (54.2%), sore throat (52.9%) and fever (45.4%) (**Fig. 3**).

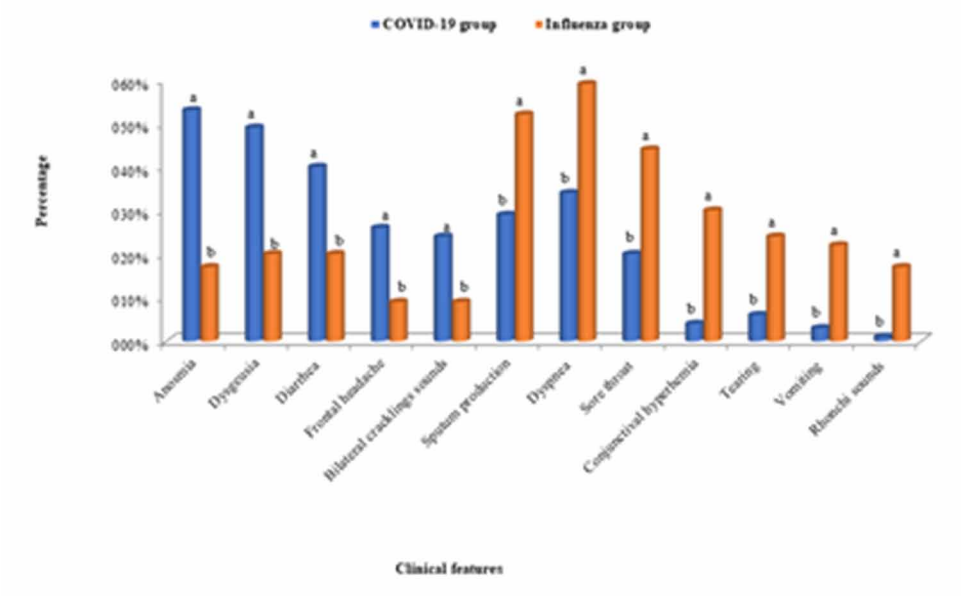
The percentages of these symptoms vary among studies; Huang et al. (2020) reported that fever is the most common symptom followed by cough and dyspnea followed by myalgia or fatigue (**Fig. 4**). However, this study was only performed on 41 patients.

Comparative Study between the Clinical Features of COVID-19 and Influenza

A study was carried out on two groups of patients including 70 patients with COVID-19 and 54 patients with influenza A / B to compare between the clinical characteristics of COVID-19 and influenza (Zayet et al., 2020). This study showed that no difference was found between the two groups in terms of age, gender and comorbidities. The comparative study shows that some clinical features (anosmia, dysgeusia, diarrhea, frontal headaches, and bilateral crackles) were statistically more frequent in the COVID-19 group, while the others (Sputum, dyspnea, sore throat, conjunctival hyperemia, hypersecretions, vomiting and rhino noises) were more common in influenza infection (**Fig. 5**).

The prevalence of mild to moderate Covid-19 symptoms varies significantly depending on the age and sex of patients (Dong et al., 2020; Lechien et al., 2020a; Ma et al., 2020).

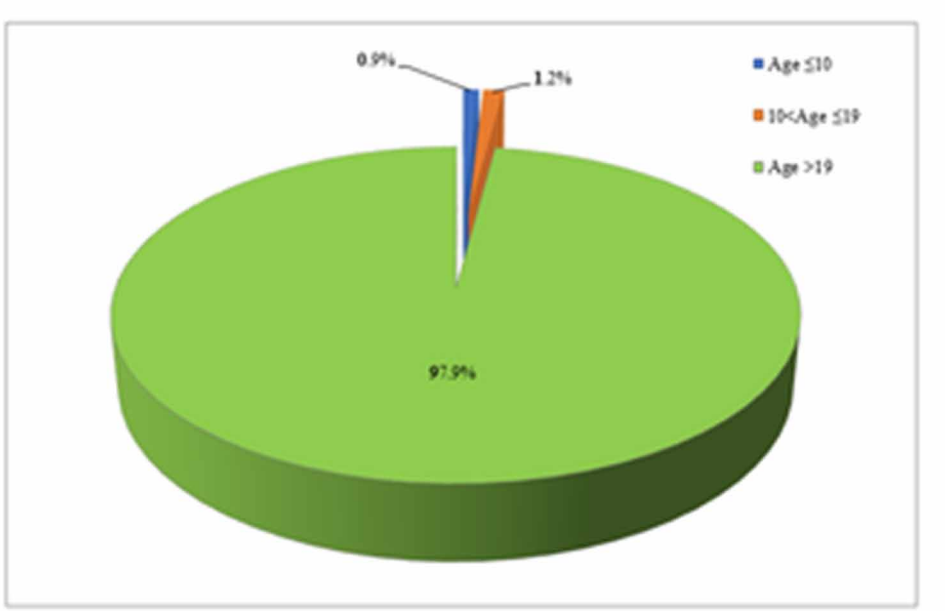
Figure 5. Comparative study between the clinical features of COVID-19 and influenza (Developed from the results of Zayet et al., 2020). The letters a and b indicate that the difference is significant or very significant between the two groups.



Age

The 19-Covid symptoms appear to be rare in children (Wang et al., 2020; Huang et al., 2020). Studies made by the Centers for Disease Control and Prevention Chinese (2020) showed that among 44,672 confirmed cases infected Covid-19, 416 were aged 1 to 10 years and 549 aged 10 to 19 years (**Fig. 6**). Children may have mild or absent symptoms more frequently than adults.

Figure 6. Number of confirmed cases infected with COVID-19 according patient age



Another study showed that clinical symptoms manifested in 12-31% of COVID-19 infections in people 10 to 19 years old, rising to 57-82% of infections in people over 70 years old (Davies et al., 2020). The clinical presentation of young COVID-19 patients more frequently included symptoms of the ear, nose and throat i.e. loss of smell, nasal obstruction, rhinorrhea, facial pain, headache and sore throat, compared to the elderly, who had fever, fatigue, loss of appetite and diarrhea more frequently ($P < 0.010$). While a study by Bi et al. (2020) showed that children are at a similar risk of infection as other people in the population, although less likely to have severe symptoms; they must therefore be taken into account in the transmission and control analyzes.

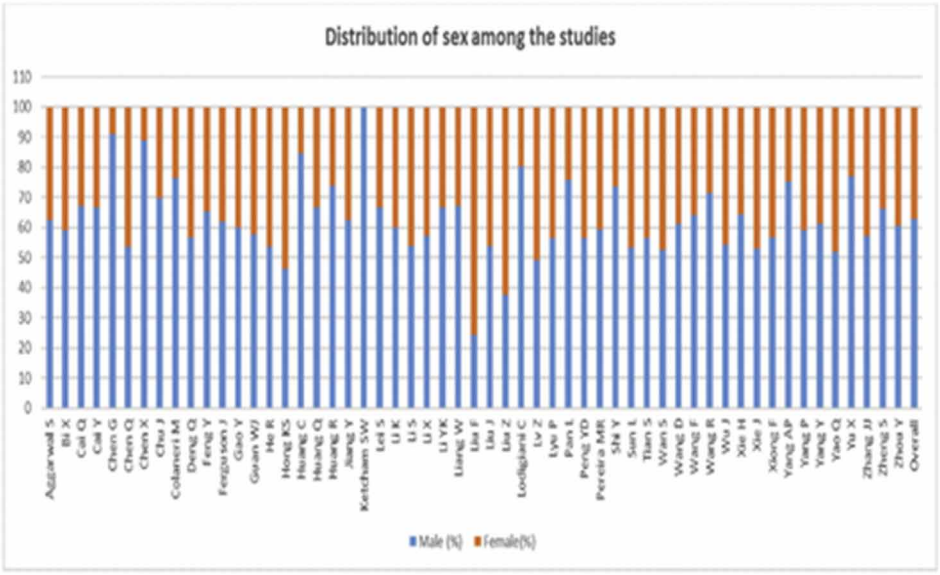
The low percentage of COVID-19 infection in children can be explained by the fact that children have a more active natural immune response, healthier airways (the duration of exposure to pollution from air is much reduced by intake to adults) and less underlying disorders. In adults, the immune response is more potent leading to a detrimental immune response associated with acute respiratory distress syndrome (Kliegman et al., 2020). Another reason for the variation in COVID-19 infection with age is likely due to the difference in the distribution, maturation and function of viral receptors.

Sex

The following symptoms were proportionately more common in women than in men: loss of smell, headache, nasal obstruction, throat pain and fatigue (P <0.001)(Lechien et al., 2020a). The men had cough and fever more frequently (P <0.001). There was no significant difference in the duration of illness with respect to sex.

To confirm the relationship between sex and the progression of coronavirus-19 disease, a study was performed on clinical features and laboratory parameters and it showed significant differences between male and female patients (Meng et al., 2020). Several independent studies have reported that men are more likely to be infected with COVID-19 and to go in severe conditions than women (**Fig. 7**; Ahmed et *al*., 2020; Barek et al., 2020; Zheng et al., 2020). This difference could be due, among other things, to the irresponsible attitude of men towards the risk of a COVID-19 pandemic (de la Vega et al., 2020), to female sex hormones, to the lower resistance of men due to the ACE2 receptor high expressing coronavirus which readily binds (Bwire, 2020) and lifestyle of men including smoking (WHO, 2020c). Sex is an important biological variable that must be taken into account in the prevention and treatment of COVID-19. The relationship between COVID-19 infection and sex is not fully visible; it may involve a complex interaction between biological, behavioral, environmental and socio-economic factors.

Figure 7. Distribution of sex of included studies to analyze the effect of sex on for the severity of COVID-19 (Barek et al., 2020)



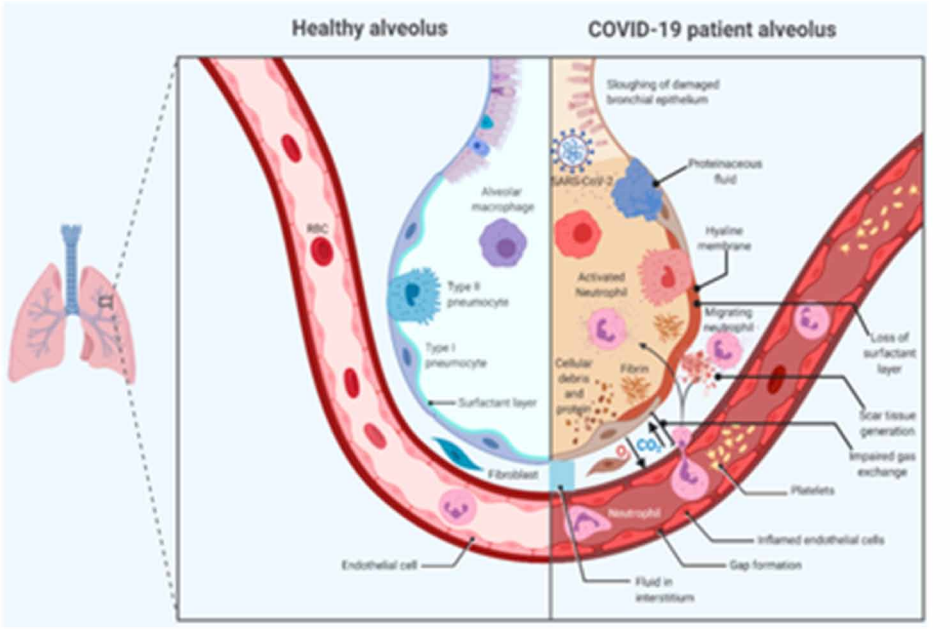
DAMAGED ORGANS

Pulmonary Pathology

In accordance with the progression of acute respiratory distress syndrome, the main targets of SARS-CoV-2 infection are the hair cells of the airway epithelium. Type II alveolar pneumocytes (Sims et al., 2005) show a nonspecific inflammatory response that plays an important role throughout the course of the disease. It is characterized by edema and cellular infiltration; also, severe exfoliation of alveolar epithelial cells, alveolar septal widening, infiltration and hyperplasia, damage to the pulmonary interstitial arteriolar walls, damage to alveolar septa and organized infiltration of the alveolar space, formation of hyaline membrane and finally necrosis (Linet al.,2020). It limits the efficiency of gas exchange in the lung, causes shortness of breath and low oxygen concentrations in the blood. Likewise, the lung becomes more vulnerable to secondary infections (Zhou P. et al., 2020; Liao et al., 2020).

Acute lung injury can occur through angiotensin converting enzyme (ACE) that converts angiotensin I (AT I) into angiotensin II (AT II), occurs when AT II binds to angiotensin II receptor 1a (AT1aR) causing tissue damage and pulmonary edema (Hendrickson &Matthay, 2020; **Fig.8**).

Figure 8. Alveolar changes in Acute Respiratory Distress Syndrome (ARDS) (Farooqi et al., 2020)



Damage to the Digestive Tract and Liver

While patients with COVID-19 often present with respiratory illness, others have reported gastrointestinal symptoms, including diarrhea, vomiting, and abdominal pain during the illness. Gao et al. (2020) reports

that the most characteristic are anorexia, nausea, vomiting (1-3.6%) and diarrhea (2-10%), which is the most common symptom. However, in Hong Kong, the presence of gastrointestinal manifestations and RNA in stool was evaluated through a meta-analysis and systematic review, which reported significant heterogeneity between studies for anorexia, nausea, vomiting, and diarrhea (74.6-85.2%), while heterogeneity was lower for abdominal pain (57.0%) (Cheung et al.,2020). Some studies suggest that between 3% and 10% of patients who develop lung infection due to SARS-CoV-2 initially had isolated and mild digestive symptoms such as anorexia, diarrhea, nausea, vomiting, and abdominal pain, preceding respiratory symptoms such as fever, cough, dryness, and dyspnea (N. Chen et al., 2020; Xu et al., 2020; Wang et al., 2020; Riddle et al., 2016). The results showed that the patients presented with vomiting in 1.7% followed by abdominal pain in 11.9% and diarrhea in 22%, this symptom is the most frequent and it was documented that in these patients a higher viral load was detected in fecal samples.

It is thought that once the virus enters the cell, RNA and virus-specific proteins are synthesized in the cell's cytoplasm to assemble new virions, which can be released into the gastrointestinal tract (Xiao et al., 2020), a theory suggesting that SARS-CoV -2 can actively infect and replicate in the digestive tract causing a host of gastrointestinal manifestations (Carvalho et al., 2020). The ACE 2 receptor is expressed in the gastrointestinal tract, especially in the small intestine and colon. These data have provided valuable information on receptor-mediated entry into host cells and provide the basis for its possible route of transmission through fecal contents (Wong SH et al., 2020; Lee et al., 2020; Xiao et al., 2020; Li Q. et al., 2020). On the other hand, it has been proposed that ACE 2 is involved in the absorption of amino acids that regulate the expression of peptides related to the homeostasis of the intestinal microbiome, which suggests that the activity of the virus can cause intestinal modifications that increase the susceptibility to colitis and diarrhea(Gao et al., 2020). Patients with gastrointestinal symptoms have a higher risk of morbidity and mortality than those who do not; That is why it is necessary to investigate symptoms such as diarrhea for the early diagnosis of COVID-19 (Cheung et al., 2020). According to recent reports in China, it has been shown that 79% of confirmed cases originate from an asymptomatic case, so we must insist on preventive measures in children (Van Doremalen et al., 2020), not excluding that there is a possible route of fecal transmission- oral, as the presence of viral RNA in the stool of healthy pediatric patients has been documented, as the virus shedding in the stool typically lasts up to 30 days (Jiehao et al., 2020; Cheung et al., 2020).

In addition to gastrointestinal symptoms, COVID-19 patients may have liver injury with elevated liver enzymes (alanine aminotransferase and aspartate aminotransferase, etc.). Although the mechanism of liver injury is not fully understood, injury may be due to the following mechanisms: direct viral infection of hepatocytes, injury related to exaggerated immune response, or drug hepatotoxicity.

Most liver injuries are mild and transient, although severe liver damage can occur. The proportion of liver injury has been reported to be higher in patients with severe COVID-19(H.Y.F.Wong et al., 2020; Chau et al., 2004; Y. Zhang et al., 2020). It is well documented that in SARS infection up to 60% of patients had liver damage, not forgetting that they had treatments with potentially hepatotoxic drugs (Leeet al., 2020; Chau et al., 2004). Data obtained by SARS-CoV-2 RNA sequencing demonstrated a significant increase in the expression of ACE 2 in cholangiocytes instead of hepatocytes, suggesting that this virus may cause direct lesions in the intrahepatic bile ducts (Chai et al., 2020).

Renal Manifestations

Renal manifestations have been described in patients with SARS and MERS-CoV infections, with a few pediatric cases reported. In the adult population, a renal impairment of 5 to 15% was found, the most characteristic finding being an acute renal failure. Currently, an incidence of renal failure is estimated between 3 and 9% in patients infected with COVID-19; however, there are other kidney changes such as albuminuria, proteinuria, and high nitrogen levels. It has been reported that patients with severe renal failure tend to have a poorer prognosis and, in most cases, associated with hospital mortality (Nadim et al., 2020; Cheng et al., 2020).

The mechanism by which SARSCoV-2 affects kidney cells is unknown, and various mechanisms are proposed (Liuet al., 2020b; Mou et al., 2020; Vaduganathan et al., 2020):

- Sepsis: due to the presence of cytokines due to the secondary systemic inflammatory response.
- Virus-induced direct cell injury.
- Viral expression in specific receptors, even viral RNA has been obtained in urine samples and kidney tissue (Naickeret al., 2020).

Since the kidney has ACE2 highly expressed in the brush border of proximal tubular cells and to a lesser extent in podocytes, it is suggested that SARSCoV-2 may have tropism towards this organ (Pericoet al., 2020).

Possible mechanisms of SARS-CoV-2 injury to the kidneys include direct infection through the bloodstream due to high ACE 2 expression as well as a sepsis-related cytokine storm (Larsen et al., 2020). One study reported in a series of 710 adult patients hospitalized with COVID19 that 26.7% had hematuria on admission, 44% had proteinuria and hematuria with elevated serum creatinine levels and elevated urea nitrogen in 15.5% and 14.1%, respectively (Cheng et al., 2020). During the period of this study, 3.2% of patients had acute renal failure, 12.3% died (Cheng et al., 2020). These data are obtained from studies carried out in adults, in the pediatric population there is still no information in this regard. However, kidney function and signs of kidney damage, mainly hematuria, proteinuria, and kidney workup such as urea and creatinine, should be monitored early. There are also no complete studies that indicate the viral influence on the clinical manifestations associated with kidney failure, rather, in the reported cases, the patients studied had a chronic renal failure (CRF), which explains the increased risk of morbidity and mortality, considering this pathology as a process chronic inflammatory disease and establishing chronic kidney disease as a risk factor for developing severe COVID-19 (Henry&Lippi, 2020; Kant et al., 2020). Even so, an increase in creatine is reported in 5% of the population compared to the previous normal baseline, which translates into acute renal impairment that could also be implicated as a factor associated with systemic deterioration (Nasr&Kopp, 2020; Betjes et al.,2013).

SARS-CoV-2 has an organotropism beyond the respiratory tract, including the kidneys and liver. Researchers have quantified the SARS-CoV-2 viral load in precisely defined renal compartments, obtained with the use of tissue microdissection from 6 patients who underwent an autopsy (Puelles, 2020). Three of these 6 patients had a detectable SARSCoV-2 viral load in all renal compartments examined, with a preferential target of glomerular cells. Renal tropism is a potential explanation for the commonly reported clinical signs of kidney injury in COVID-19 patients, even in patients with SARS-CoV-2 infection who are not critically ill (Zhou et al., 2020). Recent data indicate that kidney involvement is more common than described in early studies (Gabarre, 2020). Of the first 1,000 patients who presented at NewYork-

Presbyterian / Columbia University, 236 were admitted or transferred to intensive care units (Argenziano, 2020). Of these, 78.0% (184/236) developed acute kidney injury and 35.2% (83/236) required dialysis. At the same time, 13.8% of all patients and 35.2% of intensive care unit patients required dialysis, leading to a shortage of equipment needed for dialysis and continuous kidney replacement therapy.

The indicators of renal dysfunction in patients with COVID-19 at the biochemical level follow the guidelines for the diagnosis of renal failure in any individual. Upon admission, blood urea nitrogen and serum creatinine levels are suggested. Other parameters to monitor in patients with kidney disease are: uric acid, creatinine kinase, and lactate dehydrogenase since their increase has been shown in kidney patients with COVID-19. The urine test looks for data suggestive of proteinuria and hematuria. Its follow-up and repetition should be based on the clinical evolution and other comorbidities of the patient (Z. Liet al., 2020). Computed tomography imaging studies show alterations in the size and density of the kidneys. This demonstrates that inflammation and edema in renal parenchyma can occur in previously healthy COVID-19 patients (Z.Li et al., 2020).

Neurological Manifestations

The incidence of neurological manifestations due to SARS-CoV-2 is unknown, being identified late or retrospectively. Headache, myalgias, fatigue and drowsiness are often confused with alterations in the general state, not detailing their presentation and evolution. Propensity for neuroinvasion has been

Figure 9. (a) Human cells that express ACE2 receptors in the CNS. (b) Brain areas that express ACE2 receptors. (c) Binding of SARS-CoV-2 to a neuron (ACE2 receptors on a medullary neuron binding to the SPIKE protein on SARS-CoV-2). Source: Jha et al.,(2021)

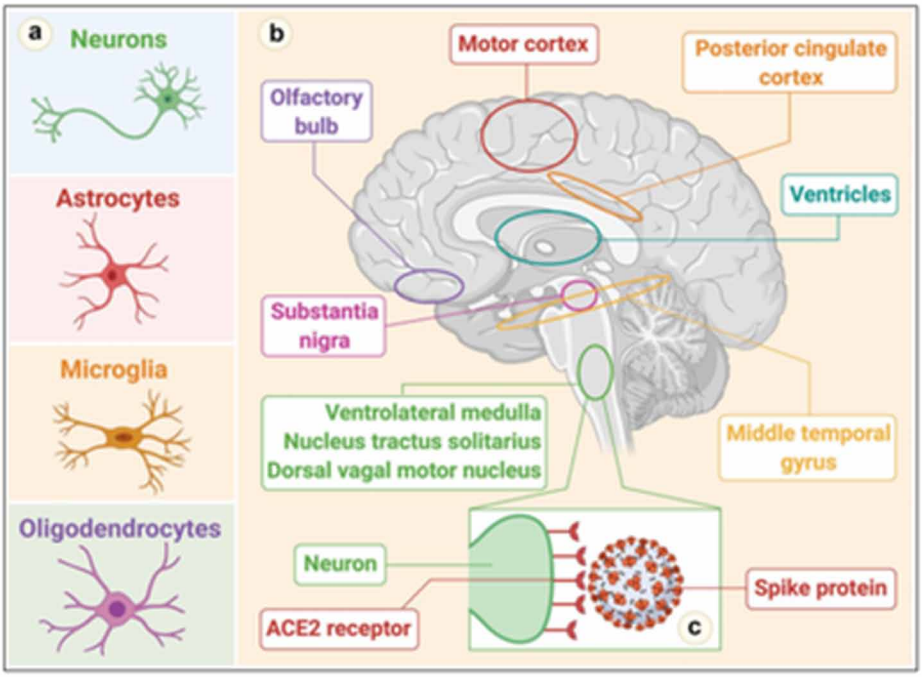
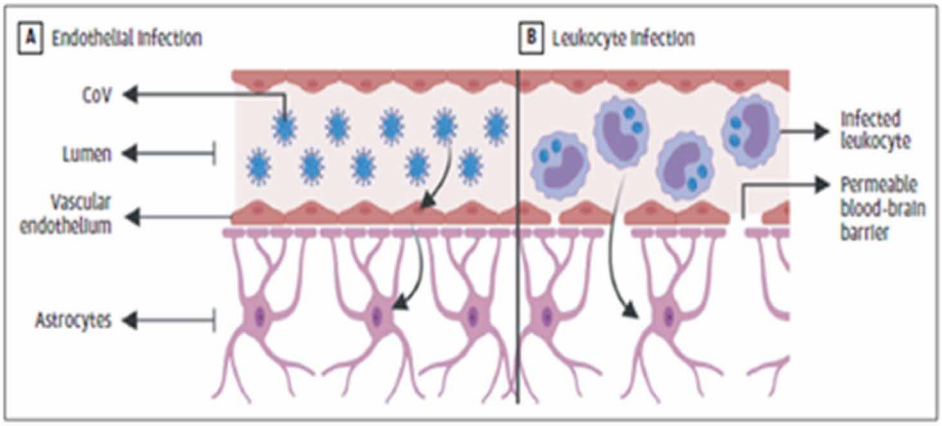


Figure 10. Mechanisms of Spread Across the Blood-Brain Barrier (A: Infected vascular endothelial cells have been shown to spread severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to glial cells in the central nervous system; B: Known as the Trojan horse mechanism, infected leukocytes can cross the blood-brain barrier to infect the central nervous system.) source: https://app.biorender.com.



shown to be a common feature of human coronaviruses. Viral neuroinvasion can be achieved by several routes, including trans-synaptic transfer through infected neurons, entry through the olfactory nerve, infection of the vascular endothelium, or migration of leukocytes across the blood-cell barrier (Zubair et al., 2020; Ellul et al., 2020, **fig. 9 & 10**).

The immune response on the part of the host may also play a role. Coronaviruses are capable of infecting macrophages, astroglia and microglia; glial cells are capable of secreting pro-inflammatory factors, IL-6, IL-12, IL-15, and TNF alpha (Bohmwald et al.,2018). The routes of spread to the central nervous system can be hematogenous or lymphatic, and by retrograde spread from peripheral nerve terminals.

The latter is carried out in the cribriform plate of the ethmoid and from the lung through the mechanoreceptors and chemoreceptors located therein and causing death due to secondary dysfunction of the cardiorespiratory control centers of the medulla oblongata (Y.C. Liet al., 2020). SARS-CoV2, in search of its ACE2 receptor, can reach endothelial cells and interact with the capillary endothelium and replicate within it and spread to neurons (Baig et al., 2020). Smell and taste disorders can be observed in 85.6 vs 88% of patients (Lechien et al., 2020b). Encephalopathy is a syndrome of transient brain dysfunction that manifests as an acute or subacute involvement. Encephalitis is a differential diagnosis from other neurotropic viruses, such as the herpes simplex family, varicella zoster or the Nile virus (Xinhua.net, 2020).

According Asadi-Pooya & Simani (2020), 25% of patients exhibited CNS manifestations, including headache (13%), dizziness (17%), and acute cerebrovascular problems (3%). In a retrospective study of 221 COVID-19 patients from Wuhan, 11 patients (5%) had ischemic stroke, one patient (0.5%) represents cerebral venous sinus thrombosis and another (0.5%) had a cerebral hemorrhage (Li Y. et al., 2020). Major risk factors for acute brain disease include advanced age (mean 71.6 years), inflammatory and procoagulant response marked respectively by the increase in C-reactive protein and D-dimer, diabetes, severe pulmonary and cerebrovascular diseases.

Frontera et al. (2020) conducted a study of 4491 patients with SARS-CoV-2 hospitalized in New York and found that 13.5% of these patients have developed a new neurological disorder. The toxic / metabolic

encephalopathy, hypoxic / ischemic injury, seizures and stroke are the most commonly used diagnoses to measure these neurological disorders. There are several series of observations of specific neurological characteristics such as Guillain-Barré syndrome (Toscano et al., 2020), myasthenia gravis (Restivo et al., 2020) or even Miller Fisher syndrome and cranial polyneuritis (Gutiérrez-Ortiz et al., 2020).

Especially in patients with severe COVID-19, neurological symptoms are common. In an observation series of 58 patients, acute respiratory distress syndrome due to SARS-CoV-2 infection was associated with prominent encephalopathy, agitation and confusion, and signs of the corticospinal tract. COVID-19 patients may experience delirium, confusion, agitation, and altered consciousness, as well as symptoms of depression, anxiety, and insomnia (Rogers et al., 2020). It remains unclear which of these features are due to disease-related critical encephalopathy, cytokines, or the effect or withdrawal of medication, which are specific to SARS-CoV-2 infection (Helms et al., 2020). However, a large comparative study between 2,132 SARS-CoV-2 patients and 1,516 influenza patients showed that there were 31 acute ischemic strokes with SARS-CoV-2, compared to 3 with influenza (Merkler et al., 2020). They also found that the likelihood of having a stroke was almost 8 times higher with SARS-CoV-2. It should be noted that there is no clear evidence that SARS-CoV-2 directly caused damage to the Central nervous system (CNS). In a study of 21 cerebrospinal fluid (CSF) samples from patients with confirmed COVID-19, all were negative (Destras et al., 2020). These data suggest that although SARS-CoV-2 is capable of replicating in neuronal cells in vitro, the test for SARS-CoV-2 in CSF is not relevant in the general population. In a large post-mortem examination, SARS-CoV-2 could be detected in the brains of 21 (53%) of the 40 patients examined, but it was not associated with the severity of neuropathological changes (Matschke et al., 2020) that appeared to be mild, with pronounced neuroinflammatory changes in the brainstem the most common finding.

Liver Manifestations

The liver is generally the organ most involved in filtering a large amount of foreign matter and therefore maintains immune tolerance through the gut-liver axis (Li & Fan, 2020). This tolerance is interrupted under conditions of psychological stress in patients with COVID-19. A study carried out in 2273 patients with SARS-CoV-2, showed that the degree of severity of liver damage is variable; i.e. 45% of patients have mild hepatic lesions, 21% moderate and only 6.4% severe (Phipps et al., 2020). Liver injury in patients with COVID-19 is usually the result of transient elevation in serum aminotransferases (Li & Fan, 2020), increase in aspartate aminotransferase (AST), alanine aminotransferase (ALAT), gamma-glutamyltransferase (GGT) and bilirubin (Chen T. et al., 2020). This hepatic injury is significantly associated with elevated inflammatory markers, such as ferritin, interleukin-6, and erythrocyte sedimentation rate (ESR) (Fan et al., 2020; Phipps, 2020). It is also due to drug toxicity or acute inflammation (Fan et al., 2020). Abnormal liver chemistry tests have been reported in patients with SARS and MERS (Chau et al., 2004; Guicciardi &Gores, 2005), implying that potential liver injury is strongly associated with COVID- infection. 19 since SARS-CoV-2 and SARS-CoV have the same receptor and the same angiotensin 2 converting enzyme (ACE2) (Li & Fan, 2020).

CONCLUSION

COVID-19 is a respiratory viral disease caused by the new SARS-CoV-2. Biologically, it is a hyperinflammatory and thrombotic condition causing severe damage to various organs. This disease represents a serious public health problem in human history and a clinical challenge. Once the SARS-CoV-2 virus enters the body after inhaling virus-laden microdroplets released by an infected person when breathing, talking, coughing or sneezing, the incubation period is highly variable depending on the immune status of the infected person (2 to 14 days). The target organ of COVID-19 is primarily the lungs, but it can directly or indirectly infect other organs (the liver, digestive tract, kidneys, neurons, etc.). The vast majority of patients has no symptoms or has mild manifestations. In this case, COVID-19 passes without major problems, sometimes even without knowing it, which results in an amplification of the number of asymptomatic reservoirs and a high transmissibility of the virus which makes it fatal on a large scale. But in some cases, the disease worsens and its development can cause a wide variety of clinical manifestations leading to complications that can worsen the prognosis and leave subsequent sequelae. The most common symptoms of COVID-19 are headache, loss of smell, nasal obstruction, cough, asthenia, myalgia, rhinorrhea, taste dysfunction, and fever. The prevalence of these symptoms varies according to the age and sex of the patients. COVID-19 can show many faces and is responsible for significant morbidity and mortality worldwide, especially in adults and people with pre-existing conditions such as cancer, diabetes, cardiovascular disease such as high blood pressure, chronic lung diseases such as asthma, are major risk factors more likely to develop serious illness after being infected with SARS-CoV-2. Certain values of laboratory biological parameters have been identified as markers allowing the identification of subjects who will present more severe forms, such as a decrease in the number of lymphocytes or an increase in the concentration of different substances in the blood (C-reactive protein, D-dimer, troponin, lactate dehydrogenase, ferritin, creatine phosphokinase, transaminase), increased erythrocyte sedimentation rate or prolonged prothrombin time.

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Chapter 4
Laboratory Methods for the Diagnosis of SARS-Cov-2

Mohamed Echchakery
Higher Institute of Health Sciences, Hassan First University of Settat, Settat, Morocco

Samia Boussaa
https://orcid.org/0000-0002-5599-1097
Higher Institute of Nursing Professions and Health Techniques, Morocco

Souad El Mouahid
Higher Institute of Nursing Professions and Health Techniques, Morocco

Maryam Mountassir
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Said El Hizazi
Ecole Supérieure de Technologie, Université Ibn Zohr, Morocco

Raymond Klevor
Mohammed VI University Medical Center, Marrakesh, Morocco

Ansumana Mohammed Keita
Arrazi Hospital, Mohammed VI University Teaching Hospital, Morocco

Mustapha Mouallif
Higher Institute of Health Sciences, Hassan First University of Settat, Morocco

Yassin Zemrani
Arrazi Hospital University Mohammed VI, Morocco

Asmae Lamrani Hanchi
Faculty of Medicine and Pharmacy of Marrakech, Cadi Ayyad University, Morocco

Soraia El Baz
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Mohamed Alouani
Faculty of Sciences, University Ibn Zohr, Morocco

ABSTRACT

The coronavirus disease 2019 (COVID-19) which has become the pandemic par excellence of our time places pressure on various aspects of human endeavor and as such requires detailed study to better combat it. However, diagnostic tests were used to provide data on the incidence of COVID-19 and to assess the immune status of infected individuals. The objective of this chapter is to describe the diagnostic methods currently used to identify SARS-CoV-2 infection. Obtaining the first SARS-CoV-2 genome sequence was

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decisive for the development of molecular diagnostic assays that currently make it possible to diagnose and screen for the Sars-CoV-2 infection. Their uses depend on the target to be detected. Antigenic tests detect the presence of a virus antigen, which usually makes a proteinaceous part of the virus surface. The serology tests detect the presence of antibodies generated against SARS-CoV-2 and are also a relevant tool for epidemiological studies.

INTRODUCTION

In December 2019, a major outbreak of Wuhan, atypical pneumonia of unknown an etiology, was reported to the World Health Organization (WHO) country office of China.The CDC's (Chinese Center for Disease Control and Prevention) country office in China has identified its etiology as a new virus belonging to the family coronaviruses (CoV) and initially received the provisional designation of the 2019 new coronavirus (2019-nCoV), which includes the alpha and gamma coronaviruses. SARS-CoV-2 is a betacoronavirus (β-CoV) that is structurally similar to other coronaviruses (SARS-CoV and MERS-CoV) from the *Coronaviridae* family (Zhu et al., 2020). Other authors have classified coronavirus into four genera, based on genetic features, namely Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus (Mavrodiev et al., 2020;Shors, 2021). This new coronavirus infects and replicates in the lung parenchyma pneumocytes and macrophages in which the ACE-2 cell receptor resides (Reina, 2020). This new virus was called SARS-CoV-2 and the disease it produces was called COVID-19 highly infectious, whose rapid global spread has put the entire world in a state of emergency, leading humans to an unprecedented global pandemic situation. On 1stJanuary 2021, there have been 81, 947, 503 confirmed cases of COVID-19, including 1, 808, 041 deaths, reported to WHO (WHO, 2021). On January 30th, 2020 the WHO declared a Public Health Emergency of International Concern (WHO, 2020a). According to data released by the WHO the country's most affected by COVID-19 are the United States of America, India, Brazil, Russian Federation, France, United Kingdom, Italy, Spain, Germany, Colombia, Argentina and Mexico their incidence has been reported by their government agencies respectively at 19,578,217; 10,305,788; 7,675,973; 3,212,637; 2,129,376; 1,893,502 (WHO, 2020a).

The virus that affects us now is very similar to those that caused the epidemics (more limited, fortunately) that we call SARS in 2003 and MERS in 2012(Del Rio et al., 2020). All three are descended from bat viruses, which evolved to acquire the ability to cause disease in humans. In fact, it is so similar to SARS that it is considered a "relative" of "SARS-CoV-2". Their helical nucleocapsid surrounds a non-segmented genome (27–32 kb) characterized by a 5′-end containing gene important for viral replication and pathogenesis in the host cell (Monchatre-Leroy et al*.,* 2017; Cui et al*.,* 2019; Saif et al*.,* 2019).The 3′-end genomic region harbours genes for nucleocapsid and membrane proteins (Yoshimoto et al*.,* 2020).

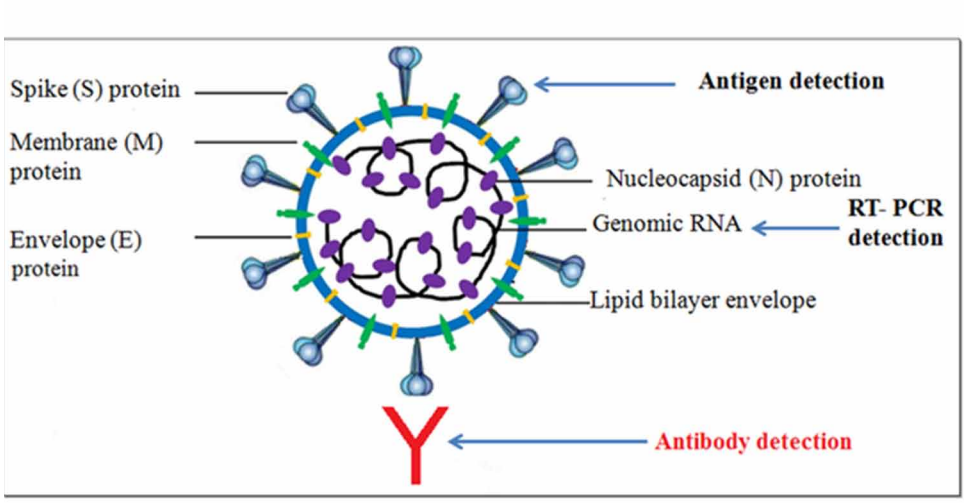
This virus has a zoonotic origin and has been transmitted to humans via an unknown intermediate host, leading to infections in humans and other mammals (Lam et al., 2020). Susceptible animals could serve as reservoirs of the virus, requiring rigorous and ongoing animal management and surveillance.

The infected person may not show symptoms and remain asymptomatic, and some may show severe symptoms in their respiratory and digestive organs (Monchatre-Leroy et al., 2017; Cui et al.,2019).

In 2003, the world was shocked by the first pandemic of the 21st century; the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) emerged in Guangdong, China (Drexler et al., 2014; Cui et al., 2018).Nine years later, a strain of CoV evolved in Saudi Arabia to cause the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Cui et al., 2018).Similar to SARS-CoV and MERS-CoV, infections SARS-CoV-2 predominate in adults and men without a confirmed underlying cause (Del Rio et al., 2020). The majority of SARS-CoV-2 infections are subclinical, whereas symptomatic patients usually present with cough, fever, fatigue, myalgia, breathing difficulties (dyspnoea), headache, pneumonia, and ground glass appearance of lungs on radiographic imaging. Other documented symptoms include productive, haemoptysis and diarrhea (Huang et al., 2020a).Some patients may have serious complications such as acute respiratory distress syndrome (ARDS) and cytokine storm, which may lead to death (Loeffelholz &Tang, 2020; Yunbao et al., 2020).Studies have shown that adults and the elderly are the most infected by SARS-CoV-2, with a slight predominance in men and a low proportion of children have contracted the infection (Guan et al., 2020; Huang et al., 2020a; Wu &McGoogan, 2020).Moreover, the presence of comorbidities such as diabetes or cardiovascular or respiratory disorders greatly affects outcomes. Indeed, being elderly or having a delay in diagnosis was found to substantially increase the case-fatality rate (Wu &McGoogan, 2020; Yang et al., 2020).

An accurate, reliable and early diagnosis is very crucial to properly manage this SARS-CoV-2 pandemic, as it provides rapid medical assistance to the infected individual and helps government agencies prevent its spread to other people and to save people's lives.

Figure 1. Schematic structure of coronavirus (CoV)



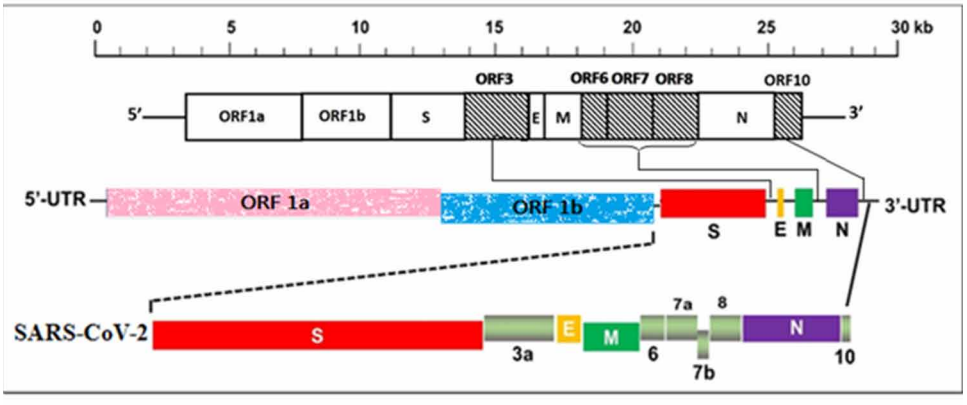
STRUCTURE OF CORONAVIRUS

Coronavirus is spherical (80–160 nm), pleomorphic, enveloped, notable for the large spike (S) glycoprotein, positive-sense single-stranded RNA (**Fig. 1**). Its name is derived from the Latin word corona, since observation under an electron microscope shows that its proteins (S) form a structure resembling a royal crown (Shors, 2021).The spike protein (S) is responsible for attaching the virus to a receptor on the surface of a host cell, and is the primary target for antibodies produced by the body as an immune defense against the coronavirus. The envelope lipid bilayer is associated with two additional transmembrane proteins, namely a small envelope protein (E) and a membrane protein (M). Nucleocapsid (N) are associated with genomic RNA.

CORONAVIRUS GENOME ORGANIZATION

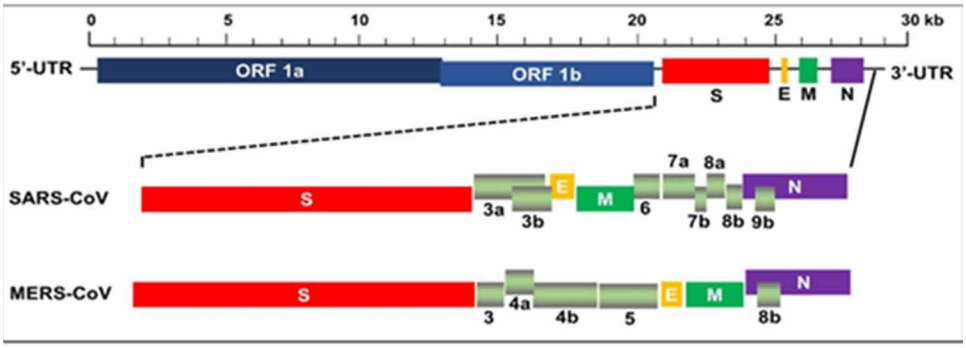
The causative virus, SARS-CoV-2 is a positive-stranded RNA virus with genome size comprised of around 30,000 nucleotides organized into specific genes encoding structural proteins and nonstructural proteins (Yang &Wang, 2020; Wu et al., 2020; Zhou et al., 2020).At the 5'terminal two-thirds of the genome consists of two open reading frames (ORF); ORF1 and ORF2 (**Fig. 2**). While the 3′a third is made up of genes encoding structural proteins including surface (S), envelope (E), membrane (M) and N core proteins. The large ORF 1ab is a replicase gene encoding polyproteins 1a (pp1a) and pp1b. In addition, SARS-CoV-2 contains 6 accessory proteins (3a, 6, 7a, 7b, 8 and 10), encoded by the ORF3a, ORF6, ORF7a, ORF7b, ORF8 and ORF10 genes (Mousavizadeh &Ghasemi, 2020; Angeletti et al., 2020).5'-UTR and 3'-UTR, untranslated regions at N- and C-terminal regions, respectively. These proteins play a crucial role in the detection and diagnosis of the virus.

Figure 2. Schematic diagram illustrates the genomic organization of SARS-CoV-2 (2019-nCoV) (Wang et al., 2020a)
Source: Wang et al., 2020a



A similarity between the genomic regions or open reading frames (ORFs) of the SARS-CoV virus, MERS-CoV and SARS-CoV-2 was observed (**Fig.2**; **Fig. 3**; Wang et al., 2020a). MERS-CoV and SARS-CoV-2 genomes encode structural (S, E, M, N) and non-structural proteins translated from ORF 1a and ORF 1b, as well as accessory proteins, including 3a, 3b, 6, 7a, 7b, 8a, 8b and 9b (for SARS-CoV) and 3, 4a, 4b, 5 and 8b (for MERS-CoV)

Figure 3. Schematic diagram illustrates the genomic organization of SARS-CoV and MERS-CoV(Wang et al., 2020a)
Source: Wang et al., 2020a



LABORATORY DIAGNOSTIC OF SARS-COV-2

Types of Specimens

The collection of appropriate samples is very crucial for the detection of most infected cases of COVID-19. For general specimen collection procedures, the WHO and CDC Interim Guides are best to consult WHO (WHO, 2020a; CDC, 2020). In addition, the diagnosis of the pathogen depends on the nature, quality, and quantity of the samples and also on the time of collection during the course of the disease. A study has shown that nasopharyngeal (NP) swabs are more recommended than oropharyngeal (OP) swabs for COVID-19 RT-PCR test since the percentage of detection of SARS-CoV-2 RNA in swabs NP (63%) was significantly higher than that of OP swabs (32%) (Wang et al., 2020b). Likewise, the Center for Disease Control and Prevention (CDC, 2020) also recommended the use of upper respiratory NP swabs or combined with OP samples in the same tube as the NP swab. And in order to avoid missing detection of COVID-19 infected cases in the nasopharyngeal swab, lower and lower respiratory tract samples such as sputum, bronchoalveolar lavage (BAL) may be the alternative choice (Wölfel et al., 2020). SARS-CoV RNA has been detected in stool, urine and blood samples, although generally less reliable than in respiratory samples (Kim et al., 2020b). All samples should be placed in a tube contain-

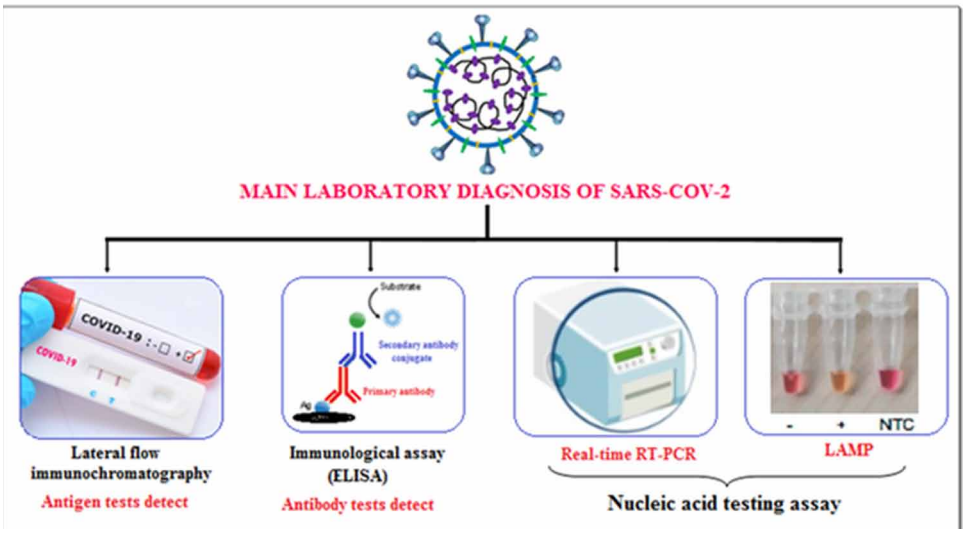
ing viral transport medium and transported to the laboratory on time. Likewise, for the serological test, the blood sample can be taken.

MAIN DIAGNOSTIC TESTS

Various SARS-CoV-2 diagnostic tests have been used to provide information on the incidence of COVID-19 and to assess the immune status of infected individuals. These tests have different degrees of specificity and are based on different target molecules of SARS-CoV-2 or the body in response to infection and each test has its own advantages and disadvantages (Loeffelholz &Tang, 2020; Jin et al., 2020). These methods include molecular and serological tests. There are three main types of detection assays relevant for COVID-19 diagnostic testing and screening, based on the target that is being detected (**Fig.4**):

- Antigen tests detect the presence of a viral antigen, typically part of a surface protein.
- Antibody tests detect the presence of antibodies generated against SARS-CoV-2.
- Nucleic acid tests detect the presence of viral RNA. Typically, these use an amplification step based on RT-PCR.

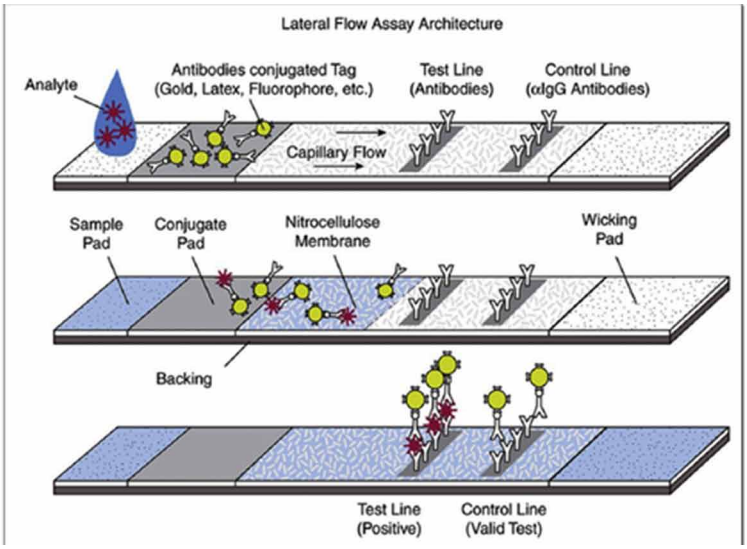
Figure 4. Main laboratory diagnosis of SARS-CoV-2



Rapid test based on the qualitative detection of SARS-CoV-2 specific antigen by lateral flow immunochromatography with colloidal gold, does not require instrumentation and results are obtained in just 10-15 minutes (**Fig.5**).Two recent studies reported a sensitivity range of 93%–100% and 100% specificity of the immunochromatography SARS-CoV-2 antigen tests targeting N protein (Porte et al., 2020; Diao et al., 2020). Rapid antigen detection kits used are generally characterized by suboptimal sensitivity and specificity (Merckx et al., 2017).The antigen test provides rapid results (after 15 min of incubation) and its sensitivity compared to RT-PCR has proven to be excellent in the studies carried out (Masia et al.,

2020; Gremmels et al., 2020) to date, indicating a correlation between the positivity of the test and the Ct value, as a semi-quantitative measure of the viral load present in the sample.

Figure 5. Principle of immunochromatography. This drawing shows lateral flow to detect an antigen (Abduljalil, 2020)
Source: Abduljalil, 2020



IMMUNOLOGICAL ASSAY

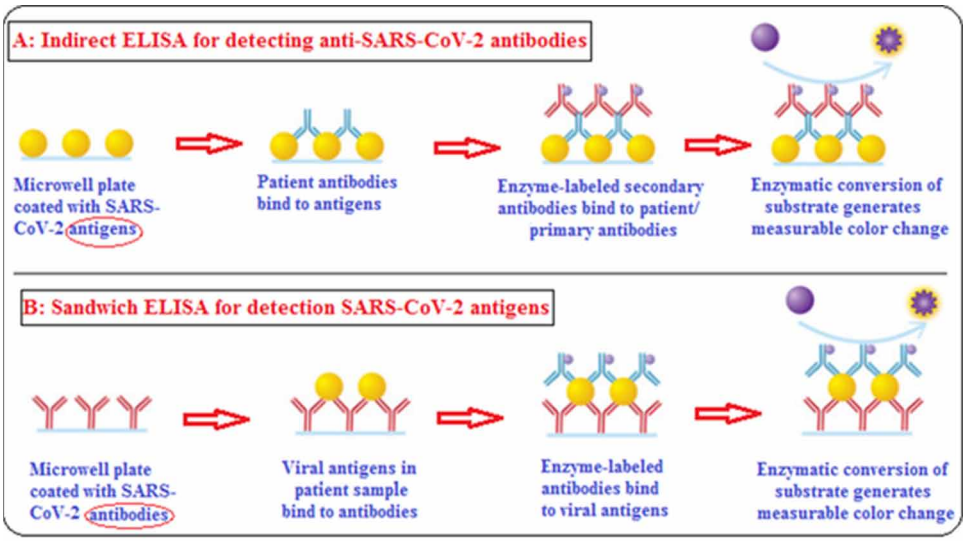
While RT-PCR-based viral RNA detection has been widely used in diagnosis of COVID-19, it cannot be used to monitor the progress of the disease stages and cannot be applied to broad identification of past infection and immunity (Carter et al., 2020).The immunological diagnostic tests that have been used are antibody tests detect the presence of antibodies generated by the immune response of the host organism against SARS-CoV-2 or measure the proteins of this virus present in respiratory samples. The most widely used immunoassays are chemiluminescence assays (CLIA), enzyme immunoassay (ELISA), lateral flow assay (LFA) and virus neutralization assay. The latter are used, which can specifically detect neutralizing antibodies, but they are mainly used for test validation and research. According to studies, preliminary reports on ELISA tests showed a good correlation between antibody assay results and virus neutralizing antibodies.

Serological assay was used earlier in SARS and other corona virus outbreaks and played important role (Chen et al., 2004; Chan et al., 2009). Although WHO has recommended that the serology testing can be used where molecular testing is not available (WHO, 2020b).Immunological tests have limitation to use in early phase of infection because that time the immune response is still building.Currently, serological tests are not recommended to use solely for the diagnosis of SARS-CoV-2 infection (FDA, 2020), but in certain situations these tests can be used to measure the amount of antibodies to support the clinical evaluation of people who show up late in their disease when used in conjunction with viral detection testing.Serological testing for SARS-CoV-2 infection is an important tool for epidemiological

studies and surveillance, such as understanding the dynamics of virus transmission in the general population. Unlike direct viral detection methods, such as antigen detection tests or nucleic acid amplification which can detect severely infected people, serologic testing helps determine if the individual being tested was already infected, even if that person has never shown symptoms.

Other diagnostic tests that have been used are rapid tests based on antigen-antibody detection. These tests are qualitative and only express one result, either positive or negative. The most commonly used technique in these is the enzyme-linked immunosorbent assay (ELISA), in which a sample of nasopharyngeal or oropharyngeal exudate is taken (**Fig.6**). In the ELISA, an antibody linked to an enzyme intentionally seeks the detection of antigens, which in this case are specific proteins of SARS-CoV-2 (protein N and the S1, S2 subunits of protein S), and then generate a signal or detectable product that can be identified if a virus antigen is found, in order to determine the positivity of the test (To et al*.,* 2020; Zhao et al*.,* 2020).

Figure 6. ELISA assays detectingantibodies (A) or antigens (B) (Carter et al., 2020)
Source: Carter et al., 2020



In the case of rapid antibody determination tests, these arise from the idea that the immune system develops immunoglobulins (Ig) against the virus, depending on the phase of the infection in which the individual is. IgM is the acute phase immunoglobulin, while IgG is the chronic, memory or recovery phase (To et al*.,* 2020).

Although to date there is no consensus among the medical community on the time in which the IgM and IgG titers increase to be detectable. It has been postulated that IgM begins to rise between 5-7 days after the moment of infection (being its detectable peak between 8-14 days), while IgG becomes detectable from day 15 to 21 (Li et al*.,* 2020; Zhao et al*.,* 2020).

At the time of the severe acute respiratory syndrome (SARS) epidemic, various reports demonstrated that the detection of two immunological markers IgM and IgG with high specificity to SARS-COV2 viruses is valid for the serological diagnosis of COVID-19 (Xiang et al., 2020).According to this study

(Xiang et al*.,* 2020), the specificity and sensitivity of IgM detection in confirmed patients infected with COVID-19, were 100% and 77.3% and for IgG detection were 95.0% and 83.3.3% respectively. Likewise, in suspected patients infected with COVID-19, the specificity and sensitivity of IgM detection were 100% and 87.5% and for IgG detection were 96.6% and 70.8% respectively. Thus, detection of both IgM and IgG with higher specificity makes them reliable and could help us diagnose COVID-19 patients.

Study has shown that, immunohistochemical assay detection of anti-viral IgM and IgG antibodies in serum of the patients and detection of antigen in lung tissue can additional evidences to confirm the COVID-19 cases (Zhu et al*.,* 2020).

Despite some limitations, these immunological tests have been used only at the points of care for research and not for the purpose of clinical decision making because, play a critical role in identifying people who have recovered from this COVID-19 infection in the past. The test result can also help us choose convalescent plasma, which can be used as a treatment option for people infected with COVID-19 (Roback&Guarner,2020).

NUCLEIC ACID TESTING ASSAY

There are two available categories for RNA amplification tests for SARS-CoV-2;rRT-PCR and loop-mediated isothermal amplification (LAMP). For SARS-CoV-2 detection, protocols of rRT-PCR were approved by WHO and the US Food and Drug Administration (FDA), whereas the isothermal amplification assays have not been authorized.

Real-Time RT-PCR

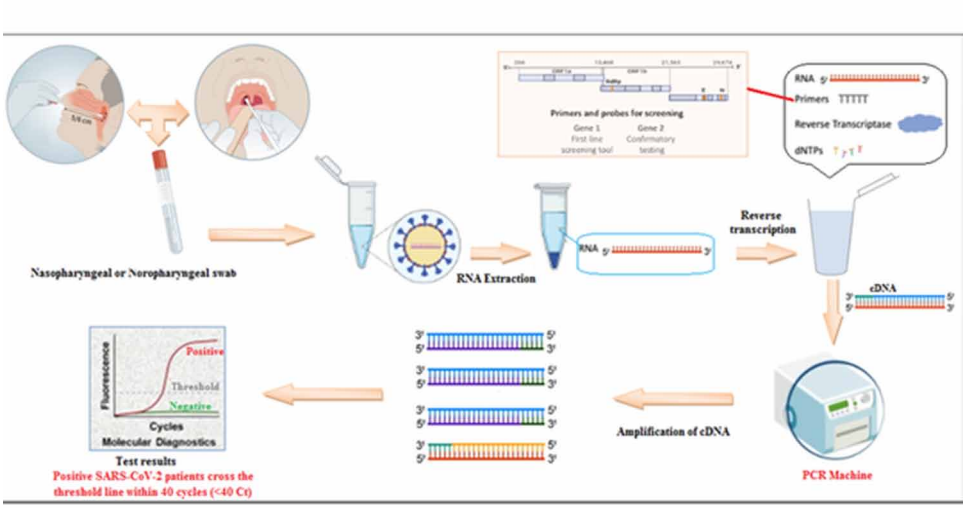
The polymerase chain reaction (PCR) is a tool of molecular biology with the objective of producing many copies (amplification) of a gene or a series of genetic sequences by using a primer sequence and DNA polymerase enzymes to exponentially increase the amount of DNA required.This technique is widely used to amplify trace amounts of DNA to allow adequate amounts required for laboratory analysis. Due to its sensitivity, high simplicity, and high sequence specificity, PCR-based methods are able to routinely and reliably detect the coronavirus in patients with COVID-19 (Shen et al*.,* 2020; Balboni et al*.,* 2012; Uhlenhaut et al*.,* 2012).For the diagnosis of COVID-19, an RT-PCR is essential. It is the diagnostic method that has been widely used around the world for its ability to detect SARS-CoV-2 in respiratory secretions (Huang et al*.,* 2020a; He et al*.,* 2020; Guan et al*.,* 2020).

According to Kubina and Dziedzic (2020), this test involves three essential steps namely extraction of viral RNA from collected samples, reverse transcription of viral RNA into single-stranded complementary DNA (cDNA) using the enzyme transcriptase inverse and the last step is the amplification of the cDNA coupled to fluorescent detection (**Fig.7**).

The sample collection from outpatients is done by nasopharyngeal or oropharyngeal exudate, while in intubated patients it is best done by bronchoalveolar lavage (Wölfel et al*.,* 2020. Once the samples are obtained, the genetic material of the virus is extracted from infected cells and is processed by RT-PCR, whose basic principle is to read or detect the virus genome, mainly from the sequences corresponding to the N, E and S proteins (Li et al*.,* 2020; Wang et al*.,* 2020b).

In addition to detecting the virus, it is important to determine the viral load that the infected have in their cells, therefore, using the so-called cycle threshold value (Ct-value [cycle threshold value]), the

Figure 7. Overview of coronavirus disease (COVID-19) diagnosis using the quantitative reverse transcription–polymerasechain reaction (RT-qPCR) technique with respiratory tract specimens



number of copies can be determined of the virus present in cells. The Ct value is the number of times that the RT-PCR has to read the genome of the virus toconsider that it is present and determines the cellular viral load (Li et al., 2020; Wang et al., 2020b; Liu et al., 2020). In some studies, the threshold Ct-value was established at 37 - 40. When the detection of SARS-CoV-2 was carried out and the sample processed by RT-PCR reported a threshold value lower than 37 cycles, the test was positive. On the other hand, if it was greater than 40 cycles, the test was negative. In cases where the Ct-value was between 37 and 40 cycles, a confirmation was required, so the test was repeated. In other words, the fewer cycles the RT-PCR performs, the higher the viral load, and vice versa(Li et al.,2020).

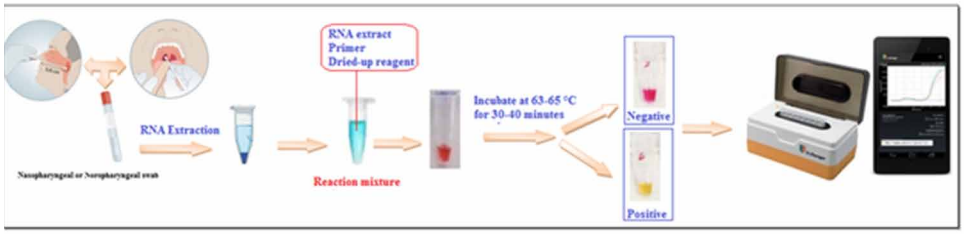
Apart from these main detection tests, whole genome sequencing can also be performed to determine the sequence of the SARS-CoV-2 virus in a sample, with possible quasi-species variants (Gorbalenya et al., 2020).

Loop-Mediatedisothermalamplification Assays (LAMP)

Another molecular method, which is the loop-mediated isothermal amplification reaction (LAMP), could serve as an alternative method to RT-qPCR to detect COVID-19. This rapid (in 30 min), simple and sensitive method paves the way for wide screening in the public domain and hospitals to obtain the detection of SARS-CoV-2 (Huang et al. 2020b). Colorimetric change was used to read the result of viral RNA amplification with the naked eye without the need for an expensive or dedicated instrument (**Fig.** 8).

LAMP reaction is a novel nucleic acid amplification technique that amplifies DNA with high specificity, efficiency, and rapidity under isothermal conditions. Compared to this new detection technique, RT-qPCR is considered a tedious and laborious technique. The LAMP method has attracted widespread attention as an alternative to real-time PCR (Notomiet al., 2000; Tomita et al., 2008; Mori&Notomi, 2002). The critical difference is that isothermal amplification does not involve thermal cycling and the polymerase can amplify the target sequence at a constant temperature (Notomi et al., 2000).

Figure 8. Schematic representation of colorimetric LAMP to quantitatively detect SARS-CoV-2



This method can also be used for both DNA and RNA targets, as it is able to detect target RNA by the reverse transcription-LAMP (RT-LAMP) reaction: by using the AMV reverse transcriptase, RT and DNA amplification can be accomplished at a constant temperature in short time (60 min) in one step (Fukuta et al., 2003). Thus, the LAMP method has advantages for rapid, on-the-spot detection of respiratory viruses. The LAMP method has been used to detect a variety of pathogens, such as influenza virus, adenovirus, RSV, severe acute respiratory syndrome, and Middle East respiratory syndrome coronavirus (Mori et al., 2009; Zhou et al., 2017; Poon et al., 2004; Lee et al., 2017).

Table 1. LAMP and PCR assays comparison (Galvez et al., 2020 ;Nguyen et al., 2020 ;Ahn et al., 2019 ; Jeon et al., 2017 ;Dham et al., 2014 ;Wang et al., 2013)

LAMP	PCR
Isothermal and continuous amplification (Smaller, simpler, hence portable).	Thermal cycling (Multiple heating and cooling cycle; hence, bulky and cumbersome).
For virus detection, for example, influenza or human Coronavirus, LAMP assay offers one-step detection.Sample preparation steps are simplified.	Always requires sample concentration and preparation (Time-consuming).
Single protocol (Faster).	Multiple protocols (Complicated and requires a skilled technician).
Tolerate inhibitors and more stable.	Inhibitors hinder the reaction.
Diagnostic sensitivity > 95%.	Diagnostic sensitivity (95%) is currently reported lower than LAMP.
Applications using LAMP assays are being explored.	Established technique
Only a heat block is required1 h until result.	Specialized thermal cyclers required4- 8 h until result.

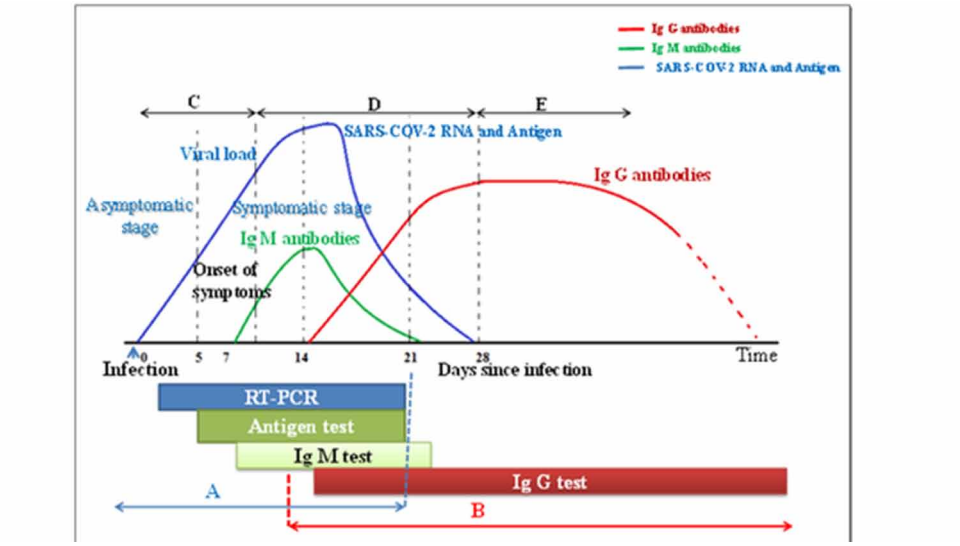
This method can be used for the diagnosis of COVId-19 without the need for specialized equipment and trained analysts. In the near future, the LAMP-based point-of-care device may be a potential diagnostic tool for the diagnosis of people infected with COVID-19 (Nguyen et al., 2020).

LAMP technology is proven to be more stable and more sensitive in detection compared to PCR. Other advantages of LAMP compared to those of PCR are shown in Table 1.

Interpretation

Rapid tests are most useful when they are used to detect SARS-CoV-2 infection in a timely manner, especially when RT-PCR is not available or cannot be carried out on a massive scale. However, it is essential that these be assessed together with the epidemiological and clinical situation of the patient. Therefore, this COVID-19 Rapid Test should not be used unit symptoms have been present for at least 7 days (**Fig.9**).

Figure 9. Schematic representation the kinetics of the COVID-19 disease caused by the SARS-CoV-2 virus from an immunological (IgM and IgG) and virological (viral RNA) point of view



A: RT-PCR test is appropriate for the acute phase of illness with asymptomatic or symptomatic infection. B: Antibody test is appropriate for convalescent phase of COVID-19 in case of asymptomatic infection. C: Asymptomatic stage. D: Symptomatic stage. E: Recuperation stage.

Virus Culture

To date, conventional culture methods are still being used to detect respiratory viruses. Numerous studies have been carried out on viral culture by standard methodology (Sims et al., 2013; Josset et al., 2013; Kim et al., 2020a). Vero E6, Vero CCL-81, HUH 7.0, 293T, A549 and EFKB3 cells were cultured in Dulbecco minimal essential medium (DMEM) supplemented with 2% fetal bovine serum at 37 ° C with

Table 2. Combined interpretation of RT-PCR result and rapid antibody detection test.

Test results			Clinical interpretation
Ig M	**Ig G**	**RT-PCR**	
Negative	Negative	Negative	Patient who has never had a SARS-CoV-2 infection
Negative	Negative	**Positive**	Patient who is currently infected by SARS- CoV-2, in a very early stage of the disease, with or without symptoms associated with COVID-19 (the most contagious stage)
Positive	Negative	**Positive**	Patient who is currently infected by SARS- CoV-2, in a subacute phase of the disease, with or without symptoms associated with COVID-19.
Positive	**Positive**	**Positive**	Patient who is currently infected by SARS- CoV-2, in a watery phase of the disease, with or without symptoms associated with COVID-19.
Negative	**Positive**	**Positive**	Patient who is currently infected by SARS-CoV-2, in a final phase of the disease and in the process of resolution of the infection, with or without symptoms associated with COVID-19.
Negative	**Positive**	Negative	Patient who is currently not infected by SARS-CoV-2 but who had a past infection and who developed memory antibodies against the SARS-CoV-2.
Positive	**Positive**	Negative	Patient who is currently infected by SARS-cov-2 and in an acute phase of the disease with or without symptoms associated with COVID-19. Or there may be a false negative for RT-PCR.
Positive	Negative	Negative	Patient who is currently infected by SARS-cov-2 and in a subacute phase of the disease with or without symptoms associated with COVID-19. Either there may be a false negative RT-PCR or a cross reaction.

5% CO2; inactivated by heat (5% or 10%) and antibiotics / antimycotics (GIBCO); used for inoculation of nasopharyngeal and oropharyngeal samples. They used standard plaque tests for SARS-CoV-2, which were based on SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) protocols (Sims et al*.,* 2013; Josset etal*.,* 2013). The results of culture methods are usually accurate; however, the operating procedures are complicated and time-consuming.

CONCLUSION

Today, the world is fighting fiercely against the most serious COVID-19 pandemic humanity has ever known. It poses a significant threat to global public health systems and has impacted people's lives and the global economy. The choice of the type of specimen for the diagnosis of SARS-CoV-2 depends on the patient's condition and the stage of disease progression. Early diagnosis is very crucial to identify infectious cases in order to prevent community transmission. Samples from the upper respiratory tract are the best choice during the first days of illness, while sputum is most sensitive in the later stages. The real-time RT-PCR test remains the molecular test of choice for the etiological diagnosis of COVID-19 cases; while antibody-based immunoassays are used as additional tools for whole community screening and confirmation with molecular testing. Real-time RT-PCR and immunoassays are helping us fight this major COVID-19 pandemic. As in other RNA viruses, mutations and other genetic changes are likely to occur, which can lead to pitfalls in nucleic acid amplification tests. The genomic homology of SARS-CoV-2 with other coronaviruses is also a challenge for serological and antigenic detection tests.

However, improvements to these point-of-care tests should contribute to better management of the pandemic because they are quick and simple to perform. In summary the proper utilization of available test in alone or in combination; we can detect the COVID-19 cases as soon as possible and saves lives of human being.

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Chapter 5
Spread of COVID-19 and Its Main Modes of Transmission

Soraia El Baz
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Ahmed Draoui
Cadi Ayyad University, Morocco

Mohamed Echchakery
Higher Institute of Health Sciences, Hassan First University of Settat, Morocco

Natalia Lopez-Gonzalez del Rey
Centre for Integrative Neuroscience A.C., University Hospital Puerta del Sur, Spain

Karima Chgoura
Faculty of Medicine and Pharmacy, Cadi Ayyad University, Morocco

ABSTRACT

The coronaviruses group can affect mammals, including humans, causing generally mild infectious disorders, sporadically leading to severe outbreak clusters, such as those generated by SARS-CoV in 2003 and by MERS-CoV in 2012 and in 2015. The current coronavirus outbreak started December 29th, 2019 in Wuhan (Republic of China) and has progressively expanded to various parts of the world. A human-to-human transmission of COVID-19 occurs directly through individuals showing symptoms. But, recent researches support the possibility of SARS-CoV-2 transmission from persons who are asymptomatic. Indirect transmission occurs via touching infected surfaces or through inhalation of small, exhaled virus in respiratory droplets. To effectively fight the spread of COVID-19, it is vital to understand the different factors that promote superspreading of COVID-19. So, the aim of this chapter is to describe the invasion of SARS-CoV-2 in the human body and the different modes of transmission (directly and indirectly).

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INTRODUCTION

The biological and ecological system changes, including anthropogenic changes, can disturb biodiversity and leading into closer contact between people and wildlife (Jones et al., 2008). Therefore, this close contact can be considered as an important factor that increase the risk of zoonotic disease transmission from animal to human and precipitate the emergence of new diseases (Hooper et al., 2012). Beside, this is not the first time that a new virus infects human populations who have close contact with wild animal (Murdoch & French, 2020).

Coronaviruses group belong to the order of Nidovirales, family of Coronaviridae, and subfamily of Orthocoronavirinae (Carlos, Dela Cruz, Cao, Pasnick, & Jamil, 2020). This group can affect mammals including humans, causing generally mild infectious disorders, leading to severe outbreaks clusters such as those generated by SARS-CoV in 2003 and by MERS-CoV in 2012 and in 2015 (Chowell et al., 2004). Since December 29th, 2019 a recent coronavirus outbreak has started in Wuhan (Republic of China), and has progressively expanded to various parts of China and has reached as well other countries (Soufi et al., 2020). So far, this new virus has infected more than 80 million people and killed approximately 7 million of them. This pneumonia outbreak was found to be linked to seafood and animal market in Wuhan (X. Xu et al., 2020). The novel coronavirus has been named Severe Acute Respiratory Syndrome Coronavirus 2 "SARS-CoV-2", while the disease associated with it is referred to as COVID-19 (Gorbalenya et al., 2020).

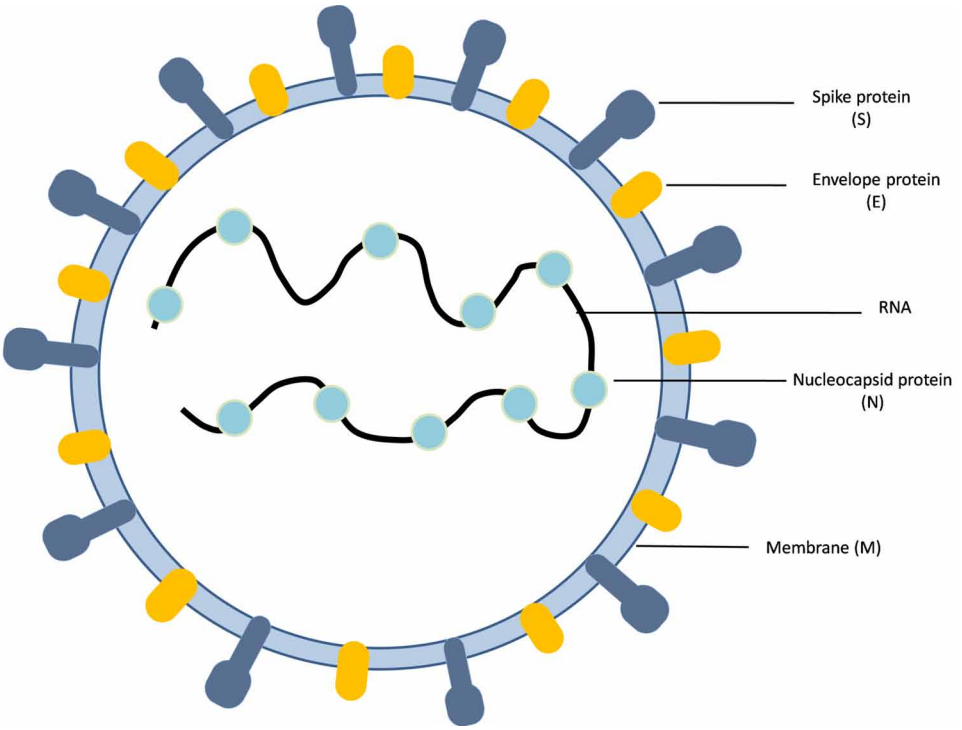
Symptoms of COVID-19 infection include fever, fatigue, and cough. Coronavirus spreads among humans predominantly via respiratory droplets (S. Ding & Liang, 2020). Based on early reports, SARS-CoV-2 can be transmitted through persons (with symptomatic or asymptomatic infection) by diverse pathways (Murdoch & French, 2020). Generally, transmission occurs by touching infected surfaces or through inhalation of exhaled virus in respiratory droplets (Weber, Rutala, Fischer, Kanamori, & Sickbert-Bennett, 2016). Persistence of human coronaviruses "hCoV" on surfaces depends on type of surface, virus strain, humidity and temperature (Kampf, Todt, Pfaender, & Steinmann, 2020). For example, SARS-Cov-2 can survive several hours on sterile sponges, aluminum, or latex surgical gloves (Qu, Li, Hu, & Jiang, 2020).

In the aim to control the spread of COVID-19, most countries have imposed a lockdown and avoid close contact in late March. Therefore, understanding the different transmission routes is a key step to control the epidemic. In this chapter, firstly we provide an overview of the pathogenesis and mechanism of entry of COVID-19 in human. Then, we focus on the potential transmission routes that have been investigated in the SARS-CoV-2 epidemic recently.

PATHOPHYSIOLOGY AND MECHANISM OF ENTRY OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS

Coronaviruses are enveloped RNA viruses first described in 1968 (Kenny & Mallon, 2021), its diameter is about 65-125 nm with a positive-sense ranging in size from 27 to nearly 32 kb in length, single-stranded RNA and viral particles resembling to the solar corona from which the name derives (Carlos et al., 2020). Structurally, SARS-CoV-2 has four main structural proteins including (fig.1): (i) spike (S) glycoprotein interacts with the receptor of the target cells favoring the virus penetration into them, (ii) small envelope (E) glycoprotein and membrane (M) glycoprotein form the envelope of the virus, (iii)

Figure 1. SARS-CoV-2 structure



the nucleocapsid (N) protein binds the viral RNA, and also several accessory proteins (Guo et al., 2020; Jiang, Hillyer, & Du, 2020; Platto, Xue, & Carafoli, 2020).

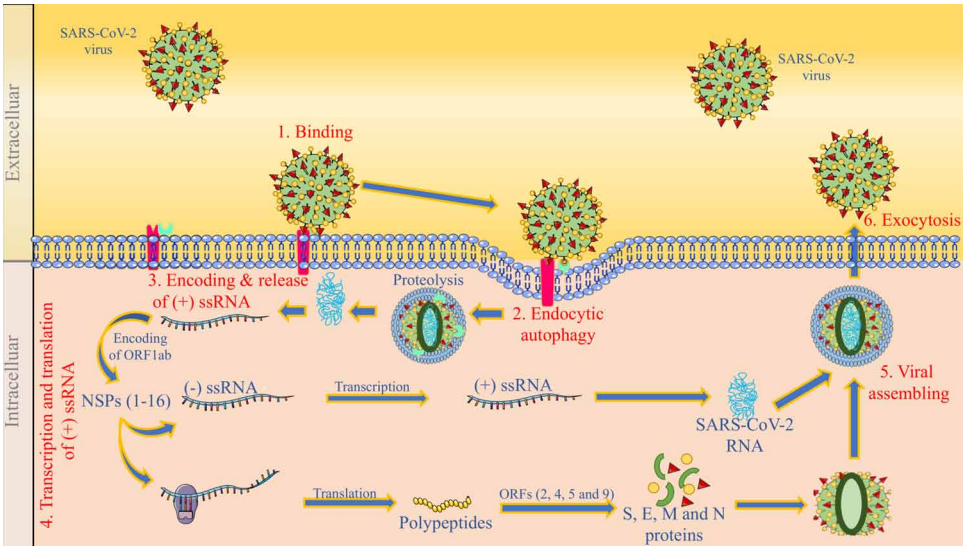
The S protein is modified in the endoplasmic reticulum (ER) of the host cell with N-linked glycans that would protect it against neutralizing antibodies (Hoffmann, Hofmann-Winkler, & Pöhlmann, 2018). This S protein comprises two functional subunits (i) subunit 1 (S1) responsible for the determination of the host virus range and for binding to the host cell receptor, while (ii) subunit 2 (S2) to mediate virus fusion and cellular membranes (Guo et al., 2020; Kirchdoerfer et al., 2016; Walls et al., 2020). For SARS-CoV-2 the angiotensin-converting enzyme 2 (ACE2) molecule has been shown to serve as a receptor, which is found on airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lung, thus facilitating viral entry into target cells (M. Hoffmann et al., 2020).

The process of CoV entering into the host cell (fig.2) begins through the attachment of the S glycoprotein to the receptor ACE2 in the host cells including human ACE2 and bat ACE, and where the virus takes control of cellular machinery for new viral particle replications (Al-Rohaimi & Al Otaibi, 2020; Rabi, Al Zoubi, Kasasbeh, Salameh, & Al-Nasser, 2020; Tai et al., 2020). When S protein is incorporated into the viral membrane, is primed into two segments: (1) the first subunit S1 contains a signal peptide and the receptor binding domain (RBD), also termed as C-terminal domain (CTD), that interact with ACE2 receptor (Soufi et al., 2020); (2) the second subunit S2, which fix the S protein to the viral membrane, and then mediates the fusion of the viral membrane with the plasma membrane of the target cell by fusion peptide (M. Hoffmann et al., 2020). The cleavage of the S protein is performed by proteases of the host cell "serine protease TMPRSS2" facilitating viral activation (Markus Hoffmann et al., 2020). The S glycoprotein is cleaved also by another protease "the furin-like protease", possibly preparing it for

the cleavage by TMPRSS2 (Astuti & Ysrafil, 2020; Markus Hoffmann et al., 2020; Kenny & Mallon, 2021). Furthermore, entered-SARS-CoV-2 into host cell will subsequently release its viral genome in the cytoplasm and become translated in the nuclei. The genomic material released by this virus is mRNA that is ready to be translated into 16 non-structural proteins (NSPs) that form the viral replicase-transcriptase complex. Next, the subgenomic proteins become translated into four structural proteins such as membrane M, spike S, nucleocapsid N and envelope E, along with several accessory proteins. Upon translation, the S, E, and M structural proteins subsequently are insulated in the endoplasmic reticulum and then moved to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC)(Astuti & Ysrafil, 2020; Guo et al., 2020; T. Tang, Bidon, Jaimes, Whittaker, & Daniel, 2020). Meanwhile, the previously replicated genome program can directly join the N protein to the nucleocapsid form and move into the ERGIC. In this compartment, the site of coronavirus structural proteins assembly, which nucleocapsids will meet with several other structural proteins and form small wallet vesicles (Fehr & Perlman, 2015). Afterwards, the virus is released from the cell via exocytosis (de Haan & Rottier, 2005; Klein et al., 2020; T. Tang et al., 2020;V'Kovski, Kratzel, Steiner, Stalder, & Thiel, 2021).

SARS-CoV-2 virus is well known to infect primarily mucosa cells in the respiratory tract, lungs, and then causes damage to cells in vasculature, brain, and other organs (H. Chen et al., 2020). In addition, other study reported the presence of ACE2 receptor on the surface of oocytes and cells in developing blastocyst (Virant-Klun & Strle, 2021). This may explain some problems with miscarriages observed during the COVID-19 infection (Ratajczak & Kucia, 2021).

Figure 2. The life cycle of SARS-CoV in host cells



1. the RBD of the viral spike bind to the ACE-2 with intervention of TMPRSS2; 2. entry of the SARS-CoV-2 via endocytosis autophagy pathway where autolysosome integrate viral contents and cut it down; 3. Viral (+)ssRNA is encoded and released in the cytosol; 4. ORF1a and ORF1ab are first genes to be encoded expressing 16 non-structural proteins (NSPs) implicated in the transcription and translation processes. Genes of the ORFs 2, 4, 5 and 9 encode successively the spike, envelope, membrane and

nucleocapside the structural proteins; 5.Assembling of the viral proteins and RNA in the host's endoplasmic reticulum and Golgi apparatus; 6. The assembled virions travel in vesicles to the cell membrane and are released by exocytosis.

DIFFERENT TRANSMISSION MODE ASSOCIATED WITH COVID-19

Animal-to-Human Transmission

Chinese people consummate the wild animal meat and their products as culinary habits, due to their medicinal value as well as the health promoting effects (Harypursat & Chen, 2020). Unfortunately, a big number of infected people by SARS-CoV-2 were exposed to the wet animal market in Wuhan City, China, so it is suggested that this is the zoonotic origin (Li et al., 2020; Rothan & Byrareddy, 2020). The first reports identified two species of snakes that could be a possible reservoir of COVID-19 disease (Rothan & Byrareddy, 2020). Until now, there has been no consistent evidence of CoV reservoirs other than mammals and birds (Bassetti, Vena, & Giacobbe, 2020; W. Wang, Tang, & Wei, 2020). So, the precise origin of the COVID-19 virus is yet ambiguous, but molecular evidence showed the virus to be most closely related to a coronavirus isolated from a horseshoe bat from Yunnan Province (Murdoch & French, 2020; Zhang, Chen, Zhang, Roy, & Shen, 2020).

Additionally, there is a close similarity between the novel SARS-CoV-2 and SARS coronavirus from pangolin (up to 99%) based on molecular biological detection, macro-genomic sequencing and electron microscopic analysis (Z. Xu et al., 2020). However, others studies reported that viruses isolated in pangolin and bats were unlikely directly linked to COVID-19 outbreak (K. Xiao et al., 2020; Zhou et al., 2020), because they are only 85.5–96.2% overall genome sequence identity with SARS-CoV-2 (X. Zhang et al., 2020). Also, other animal species reported harbouring CoVs such as cattle, horses, swine, pets, camels, rodents, ferrets, mink, bats, snake, frogs, marmots and Malayan pangolin, so their role as natural reservoir host needs more attention (Dhama, Patel, Pathak, et al., 2020; Dhama, Patel, Sharun, et al., 2020; Monchatre-Leroy et al., 2017). Furthermore, the future explorations might reveal the real intermediate host of SARS-CoV-2 responsible for this zoonotic transmission (Almendros & Gascoigne, 2020).

Human-To-human Transmission

Direct Transmission of Coronavirus Disease 2019

Human to human coronavirus transmission has been described both in hospital and house. The transmission of COVID-19 occurs via symptomatic individuals (in the incubation stage or showing symptoms), and via asymptomatic individuals (remain contagious while remaining superspreaders) (Qu et al., 2020). World Health Organization (WHO) suggest that respiratory secretions or droplets expelled face-to face by infected individuals during talking, coughing, or sneezing is the most common mode of transmission (WHO, 2020b). Therefore, a close contact with an infected person (within about 1m for a total of 15 minutes) or briefer periods of exposure to symptomatic persons (eg, coughing) are associated with higher risk for transmission. Contrariwise, brief exposures to asymptomatic persons (less than 10 minutes) are less likely to result in transmission (Chu et al., 2020). Current estimates for the mean incubation period

range from 4 to 6 days, while is 4.4 days for SARS-CoV and 5.5 days for MERS-CoV (Park, Cook, Lim, Sun, & Dickens, 2020). It is almost certain that during this incubation period, asymptomatic and presymptomatic carriers (individuals who will later develop symptoms) can transmit SARS-CoV-2, because viral shedding begins between 2-3 days before the onset of symptoms (Wei et al., 2020). The existence of persons with asymptomatic SARS-CoV-2 infection, who are able of transmitting the virus to others, has several implications. For that, CDC recommended key interventions including social distancing and wearing aface maskin indoor public areas to prevent transmission by asymptomatic and symptomatic persons with SARS-CoV-2 infection (Furukawa, Brooks, & Sobel, 2020).

Secondary Transmission of Coronavirus Disease 2019

Inanimate surfaces: this outbreak its spread also via contaminated hands or by feces, and via touching infected surfaces including self- inoculation of the mucous membrane of the nose, eyes, or mouth (Chan et al., 2020; Otter et al., 2016). SARS-CoV-2 virus is thought to persist and to survive on inanimate surfaces for several hours, such as aluminum or sterile sponges, increasing the opportunity for transmission via touch (Kampf et al., 2020; Qu et al., 2020). Other studies like Chatterjee, Murallidharan, Agrawal, and Bhardwaj (2021) and van Doremalen et al. (2020) suggest that virus persist on impermeable surfaces (e.g. steel and plastic) for up to 3- 4 days after inoculation, than permeable surfaces (e.g. cardboard) and porous surfaces (e.g. cloths). In addition, it was reported that SARS-CoV-2 was also founded on the surface of cell phones, the door handles, and other items in the residential sites of infected cases (Han, Lin, Ni, & You, 2020).

Airborne transmission: the airborne transmission and aerosol transmission are the same phenomenon, the first isfocusing on the air that transfers the aerosol and the second is focusing on the particles that transfer the pathogen (Ram et al., 2021). According to WHO the "Respiratory droplets are >5-10 μm in diameter whereas droplets <5μm in diameter are referred to as droplet nuclei or aerosols" (WHO, 2020b). Spread by aerosol is suspected to be another important route of SARS-CoV-2 transmission (Han et al., 2020), which operates in parallel with droplet and fomite routes (L. Morawska & Milton, 2020). At the beginning, WHO has refused to admit airborne transmission as another route of transmission for the spread of COVID-19. However, recently WHO has accepted the possibility of airborne transmission, but is conditioned by specific circumstances (WHO, 2020a), especially in indoor environments with poorly ventilated air-conditioned such as restaurants and supermarkets (Lidia Morawska et al., 2020; Ram et al., 2021). Inhalation of microdroplets (microscopic aerosol droplets) could be a potential factor of human-to-human transmission. It is considered that heavy breathing, talking, and coughing generate numerous aerosols containing infective viral materialand remained for prolonged period (Wilson, Corbett, & Tovey, 2020). As many aerosols are smaller particles, so they can be exhaled to several meters and therefore they disperse more widely (Borak, 2020). There are many factors that control the movement of aerosols in air, such as their size, the characteristics of the air flow (including turbulence, temperature, speed, direction and humidity) and the momentum of air (J. W. Tang et al., 2021). For example, RNA viral was sampled from air within a patient's room during SARS-CoV-1 epidemic (Booth et al., 2005). Another epidemiological study suggested that many residents of a tower block were infected by airborne spread of contaminated air in a ventilator shaft through a rising plume during the same SARS-CoV-1 epidemic (Yu et al., 2004). Nevertheless, many studies have detected SARS-CoV-2 RNA in collected particles. In addition, this virus is able to remain stable and viable in aerosols (< 5 μm) for up to 3 hours whereas maintaining her infectious titre (Liu et al., 2020; Shao et al., 2021; van Doremalen et al., 2020).

Nishiura et al. (2020) found in their results that closed environments contribute to secondary transmission of COVID-19 and promote superspreading of COVID-19 as facilitators for transmission. They suggested also in their study to reduce of unnecessary close contact in closed environments, which may help prevent large case clusters and superspreading events (Nishiura et al., 2020).

Fecal transmission: several studies reported intestinal tissue involvement in patients with SARS-CoV and MERS-CoV outbreak and they can survive in stool samples for 4 days (Corman et al., 2016; Y. Ding et al., 2004; Weber et al., 2016). Recently, many studies detected the presence of SARS-CoV-2 (almost 55%) in fecal specimens from patients with COVID-19 (Cheung et al., 2020; W. Wang, Xu, et al., 2020; Wu et al., 2020;F. Xiao et al., 2020). In contrast, other analysis localized ACE2 and TMPRSS2 in esophagus upper and stratified epithelial cells and absorptive enterocytes from ileum and colon (H. Zhang et al., 2020). Therefore, digestive system will be vulnerable to SARS-CoV-2 infectionand which increase gastrointestinal wall permeability and then leads enteric symptoms like diarrhea (Gu, Han, & Wang, 2020). Further, the duration of positivity for SARS-CoV-2 in stool tends to continue between 1 and >30 days post onset of illness (F. Xiao et al., 2020; Y. Zhang et al., 2020). Therefore, fecal transmission should be considered as another potential transmission route of SARS-CoV-2 (Chen, Guo, Pan, & Zhao, 2020; F. Xiao et al., 2020), because recent study has demonstrated that patients with COVID-19, discharge its etiologic SARS-CoV-2 virus through their excrement (Bivins et al., 2020). It is not easy for some people to maintain their proper hand hygiene after open defecation (Caruso and Freeman 2020). These can be as a potential fecal-associated transmission of virus for toilet users in public places especially in schools, hospitals, and airports (Sun and Han 2020; Welling et al. 2020). In addition, the transmission can be through shoes, feet and clothes contaminated during human activities in the open environment (e.g. defecating outside) (Sun & Han, 2020). It is reported previously the important role of water in the transmission of respiratory infectious diseases and specially the effect of hand washing (Cairncross, 2003).Virus-laden aerosols may generate from flushing activities including toilets and wastewater, which expels bioaerosols in the air (Sun & Han, 2020). However, existence of SARS-CoV-2 in wastewater systems could affect directly the environmental transmission of COVID-19 (Lodder & de Roda Husman, 2020; M. Usman, Farooq, & Hanna, 2020). Also, recent research was found SARS-CoV RNA in the sewage water of two hospitals in Beijing treating patients with SARS (X. W. Wang et al., 2005). Another recent study reported that coronavirus stay infectious for days to weeks in water and sewage (Casanova, Rutala, Weber, & Sobsey, 2009), and low viral loads in stool could still be a concern for transmissibility (Amirian, 2020). Indeed, bioaerosols can be generated at cooling towers and wastewater treatment plants, especially in uncovered aerobic wastewater treatment facilities like an aerobic tank and activated sludge process (Muhammad Usman, Farooq, & Anastopoulos, 2021). Inhalation of droplets or fecal aerosols may be a possible faecal-transmission route of SARS-CoV-2 via wastewater plumbing systems, as happened in Hong Kong during SARS outbreak 2003 in a 50-storey residential building through sewage aerosols (Heller, Mota, & Greco, 2020; Yu et al., 2004). It remains commonly known that coronaviruses group are susceptible to ethanol, chlorine and bleach (Geller, Varbanov, & Duval, 2012). So, important measures must be made with stools of patients infected with coronavirus, and also sewage from hospitals and houses should be properly disinfected.

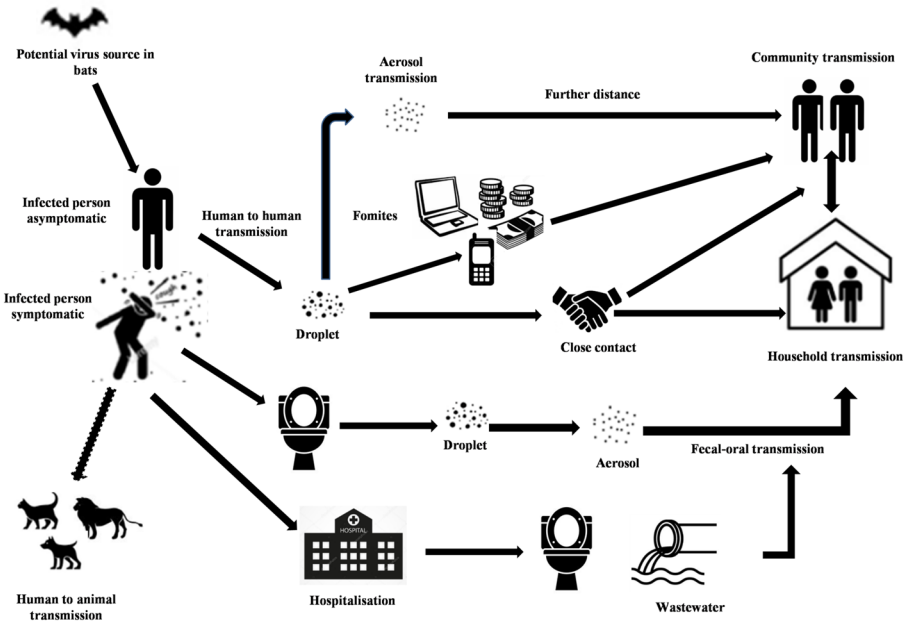
Human-to-Animal Transmission

Various studies have demonstrated the susceptibility of animals in close contact with humans to SARS-CoV-2 such as ferrets, cats and dogs (Almendros, 2020; Goumenou, Spandidos, & Tsatsakis, 2020;

Kiros et al., 2020; Shi et al., 2020). The first isolation of SARS-CoV-2 from pets is reported on February 28, and March 18, 2020, which two dogs were tested positive for COVID-19 in Hong Kong and this infection was due to transmission from his infected owner (El Baz & Imziln, 2020; OIE, 2020b, 2020c). Another case was reported in Belgium by the Federal Public Service (FPS) Health, Food Chain Safety and Environment on March 27, 2020 which a cat declared positive for the coronavirus from its owner (FPS, 2020; Mallapaty, 2020).Second cat in the world infected with SARS-CoV-2 also from its owner was detected in Hong Kong on March 31, 2020 (AFCD, 2020). It is known that dogs have an ACE2 similar to human ACE2 as a SARS-CoV receptor (Goumenou et al., 2020). The latency period for SARS-CoV-2 in animals is similar to humans, ranges from 3 to 7 days and up to 14 days. Therefore, animals could act as silent sources of transmission because they may remain asymptomatic for SARS-CoV-2 (Ng & Hiscox, 2020). In addition, domestic animals and wildlife housed in zoological centers are at a higher risk of infection with SARS-CoV-2 from infected humans (Zhao, Cui, & Tian, 2020). For example, Centers of Diseases Control and Prevention (CDC) announced on March 27, 2020 the infection of the first tiger in the Bronx Zoo, New York. On April 3, 2020, two others tigers and three African lions has been reported in the same Zoo (CDC, 2020). Their infections by SARS-CoV-2 were supposed due to anasymptomatic zoo-keeper directly or indirectly (by food preparation, respiratory droplet, fomite) (McAloose et al., 2020).

Additionally, some minks in Netherlands farms were infected by SARS-CoV-2 on 23 and 25 April 2020. On further investigation, these minks were infected by the farm owners and workers who have respiratory disease symptoms for SARS-CoV-2 infection (MANF, 2020). So, these results confirm the

Figure 3. The main transmission routes of COVID-19 (El Baz & Imziln, 2020)



possibility of transmission of COVID-19 between humans and animals, through the food or the bedding material, infected droplets or by the contaminated fecal matter (Oreshkova et al., 2020).

The World Organization for Animal Health (OIE) announced that there is a possibility for some animals tobecome infected through close contact with infected humans, but at the same time OIE declared that there is no evidence that pets like dogs and cats can spread COVID-19 (Goumenou et al., 2020; OIE, 2020a). Generally, vulnerable animal to SARS-CoV-2 include: (i) animals in contact with humans infected with SARS-CoV-2, (ii) species housed in zoological centers, and (iii) livestock housed in high densities on farms.

CONCLUSION

Up to now, the different of SARS-CoV-2 transmission routes have not yet been determined. The most main transmission routes of COVID-19 can be through (fig.3): i) animal to human transmission; ii) human-to-human by respiratory transmission, oral-fecal transmission, asymptomatic patients transmission, mother-to-child transmission (in the uterus) and children-adult transmission; iii) air, surface-human transmission. But, further studies are warranted to study all different potential transmission, so that health measures can be adopted to reduce further spread of SARS-CoV-2.

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Section 3

COVID-19 Pathophysiology: Paths to Destruction

Chapter 6
COVID-19:
Lungs Facing the Storm

Ahmed Draoui
Cadi Ayyad University, Morocco

Hicham Chatoui
https://orcid.org/0000-0002-4707-1645
LBI, FST BM, University Sultan Moulay Slimane. Morocco & Private University of Marrakech (UPM), Morocco

Soraia El Baz
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Hanane Rais
Cadi Ayyad University, Morocco

Bilal El-Mansoury
Chouaib Doukkali University, Morocco

My Abdelmonaim EL Hidan
Ibn Zohr University, Agadir, Morocco

Abdelmohcine Aimrane
Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco

Nadia Zouhairi
Cadi Ayyad University, Morocco

Mohamed Echchakery
Hassan First University of Settat, Settat, Morocco

Abdelaati EL Khiat
Cadi Ayyad University, Morocco

Lahcen Tamegart
Cadi Ayyad University, Morocco

Radouane El Fari
Cadi Ayyad University, Morocco

Hind Benammi
Cadi Ayyad University, Morocco

Karima Lafhal
Cadi Ayyad University, Morocco

Miloud Hammoud
Cadi Ayyad University, Morocco

Halima Gamrani
Cadi Ayyad University, Morocco

ABSTRACT

SARS-CoV-2 infection is characterized by its high contagiousness and unusual potential lethality. Microscopically, diffuse alveolar damage is the main histologic lung injury dominated by alveolar destruction. At the early stage, the authors note non-specific lesions similar to lesions of diffuse alveolar damage. In particular, the alveoli dilated and filled with exudative fibromyxoid material, the thickening

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of the interalveolar partitions by edema and an essentially mononuclear inflammatory infiltrate with eosinophilic hyaline membranes covering the alveoli. Viral inclusions are not generally found, and at an advanced stage, the installation of pulmonary fibrosis is noted. The place of non-invasive and/or invasive ventilation is undetermined in hypoxemic respiratory failure secondary to SARS-Cov-2 pneumonia, whereas in the most severe cases of COVID-19, the use of oxygenation by extracorporeal membrane is immediate. The cytokine storm in the lungs prompted clinicians to administer immunomodulators, the results of which was a reduction in hospital mortality.

INTRODUCTION

In December 2019, cases of pneumonia linked to a novel coronavirus were reported in China(Ren et al., 2020)before spreading to the whole world, creating the largest infectious pandemic since the Spanish flu of 1918. This coronavirus, called SARS-CoV-2, causes a disease called COVID-19 (Corona Virus Disease of 2019). It is an emerging infectious disease of the viral zoonosis type. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic (World Health Organisation, 2020). SARS-CoV-2 infection is characterized by its high contagiousness and unusual potential lethality. Responsible for a clinical picture associating several organ damages but mainly an attack on the upper and lower airways. The objective of this chapter is to recall the main lines of the pathophysiology of pulmonary involvement with SARS-CoV-2, to detail the respiratory damage linked to SARS-CoV-2 by discussing the particularities of acute respiratory distress syndrome from COVID-19, and to take stock of the management of patients with moderate and severe forms of COVID-19 and finally to discuss some therapies capable of relieving the pulmonary aggravations described in this disease.

CLINICAL FORMS OF RESPIRATORY DAMAGE ASSOCIATED WITH SARS-COV-2

Many symptoms of COVID-19 have been described to date. Among the most common are: fever in about 50% of non-severe forms and 85% of severe forms; a dry cough between 30% and 60%; fatigue 40%; sputum 30%; dyspnea (in 20 to 40%); and myalgia 40–50%. Headaches seem to be more frequent in patients with a mild form not requiring oxygen therapy (approximately 55% of cases versus 10% in hospitalized patients)(Cao, Liu, Xiong, & Cai, 2020; Kumar et al., 2020). Anosmia and ageusia, although not specific for COVID-19, are found in approximately 50% and 40% of cases (Tong, Wong, Zhu, Fastenberg, & Tham, 2020). Disorders of smell and taste without anosmia or ageusia total would be even more frequent in the order of 85% of patients would affect more women than men, and could be the inaugural symptom in about 15% of cases(Lechien et al., 2020; Tong et al., 2020). More rarely, the following have been reported: chest pain (in about 15% of cases); sore throat (15%); diarrhea (7.5%); nasal congestion or rhinorrhea (7%); nausea and / or vomiting (5%); abdominal pain (5%); and hemoptysis (less than 2%) (Kumar et al., 2020). Among the clinical signs, the presence of fatigue, sputum, and dyspnea are associ-

ated with a poorer prognosis; while the presence of nasal congestion would be associated with a better prognosis(Cao et al., 2020; Kumar et al., 2020; Lechien et al., 2020; Li et al., 2020; Tong et al., 2020).

Multiple clinical forms have been described, with very variable incidences, ranging from the digestive picture to isolated neurological manifestations, including skin rashes(Abobaker, Raba, & Alzwi, 2020; Baj et al., 2020). However, respiratory involvement is the predominant clinical form, the other organs being less frequently affected. Among affected patients, approximately 5% require admission to an intensive care unit, 2 to 3% are ventilated invasively, and 1.5 to 2.5% die from severe COVID-19(Guan et al., 2020; Wu & McGoogan, 2020). The most common respiratory symptom is a dry cough (about 60% of cases); the patients are not very "sputtering"(Chen et al., 2020; Guan et al., 2020; Huang et al., 2020). The scanner data showed bilateral pulmonary involvement in about 75% of cases with peripheral predominance (more than 75% of cases). The most frequent radiological lesion is "ground glass" (68 to 83% of cases), followed by "crazy-paving" lesions (15 to 34%). Consolidations are present in 32 to 58% of cases(Zhu et al., 2020). The presence of a pleural effusion is unusual (5% of cases). Despite these lesions, which are often extensive on the scan, some patients present with radio clinical discordance with moderate dyspnea, even though there is sometimes profound hypoxemia. This phenomenon, called "silent hypoxemia" or "happy hypoxemia", has been described in certain cases of atelectasis or of right-to-left intra-cardiac or intra-pulmonary shunt, but is all in all quite unusual and rarely encountered outside of the body. COVID-19. The pathophysiology of this phenomenon is multifactorial and involves, among other things, a discrepancy between the mechanisms leading to hypoxemia at the onset of the disease (dysregulation of hypoxemic pulmonary vasoconstriction, diffusion anomaly, intravascular microthrombi, etc.) and the mechanicsbreathing preserved without increasing dead space or airway resistance not stimulating breathing centers(Dhont, Derom, Van Braeckel, Depuydt, & Lambrecht, 2020). Another hypothesis is that of the direct attack by the virus or indirect by the inflammation of the cytokine storm of the afferents of the autonomic nervous system traveling through the vagus and glossopharyngeal nerves(González-Duarte & Norcliffe-Kaufmann, 2020)or their relay at the level of the nucleus of the solitary tract in the bulb and no longer transmitting the signals of hypoxemia coming from the carotid bulbs or the sensation of dyspnea coming from the tracheobronchial tree and the pulmonary parenchyma(Ur & Verma, 2020).

PATHOPHYSIOLOGY OF PULMONARY INVOLVEMENT

Detection of SARS-COV-2 within the Lung Parenchyma

The detection of Sars-CoV-2 (RNA or viral proteins) on fixed tissue can be done using immunohistochemical techniques, in situ hybridization, molecular biology and / or electron microscopy. The interest is to be able, at least in part, to associate the histological lesions observed with the viral infection, and to eliminate other "non-specific" causes such as cardiovascular failure, consequences of intensive care or drug treatment and / or other associated infections.Several antibodies, some of which are commercially available, make it possible to detect Sars-CoV-2 viral proteins on dewaxed tissue sections. These may be antibodies directed against the core proteins or against other proteins, such as the spike protein or the Rp-3 NP protein(Zhang et al., 2020). Viral antigens have been demonstrated in the cytoplasm of several cell types, primarily the ciliated epithelial cells of the respiratory tree, present from the nasopharynx to the bronchi. Different viral proteins can be identified in other cell types, such as pulmonary alveolar cells, glandular cells and in endothelial cellsin recent studies.(Skok, Stelzl, Trauner, Kessler, & Lax,

2021; Varga et al., 2020). In situ hybridization techniques have detected fragments of Sars-CoV-2 RNA in the cytoplasm of ciliated epithelial cells of the respiratory tree. By combining the two techniques it is possible to simultaneously identify proteins and viral RNA (Liu et al., 2020).

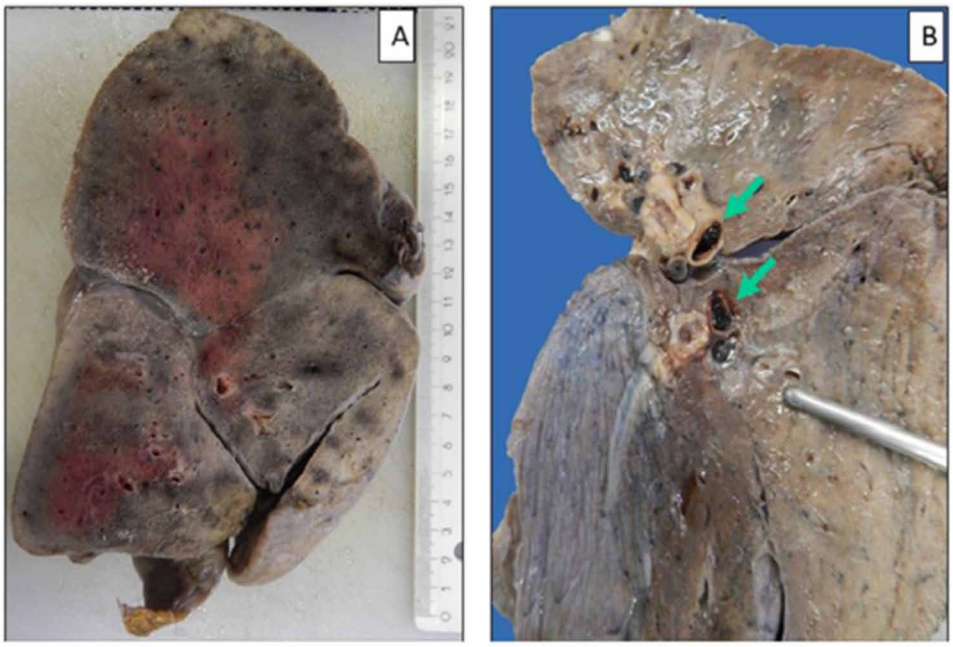
RT-PCR approaches have been developed to demonstrate the presence of Sars-CoV-2 at several organs, particularly in the respiratory tract(Remmelink et al., 2020; Wang et al., 2020). These techniques are possible to perform on dewaxed tissue sections fixed with formalin. Sars-CoV-2 has been identified in other organs as well, such as the central nervous system, heart, liver, kidney, intestine, or spleen(Wang et al., 2020). Molecular biology techniques must be carried out systematically using positive and negative controls, considering the possibility of false positive or negative results. False negative results are due to a degradation of the viral RNA following formalin binding, to a small quantity of viral RNA to be amplified or to an alteration of the viral RNA following unsuitable storage conditions for the blocks of paraffin.False positives have also been reported, especially when using quantitative PCR methodology. It should be noted that the demonstration of Sars-CoV-2 by molecular biology must always be compared with the results of the histological analysis, in particular the presence of an inflammatory reaction and / or necrotic lesions, in order to be able to a link between the presence of the virus and a pathogenic effect (Hofman & Copin, 2021).

Parenchymal Lung Lesions

Macroscopic lesions of the lungs during autopsies are not specific and correspond to hemorrhagic or infarct foci, or to areas of parenchymal condensation (Fig. 1A). More frequently, the observation quite characteristically shows the presence of thrombi in various pulmonary vessels (Fig. 1B). The images described for a large majority of patients correspond to lesions of diffuse alveolar damage and acute fibrinous organized pneumonitis (Barton, Duval, Stroberg, Ghosh, & Mukhopadhyay, 2020; Copin et al., 2020; Heinrich et al., 2020). There are thus hyaline membranes lining the surface of the alveoli, often associated with fibromyxoid cell exudates (Fig. 2A, B), and desquamation of the pneumocytes usually noted in the early stages of acute respiratory distress syndrome(Fig. 2C)(Mohanty et al., 2020; Xu et al., 2020). These lesions of diffuse alveolar damage are quite similar to those described in other etiological circumstances that may induce such lesions (Konopka et al., 2020). Acute organized and fibrinous pneumonia is also frequent, as well as more or less extensive foci of pulmonary infarction, especially in the very severe forms of the disease. Several images can be more or less completely associated with these lesions; this is a significant interstitial edema of intra-alveolar hemorrhagic foci (Fig. 2D), intra-alveolar polynuclear neutrophil infiltration, type II pneumocyte hyperplasia, interstitial lymphocyte or pleural infiltration, the presence of large atypical pneumocytes and multinuclear syncytial cells with large nucleoli and amphophilic cytoplasmic granulations suggesting a cytopathic effect of viral origin, and an increase in the number of stromal cells (fibroblasts) . Other observations have shown that in some patients who died after a fairly prolonged period in the intensive care unit, inflammatory interstitial fibrosis, associated with pneumocytic hyperplasia with a few binucleated pneumocytes(Hofman & Copin, 2021). Lung vascular damage is one of the hallmarks of SARS-CoV-2 infection(Ackermann et al., 2020; Lax et al., 2020). The lesions concern vascular structures of various sizes, such as capillaries and arterioles, but also venules, veins, and more rarely large arteries. They are sometimes minimal, being limited to congestion of the various vessels. It can also be recent or hyaline thrombi, sometimes in the process of fibrous organization, but also parietal inflammation with endothelitis or capillaritis (Fig. 2E, F)(Hofman & Copin, 2021). These vascular lesions would be the consequence:

- Direct damage to endothelial cells by the virus.
- A "cytokine storm" induced by an innate immune response inadequate to viral infection.
- a sudden formation induced by the extracellular neutrophilic virus (Magán-Fernández et al., 2020).

Figure 1. Post-mortem parts of pneumonectomy

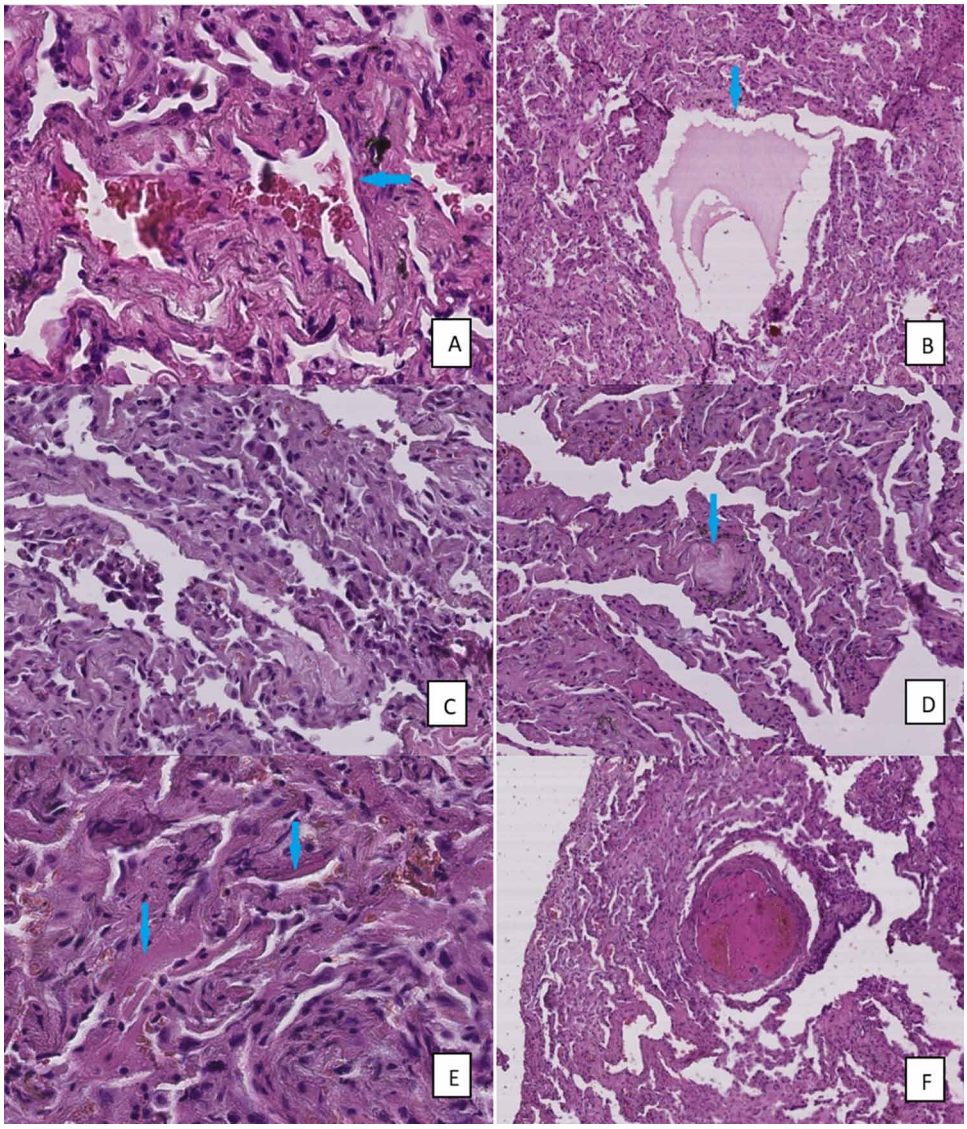


A. 88-year-old diabetic patient who died suddenly. Lung parenchyma condensed and "hepatized" as a whole. B. 70-year-old patient, with diabetes and hypertension, died suddenly. Presence of thrombi (arrows) in the pulmonary vessels (A and B). Modified according to(Hofman & Copin, 2021).

Thrombotic Events

Alterations in hemostasis and the resulting state of hypercoagulability are associated with a significant increase in thrombotic complications ranging from classic deep vein thrombosis (Fig. 2F) and pulmonary embolism, to totally unusual thrombosis of central line catheters. or arterial route, very early thrombosis of extra-renal purification filters. Conversely, very few bleeding complications have been reported, which reinforces the idea of hypercoagulability complicating COVID-19. Several autopsy data also underline the vascular dimension of the disease. The first analyzes found in the advanced forms, pulmonary infarctions and diffuse pulmonary, glomerular and dermal micro-thromboses(Fox et al., 2020). A prospective study, on twelve consecutive complete autopsies of patients who died from SARS-CoV-2 infection, noted 58% deep vein thrombosis with massive pulmonary embolism as the cause of death in one third of cases. In addition, in all patients with deep vein thrombosis, the thrombosis was bilateral(Tazi Mezalek, 2021).

Figure 2. Histological pulmonary lesions of a COVD-19 positive patient hospitalized in intensive care at the Mohammed VI University Hospital in Marrakech (Image: LEICA SCN400)



A: exudate and alveolar hemorrhage (HEx40) B: exudate of protein and intra-alveolar fibrin (arrow) with thickening of the inter-alveolar partitions (HEx10) C: intra-alveolar protein globule (HEx20) D: desquamation and hyperplasia of pneumocytes II (HEx40) E: hyaline membrane (HEx40) F: vascular thrombus (HEx10).

THERAPEUTIC MANAGEMENT

Ventilatory Management: Non-Invasive/Invasive Ventilation, and Extra-Corporeal Membrane Oxygenation

The place of non-invasive ventilation is undetermined in hypoxemic respiratory failure secondary to SARS-Cov-2 pneumonia and only the indications demonstrated for non-invasive ventilation (hypercapnic decompensation of obstructive pulmonary disease and acute lung edema occurring in a COVID-19 patient) are indisputable. If the decision to still opt for a non-invasive ventilatory support strategy other than the administration of oxygen, one should be aware that patients with SARS-Cov-2 pneumonia are at high risk of sudden deterioration, deterioration which can lead to cardiac arrest of hypoxic origin.It is therefore essential to ensure that patients treated with non-invasive ventilatory support are monitored and that the equipment necessary for emergency intubation is available(Krähenbühl, Oddo, Piquilloud, & Pantet, 2020).

In the initial acute phase, it is important to ventilate patients with severe SARS-Cov-2 lung disease on a controlled basis, possibly for at least 72 hours. In these patients who present, in the acute phase, a frequently increased neural ventilation control, this makes it possible to avoid the occurrence of secondary pulmonary lesions of the patient type self-inflicted lung injury.These lesions are likely to occur when switching to assisted or controlled assisted mode if the ventilatory control remains high (significant inspiratory efforts leading to significant negativation of pleural pressure and elevated transpulmonary pressures. This is frequently the case with the waning of severe respiratory failure and appears to be particularly marked in patients with respiratory failure Covid-19(Krähenbühl et al., 2020).Finally, in the most severe cases of acute respiratory distress syndrome COVID-19, when protective ventilation can no longer be provided, the recourse to extracorporeal membrane oxygenationshould be considered. Extracorporeal membrane oxygenation venovenous is reserved for refractory hypoxaemias that do not respond to other measures and in particular to prone decubitus(Garnier, Quesnel, & Constantin, 2021; Krähenbühl et al., 2020).

Anti Coagulants

More specifically, the high thrombotic risk presented by these patients leads to particular vigilance in the preventive or even curative anticoagulation of these patients (Garnier et al., 2021). Anti-thrombotics are probably a full-fledged treatment in patients hospitalized for COVID-19. The benefit of anticoagulant therapy is reported by Tang et al. In 99 patients who received low molecular weight heparin thromboprophylaxis. Despite several important limitations, the authors concluded that treatment with LMWH appeared to be associated with lower mortality in patients with DD levels six times higher than normal or $\geq$ 3000 ng / mL (32.8% vs.52. 4%, $p = 0.017$)(Tang et al., 2020). The benefits of anticoagulation are also reported by another study of nearly 3,000 patients hospitalized with severe COVID-19, 28% of whom received thromboprophylaxis. Hospital mortality was significantly lower in ventilated patients on anticoagulants vs. without anticoagulants (29.1% vs. 62.7%). In multivariate analysis, a prolonged duration of anticoagulation was associated with a reduction in mortality (HR 0,86 per day of anticoagulant, 0,82–0,89, $p < 0,001$)(Paranjpe et al., 2020). Finally, Klok et al. report that prophylactic anticoagulation at admission was associated with significantly fewer thromboses at follow-up.(Klok et al., 2020).

Immunomodulatory Treatments

The pathophysiology of the cytokine storm suggests the use of immunomodulatory treatments. Among the different treatments used, tocilizumab is a recombinant monoclonal antibody directed against the soluble and membrane receptors of IL-6, already commonly used in certain inflammatory pathologies such as rheumatoid arthritis, giant cell arteritis or arthritis. idiopathic juvenile. The significant increase in IL-6 concentrations appearing to be one of the cytokines most associated with the clinical prognosis of severe forms of COVID-19 has motivated its use in this context. Numerous comparative observational studies have evaluated its effectiveness in compassionate use (Garnier et al., 2021). Considering, only COVID-19 patients with respiratory distress admitted to critical care units, an American series of 210 patients treated with tocilizumab and 420 unexposed patients, analyzed by propensity score, reports a decrease in hospital mortality in all patients. patients (HR 0.64 [0.47–0.87] - p = 0.004) and in the mechanically ventilated patient subgroup (HR 0.63 [0.46–0.85] - p = 0.003)(Biran et al., 2020).

CONCLUSION

The practice of autopsies has made it possible to better understand new diseases and being able to carry out regular autopsies during an epidemic or pandemic linked to the emergence of an infectious agent is a necessity, even a scientific obligation. SARS-CoV-2, responsible for COVID-19, is a new beta-coronavirus responsible for primarily respiratory infection. SARS-CoV-2 induces an intense inflammatory reaction that can go as far as a cytokine storm, responsible for severe epithelial pulmonary involvement and an array of pulmonary intravascular coagulopathy. The polymorphic clinical picture in symptomatic patients can range from ENT and general nonspecific symptoms to acute respiratory distress syndrome with typical pathology, but with some clinical presentation atypia. Its non-specific management in critical care, and in particular ventilation, is to date like that recommended for acute respiratory distress syndromes of other origins.

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Chapter 7
COVID-19 Beyond the Lungs:
How SARS-Cov2 Invades the Human Nervous System

Omar El Hiba
FSJ, University Chouaib Doukkali, Morocco & Moroccan Society for Ethics and Animal Research (MoSEAR), Morocco

Hicham Chatoui
https://orcid.org/0000-0002-4707-1645
Faculty of Sciences and Techniques (FST), University Sultan Moulay Slimane, Morocco & Private University of Marrakech, Morocco

Nadia Zouhairi
FSJ, University Chouaib Doukkali, Morocco

Lahoucine Bahi
Faculty of Sciences and Techniques (FST), University Sultan My Slimane, Morocco

Lhoussaine Ammouta
Faculty of Sciences and Techniques (FST), University Sultan My Slimane, Morocco

Tiziano Balzano
https://orcid.org/0000-0001-6523-2206
Centre for Integrative Neuroscience A.C., University Hospital HM Puerta del Sur, Spain

Moulay Abdelmonaim El Hidan
Faculty of Applied Sciences, Ibn Zohr University, Morocco

Faical Isbaine
Emory University, USA

Arumugam R. Jayakumar
University of Miami School of Medicine, USA & South Florida VA Foundation for Research and Education, USA

Michael D. Norenberg
Departments of Pathology, Biochemistry, and Molecular Biology, University of Miami, USA

Amira Zaky
Faculty of Sciences, Alexandria University, Alexandria, Egypt

Halima Gamrani
Faculty of Sciences, Cadi Ayyad University, Morocco

ABSTRACT

Since December 2019, the world has been shaken by the spread of a highly pathogen virus, causing severe acute respiratory syndrome (SARS-Cov2), which emerged in Wuhan, China. SARS-Cov2 is known to cause acute pneumonia: the cardinal feature of coronavirus disease 2019 (COVID-19). Clinical features of the disease include respiratory distress, loss of spontaneous breathing, and sometimes neurologic signs

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such as headache and nausea and anosmia, leading to suppose a possible involvement of the nervous system as a potential target of SARS-CoV2. The chapter will shed light on the recent clinical and experimental data sustaining the involvement of the nervous system in the pathophysiology of COVID-19, based on several case reports and experimental data reporting the possible transmission of SARS-CoV2 throughout the peripheral nerves to the brain cardiorespiratory centers. Thus, understanding the role of the nervous system in the course of clinical symptoms of COVID-19 is important in determining the appropriate therapeutic approach to combat the disease.

INTRODUCTION

In December 2019, the republic of China had officially announced a new epidemic which emerged in Wuhan, following the discovery of a cluster of persons with viral pneumonia of unknown agent. Later, the mysterious agent was identified as a previously unknown coronavirus which was named by 2019 novel coronavirus (2019-nCoV) (Schwartz and Graham, 2020; Ma et al., 2020). One month later, the respiratory disease had spread to other countries including Japan, Italy, USA, Korea, Iran and others (Zhou, 2020).

On February 11, 2020, the World Health Organization (WHO) attributed the name of COVI-19 to the mysterious pulmonary disease, while the International Committee on Taxonomy of Viruses (ICTV) adopted the term SARS-Cov2 to designate the virus responsible for COVID-19 (Gorbalenya et al., 2020). One month later, on March 11, 2020, the WHO declared officially COVID-19 as a pandemic and a public health emergency of global concern (WHO, 2020).

On April 9, 2021, COVID-19 had affected up to 216 countries worldwide with around 133 146 550 infected individuals and 2 888 530 deaths (WHO, 2020). Official statistics showed that Americas are the still the most affected countries followed by Europe, then South-East Asia, Eastern Mediterranean region, Africa and Western Pacific (WHO, 2020).

In humans, clinical features of COVID-19 patients differ widely from asymptomatic to severely symptomatic manifestations. However, the main reproducible symptoms in COVID-19 patients are fever, headache, myalgia, cough, diarrhea, dyspnea, and pneumonia. Other symptoms may appear including acute respiratory and heart injuries, especially during the severe forms of the disease (Wu et al., 2020; Huang et al., 2020).

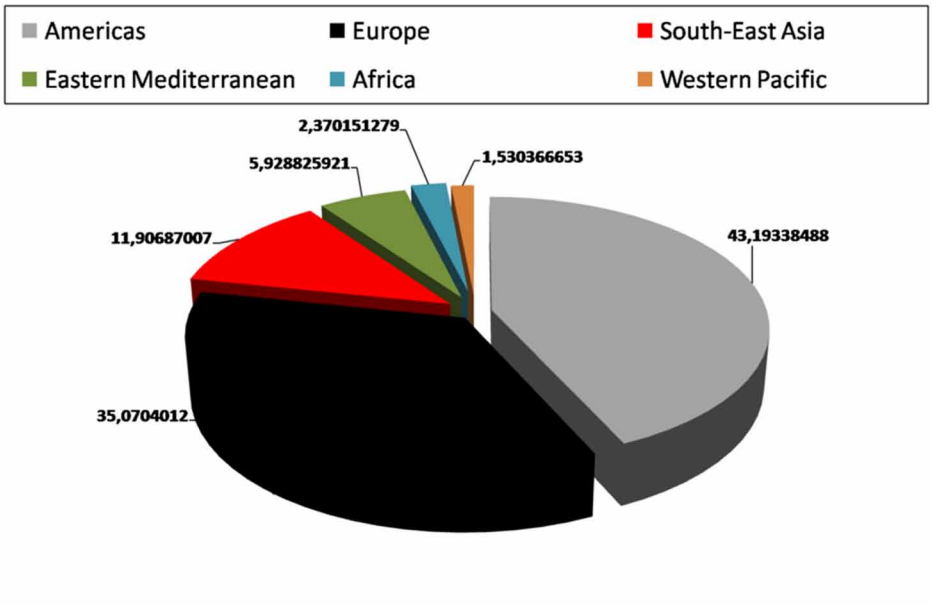
The ability of SARS-Cov2 to affect the human cells depends on the viral tropism which allows it to replicate within particular tissues but not others (McFadden et al., 2009). Accordingly, such selectivity results from the specific virus-host cell recognition involving particular proteins. Previous studies reported the main role of the virus Spike (S) protein and the angiotensin-converting enzyme 2 (ACE2) receptor as the key to the host cell entry for the virus (Hoffmann et al., 2020). ACE2 is found in different organs and tissues such as lungs, intestines, kidneys, endothelial cells, as well as the airway epithelial cells of the olfactory tract, leading to suppose that SARS-Cov2 may invade the human nervous system and therefore being behind the neurological manifestations in some COVI-19 patients (Hamming et al., 2004).

Through the current chapter, we will bring evidences of a nervous system invasion by SARS-Cov2 in COVID-19 patients, together with the underlying mechanisms behind the various neurological complications ranging from anosmia and ageusia to stroke.

HISTORY OF THE PANDEMIC

Since December 2019, the Chinese government had declared an uncontrolled mysterious outbreak of pneumonia in Wuhan city. First reports have suspected the emergence from Huanan; a wholesale market for aquatic and live animals sale (Li et al., 2020). Preliminary studies in patients with the respiratory disease revealed the presence of non-identified betacoronavirus sampled from lower respiratory tract. Otherwise, the virus was isolated from the human airway epithelial cells and was then named as 2019–novel Coronavirus (2019–nCoV) (Zhu et al., 2020). Later, electron microscopy observations showed that the virus structure allows it to be classified as a member of the Coronoviridae family. Surprisingly genetic studies showed 88% sequence similarity with 2 derived strains of coronavirus found in bats (RaTG13), while it appears to be more distant from humans SARS (79% similarity) and MERS (50% similarity). (Lu et al., 2020). On February 11, 2020, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses attributed the name of SARS–CoV2 (Severe Acute Respiratory Syndrome-CoV2) to the newly discovered virus (Gorbalenya et al., 2020). Accordingly, the World Health Organization (WHO) attributed the term COVID-19 to the associated disease (WHO, 2020).

Figure 1. Geographic distribution of COVID-19 confirmed cases worldwide (WHO, 2020)



COVID-19 EPIDEMIOLOGY

On April 9, 2021, the pandemic of COVID-19 had spread worldwide affecting up to 216 countries and territories and reached 133 146 550 confirmed cases with 2 888 530 deaths worldwide (WHO, 2020). The regional distribution of COVID-19 confirmed cases showed that the Americas are still the most affected countries followed by Europe, then South-East Asia, Eastern Mediterranean region, Africa and Western Pacific (figure 1) (WHO, 2020).

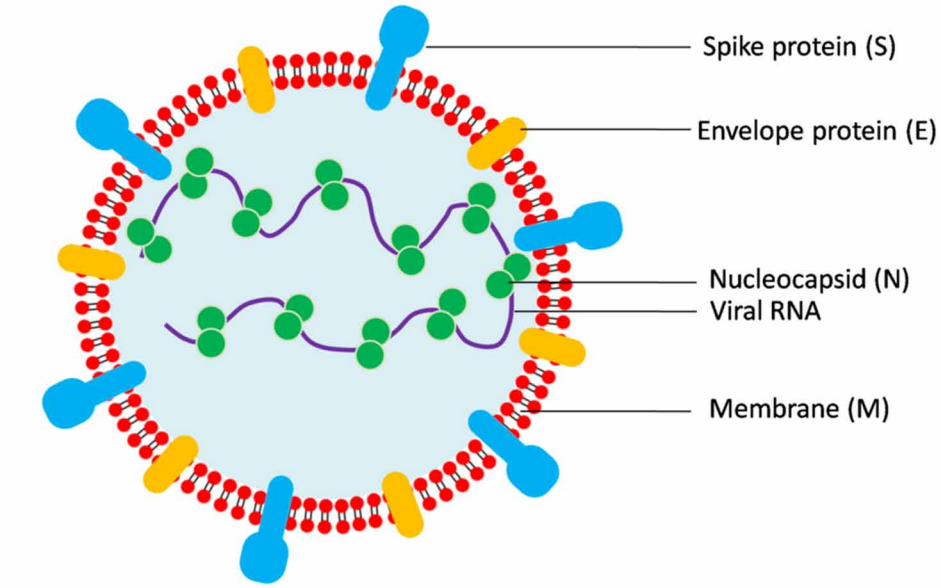
TRANSMISSION AND INFECTIVITY OF COVID-19

At the beginning of the disease in Wuhan, zoonotic transmission was thought to be the main cause of COVID-19 infection due to the fact that most infected individuals had a prior contact with wet markets (Li et al.,2020). Later, the number of infected individuals without confirmed contact, either with the Wuhan markets or another COVID-19 patient, increased drastically along with healthcare staff, which lead scientists to suggest a person-to-person transmission of the virus (Ralph et al., 2020; Chan et al., 2020).

Studies on the transmission routes of SARS-CoV2 emphasized the involvement of respiratory droplets containing the virus originating from COVID-19 patients generated by coughing, sneezing, singing, breathing, and speaking through direct or indirect contact (Rothan and Byrareddy, 2020).

Otherwise, indirect viral contamination is another route which should not be underestimated,. Indeed, airborne SARS-Cov2 transmission occurs generally in the case of evaporation of large respiratory droplets or dust particles contaminated (< 5 µm size). The physical characteristics of those particles allow their air suspension and maintaining in the air for longer periods and may be transported for long distance reaching 1m (WHO, 2020).

Figure 2. SARS-CoV2 structure (modified according to Das, 2020)



In addition, contact with contaminated objects or fomites is considered as another route for the virus transmission. Support of such view is the ability of SARS-CoV2 to still alive in different object surfaces (Van Doremalen et al., 2020).

A body of evidence sustains the possible fecal-oral transmission of SARS-Cov2. In fact, the gastro-intestinal tract expresses the two main proteins involved in the specific viral entry to host cells namely Angiotensin Converting Enzyme 2 (ACE2) and Transmembrane protease serine 2 (TMPRSS2) (Zhang et al., 2020; Iwata-Yoshikawa et al., 2019). Furthermore, previous data reported a delay in the virus shedding in the feces of COVID-19 patients (Liu et al., 2020).

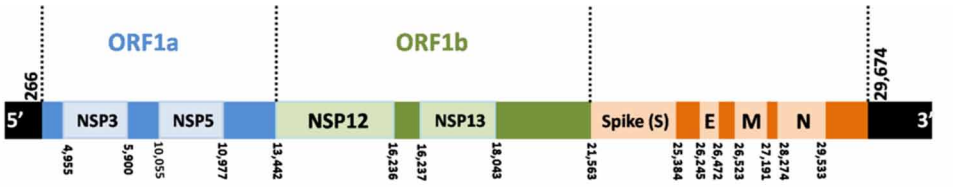
Controverted data suggested the possible transplacental (vertical) SARS-Cov2 transmission. Indeed, hematological analysis of blood samples from neonates born to mothers with confirmed COVID-19, revealed the presence of specific SARS-Cov2 IgM antibodies at the day of birth (Kimberlin and Stagno, 2020; Dong et al., 2020; Zeng et al., 2020).

Few evidence may imply the potential SARS-Cov2 transmission though sexual route. Analysis of semen samples from a cohort of COVID-19 patients showed that 6/38 of the investigated males were judged positive. Among the 6 patients, 2 were at the recovery stage and 4 in the acute one (Li et al., 2020).

SARS-COV2 STRUCTURE

Genetic studies classify SARS-Cov2 as a member of the subfamily of Coronavirinae belonging to the family of Coronaviridae, particularly, Betacoronavirus genus. Molecular biology data confirm that SARS-Cov2 genome is a single-stranded positive-sense RNA (+ssRNA) with around 29.9 kb according to NCBI genome database (NC_045512.2), with GC nucleotides percentage estimated as 38% (Lu et al., 2020). The genetic material of the virus is encapsulated in the nucleocapsid protein (N), while the periphery is constituted of an envelope containing the main important viral proteins for specific virus-host recognition; the membrane (M), the spike (S) and the envelop (E) proteins (figure 2) (Brian and Baric, 2005). Other non-structural proteins such as Nsp (1 to 16) are involved in different functions ensuring the formation of replication–transcription complex (RTC) essential for the genome transcription and replication within the host cell (Banerjee et al., 2020, Zhao et al., 2020).

Figure 3. SARS-CoV2 genome structure (Masters, 2006; Demogines, et al., 2012; Neuman et al., 2011; DeDiego et al., 2007)



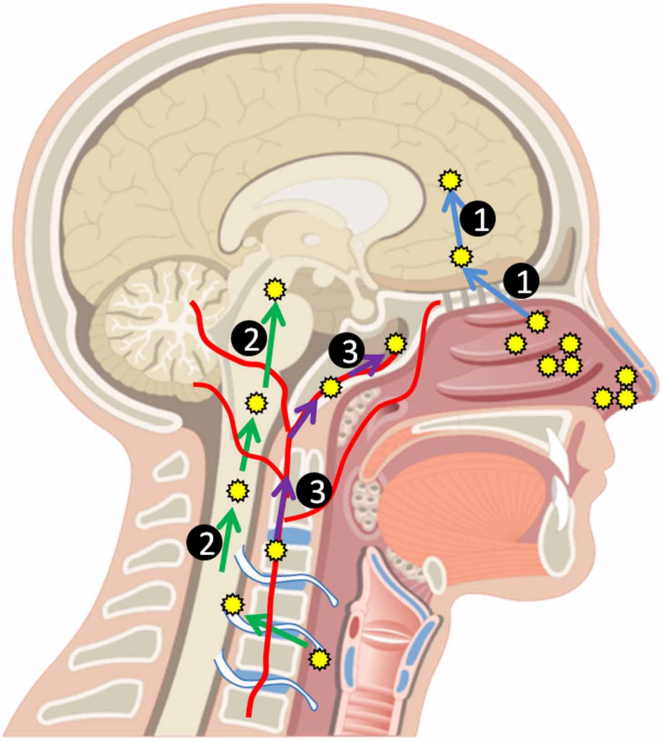
GENOMIC ORGANIZATION

SARS-Cov2 genome is organized in at least 6 open reading frames (ORFs). The first one ORF1a/b which is located at the 5′ end and represents nearly 2/3 of the total viral genome length whole genome length and encodes a polyprotein1a,b (pp1a, pp1b) (Masters, 2006). The other ORFs encode for structural proteins such as S, M, N, E proteins (figure 3) which are mainly involved in the host entry and invasion (Tong, 2009), accordingly, these proteins constitute the main targets of drugs and vaccines.

EVIDENCE OF SARS-COV2 INVASION OF THE HUMAN NERVOUS SYSTEM

A body of evidence sustains the theory of a possible lesion of the central nervous system (CNS) following SARS-Cov2 infection in humans. Indeed, clinical reports indicated, in COVID-19 patients, the exacerbation of particular symptoms including headache, epilepsy, and disturbed consciousness, generally associated to intracranial infections. While the majority of patients exhibit an anosmia and dysgeusia (Giacomelli et al., 2020). In a clinical case report on one patient in China, authors documented viral encephalitis arising from SARS-Cov2 which was found in the CSF of the patient (Xiang et al., 2020),

Figure 4. The three major routes for SARS-Cov2 entry into the CNS. 1: retrograde axonal transport from the olfactory bulb. 2: central or peripheral nerve transport. 3: systemic circulatory transport (modified according to Wang et al., 2020)



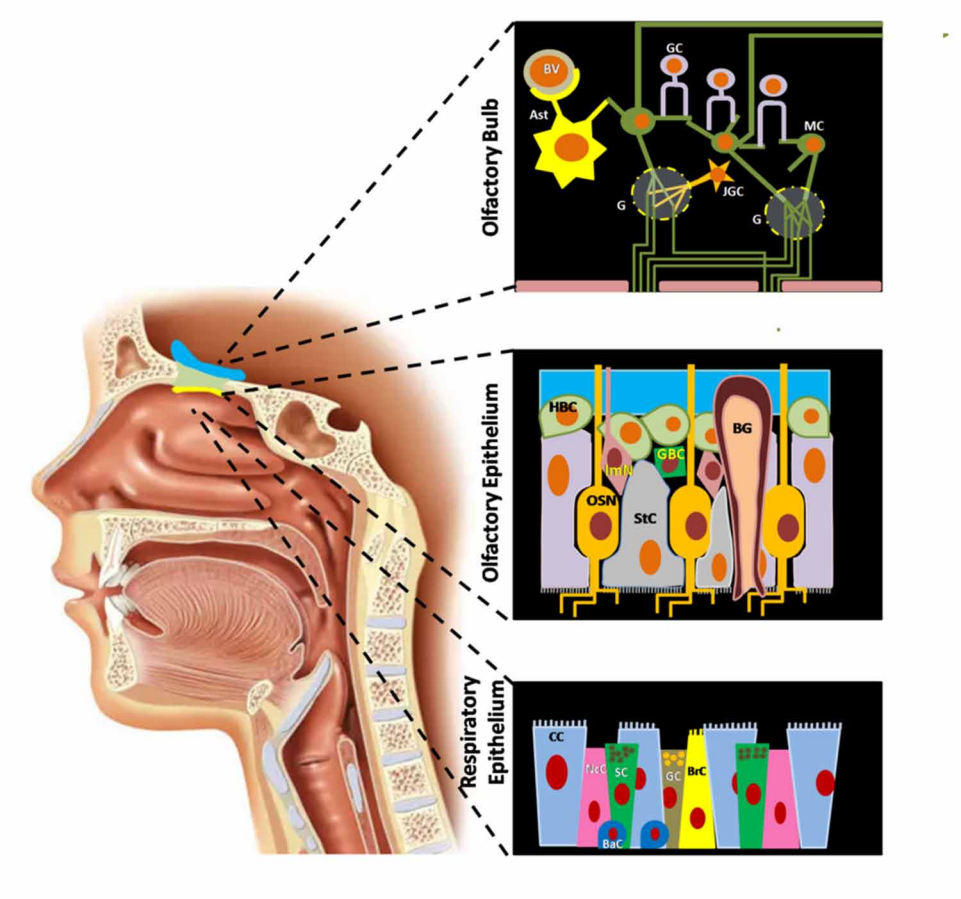
suggesting that the virus may invade the nervous parenchyma and trigger its neurological damages through divers mechanisms.

SARS-Cov2 may share, with other respiratory viruses like MERS and SARS, the same pathways to reach the nervous system; mainly, the hematogenous pathway, the retrograde axonal transport through the olfactory bulb and the viral transport via the central or the peripheral nerve terminals (figure 4).

Following lungs infection and increased viremia, SARS-Cov2 may reach the nervous system via cerebral circulation (Baig et al., 2020). Support of such view is provided by a postmortem study showing in a COVID-19 patient, the presence of active viral particles budding on endothelial cells (Paniz-Mondolfi et al., 2020). Another way to enter the CNS is via retrograde axonal transport from the olfactory bulb, while the direct nerve (peripheral and central) transport of the virus is also probable (Lechien et al., 2020; Menni et al., 2020; Baig, 2020).

A body of evidence sustains the presence of ACE2 receptors within the brain tissue, accordingly, the CNS may host the virus during its replication and therefore is considered as a target of the viral invasion (Baig et al., 2020; Xia, and Lazartigues, 2008; Xu et al., 2005). The specific interaction between

Figure 5. Cell types composing the nasal epithelium (olfactory and respiratory epithelia and olfactory bulb). Axons from olfactory sensory neurons (within the olfactory bulb) coalesce into glomeruli further innervated by mitral and juxtaglomerular cells (Hedrich et al., 2004; Reznik, 1990).



the SARS-Cov2 Spike (S) protein and the capillary endothelium ACE2 protein may trigger blood brain barrier (BBB) lesion allowing the virus to enter the CNS through the damaged vascular system (Baig et al., 2020).

NEUROLOGICAL COMPLICATIONS ASSOCIATED TO SARS-COV2 INFECTION

Anosmia and Ageusia

Previous reports in COVID-19 patients showed the presence of several disturbances in smell (anosmia) and taste (ageusia) perceptions in the absence of possible nasal inflammation (Bagheri el al., 2020; Giacomelli et al., 2020; Wölfel et al., 2020; Lechien et al., 2020; Menni et al., 2020; Spinato et al., 2020). Additionally, comparison of the recovery durations from COVID-19 associated to anosmia and typical post-viral anosmia (damage in the olfactory sensory neurons (OSNs)), shows that the first form takes few weeks, while the second one takes generally several months (Welge-Lüssen and Wolfensberger, 2006, Duncan and Seiden, 1995; Cavazzana et al., 2018).

Literature reports indicate that the two main components of the nasal epithelium are respiratory and olfactory epitheliums. The respiratory epithelium which ensures humidification of air within the respiratory tract, is constituted of 4 different cell types mainly: ciliated cells, secretory cells (goblet cells), and brush cells (figure 5) (Hedrich et al., 2004). Whereas, the olfactory epithelium ensures the odor detection through specific receptors on olfactory sensory neurons (OSNs) (Suzuki et al., 1995; Suzuki et al., 1996; Vogalis et al., 2005).

Otherwise, substantial evidences support the role of the two major proteins involved in the specific interaction between SARS-Cov2 and the host cell; such as the viral spike (S) protein and the ACE2 protein of the target cell. As the process begins by the cleavage of the spike by the cell surface protease TMPRSS2, other proteins may be also involved such as the proteases: Cathepsin B and L, CTSB/CTSL (Zhou et al., 2020; Ceccarelli et al., 2020; Zumla et al., 2016; Hoffmann et al., 2020; Li et al., 2003; Li et al., 2004; Kuba et al., 2005).

Recent evidence showed that cells from the respiratory epithelium (in particular goblet and ciliated cells) are expressing ACE2 and TMPRSS2 in a high level, leading to suppose that these cells are able to host the SARS-Cov2 during infection (Sungnak et al., 2020; Hou et al., 2020). Nevertheless, the absence of OSNs and sustentacular cells in the studied samples lead to exclude the olfactory epithelium from the study (Deprez et al., 2020; Braga et al., 2019). While a study performed by Brann et al., (2020), using single cell RNA sequencing, revealed that human olfactory mucosa cells express ACE2 and TMPRSS2. Whereas, support cells, stem cells, and perivascular cells express exclusively ACE2. Accordingly, the authors concluded that SARS-Cov2 infection of non-neuronal cells underlies anosmia in COVID-19 patients (Brann et., 2020).

Infectious Toxic Encephalopathy (ITE)/ Acute Toxic Encephalitis (ATE)

ITE/ATE is a particular type of brain dysfunctions resulting from metabolic disorders, hypoxia and toxemia especially during acute infection (Mizuguchi et al., 2007; Tauber et al., 2017; Young, 2013). At the neurological level, ITE patients exhibit cerebral edema in the absence of neuroinflammation. The mild form of the disease is associated with headache, dysphoria, mental disorder, and delirium. While

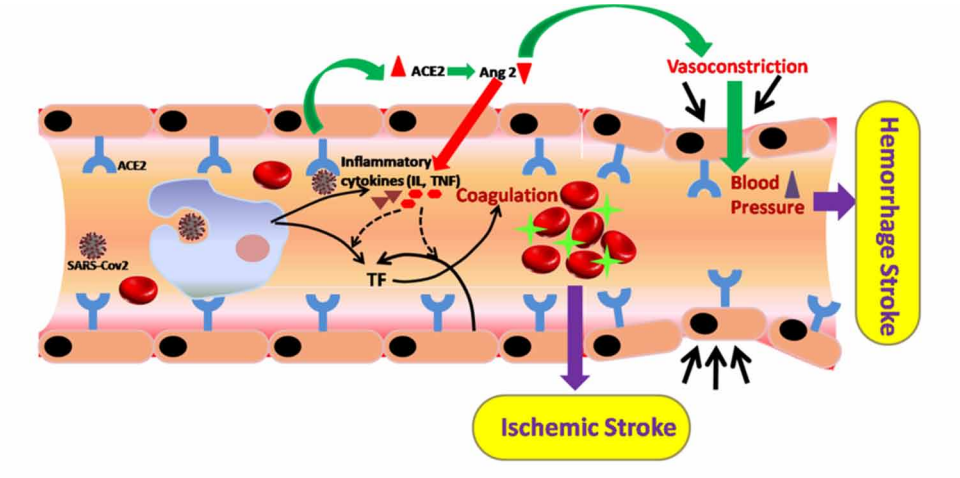
during the severe form, patients manifest a wide range of symptoms including disorientation, impaired consciousness, sometimes paralysis and coma (Dobbs, 2011; Mizuguchi et al., 2007). Other studies have brought evidence of the possible involvement of viral infection, including SARS-Cov2, in the neuropathology of ITE taking into consideration the high rate of COVID-19 patients exhibiting hypoxia and viremia (Guo et al., 2020). The high similarity between clinical manifestations of COVID-19 and ITE, which include headache and disturbed consciousness, along with the presence of brain edema, sustain the hypothesis that SARS-Cov2 may elicit an ITE in COVID-19 patients (Xu et al., 2020).

Cerebrovascular Disease (ACD)

Several case reports on the neurological symptoms of COVID-19 emphasized the existence of cerebrovascular diseases due to their higher prevalence in COVID-19 patients, particularly those with severe manifestations (Mao et al., 2020). At the cellular level, SARS-Cov2 binding to the ACE2 lead to its inactivation, and consequently, an impaired blood pressure control (Zhao et al., 2020; Wang et al., 2020), increasing therefore the risk of hypertensive peaks induced stroke (intra-cerebral hemorrhage) (figure 6). While ACE2 dysfunction resulting in ACE2 accumulation, is involved in the inflammation cascade following ischemia and lower perfusion of the ischemic zones associated to the development of larger infarct volumes (Arroja et al., 2016; Kaushik et al., 2020).

Otherwise, combination of impaired ACE2 function and cytokine storm together with hypoxia, may underlay heart injuries particularly myocardial ischemia and cardiac arrhythmias such as atrial fibrillation in COVID-19 patients (Kochi et al., 2020), contribute as well to the development of cardio-embolism and therefore ischemic stroke (figure 6).

Figure 6. Schematic representation of the mechanism of SARS-Cov2 induced vascular pathologies



Activation of monocyte-derived macrophages (MDM) by SARS-Cov2 elicits the release of pro-inflammatory cytokines (IL and TNF). SARS-Cov2 binding to endothelial ACE2 receptors repressed its function increasing therefore angiotensin II (Ang2) concentration; a further proinflammatory factor.

Consequently, tissue factors (TF) are expressed both by MDM and endothelial cells, which activate the extrinsic coagulation pathway. Such activation may elicit fibrin accumulation and formation of blood clots, increasing therefore the risk of acute ischemic stroke. Cytokine storms are also able to trigger fragilization of BBB responsible of the hemorrhagic stroke onset. While the elevated amounts of Ang2 may cause blood hyper-pressure; a risk of hemorrhagic stroke (Wang et al., 2020)

Additionally, another factor which may increase the risk of cerebral venous thrombosis or ischemic stroke is the hypercoagulability, which has been widely documented in COVID-19 patients, especially in the severe episodes of the disease. Hypercoagulopathy involve several factors such as immobilization, dehydration, inflammation as well as increased fibrinogen, endothelial cell injury and platelet activation (Becker, 2020; Zhang et al., 2020; Klok et al., 2020; Helms et al., 2020).

CONCLUSION

The cumulating evidences available till now, sustain the hypothesis of a possible neurotropic potential of SARS-CoV2, which may be considered as neuro-invasive for humans and may underlay the variable neurological manifestations observed prior, during and even after the onset of common COVID-19 symptoms, particularly the long-term persistent neurological disorders. Hence, understanding the exact mechanisms through which the virus may interact with the different nervous system components (peripheral and central), is of crucial importance for the management of COVID-19. The rare and confluents data available lead to conclude that further studies involving in vitro and in vivo experimental investigations are required to complete our knowledge on SARS-CoV2 invasion of the human nervous system.

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Chapter 8
Gastrointestinal Tract and COVID-19:
Insights Into the Role of Gut Microbiome

Aaron Lelo Pambu
University of Kinshasa, DRC

Abdellah Zinedine
https://orcid.org/0000-0002-8632-0536
Faculty of Sciences, Chouaib Doukkali University, Morocco

ABSTRACT

The current outbreak of the novel coronavirus, SARS-CoV-2 (coronavirus disease 2019; previously 2019- nCoV), epi-centered in Hubei Province of the People's Republic of China, has spread to many other countries caused an extreme burden for healthcare systems globally. Coronaviruses are traditionally considered nonlethal pathogens to humans, mainly causing approximately 15% of common colds. In this century, we have encountered highly pathogenic human CoVs twice. In this chapter, the authors propose to focus the gastrointestinal physiopathology of the infection of SARS-Cov2. This chapter will develop subject like the gastrointestinal manifestations of the infection to SARS-Cov2. The second part of this chapter will develop the role of the gut microbiome in the SARS-Cov2 diseases susceptibilities. And then the authors will show the etiopathogenesis of SARS-Cov2 associated diarrhea. As reported by previous studies, the SARS-Cov virus entry into host cell is mediated by the interaction between the envelop-anchored viral spike protein and the host receptor named angiotensin-converting enzyme 2 (ACE2).

INTRODUCTION

The current outbreak of the novel Coronavirus, Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) (Coronavirus disease 2019; previously 2019-nCoV), epi-centered in Hubei Province of the People's Republic of China, has spread to many other countries and caused an extreme burden for health care systems globally. Coronavirus have been traditionally considered as non-lethal pathogens to

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humans, mainly causing approximately 15% of common colds. However, in this century, we have encountered highly pathogenic human CoVs twice, i.e., SARS-CoV and Middle East respiratory syndrome Coronavirus (MERS-CoV), which caused outbreaks respectively in China in 2003 and Saudi Arabia in 2012 (Assiri et al., 2013; Hoffmann et al., 2020a).

Although this viral infection is mainly manifested with fever, dry cough and shortness of breath, respiratory symptom and inflammation. Symptoms like Gastrointestinal manifestations have been reported to be associated to the infection to SARS-Cov2 (Del Rio and Malani, 2020). This virus uses the Angiotensin-Converting Enzyme 2 (ACE2) receptor in order to invade cells, and these receptors have been reported to be highly expressed in both respiratory and gastrointestinal tracts (Xiao et al., 2020; Wang et al., 2020),suggesting that the digestive tract might be an extra-pulmonary site for virus replication and activity (Wolfel et al., 2020; Xu et al., 2020).Accumulating evidence in these days suggest that, this coronavirus, may also be considered as an enteric virus, which can be spread via the fecal-oral route (Guan et al., 2020; Holshue et al., 2020). The most commonly reported Gastrointestinal(GI) manifestation of Covid-19are diarrhea, abdominal pain, nausea or vomiting, which are reported in a third to up even more than half of the patients (Parasa et al., 2020).

The gut microbiota demonstrates tremendous diversity and variation of commensal bacterial populations, and this explains how the gut microbiota plays a vital role in the outcome of diseases. Several studies have confirmed that gut microbiota plays a key role in health through the immunity building mechanism (Chung et al., 2012; Bouskra et al., 2008; Mazmanian et al., 2005). This commensal microbiota in the gut tract ecosystem is dynamic and can be regulated by invading viruses to facilitate a stimulatory or suppressive response (Ma et al., 2019). Mounting evidences have supported the hypothesis that, the composition of the gut microbiome could partially explain the difference in susceptibility of Covid-19 patients. There are few cues that support this possibility of the gut microbiota link to Covid-19. The first one is the presence of many SARS-Cov2 viral RNA in the faeces of many patients. Secondly, the various gastrointestinal symptoms reported by patients. Thirdly, the fact that most vulnerable patients were the old people, immune-compromised and patients with co-morbidities And the fourth one is the greater evidences of the Gut-lung axis. Where it is emphasized the role played by gut microbiome diversity and abundance in SARS-Cov2 susceptibility (Busra and Belma, 2020). In all such people, studies have revealed a gut dysbiosis and decreased gut diversity.

SARS-CoV have been reported to entry into host cell through a mediated interaction between the envelop-anchored viral spike protein and the host receptor ACE2.This invasion requires priming by cellular Serine proteases (TMPRSS2), which allow spike protein cleavage, regulating the entire mechanism showing that the virus infectivity mainly depends on binding affinity with human ACE2.Other studies have shown high expression of ACE2 in the enterocytes, suggesting these cells are also potential target of the virus in the GI tract. More recently, ACE2 has been reported to be important in controlling intestinal inflammation and gut microbial ecology (Hashimoto et al., 2012). This can explain the mechanism of the physiopathogenesis of SARS-Cov2 associated diarrhea. In this chapter we will develop the molecular mechanism underling the infection of SARS-Cov2 in the GI tract.

GASTROINTESTINAL PHYSIOPATHOLOGY OF COVID-19

Gastrointestinal Tract Structure and Function

The gastrointestinal tract (GIT) consists of an echoing muscular tube starting from the oral cavity, where food enters the mouth, continuing through the pharynx, esophagus, stomach and intestines to the rectum and anus, where faeces are expelled (Ma et al., 2019). The GIT is divided into upper and lower tracts, which has two surfaces referred as the *mucosa* and the *serosa*. Although the outer surface or serosais a thin layer of connective tissue covered with a single layer of squamous epithelial cells, the inner or mucosal surface is quite complex. It actually consists of three components, namely: a single layer of epithelial cells called the *epithelium*, the *lamina propria*, and the *muscularis mucosae*. Even though the structure of the GIT differs substantially from region to region, most of that variation is within the mucosa. The epithelial cells themselves are the primary source of variation and are specifically modified to carry out the functions of each region of the tract (Ma et al., 2019).

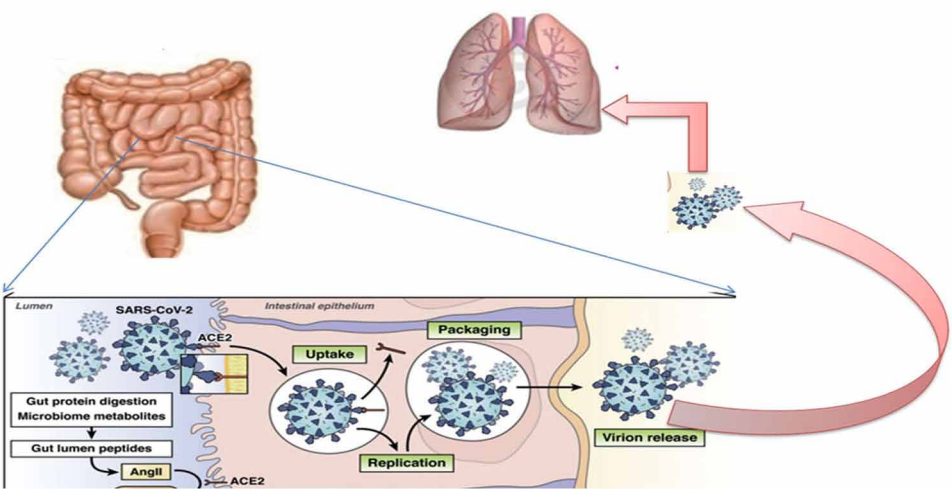
SARS-CoV Infection Mechanism

The pre-requisite for SARS-CoV-2 infection is the entry into host cells, which is dependent on dense glycosylated spike protein (S protein). The S protein is a type I trimeric transmembrane protein with an N terminal cleavable signal peptide, one large and heavily N-glycosylated ectodomain (60–90carbohydrates per trimer), a transmembrane region, and a cytoplasmic tail containing a cluster of S-acylated cysteine residues. This S protein contains two functional subunits S1 and S2. The S1 subunit is responsible for the binding of the virus to host cell receptors, whereas the S2 subunit is responsible for the fusion of viral and cell membranes (Peijie et al., 2020; Wrapp et al., 2020). The S1 domain is further divided into an N terminal domain (NTD) and a C terminal domain (CTD). The NTD exhibits a structural fold as human galectins, galactose-binding lectins, and hence, in most CoVs, a sugar present at the cell surface serves as an attachment factor. The CTD is responsible for binding to the host receptor ACE2 in the case of SARS-CoV and 2019-nCoV. The CTD contains two subdomains: a core structure (a five-stranded antiparallel β-sheet) and the actual receptor-binding motif (RBM), which determines the receptor binding specificity (Peijie et al., 2020; Sun et al., 2020).

After the binding to its receptor, the virus must access to the host cell cytosol. The S protein catalyzes fusion of the viral and cellular membrane to allow access of the viral genome to the cytosol. A pre-requisite for this activity is the cleavage of S into subunits, the process is called priming. This is generally accomplished by acid-dependent proteolytic cleavage. The first cleavage site is located at the S1/S2 boundary and another site (called S2′) within S2. CoVs have evolved multiple strategies for proteolytic activation of S, and a large number of host proteases, such as furin, trypsin, trans-membrane protease/serine (TMPRSS), and cathepsins have been identified to process the spike protein. Cleavage by trypsin and TMPRSS family members occurs at monobasic cleavage sites and likely takes place in the extracellular space and at the cell surface, followed by fusion of the viral and cellular membranes (Belouzard et al., 2009). The S protein is initiated by the serine protease TMPRSS2, which is essential for SARS-CoV-2 to enter cells. The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus. In particular, the receptor-binding domain (RBD) of the S protein domain is directly involved in the recognition of host receptors (Lan et al., 2020; Jian et al., 2020).

The infection of SARS-CoV-2 depends on the combination between S protein and ACE2. If the S protein of SARS-CoV-2is considered key, ACE2 in the human body is like a lock that can be unlocked by S protein as shown in the figure 1. Other host cell receptors may also mediate SARS-CoV-2infection. Using genomic receptor profiling with SARS-CoV-2 S protein as the target, including ACE2. Among them, ASGR1 and KREMEN1can directly mediate SARS-CoV-2 infection independent of ACE2,hence may be specific receptors of SARS-CoV-2 infection (Gu et al., 2020). These multiple host cell receptors of SARS-CoV-2 may explain why SARSCoV-2 can invade multiple body organs, thus causing complex clinical manifestations (Wrapp et al., 2020; Walls et al., 2020).

Figure 1. Gut-lung infection mechanism of SARS-CoV-2



The availability and activity of the proteases in a certain cell, tissue, and host species regulates the tropisms of CoVs. However, the fact that S can easily acquire new protease cleavage sites and that various (some of them ubiquitous) proteases can fulfil the same task suggests that CoVs are naturally equipped or can easily adapt to multiply in several cell types.

Gastrointestinal Covid-19

SARS-CoV-2 infection causes primarily a respiratory-based constellation of symptoms. This is probably due to the respiratory nature of symptoms, leading to the hypothesis that the virus infects respiratory epithelial cells, and is transmitted via respiratory droplets from human to human. Moreover, despite the fact that COVID-19 is mainly a pulmonary disease, gastrointestinal symptoms and signs are prevalent in patients with COVID-19 (Peijie et al., 2020). Also a recent case report detected transcriptional activity of SARS-CoV-2 viral RNA in stool samples after analysis by shotgun metagenomics sequencing, thus challenging these hypotheses and attesting the presence of SARS-CoV-2 in the gut of a subset of patients raising the question of viral gastrointestinal infection and a fecal-oral transmission route (Zuo et al., 2021). Fecal shedding of SARS-CoV RNA has been reported in 86%–100% of patients during days 6–14 of illness and could persist for more than 30 days of illness. There might be a potential explana-

tion for relatively high prevalence of these gastrointestinal symptoms. Mounting studies reported that both SARS-CoV and SARS-CoV-2 have a high affinity for ACE2 because the virus enters target cells through ACE2 (Zhou P et al., 2020), a receptor found in both the upper and lower gastrointestinal tract where it is expressed in enterocytes and intestinal cells (Xiao et al., 2020; Guan W et al., 2020; Zou et al., 2020; Wang et al., 2014).

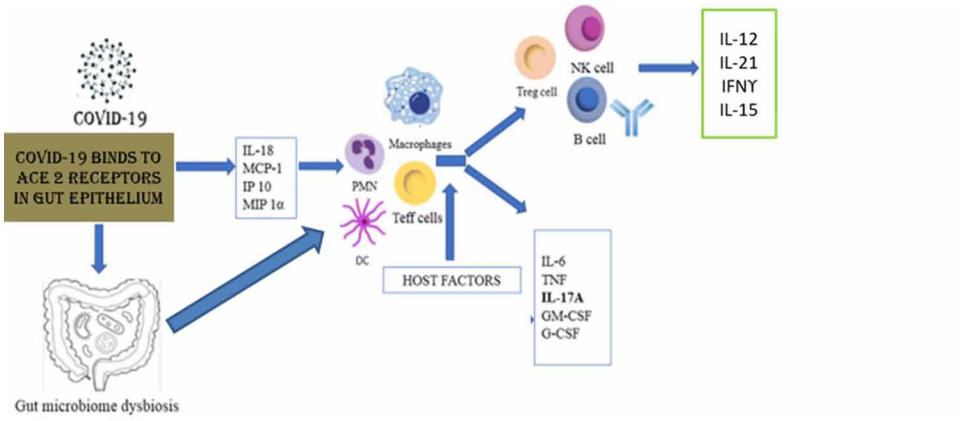
The key step of the virus entry into the host cell is via the ACE-2 receptors (Wan et al., 2020a,b) and ACE-2 is an important regulator of intestinal inflammation (Hashimoto et al., 2012). Besides the presence of ACE-2 receptor, successful virus entry requires transmembrane protease/serine 2 (TMPRSS2), which cleaves the S-protein of SARS-CoV-2 on the cell membrane and enables viral fusion [(2)] ACE-2 and TMPRSS2 were not found only in the lung alveolar cells and esophageal epithelial cells but also in the absorptive enterocytes of ileum and colon with interestingly higher expression (Zhang et al., 2020). Using single-cell RNA sequencing, Liang et al demonstrated that ACE-2 was highly expressed in the proximal and distal intestine (Liang et al., 2020). Thus, the greater invasive nature of the virus and the abundance of its attaching receptors along the GIT can explain its GI manifestations. Both biopsy of small intestine and rectal swabs have been detected to be positive for SARS-CoV-2 virus (Xu et al., 2020).

Several mechanisms of Gastrointestinal invasion have been postulated for causation of diarrhea in COVID-19 infection. It is estimated that 16%–73% of patients had diarrhea during the course of SARS illness. The first one is the direct virus entry through ACE-2 receptor causing malabsorption, unbalanced intestinal secretion, and activated enteric nervous system. Secondly is the direct/indirect damage to the intestinal epithelium by inflammatory response (Xie et al., 2020); the third mechanism is the antibiotic and/or antiviral drugs-induced intestinal dysbiosis; and the fourth one is the fact that the virus has induced disorders of the intestinal flora (Xiao et al., 2020). The binding of SARS-CoV-2 with ACE2 in the GIT reduces the level of available receptors, which affects the absorption of tryptophan, and ultimately destroys the steady state of the intestinal flora. This is one of the causes of gastrointestinal symptoms such as diarrhea. The fifth one is the existence of the "gut–lung axis" disturbances wherein respiratory flora alteration affects the digestive system by the immune regulation (Budden et al., 2017). Changes in the composition and function of the gastrointestinal flora affect the respiratory tract through the common mucosal immune system.

The evidence of shedding of the virus through feces is another definitive proof of GI involvement and a potential route for transmission. One study found that SARS-CoV-2 cannot always be detected in the stool of Covid-19 patients with gastrointestinal symptoms, so it has been speculated that the gastrointestinal symptoms of some patients may not be caused by direct damage due to the viral infection. Effector CD4+ T cells entering the intestinal mucosa are recognized as key for mucosal immunity and chronic enteritis. C-C chemokine receptor type 9 (CCR9) is a necessary chemokine receptor for CD4+ T cells to enter the small intestine (Wang et al., 2014). In Wang et al. (2014), found that lung-derived CCR9+CD4+ T cells were increased after viral infection. It has been revealed that the small intestinal epithelium can express CCL25, which in turn promotes the recruitment of CCR9+CD4+T cells into the small intestine (Stenstad et al., 2006), leading to intestinal immune damage and destroying the homeostasis of the intestinal flora. This disturbance of the intestinal flora will promote the polarization of Th17 cells in the small intestine, and the production of too much IL-17A as shown in figure 2 which will lead to the recruitment of neutrophils (Crowe et al., 2009), causing intestinal immune damage, diarrhea, and other gastrointestinal symptoms.

When inflammation occurs in the intestine, cytokines and bacteria also can enter the lung through the bloodstream, further affecting the lung immune response and inflammation (Zhang D et al., 2020).

Figure 2. The host gastrointestinal infection by Covid-19 and gut microbiome dysbiosis induce pro inflammatory cytokines and interferons are released



Intestinal mucosal damage and bacterial imbalance can also influence the gut-liver axis (which refers to the bidirectional relationship of the portal vein between the intestine, microorganisms and liver through the portal vein). In the intestine, host and microbial metabolites are transferred to the liver through the portal vein and affect liver function. The liver releases bile acids and bioactive media into the biliary and systemic circulation and transports them to the intestine (Tripathi et al., 2018). This leads to liver function damage in patients, which may also explain the abnormality of liver function indicators in COVID-19 patients in some studies (Hu et al., 2020).

GUT MICROBIOME AND COVID-19 INFECTION

Human Gut Microbiome

Human microbiome is an all-encompassing term that refers to all microorganisms on or in the human body. Human beings are therefore regarded as ecosystems that are comprised of distinct ecologic niches or habitats, each housing a discrete collection of co-evolved bacteria, archaea, viruses, and lower and higher eukaryotes interacting extensively with each other and with the human host (Belkaid and Segre, 2014). The co-evolution of human and its microbiome has led to an interdependence where the human microbiome contributes to a vast array of essential functions to the human host and influences a variety of physiologic, immunologic, and metabolic processes.

These microorganisms are found in large numbers on skin, mucosal surfaces and the gut. The GIT contains trillions of microbes dwelling in our gut, with different species of bacteria, fungi, parasites, and viruses playing divers roles in maintaining and regulating genes involved in the immune health and metabolism (Zhu et al., 2017).Thus, research is showing that the human microbiome is fundamental in the maintenance of the human health, and microbial perturbations are being linked to an ever-increasing array of neurologic, gastrointestinal, metabolic, oncologic, hepatic, cardiovascular, psychologic, respiratory, and autoimmune disorders (Susan et al., 2016).

The human gut microbiota is composed of approximately $10^{11–14}$ microorganisms per gram of content, including diverse populations of bacteria, mainly anaerobes (95% of the total), which is 10 times higher than the total number of human cells. At the phylum level, the dominant intestinal bacteria are *Firmicutes* and *Bacteroidetes* in healthy human subjects, whereas other minor phyla include *Proteobacteria*, *Actinomycetes*, *Verrucomicrobia*, and *Fusobacteria* (Hall et al., 2017).

While the microbes get a habitat and nourishment from the host, these microbes in turn help the host by regulating various host physiological functions, including dietary digestion, and imparting protective immunity against pathogens. Alterations of gut microbiota sometimes collectively called as "gut dysbiosis" have been shown to be associated with various diseases and disorders like inflammatory bowel disease (IBD) (Khan, 2019), type 2 diabetes (Gurung, 2020), depression (Zalar et al., 2018), cardiovascular diseases (Tang et al., 2017).The composition of the human gut ecosystem is influenced by multiple and diverse factors, some physiological (age, origin, environment) and others linked to external factors, such as dietary habits, antibiotics, and probiotics.

Gut Dysbiosis and Covid-19 Infection

Diversity in the gut microbiota decreases during aging and microbiome composition altered to an imbalance state, so called dysbiosis, leads to an immune dysfunction and generalized inflammation (Aleman and Valenzno, 2019). Primarily, the gut microbiota in healthy individuals is dominated by four phyla *Actinobacteria, Firmicutes, Proteobacteria,* and *Bacteroidetes* (Villanueva et al., 2015; Gill, 2006). The colon harbours an extremely high density of bacteria in the families *Bacteroidaceae*, *Prevotellaceae*, *Rikenellaceae*, *Lachnospiraceae* and *Ruminococcaceae* (Hall et al., 2017).

The metabolic products of the microbiome shape the microenvironment and exerts a strong selective pressure on microbial colonization. In the gut *Bacteroidetes* and *Firmicutes* are predominant while *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* preponderate in the lung (Zhang D et al., 2020). Dysbiosis considered as an indicator of unhealthy microbiome has been linked to various chronic conditions such as asthma, arthritis, obesity, and type 2 diabetes (Aleman and Valenzano, 2019; Hufnagl et al., 2020). People older than 65 years old have been found to be at higher risk of death from Covid-19 than those of <65 years old (John et al., 2020). The incidence of diarrhea in Covid-9 patients and the high mortality rate in elderly patients, taken together, point to a possible involvement of gut-lung axis in Covid-19 with association of dysbiosis. These may imply that directed alteration of gut microbiota could be utilized to prevent or treat unhealthy conditions in humans. Like for the gut microbiota, there are evidences now that suggest the presence of distinct microorganisms in the lung (Bingula, 2017).

Interestingly, the gut microbiota has been shown to affect pulmonary health through a vital cross-talk between the gut microbiota and the lungs which is referred to as the "gut-lung axis" (Keel et al., 2012). The gut-lung axis is supposed to be bidirectional, meaning the endotoxins, microbial metabolites can impact the lung through blood and when inflammation occurs in the lung, it can affect the gut microbiota as well (Dumas, 2018). This raises an interesting possibility that novel SARS-CoV-2 might also have an impact on the gut microbiota.

Microbiota-virus interactions have been studied, as well as the positive and negative effects of microbiota on viruses (Robinson and Pfeiffer, 2014). Bacterial surfaces are able to interact with viral proteins, which differ for structures and folds. Viral infection is facilitated by the interaction with the main bacterial envelope components, the lipopolysaccharides (LPS) in Gram-negative and peptidoglycans (PG) in Gram-positive. Poliovirus and other viruses, including Reovirus, mouse mammary tumor virus, and

murine norovirus, have been shown to use both LPS and PG to enhance their thermostability, receptor affinity and similar mechanisms to facilitate the *in vivo* infection (Karst, 2016). Together, these results indicate a key role for commensal bacteria in improving viral adherence, stability and infectivity toward eukaryotic cells. On the other hand, microbiota could confer protection against viral infections by inducing the immune response to avoid infection. Microbiota impacts directly and indirectly on virus biology and in turn eukaryotic viruses can influence the bacterial biology (Neu and Mainou, 2020).

The patients' fecal samples were tested for viral presence and 11 were positive upon admission, of these, 6 were still positive at the time of hospital discharge. Over time, 14 bacterial species were associated with the fecal viral load, *Bacteroidesdorei*, *Bacteroidesthetaiotaomicron*, and *Bacteroidesmassiliensis*. *Bacteroidesovatus*, known to downregulate expression of ACE2 in murine gut, showed an inverse correlation, while the Firmicutes *Erysipelotrichaceae* showed a positive correlation. The results suggest that dysbiosis lasts even in remission (Zuo et al., 2021).

Complications of Covid-19 are more frequent in people with a pro-inflammatory condition and/or an impaired immune response. Low-grade chronic systemic inflammation accompanies several comorbidities such as obesity, atherosclerosis, type 2 diabetes, and hypertension that adversely affect the outcomes of patients with Covid-19 (Chiappetta et al., 2020). The gut-microbial–host-immune axis is likely to play a significant role for inflammatory status, and fecal metabolomics analysis by Gou et al. (2020) revealed amino acid-related pathways linking gut microbiota to inflammation and Covid-19 severity. Increased low-grade inflammation is related to lower bacterial diversity. Furthermore, gut microbiota modification during ageing can trigger inflammation; transferring gut microbiota from old mice to young germ-free mice triggers responses mimicking "inflammaging" (Fransen et al., 2017) that includes higher expression of pro-inflammatory cytokine genes, such as TNF-α, and increased circulation of pro-inflammatory bacterial compounds probably linked to permeabilization of the intestinal epithelium by inflammation. Chronic inflammation can cause dysbiosis that, in turn, can cause altered epithelial functioning and consequent disease and infection. LPS are endotoxins derived from the outer cell membrane of Gram-negative bacteria, triggering inflammation-related processes, when endotoxemia is present (Gunness and Gidley, 2010).

Dysbiosis may affect gut permeability leading to the increase at the systemic levels of bacterial products such as LPS that are able to cross the gastrointestinal mucosa via leaky intestinal tight junctions (Gunness and Gidley, 2010). Also indole, one of the major tryptophan-derived microbial metabolites, produced by the action of bacterial tryptophanase, can interact with inflammation-related processes in the human host [(63)].Furthermore, indole-3-propionate indirectly limits LPS infiltration, reducing metabolic endotoxemia and host inflammation (Venkatesh et al., 2014; Cani et al., 2012).

Since the intestinal microbiome is likely to influence Covid-19 severity, and Covid-19 impact the intestinal microbiome with an increase in opportunistic pathogens, the microbiota health might be important to counteract this disease

As reported, the loss of gut microbiome diversity can lead to dysbiosis which in turn may be associated with many diseases (Mosca et al., 2016). In that fact, people whom have less diverse gut microbiota and beneficial microorganisms are subject to several illnesses (Nagpal, 2018). As reported, many elderly and immune-compromised patients progress to serious adverse clinical outcomes. It is therefore tempting to speculate that in Covid-19, there is a possible cross-talk taking place between the lung and the gut microbiota which might influence the outcome of the clinical manifestation.

ETIOPATHOGENESIS OF SARS-COV-2 ASSOCIATED DIARRHEA

Diarrhea is a frequent presenting symptom in patients infected with SARS-CoV-2.The virus infectivity primarily is determined by its binding affinity with ACE2 receptor. Structural studies indicated that the new SARS-CoV-2 not only binds ACE2, but its binding affinity for human ACE2 is significantly stronger (10–20 times more) than its 2003 SARS-CoV predecessor (Liang et al., 2020). A bioinformatics analysis based on single-cell transcriptomes revealed that ACE2 was expressed in lung AT2 cells, upper esophagus, and in absorptive enterocytes from ileum and colon. Moreover, other studies provided supplementary evidence that coronaviruses may infect the GIT, because a high co-expression of ACE2 and TMPRSS2 was noticed in enterocytes, and in the esophagus and lungs (Zhang et al., 2020).

Although the specific mechanisms involved in diarrhea pathogenesis are not entirely known, viral infection is likely to cause an alteration of intestinal permeability, resulting in enterocyte malabsorption (Gu et al., 2020). In addition, it has been proposed that intestinal ACE2 is involved in the uptake of dietary amino acids, regulating the expression of antimicrobial peptides and promoting the homeostasis of the gut microbiome. Moreover, ACE2 expression is high in epithelial cells of the proximal and distal intestines. The intestinal epithelium is in direct contact with exogenous pathogens, and small intestinal epithelial cells are the first affected by the virus, and diarrhea may be an important sign of infection and clinical manifestation (Zhang et al., 2020). Mouse models showed that the presence of ACE2 alterations was associated with colitis, suggesting that virus activity may cause enzyme modifications, increasing the susceptibility to intestinal inflammation and diarrhea (Hoffmann et al., 2020b). Further studies are needed to clarify the mechanisms underlying diarrhea in these viral infections and to define the correlation between respiratory and gastrointestinal symptoms.

CONCLUSION

In conclusion, the respiratory system is the primary route for transmission of Covid-19 .However, several studies have reported that the GI tract is also affected by SARS-CoV-2, but an oral-fecal route of transmission has not yet been clearly documented and demonstrated. Patients with Covid-19 may develop a variety of GI manifestations, which may pre-exist or not be accompanied by respiratory symptoms. The presence of this gastrointestinal manifestation generate suspicion of a possible SARS-CoV-2 infection and should be investigated to reach an early diagnosis of Covid-19. The incidence of diarrhea is currently underestimated and further studies are needed to quantify the exact burden of diarrhea to compare the sensitivity of fecal and nasopharyngeal tests, to evaluate whether diarrhea is a predictive factor for prognosis, and to clarify the effects of Covid-19 in patients with underlying gastrointestinal diseases.

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Chapter 9
Liver Injury in COVID-19 Patients:
An Overview of the Current Evidence

Tiziano Balzano
https://orcid.org/0000-0001-6523-2206
Centre for Integrative Neuroscience A.C., University Hospital HM Puerta del Sur, Madrid, Spain

Omar El Hiba
FSJ, University Chouaib Doukkali, Morocco & Moroccan Society for Ethics and Animal Research (MoSEAR), Morocco

Natalia López-González del Rey
Centre for Integrative Neuroscience A.C., University Hospital HM Puerta del Sur, Madrid, Spain

Souad El Amine
Ecole Normale Supérieure (ENS), Cadi Ayyad University, Morocco

Kamal Smimih
Faculty of Sciences, University Chouaib Doukkali, Morocco

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) preferentially infects cells in the respiratory tract, but several studies have also demonstrated low levels of SARS-CoV-2 copies in the liver. The hypothesis that patients with COVID-19 may develop liver dysfunction is supported by findings showing abnormal liver test results in such patients, but the exact mechanisms by which SARS-CoV-2 induces liver damage remain unclear. Liver injury in COVID-19 patients has probably a multifactorial etiology including the rapid onset of a systemic pro-inflammatory state due to viral infection, the use of potentially hepatotoxic drugs, pneumonia-associated hypoxia, and the eventual direct injury of the liver by SARS-CoV-2. This chapter will discuss the potential pathophysiological mechanisms for SARS-CoV-2 hepatic tropism and an overview about the main biochemical and histopathological findings observed in liver from COVID-19 patients. Finally, the effects that this infection can produce in patients with chronic liver disease will be also discussed.

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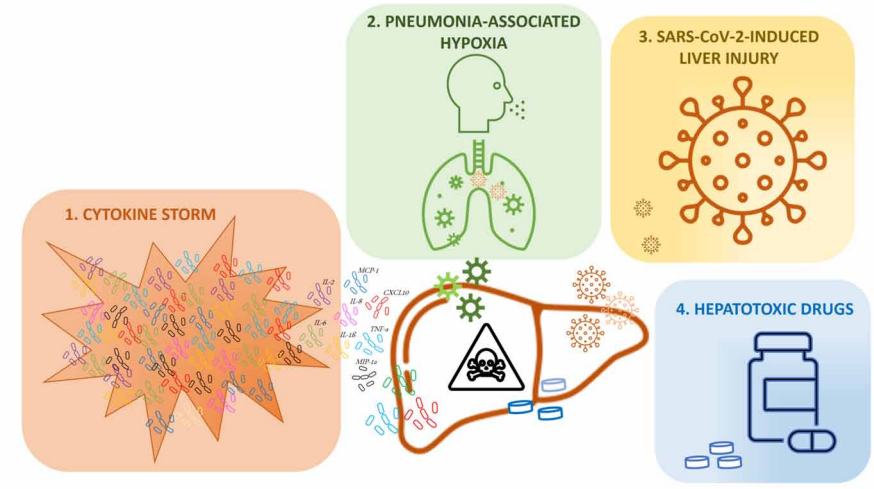
INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) preferentially infects cells in the respiratory tract but several studies have also demonstrated low levels of SARS-CoV-2 copies in the liver (Lubnow et al., 2021; Puelles et al., 2020). This is supported by the finding that 14–53% of patients with COVID-19 have evidence of liver dysfunction (Grace et al., 2020), showing abnormal liver test results (Cai et al., 2020). However, the exact cellular site of replication in the liver remained unclear. Studies involving transmission electron microscopy approach showed numerous coronavirus particles in the cytoplasm of hepatocytes. Infected cells displayed a cytopathic phenotype with glycogen granule decrease and canalicular impairment with shedding of microvilli (Y. Wang et al., 2020). SARS-CoV-2 virions were also detected by in situ hybridization methods in vessel lumens and endothelial cells of portal veins of COVID-19 liver samples(Sonzogni et al., 2020).If the viral infection per se is enough to induce liver injury remain to investigate. Liver injury in COVID-19 patients has probably a multifactorial etiology (Figure 1) including the rapid onset of a systemic pro-inflammatory state due to viral infection, the use of potentially hepatotoxic drugs, pneumonia-associated hypoxia and the eventual direct injury of the liver by SARS-CoV-2 (Feng et al., 2020; Zhong et al., 2020).

This book chapter will discuss the potential pathophysiological mechanisms for SARS-CoV-2 hepatic tropism and an overview about the main biochemical and histopathological findings observed in liver from COVID-19 patients. Finally, the effects that this infection can produce in patients with chronic liver disease will be also discussed.

Figure 1. Potential mechanisms of liver injury in patients with COVID-19



1: Cytokine storm, observed in the early phase of COVID-19 infection and is probably the main event altering liver function and integrity. It is characterized by increased interleukin (IL)-2, IL-6, IL-8, IL-1ß, granulocyte colony stimulating factor, interferon-γ inducible protein 10 (CXCL10), monocyte

chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), and tumor necrosis factor-α (TNF-α);

2: COVID-19 patients showing hypoxia and shock caused by respiratory distress syndrome can develop pneumonia-associated hypoxiaand increasing the possibility to suffer from acute liver injury.

3: SARC-CoV2 may directly bind to angiotensin converting enzyme II predominantly expressed in cholangiocytes and at lower levels in hepatocytes to dysregulate liver function;

4: Drugs including antipyretics, antiviral medications (lopinavir/ritonavir), antibiotics (azithromycin) and anti-inflammatory agents (tocilizumab) may have potential hepatotoxicity and lead to abnormal liver function.

MECHANISMS OF LIVER INJURY IN COVID-19

Direct Effects of SARS-CoV-2 on Liver

SARS-CoV-2 is an enveloped, positive-sense RNA virus with a large genome of about 30 kbp coding for 16 non-structural and four structural proteins (Saviano et al., 2020). The main surface glycoprotein, the spike (S) protein facilitates viral entry into target cells by binding the primary host receptor, the angiotensinconverting enzyme 2 (ACE2) (Hoffmann et al., 2020) and the co-receptor Neuropilin-1 (NRP1) (Cantuti-Castelvetri et al., 2020; Daly et al., 2020). It is then processed by serine protease TMPRSS2 for S protein priming (Hoffmann et al., 2020).

In healthy livers, ACE2 and TMPRSS2 protease are predominantly expressed in cholangiocytes and at lower levels in hepatocytes (Aizarani et al., 2019; Chai et al., 2020), pointing the parenchymal cells as a possible route of entry for SARS-CoV-2. Furthermore, it has been demonstrated that ACE2 expression is significantly increased in liver injury in both humans and animal models (Paizis et al., 2005).

ACE2 is one of the main components of renin–angiotensin system (RAS) and it catalyzes the conversion of AngII into Ang-(1–7) [angiotensin-(1–7)] producing anti-fibrotic, vasodilatory and anti-proliferative effects. On the other hand, ACE and its product angiotensin II have opposite effects promoting vasoconstriction, inflammation and fibrosis (Grace et al., 2012). Therefore, it is plausible that the binding of SARS-CoV-2 to ACE2 results in downregulation of ACE2 activity and leading to unopposed ACE activity and angiotensin II-mediated tissue injury (Grace et al., 2020). This is supported by the observation that angiotensin II level in the plasma sample from COVID-19 infected patients was markedly elevated and linearly associated to viral load and lung injury (Liu et al., 2020). In addition, SARS-associated coronavirus patients with liver impairment display marked accumulation of cells in mitosis and apoptosis via a caspase-dependent pathway (Chau et al., 2004), suggesting that liver injury in patients with SARS-CoV-2 infection can be induced by similar mechanisms. Reinforcing this concept, Zhao et al., demonstrated that SARS-CoV-2 infection can induce tissue damage at the cellular and molecular levels by using an ex-vivo approach employing human liver ductal organoids(Zhao et al., 2020). All these data support the hypothesis that SARS-CoV-2 can directly induceliver injury but in absence of more evidences and supportive studies, the mechanisms suggested here could remain just speculations. In addition, considering the circulation of novelSARS-CoV-2 variants, such as B.1.1.7(in UK, Volz et al., 2021), B.1.351 (in South Africa,Tegally et al., 2020) and P.1 (in Brazil,Faria et al., 2021), more studies evaluatingthe possible effects of these variants on liver functionshould be also conducted.

Pneumonia-Associated Hypoxia

Also known with the name of hypoxic hepatitis (HH), pneumonia-associated hypoxia has been suggested as another possible contributor of liver injury during SARS-CoV-2 infection. This condition is commonly seen in patients with cardiac failure (49.1%), septic shock (29.8%), hypovolemic shock (9.4%), acute respiratory failure (6.4%), acute on chronic respiratory failure (3.3%), pulmonary embolism (1.4%) and hyperthermia (0.5%) (Van den Broecke et al., 2018). COVID-19 patients showing hypoxia and shock caused by respiratory distress syndrome can develop hypoxic hepatitis and increasing the possibility to suffer from acute liver injury (Han et al., 2021). A study involving 51 intensive care units (ICU) patients with COVID-19 has demonstrated an HH incidence two-fold higher (H. Huang et al., 2020) (5,9% vs 2,4%) than ICU patients with liver injury and without COVID-19 (Henrion, 2012). Hypoxic hepatitis is often accompanied by an elevated mortality. In fact, a recent study based on 1116 ICU patients reported a 28-day mortality associated with HH of 45.0% (Van den Broecke et al., 2018). These dramatic numbers can be even higher in COVID-19 patients with hypoxic hepatitis. Biochemically, it has been associated to massive but transient elevated alanine aminotransferase (ALT) level (more than 20-fold the upper limit of normal) (H. Huang et al., 2020). In spite of that, hypoxic hepatitis remains a fascinating and mysterious condition for hepatologists and from a COVID-19 point of view, its prompt identification and management remain crucial to decrease the high mortality rate observed in these patients.

Cytokine Storm

No single definition of cytokine storm is widely accepted but it can be considered as a systemic inflammatory syndrome involving elevated levels of circulating cytokines and immune-cell hyperactivation precipitated by various therapies, pathogens, cancers, autoimmune conditions, monogenic disorders and leading to multiorgan dysfunction (Fajgenbaum& June, 2020).

The cytokine profile observed in the early phase of COVID-19 infection includes increased interleukin (IL)-2, IL-6, IL-8, IL-1ß, granulocyte colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α. These inflammatory mediators are mainly released by innate cells including neutrophils, macrophages, and NK cells and adaptive immune cells such as activated T-cells that differentiate into a number of subsets (Type 1 helper T (Th1) cells and cytotoxic T lymphocytes as the most involved) (Anirvan et al., 2021; Mehta et al., 2020). Other biomarkers that may be indicative of cytokine storm such as C-reactive protein and ferritin are usually also elevated (Clark et al., 2021).

These events may be followed by an anti-inflammatory response, mainly caused by an increase of IL-10 with concurrent downregulation of neutrophil and T lymphocyte (Anirvan et al., 2021). T cell lymphopenia, with absolute numbers of T lymphocytes, CD4+ T cells, and CD8+ T cells has been observed to be markedly lower in severe cases than moderate cases representing a potential prognostic marker to be included in the monitoring of COVID-19 patients (Riva et al., 2020).

Chemokines are the main molecules coordinating immune responses. Symptomatic, but not asymptomatic, infected individuals show elevated monocyte-macrophage-directed CCL2, neutrophil-directed CXCL1 and CXCL8 and Th1 cell-directed CXCL9 levels in serum.Symptomatic and (to a lesser extent) asymptomatic infected individuals have increased levels of Th1 cell-directed CXCL10 in comparison withuninfected controls. On the other hand, CCL5 levels were significantly lower in plasma of fatal cases compared to mild and severe cases(Majumdar & Murphy, 2021).However, some studies reported

contradictory results where severe patients with liver and kidney injuries showed elevated levels of CCL5 in comparison with healthy controls or mildly and moderately SARS-CoV-2 infected patients (Khalil et al., 2021). This agrees with previous reports showing that high levels of CCL5 can promote the development of various liver diseases (L. Chen et al., 2020).

The liver is extremely sensitive to disturbances of systemic homoeostasis and cytokine (and chemokines) storm can alter liver function and integrity by inducing several alterations such as higher vascular permeability, liver hypoxia and elevated generation of reactive oxygen species (ROS) which, in turn, may cause cellular injury and death (Anirvan et al., 2021).

A randomized, double-blind, placebo-controlled, phase 3 trial using tocilizumab, an anti–interleukin-6 receptor antibody, reduced the likelihood of progression to the composite outcome of mechanical ventilation or death among hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation (Salama et al., 2021). Similarly, also other anti-inflammatory agents such as anakinra (a recombinant IL-1 receptor antagonist) and baricitinib (a JAK inhibitor) have been demonstrated to be promising options to improve the prognosis and reduce the risk of death in COVID-19 patients (Cavalli et al., 2020; P. Richardson et al., 2020). Thus, an early detection and the correct management of cytokine storm in severe COVID-19 patients would reduce not only the possibility to suffer from liver damage and dysfunction but it would also allow obtaining better outcome in such patients.

Drug-Induced Liver Injury

Drug-induced liver injury is an uncommon but clinically important form of liver disease caused by various medications (Hoofnagle&Björnsson, 2019). It has been demonstrated that many of approved drugs used to treat COVID-19 patients have hepatotoxic properties.

To date, no specific therapy has been proven to be effective for SARS-CoV-2 infection. Many patients, especially severe and critical ones, were often treated with multiple drugs including antipyretics, antiviral medications, antibiotics and steroids in clinical practice.

Among the antiviral medications, the lopinavir–ritonavir combination has been largely used to be relatively safe and easily mobilized against COVID-19 (Kunz, 2020) although no benefits have been observed (Cao et al., 2020). Liver tests in patients with COVID-19 showed that the use of lopinavir/ritonavir increased the odds of liver injury by 4-fold (Cai et al., 2020).

Interferon beta has also been demonstrated to be effective as antiviral if administered shortly after infection (Monk et al., 2021; Peiffer-Smadja&Yazdanpanah, 2021). Furthermore, a randomized clinical trial found that triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir and ribavirin were safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19 (Hung et al., 2020). Besides its promising outcomes, all forms of interferon beta have been shown to cause asymptomatic and mild hepatic injury and it is associated with transient elevations in serum aminotransferase and alkaline phosphatase levels (Olry et al., 2020).

Hydroxychloroquine with or without azithromycin, a broad-spectrum antibiotic, have been used as treatment for SARS-CoV-2 infection for their anti-inflammatory properties beyond to be widely available and safe(Oldenburg & Doan, 2020). However, both hydroxychloroquine and azithromycin may cause idiosyncratic acute liver injury. In addition, azithromycin was also associated with hepatocellular injury, with a short latency (a few days) (Olry et al., 2020).

A high percentage of patients with COVID-19 on admission and during hospitalization in patients may present fever. The use of antipyretics such as paracetamol or other analgesics, has been shown to present potential hepatotoxicity, which associated with the risk of liver damage that may occur in the most severe stages of COVID-19 infection can result in a very dangerous synergy (Vitiello et al., 2021).

As described above, cytokine storm has been suggested as the most contributive cause of liver damage in COVID-19 patients. Tocilizumab, an anti–interleukin-6 receptor antibody and one ofthe more promising treatment used to treat the systemic inflammatory syndrome in SARS-CoV-2 infection, can induce in rare cases acute liver failure and hepatitis (Drepper et al., 2013; Mahamid et al., 2011).

Considering all these evidences, the risk of suffering from drug-induced liver injury during COVID-19 infection should not be neglected. Therefore, it makes crucial to generate more and better evidences with regard to the safety and efficacy of the treatments and at the same time, to consider more targeted and specific protocols specially when the current ones are associated with the onset of other complications how can be the case of drug-induced liver disease.

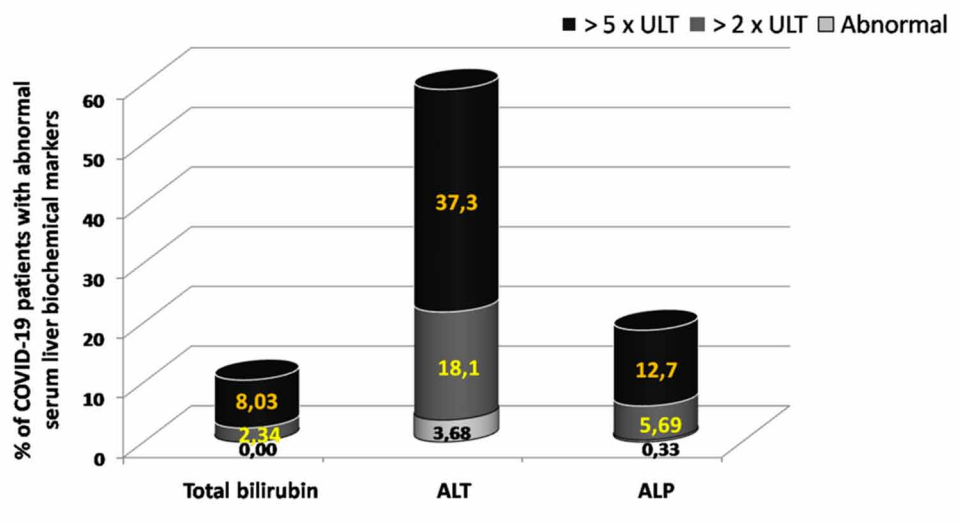
ABNORMAL LIVER BIOCHEMICAL PARAMETERS IN COVID-19 PATIENTS

A meta-analysis study performed by(Wu et al., 2020) assessed the eventual hepatic biochemical abnormalities in COVID-19 patients including; aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGT), total bilirubin and albumin together with the possible association with the severity of COVID-19 (Wu et al., 2020). The estimated pooled incidence of impaired biochemical markers of hepatic function in COVID-19 patients, at the admission for hospitalization and during the course of the disease was at 27.2% and 36% respectively, leading to admit that altered hepatic biochemical profile is common in COVID-19 patients and seems to be positively correlated to the severity of the pulmonary disease(Wu et al., 2020).

A support of such view is provided by a series of case report studies sustaining a liver function alteration in COVID-19 patients (Bloom et al., 2021; N. Chen et al., 2020; S. Richardson et al., 2020; D. Wang et al., 2020; L. Xu et al., 2020), particularly in severe COVID-19 manifestations where liver injury may occur(Cai et al., 2020; C. Huang et al., 2020; L. Xu et al., 2020). However, it should be considered the fact that the majority of studies addressed the possible liver function injuries in COVID-19 patients, were carried out in China where the liver hepatitis B is of high incidence (H. Wang et al., 2019)along with the use of drugs susceptible to trigger liver injuries like lopinavir–ritonavir (Cai et al., 2020; Fan et al., 2020). Otherwise, a clinical investigation realized in the Kingston Hospital, UK, investigated a total of 299 COVID-19 patients without a history of eventual liver diseases. The study showed that 29.4% exhibited an impaired liver function upon their admission in the hospital, while 15.4% showed liver abnormalities during the course of the COVID-19 disease. Additionally, a significant correlation was found between liver dysfunction and an elevation of serum levels of lactate dehydrogenase (LDH), C reactive protein and ferritin(Lok&Gess, 2020), while the main documented biochemical abnormalities were the increased levels of ALT, ALP and total bilirubin (Figure 2).

The same study reported a positivecorrelation between the development of respiratory complications (ventilator support), the degree of impaired liver function and the duration of hospital stay. (Lok&Gess, 2020). Other important retrospective study carried out on 417 COVID-19 patients from Shenzhen, China, from January 11 to February 21, 2020 and followed up to March 7,2020, revealed that 76.3% of patients had abnormal liver biochemical profile while 21.5% had liver injury during hospitalization.

Figure 2. Biochemical profile of liver function in COVID-19. ULT: upper limit; ALT: alanine aminotransferase, ALP: alkaline phosphatase. Graph generated with data from (Lok&Gess, 2020).



Otherwise, 2 weeks hospitalization appeared to aggravate the liver tests with 3 folds ULT elevation of ALT (23.4%), AST (14.8%), total bilirubin (11.5%), GGT (24.4%). In any case, hepatocellular test abnormalities at the admission were associated to increased risk of progression to severe complication of COVID19 (Cai et al., 2020).

Otherwise, the ethnicity and origin of COVID-19 patients may also be involved in the occurrence of clinical complications. Indeed, it has been reported an increased proportion of Asian patients with liver complication compared to those of white ethnicity (Lok&Gess, 2020).

EVIDENCE OF POSSIBLE LIVER TISSUE INJURIES IN COVID-19 PATIENTS

Some limited clinical reports in COVID-19 patients, documented the evidence of liver tissue injuries associated to the viral infection. Indeed, a series of studies reported the accumulation of fat in hepatocytes which was associated to macrovesicularsteatosis(Z. Xu et al., 2020).

In a post-mortem study performed by Xu et al., the authors reported features of liver tissue lesions in a patient with severe COVID-19 including moderate microvesicularsteatosis and mild inflammatory infiltrates within the hepatic lobules and portal tracts. Concomitantly, the authors reported a reduction and hyper-reactivity of immune cells such as CD4 and CD8 along with increased CCR6+ Th17 CD4 T cells and cytotoxicity granulations in CD8 cells, leading to hepatocellular dysfunctions (Z. Xu et al., 2020). Other studies showed, in liver biopsies from 4 patients with COVID-19, minimal sinusoidal dilatations and focal macrovesicularsteatosis. Additionally, mild lobular lymphocytic infiltration was also documented (Tian et al., 2020).

In a recent study, 40 autopsied patients, dead from complication of COVID-19 in USA, were autopsied to delineate the presence of liver dysfunction evidences. Indeed, authors showed elevated liver biochemical markers such as ALT and AST which were correlated to macrovesicularsteatosis considered as the most

common liver injury found in the autopsied patients (75%), followed by mild lobular necroinflammation and portal inflammation (50%), while 15% of patients exacerbate sinusoidal microthrombi. Whereas, viral analysis using PCR, revealed 55% positivity among all studied liver samples (Lagana et al., 2020).

In Italy, a post-mortem histopathological study on liver biopsies, from 48 patients dead from COVID-19 complication without prior liver disease, revealed the existence of mild inflammation along with vascular pathology in all the studied samples. Additionally, authors reported the presence of portal vein branches with lumen massive dilatation, together with partial or complete luminal thrombosis of portal and sinusoidal vessels, as well as portal tract fibrosis, while 68,18% of liver samples were positive for SARS-CoV-2 (Sonzogni et al., 2020). However, liver failure was not thought to be the main concern or the target of important inflammatory damage (Sonzogni et al., 2020).

EFFECTS OF COVID-19 ON PATIENTS WITH LIVER DISEASE

Cirrhosis

The liver plays an important role in regulating immune homeostasis. Patients with chronic liver diseases may have dysregulated innate and acquired immunity, increasing their risk to be infected by SARS-COV-2 and suffer from most severe COVID-19 related complications, including death.

A study involving 745 patients from 29 different countries with chronic liver disease and SARS-CoV-2 (386 with and 359 without cirrhosis) found that mortality from COVID-19 was particularly high among patients with more advanced cirrhosis and those with alcohol-related liver disease (Marjot et al., 2021). Interestingly, a multicenter study involving 37 cirrhosis+COVID-19 patients, 127 cirrhotic patients (without COVID-19) and 108 COVID-19 patients (without cirrhosis) revealed that patients with cirrhosis+COVID-19 had similar mortality compared with patients with cirrhosis alone but higher than patients with COVID-19 alone (Bajaj et al., 2021). Completing these results, a research based on liver transplant recipients demonstrated that they did not appear to be at increased risk of death from SARS-CoV-2 infection (Webb et al., 2020).

Considering the huge global burden of cirrhosis, with an estimated 112 million people affected (Sepanlou et al., 2020), all together these interesting results suggest the importance to give enhanced attention and protection for patients with advanced cirrhosis and more importantly, it is crucial to continue liver transplant services during the pandemic.

Non-Alcoholic Fatty Liver Disease

Among the population with chronic liver disease, the global prevalence of people suffering from non-alcoholic fatty liver disease (NAFLD) is increasing; this may suggest that there is a large proportion of our population which could be at risk of severe COVID-19. NAFLD is considered a multisystem disease, affecting both extra-hepatic organs and regulatory pathways. In fact, NAFLD can increase the risk of type 2 diabetes mellitus, cardiovascular and cardiac diseases, and chronic kidney disease (Byrne &Targher, 2015). Considering all these issues, NAFLD patients may have a higher predisposition to suffer from severe complications of COVID-19 in case of infection. In agreement with this hypothesis, a multicenter retrospective study including sixty-six COVID-19 patients with NAFLD (45 patients with obesity and 21 patients without obesity) showed that the risk of severe illness in NAFLD patients with

co-existing obesity was >6-fold greater (Zheng et al., 2020). In line with these results, Sachdeva et al., found that NAFLD is associated with an increased risk of severe COVID-19, even after adjusting for obesity as a possible confounding factor (Sachdeva et al., 2020). Besides obesity, hypertension has been demonstrated to be one of the most prevalent metabolic risk factors in NAFLD patients to suffer from severe complications during SARS-CoV-2 infection. A retrospective population-based study estimated around a 21% the cumulative prevalence of hypertension among the study population (Ghoneim et al., 2020).Similarly, Guo et al., reported that COVID-19 patients without other comorbidities but with diabetes were at higher risk of severe pneumonia, more susceptible to an inflammatory storm and hypercoagulable state associated with dysregulation of glucose metabolism which may contribute to a poorer prognosis of COVID-19 (Guo et al., 2020).

The expression of ACE2 can be increased in patients with type 1 or type 2 diabetes or hypertension, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). Consequently, the increased expression of ACE2 induced by diabetes and hypertension treatment would increase the risk of developing severe and fatal COVID-19(Fang et al., 2020).

All these evidences with the increasing global prevalence of NAFLD may suggest that a large proportion of our population could be at risk of severe complications induced by COVID-19 infection.

Hepatitis B Virus

Lymphopenia induced by SARS-CoV-2 may trigger hepatitis B virus (HBV) reactivation in coinfected SARS-CoV-2/HBV patients (Saviano et al., 2020). Though just a few studies were performed to assess the effects of SARS-CoV-2 on HBV patients, most of them agree in suggesting that coinfection of HBV do not increase viral shedding, disease severity or duration of hospitalization (Lens et al., 2020; Rodríguez-Tajes et al., 2021; Yu et al., 2021; Zou et al., 2021). However, these remain very poor studies performed on small populations, thus further large-scale studies are needed to investigate the exact interactions between SARS-CoV-2 and HBV coinfection.

CONCLUSION

Studies reported in this chapter strongly suggest that the presence of liver injury can be considered as a marker for more severe disease and higher mortality in patients with COVID-19.

SARS-CoV-2 particles and RNA copies have been detected in hepatocytes and cholangiocytes from liver of COVID-19 patients. These data are supported by abnormal liver biochemical tests observed in COVID-19 patients. Furthermore, the presence of impaired biochemical markers of hepatic function in COVID-19 patients is positively correlated to the severity and prognosis of the pulmonary disease.

Despite these clinical results, the exact mechanisms by which SARS-CoV-2 induces liver damage remain unclear. Liver injury in COVID-19 patients has probably a multifactorial etiology including the rapid onset of a systemic pro-inflammatory state due to viral infection, the use of potentially hepatotoxic drugs, pneumonia-associated hypoxia and the eventual direct injury of the liver by SARS-CoV-2.

Risk to suffer from liver injury appears limited in patients without chronic liver disease. Otherwise, NAFLD patients have been demonstrated to have a higher predisposition to suffer from severe complications of COVID-19 in case of infection. The risk is higher in those suffering from obesity or hypertension.

Mortality from COVID-19 was observed to be particularly high among patients with more advanced cirrhosis and those with alcohol-related liver disease. Importantly, while liver transplanted patients have higher risk of contracting the disease, a research based on liver transplant recipients demonstrated that they did not appear to be at increased risk of death from SARS-CoV-2 infection.

Considering the huge global burden of chronic liver disease, all these evidences suggest to give enhanced attention and protection for the large proportion of our population suffering from these conditions and to continue liver transplant services during the pandemic. Finally, it is crucial to continue investigating the interplay between SARS-CoV-2 and liver function in order to obtain safer and more effective treatments and at the same time, to develop more targeted and specific protocols specially when the current ones are associated with the onset of other complications how can be the case of drug-induced liver disease.

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KEY TERMS AND DEFINITIONS

Apoptosis: Biological process of programmed cell death.
Cholangytes: Epithelial cells lining the bile duct.
Diabetes: Metabolic disease characterized by elevated levels of blood glucose.
Fibrosis: Formation of an abnormal amount of fibrous connective tissue in an organ.
Hepatocyte: Main parenchymal cell in the liver.
Hypertension: Clinical condition characterized by persistent high blood pressure.
Hypoxia: Lower-than-normal level of tissue oxygenation.
Mitosis: Biological process of cell duplication, in which one cell divides into two genetically identical daughter cells.
Steatosis: Abnormal accumulation of lipids (more than 5%) within the hepatic cells.

Chapter 10
SARS-Cov-2 and Associated Heart Failure:
An Overview of the Possible Mechanisms

Abdelmohcine Aimrane
Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco

Bilal El-Mansoury
Faculty of Science, Chouaib Doukkali University, Morocco

Said Sabir
https://orcid.org/0000-0003-2246-5645
Faculty of Medicine and Pharmacy, Marrakech, Morocco

Soraia El Baz
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Nadia Zouhairi
Faculty of Sciences, Chouaib Doukkali University, Morocco

Mohamed Echchakery
Institut Supérieur des Science de la Santé, University Hassan I, Morocco

Ahmed Draoui
Faculty of Sciences Semlalia, University Cadi Ayyad, Marrakesh, Morocco

Chatoui Hicham
https://orcid.org/0000-0002-4707-1645
BEL, FST, Sultan Moulay Slimane University, Morocco & Private University of Marrakech (UPM), Morocco

Naima Fdil
Faculty of Medicine and Pharmacy, Marrakech, Morocco

Souad Sellami
Centre Hospitalo, Universitaire Mohammed VI, Marrakech, Morocco

Abdesslam Ferssiwi
Faculty of Science, University Chouaib Doukkali, Morocco

Abdelali Bitar
Faculty of Science, University Chouaib Doukkali, Morocco

Hanane Rais
Faculty of Medicine and Pharmacy, Marrakech, Morocco

ABSTRACT

The newly emerged pandemic of coronavirus-induced disease of the year 2019 (COVID-19) has become the utmost health concern worldwide. Patients with COVID-19 are highly susceptible to develop hypercoagulable state increasing the risk of causing venous and arterial thrombosis at both small and large

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vessels. Additionally, in patients showing co-morbidities, for instance patients with inborn errors of metabolism linked to heart failure, the complications and mortalities are even higher than in any other case. In such frail patients already showing health concerns, the COVID-19-induced pneumonia may cause acute or chronic cardiovascular complications. Indeed, several reports of thrombotic complications in association with other complications has been presented, such as large vessels storks, clotting of catheters, and myocardial injury. Nevertheless, knowledge on the COVID-19-associated cardiovascular diseases remains scarce. Thus, in this chapter, the authors represent an overview of the available data on the induced heart failure related to COVID-19.

INTRODUCTION

The newly emerged coronavirus disease of 2019 (COVID-19) pandemic has urged the world, and especially the scientific and medical comities. As is well known, the primary cause of death from COVID-19 cases is due to acute respiratory distress syndrome (Gibson, Qin, & Puah, 2020). Nevertheless, a number of mortality and complicated cases exhibit cardiovascular pathologies (Xiaokuni Li, Hu, Su, & Dai, 2020; Y. Li, Bai, & Hashikawa, 2020; Y. Liu et al., 2020; Yang et al., 2020b). Interestingly, relevant evidence highlighted the potential implication of myocardial injury and heart failure in mortality from COVID-19, either among patient with or without cardiovascular comorbidities(Freaney, Shah, & Khan, 2020). The mechanism of such complications not being fully understood, urgent studies are needed to strength knowledge on the interplay between COVID-19 and myocardial injury.

Moreover, patient with basic comorbidities of heart failure, especially inborn errors of metabolism linked to heart failure have shown higher vulnerability toward infection with COVID-19(Assessment, 2020), the incidence of these cases being important as well; 1:800–2500 live births (Ismail, Showalter, & Fiehn, 2019).

Thus, the following chapter shed light on the most relevant theories on the mechanisms of cardiac injury in the pathogenesis of COVID-19, as to explain the potential relationship between the severe of acute respiratory syndrome corona-virus-2 (SARS-CoV-2) and cardiovascular complications.

EVIDENCE ON THE INTERPLAY BETWEEN CARDIOVASCULAR COMPLICATIONS AND COVID19

COVID19 infection and fatality increase in patients with comorbidities, especially of cardiovascular concerns. In fact, cardiovascular disease (CVD) is the most common co-morbidity associated with COVID-19 and the fatality rate in COVID-19 patients with CVD is higher compared to other comorbidities, such as hypertension (HTN) and diabetes (Unudurthi, Luthra, Bose, Mccarthy, & Irene, 2020). Conversely and interestingly, cardiovascular diseases may precipitate from the infection with COVID19(Freaney et al., 2020). In order to understand such interplay between cardiovascular complications and COVID19 infection, several studies has put the line on the probable interacting factors with various viewpoints.

The mortality rate among patients with elevated a cardiac injury biomarker Troponin T (TnT), was ~60%, whereas the mortality rate in patients with normal TnT levels was ~9% (Unudurthi et al., 2020), and it was demonstrated that high levels of troponin are associated with higher mortality rates of up to 50% (Kermali, Khalsa, Pillai, Ismail, & Harky, 2020). In addition, COVID-19 patients with CVD have a higher mortality rate (around 10.5%) as compared to other comorbidities such as hypertension (6%), diabetes (7.3%), or chronic respiratory disease (6.3%) (Yang et al., 2020a). In severe cases, direct acute myocardial injury characterized by concentric left ventricular hypertrophy with a dilated, severely hypokinetic right ventricle and cardiac amyloidosis has been reported(Hu et al., 2004). In addition, preliminary autopsy reports from patients that succumbed to severe COVID-19 infection show severe right ventricular dilation, cardiac necrosis and infiltration of immune cells into the myocardium (Unudurthi et al., 2020).

In patients with cardiovascular diseases, the risk of infection with SARS-CoV-2 and death may increase in comparison with normal patients. Asystematic review and meta-analysis have revealed that COVID19 inpatients with cardiovascular comorbidities, represented by increased troponin levels, shows greater risk to develop most commonly acute cardiac injury associated with mortality (Santoso et al., 2020). Furthermore, the meta-analysis of six studies has supported this reportingHTN and cardio-cerebral vascular diseases prevalence of 17.1% and 16.4%, respectively. In fact, patients with preexisting CVD who develop COVID-19 have worse outcomes than patients without CVD (Freaney et al., 2020).

Moreover, infection with SARS-CoV-2 can directly or indirectly lead to myocardial injury and recent data, suggest that direct myocardial injury may occur in some individuals (Freaney et al., 2020). In addition to being widely prevalent, and even being a prognostic comorbidity, CVD can also be triggered and caused by COVID-19 in patients with no prior history of heart disease(Mao et al., 2020). Laboratory analysis of COVID-19 positive patients had revealed presence of tissue damage indicators in their blood, such as creatinine kinase, and lactate dehydrogenase that are associated with abnormal myocardial zymogram and muscle damage (Mao et al., 2020).

Some clinical data from COVID-19 patients with no basic COVID19 comorbidities indicate elevated levels of cardiac injury biomarkers, such as NT-proBNP, high sensitivity cardiac troponin I and C-reactive protein (CRP) (Madjid, Safavi-Naeini, Solomon, & Vardeny, 2020). Moreover, recent articles report the presence of SARS-Cov2 viral particles in cardiac tissue including cardiomyocytes, endothelial cells, mesenchymal cells, and inflammatory cells (Dolhnikoff et al., 2020). In severe cases, direct acute myocardial injury characterized by concentric left ventricular hypertrophy with a dilated, severely hypokinetic right ventricle and cardiac amyloidosis has been reported(Hu et al., 2004). In addition, preliminary autopsy reports from patients that succumbed to severe COVID-19 infection show severe right ventricular dilation, cardiac necrosis and infiltration of immune cells into the myocardium (Unudurthi et al., 2020). Moreover, findings from SARS epidemics, showed viral RNA SARS-CoV in the myocardium of 35% (7/20) of patients who died from SARS, as well as prominent macrophage infiltration (Oudit et al., 2009). Patients with preexisting CVD who develop COVID-19 have worse outcomes rather than patients with no CVD.

The underlying mechanisms of COVID-19 associated myocardial injury are not completely understood. To date, proposed hypotheses of COVID-19 related myocardial injury consider the role of direct ACE-2-mediated cardiomyocyte damage by the virus; microvascular disease with vascular leakage and hypercoagulation due to endothelitis; systemic hyperacute inflammatory response syndrome and pneumonia related oxygen supply-demand imbalance with ischemia (Li et al., 2020; Shi et al., 2020). Even though there is increasing need of advanced studies to better understand the underlying mechanisms, the actual finding on COVID-19 pandemic proclaim the requirement of higher alertness of its possible

cardiovascular ramification. Increasing evidence shows indeed the possibility ofdevelopingcardiac complications during COVID-19 hospitalization.

INSIGHT INTO THE POSSIBLE MECHANISMS UNDERLYING COVID-19-RELATED CARDIOVASCULAR SEQUELS

To date, proposed hypotheses of COVID-19-related myocardial injury consider the role of direct angiotensin converting enzyme-2 (ACE-2)-mediated cardiomyocyte damage by the virus; microvascular disease with vascular leakage and hypercoagulation due to endothelitis; systemic hyperacute inflammatory response syndrome and pneumonia related oxygen supply-demand imbalance with ischemia (Li et al., 2020; Shi et al., 2020). Nevertheless, further research are needed to better understand the underlying mechanisms.

As is well-known, ACE-2 is a part of the renin-angiotensin system (RAS) that protects many organs from fibrogenesis and inflammation(Xiaopeng Li et al., 2008; Österreicher et al., 2009). Among others, Angiotensin-II (Ang-II) is a protein of the RAS system that binds to its receptors, Ang II type 1 and type 2 receptors (AT1 and AT2),setting off high blood pressure and inflammation. The ACE-2 controls the activity of Ang-II by convertingit into Ang-(1-7), which counterbalance its effects protecting the organism from cell death, tissue injury and inflammation(Sriram & Insel, 2020). Additionally and interestingly, Ang-(1-7) has a potent antitrophic and peripheral vasodilatatory effect(Schindler, Bramlage, Kirch, & Ferrario, 2007). Thus ACE-2 may counterbalance the function of ACE-1 either through the conversion of Ang-II into Ang-(1-7) or via competition with ACE-1 for Ang-I(Crackower et al., 2002).

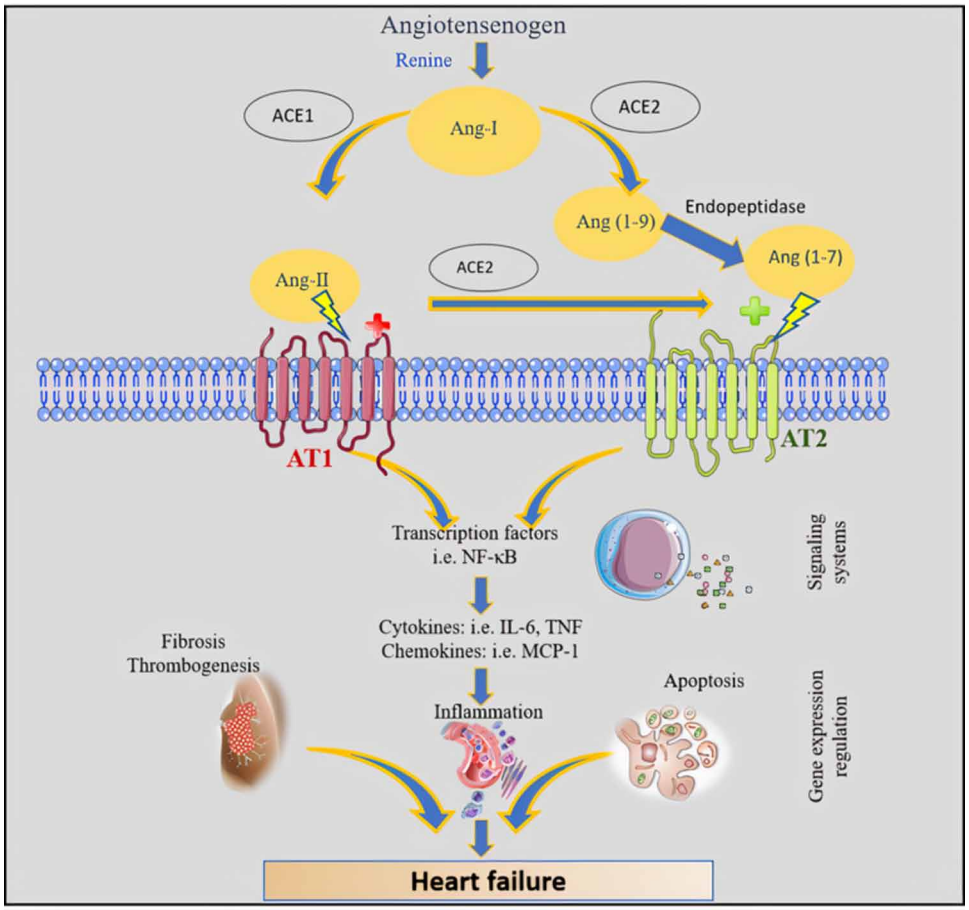
Besides, the potential mechanisms underlying COVID-19 induced cardiovascular dysfunction might be divided into ACE-2 related mechanisms and various other indirect mechanisms. In addition to ACE-2 receptor, which serves as the main anchor point for SARS CoV-2, cellular proteases such as serine protease TMPRSS2 and cathepsins (cathepsin B and cathepsin L) play an important role in viral entry by promoting viral fusion with host cells (Hoffmann et al., 2020). Nevertheless, the main scope will be given to ACE-2 receptors as their implication is major in the discussed pathophysiology. Besides,the indirect mechaSnisms may trigger cardiac damage in COVID-19 patients, especially systemic hyper-inflammation.

Down Regulation of ACE-2: Possible Direct Mechanisms Leading to Heart Failure

The distribution of the membrane proteins ACE-2 is broad and extends into many organs. It is widely expressed especially in the heart, endothelial cells of the kidneys, and brain tissues, which expression has been revealed to crucially protect and compromise cardiac function, either with or without viral infection (insert ref see (Crackower et al., 2002; South, Diz, & Chappell, 2020). However, as SARS-CoV-2 integrates the organism it binds to ACE2 downregulating its function, which leads to the accumulation of Ang II. This later binds to AT1 receptor inducing cytokines storm and tissues damage (Murakami, Kamimura, & Hirano, 2019) (figure 1).

On the central nervous system, interesting reports have stated an increase of SARS-CoV-2 viral load in the brain steam, which may reveal a potential internalization via ACE-2 and transport to several nerves of the brain. The interruption of the vital function of ACE-2 leads consequently to neuronal cell death. Moreover, the cardiovascular centers of the brain may potentially be subject to cell death due to their loss

Figure 1. Inderect mechanisms of COVID-19-induced heart failure



of ACE-2 activity causing impaired proper autonomic nervous system regulation of blood pressure. In the brainstem, the SARS-CoV-2 blockage of ACE-2 may promote increased sympathetic drive, alteration of baroreflex cardiovascular response, as well as intensification of hypertension(South et al., 2020).

In the tubular epithelium of the kidneys, the SARS-CoV-2 induced blockage of ACE-2 may set off altered sodium transport and consequently increased blood volume and pressure, in addition to chronic effects on kidney injury(South et al., 2020).

Additionally, ACE-2 pulmonary infection could be considered as a factor that exacerbate hypertension (Imai et al., 2005; Kuba et al., 2005). It is worthy to note that the first noted pulmonary complication in COVID-19 patients are linked mainly to the resulting vascular barrier breach causing tissue oedema, endotheliitis, and promotion of coagulation pathways. Interestingly, this may results in a potential disseminated intravascular coagulation (DIC) (Teuwen, Geldhof, Pasut, & Carmeliet, 2020). Otherwise, vascular occupation of ACE-2 by the virus may intensify hypertension as this increase vascular permeability via activation of the kallikrein–bradykinin pathway(Pober & Sessa, 2007).

Directly related to the myocarditis, the proposed hypothesis consider the direct ACE-2 mediated damage of the cardiomyocyte (Shchedrygina, Nagel, & Puntmann, 2021; Shi et al., 2020). In fact, in human myocarditis, ACE-2 is expressed at high amount in the pericytes. Interestingly, this expression is even

more important in patients with preexisting heart failure, which may shows a higher vulnerability of these patients to infection with COVID-19 (Chen, Li, Chen, Feng, & Xiong, 2020). Nevertheless, other mechanisms may have similar impact on the pathophysiology of heart failure related to COVID-19 infection.

Other Indirect Mechanisms

Cytokine Storm and Hyper-Inflammation

Several clinical reports on COVID-19 patients reported significantly elevated inflammatory biomarkers in the bloodstream, including interleukin (IL)-2, IL-6, IL-7, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), tumor necrosis factor-α (TNF-α), interferon-γ inducible protein (IP)-10, CRP, ferritin and procalcitonin (Richardson et al., 2020). Even though triggered by local infection in the lungs, the increased systemic levels of these inflammatory cytokines activate inflammatory and maladaptive remodeling pathways in multiple organs, including the heart (Unudurthi et al., 2020).

The increase in proinflammatory cytokines are involved in the development of cardiac disease and it is known that, aberrant expression of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and matrix metalloproteinases (MMPs) in the heart are thought to contribute to the onset of myocardial infarction (MI) (Wang et al., 2016).

Thus, the exacerbated inflammation is involved in the development and progression of heart failure, and again, innate immune responses and complement seem to participate in these responses. Importantly, during recent years complement mediated inflammation has been shown to act as a pertinent factor in a variety of heart diseases (Lappegård et al., 2014).

Complement

The complement system plays a key role in the host immune response to viruses by opsonization of viral particles, recruitment of inflammatory cells, and ultimately lysis of infected cells (Mastellos, Ricklin, & Lambris, 2019). However, complement activation can also damage host cells. SARS-CoV infection in mice activates the complement system (Gralinski et al., 2018) and the activation of this complement system might be involved in the pathophysiology of a diverse range of cardiac conditions (Lappegård et al., 2014).

This complement system plays a key role in the host immune response to viruses by opsonization of viral particles, recruitment of inflammatory cells, and lysis of infected cells (Mastellos et al., 2019). However, uncontrolled complement activation can induce tissue damage in the host (Barratt-Due et al., 2012) because of its contribution into acute and chronic inflammation, intravascular coagulation, cell injury and ultimately leads to multiple organ failure and death (Noris & Remuzzi, 2013).

Importantly, mice infected with SARS-CoV activates the complement system (Gralinski et al., 2018). C3−/− mice exhibited reduced recruitment of neutrophils and inflammatory monocytes into the lung and less respiratory dysfunction after SARS-CoV infection compared to controls (Gralinski et al., 2018). Similarly, inhibition of the C5a receptor reduced lung injury in hDPP4 mice infected with MERS-CoV (Middle East respiratory syndrome) (Jiang et al., 2018).These results indicate that the complement system contributed to the lung pathology after SARS-CoV infection in mice. Importantly, significant deposits of terminal complement components have been noted in the lung microvasculature of COVID-19 patients

(Magro et al., 2020). Complement system inhibition with eculizumab, which binds to C5, might be beneficial for COVID-19 patients (MacKman, Antoniak, Wolberg, Kasthuri, & Key, 2020).

Determination of the exact role of complement in the various heart diseases will hopefully help to identify patients that might benefit from therapeutic complement intervention (Lappegård et al., 2014). Pathogenic role of complement in heart failure development C5a-C5a receptor interaction has previously been shown to be centrally involved in sepsis-induced cardiomyocyte dysfunction and heart failure (Atefi et al., 2011). This relevant evidence is emerging that could be of help in orienting anti-complement therapy. However, more studies are required to fully elucidate the relative role of each complement component and pathway in the pathophysiology of COVID-19.

Moreover, there is an intensive crosstalk between the coagulation and the complement systems, and if this "immunothrombosis" is uncontrolled, it is may lead to thrombotic complications including myocardial infarction and stroke (Engelmann & Massberg, 2013).

Coagulation Abnormalities

Platelets play an essential role in maintaining vascular integrity. More recently, platelets have been found to participate in the immune response to viruses (Koupenova, Clancy, Corkrey, & Freedman, 2018). However, platelet activation during viral infection may also increase the risk of thrombosis. The innate immune response is activated in response to invading pathogens to counteract the infection and this is generally accompanied by activation of coagulation that serves to localize the infection (Antoniak, Mackman, Antoniak, & Mackman, 2021). Nevertheless, excessive and widespread activation of coagulation can lead to disseminated intravascular coagulation (DIC), defined as fulminant activation of coagulation, consumption of coagulation factors, and bleeding (Jr, Toh, Hoots, Wada, & Levi, 2001).

The high mortality and its relationship with thromboembolic diseases in COVID-19 have increasingly attracted attention (Haematol, 2020; Jennifer, 2020). It is believed that COVID-19 can activate coagulation cascade through various mechanisms, leading to severe hypercoagulability. Early anticoagulation may block clotting formation and reduce microthrombus, thereby reducing the risk of major organ damages (T. Li, Lu, & Zhang, 2020). In addition, tissue factor expression on monocytes/macrophages, neutrophil activation, and neutrophil extracellular traps (NETs) produce activation of thrombosis (Liaw, Ito, Iba, Thachil, & Zeerleder, 2016). This thromboinflammatory response might cause endothelial damage that further increase thrombin generation (Iba et al., 2020).

Recent studies suggest that SARS-Cov2 can directly infect and kill endothelial cells exposing the thrombogenic basement membrane and activating the coagulation cascade (Maier et al., 2020), which can contribute to hypercoagulable state in COVID-19 patients. It has been reported that there is an association between thrombocytopenia and risk of in-hospital mortality in COVID-19 patients (MacKman et al., 2020). Coagulation abnormalities triggered by COVID-19 can also directly and indirectly lead to cardiovascular problems. Recent reports highlighted the presence of coagulation abnormalities in COVID-19 patients that causes blood clots leading to multiorgan failure, including HF. Once formed these blood clots are systematically degraded by specific enzymes such as plasmin, resulting in the formation of fibrin degradation products such as D-dimer. In fact, D-dimer is a protein fragment formed when blood clot are released in the body, and additionallyone of the main fibrin degradation products and is used as a clinical marker for deep vein thrombosis (DVT), pulmonary embolism (PE) or disseminated intravascular coagulation (DIC).

Interestingly, patients with COVID-19 often have elevated D-dimer levels and high D-dimer levels correlate with disease severity and increased risk of death (Guan et al., 2020; Zhou et al., 2020). This product (D-dimer) has attracted attention as a prognostic marker in COVID-19 patients (Helms et al., 2020; Huang et al., 2020; Panigada et al., 2020; To & Editor, 2020) and has been repeatedly reported to be a useful biomarker associated with the severity of disease (Guan et al., 2020) and is a predictor of adverse outcomes (Iba et al., 2020). A series of articles from China reported higher D-dimer levels in severely affected patients compared with those with a non-severe disease (MacKman et al., 2020) and its high level was associated with increased mortality (Zhou et al., 2020). Micro-emboli caused by damaged endothelium or a hypercoagulable state could destabilize existing coronary artery plaques precipitating a type I myocardial ischemia (MI) (Unudurthi et al., 2020). Coagulation profiles observed this study population reflect a severe hypercoagulability rather than a consumptive coagulopathy (e.g., disseminated intravascular coagulation). Such a laboratory pattern and association can belinked to both markedly increased levels of fibrinogen and an excessivefibrin polymerization due to the infection. SARS-CoV-2 is likely to promote massive fibrin formation and deposition which can also account for the very high D-dimer levels found in these patients (Spiezia et al., 2020). In this regard, anticoagulant therapy may improve the prognosis in COVID19 patients.

COVID-19 IN PATIENTS WITH BASIC HEART FAILURE DISEASE: EXAMPLE OF INBORN ERRORS OF METABOLISM LINKED TO HEART FAILURE

Inborn errors of metabolism (IEM) are a vast group of genetic disorders caused by pathogenic variants in genes controlling enzymes, structural proteins or cofactors affecting various metabolic pathways (Ismail et al., 2019). Although most IEM are individually rare, more than 1000 well characterized IEM disorders have been recently classified (Ferreira, van Karnebeek, Vockley, & Blau, 2019), with an estimated overall incidence of 1:800–2500 live births (Ismail et al., 2019). Despite the great diversity in the clinical presentations and management strategies of different IEM, they mostly share in common their need for challenging diagnostic procedures requiring specialized laboratories and for multidisciplinary collaborative medical teams for acute and long-term treatment and patient monitoring.

The inborn errors of metabolism exhibit protean clinical manifestations. Cardiac disease either in isolation or as part of a wider multisystem disease process, are frequently observed in the IEM. Cardiac presentations associated with the IEM include, arrhythmias, dilated cardiomyopathy, hypertrophic cardiomyopathy, non-compaction, valvular disease, endocardial fibroelastosis, and aortic root pathology. IEM groups commonly associated with cardiac disease include the mitochondrial respiratory chain defects, fatty acid oxidation defects, glycogen storage diseases, lysosomal storage diseases, defects of organic acid and amino acid metabolism, and defects of post-translational modification. This presentation will provide an update of the IEM disease process associated with cardiac disease, outlining a simple clinical approach to delineating an overarching diagnosis; especially in disease processes where a rapid diagnosis is essential, e.g., Pompe Disease(Kishnani et al., 2006).

IEM are responsible for around 5% of all cases of cardiomyopathy (CM) ; similarly, around 5% of all IEMs are associated with CM (Cox, 2007). IEM account for around 27% of cases of Hypertrophic cardiomyopathy HCM (Cox, 2007), and HCM as the primary presenting feature of a metabolic disease has been described (Arad et al., 2005).In many cases of HCM there can be few if any symptoms, however signs of congestive cardiac failure can be present if diastolic dysfunction is severe. The most common

IEM causing HCM are the glycogen storage diseases, accounting for around half of all cases (Cox, 2007). The most common of these is **Pompe disease** (glycogen storage disease type II). This generally presents in infancy with hypotonia, muscle weakness and respiratory failure. Congestive cardiac failure may be present due to impaired myocardial relaxation associated with gross hypertrophy and typically cause hypertrophic cardiomyopathy, whereas the accumulation of toxic metabolites, as seen in the organic acidurias, is associated with dilated cardiomyopathy (DCM). Advanced DCM presents with signs and symptoms of heart failure, including tachypnoea, increased work of breathing, tachycardia, and signs of reduced cardiac output. Mixed pathology is also possible, particularly in late presentations. IEM such as, **Barth syndrome,** first described in 1983(Barth et al., 1983), is an X-linked disorder affecting the stability of cardiolipin, a mitochondrial membrane protein, with increased urinary excretion of 3-methylglutaconic acid. It consists of a triad of cardiomyopathy, neutropenia and skeletal myopathy. A disorder of cardiolipin stability usually associated with DCM, have been associated with rarer types of CM such as endocardial fibroelastosis (EFE) and left ventricular noncompaction. No specific treatments for Barth syndrome have been proven. Cardiac management consists of medical management of heart failure and surveillance for ventricular arrhythmias with appropriate risk reduction therapies, including implantable cardiac defibrillators (Spencer et al., 2006). Cardiac screening of patients with metabolic diseases is important to guide treatment and stratify risk. Supportive cardiac treatment may be required, and whilst associated myocardial disease may improve or even resolve with correction of the metabolic disturbance(Lloyd, Vara, & Mathur, 2017).

Inborn Errors of Metabolism Linked to COVID19

The coronavirus pandemic has taken healthcare system all over the world by surprise: totally unprepared, HCPs had to rapidly change the way they organize and deliver medical care, not only to assist COVID-19 cases, but for all patients. As such, the pandemic is having a significant impact on patients affected by chronic and multiorgan disorders such as IEM. In the general population, the most severe and fatal cases of COVID-19 are observed in patients 60+ years of age and in those with underlying health conditions (diabetes, hypertension, cardiac disorders, chronic lung disease), while children are less frequently infected and present milder symptoms than adults (Assessment, 2020).

Incidence of COVID-19 in Rare Metabolic Patients

At the beginning of the pandemic, the healthcare providers (HCPs) expressed some concerns regarding the risks of severe forms of COVID-19 in IEM patients; indeed, the following IEM are considered a major risk factor for the coronavirus disease by MetabERN ***(MetabERN is a network of 69 medical centres specialised in rare metabolic diseases located in 18 European Member States)*** experts. amino and organic acids-related disorders (AOA) (at high risk according to 57.5% of centers); disorders of pyruvate metabolism, Krebs cycle defects, mitochondrial oxidative phosphorylation disorders, disorders of thiamine transport and metabolism (56.2%); lysosomal storage disorders (LSD) (52%); and carbohydrate, fatty acid oxidation and ketone bodies disorders (C-FAO) (45.2%).(Lampe et al., 2020)

Children and adults with an IEM are particularly at higher risk of morbidity and mortality when infected with SARS-CoV-2 due to their chronic preexisting conditions and potentially vulnerable immune system (McGuire, 2020; Parvaneh, Quartier, Rostami, Casanova, & de Lonlay, 2014). Furthermore, due to the pandemic itself or due to the forced reorganization of health care system activities needed to face

the pandemic in many countries (Zhao et al., 2007), medical services dedicated to IEM patients have also been impacted. Current available data about the impact of COVID-19 on patients suffering from inborn errors of metabolism are very scarce. Published reports concerning the pandemic are mainly describing expert opinions about management challenges and guidelines for IEM disorders (Brunetti-Pierri, Fecarotta, Staiano, Strisciuglio, & Parenti, 2020; S. Liu et al., 2020; Mistry et al., 2020; Politei, 2020), and few patient surveys investigating management problems and satisfaction (Andrade-Campos, Escuder-Azuara, de Frutos, Serrano-Gonzalo, & Giraldo, 2020; Riccio, Pieroni, Limoneglli, & Pisani, 2020; Sechi et al., 2020). Case reports of IEM patients with confirmed viral infection have also been published recently (Andrade-Campos et al., 2020; Mercolini et al., 2020).

CONCLUSION

The interaction between the viral infection with COVID-19 and cardio-vascular sequela is clearly relevant. Thus, it is important to emphasize the urgent need to investigate the potential leading mechanisms, particularly the viral entry to the myocardial tissue through ACE-2. Moreover, further data are needed to stretch knowledge on the potential infection of patients with inborn metabolic diseases. In the present situation, rare metabolic patients need in fact to be protected not only from the risk of coronavirus infection, but also from the possible degeneration of their disease.

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Chapter 11
Viral Infection of the Reproductive System in Times of COVID-19

Khaled Kahloula
Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria

Djallal Eddine Houari Adli
Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria

Nadia zouhairi
Faculty of Sciences, Chouaib Doukkali University, Morocco

Kaddour Ziani
Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria

Miloud Slimani
Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria

Wafaa Arabi
Department of Biology, Faculty of Sciences, University Dr. Moulay Tahar, Saida, Algeria

Abdelmohcine Aimrane
Faculty of Sciences, University Chouaib Doukkali, Morocco & Faculty of Medecine and Pharmacy of Marrakech, Morocco

Soraia El Baz
Faculty of Sciences Semlalia, Cadi Ayyad University, Morocco

Ahmed Draoui
Cadi Ayyad University, Morocco

Mohamed Echchakery
Institut supérieur des Sciences de la santé (ISSS), University Hassan I, Morocco

Abdelali Bitar
Faculty of Sciences, Chouaib Doukkali University, Morocco

ABSTRACT

Coronavirus (SARS-COV2) caused several deaths worldwide. This virus infects the target cell by binding to angiotensin-converting enzymes 2 (ACE2) receptor through its receptor-binding domain (RBD) and replicates. Thus, a high level of ACE2 expression is detected in the testicular cells so that the testis is believed to count as a potential target for direct damage by COVID-19. Moreover, the possibility of testicular damage may be caused by either direct viral invasion through interaction with ACE2 recep-

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tors or because of inflammatory response. Similarly, in women, literature reported the distribution and function of ACE2 in the female reproductive system, which is widely expressed in the ovary, uterus, vagina, and placenta. It regulates follicular development and ovulation, modulates luteal angiogenesis and degeneration, and influences regular changes in endometrial tissue and embryo development. Taking these functions into account, COVID-19 may disturb the female reproductive functions through regulating ACE2, resulting in infertility, menstrual disorder, and fetal distress.

INTRODUCTION

Coronaviruses have caused large health epidemics in the past, as SARS-CoV (Severe Acute Respiratory Syndrome CoronaVirus) caused a health epidemic in 2003, and another large pandemic outbreak caused by the Middle-East Respiratory Syndrome CoronaVirus (MERS-CoV) in 2012 (Di Mascio et al., 2020). The COVID-19 (SARS-CoV-2) virus has created a global pandemic and economic suffering. Attention has rightly focused on the respiratory system because this is where a life-and-death battle is waged between the viral horde and the host's immune system. However, other tissues are also susceptible to viral attacks including the kidney, heart, and brain, and also reproductive system (Aitken, 2021). The purpose of this chapter is to highlight the evidence that the male and female reproductive system constitutes another vulnerable target, raising the possibility that COVID-19 might ultimately induce infertility and/or facilitate the sexual transmission of this virus.

Male infertility is linked to some viral infections including human papillomavirus (HPV), herpes simplex viruses (HSV), and human immunodeficiency viruses (HIVs). Almost nothing is known about the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) effect on fertility. The possible risk factors of coronavirus disease 2019 (COVID-19) infection on fertility comes from the abundance of Angiotensin-Converting Enzyme-2 (ACE2), receptor entry of the virus, on testis, a reduction in important sex hormone ratios, and COVID-19-associated fever. Recent studies have shown a gender difference for COVID-19 rates and comorbidity (Batiha et al., 2020).

CELLULAR ENTRY MECHANISM OF THE VIRUS

A novel CoV emerged in December 2019, termed SARS-CoV-2 by the International Virus Taxonomy Committee (Gorbalenya et al., 2020) due to its genetic similarities to the SARS-CoV-1 virus (79.5%) (Guo et al., 2020). The infection has been termed "COVID-19" (coronavirus disease-19), as this is a CoV-related disease that was discovered originally in 2019 (Ashour et al., 2020; Guarner, 2020) SARS-CoV-2 has been identified as a member of the β-coronavirus subgroup, with a positive-sense single-strand RNA, located within a nucleocapsid contained in an envelope Ashour et al., 2020; Lu et al., 2020; Zhou, 2020). The viral structure includes characteristic spike (S) proteins that are projected from the virion surface and assist viral cell entry, membrane (M) and envelope (E) proteins that assist in viral assembly, and the N protein which forms the nucleocapsid (Ashour et al., 2020). The S protein mediates viral transfer into

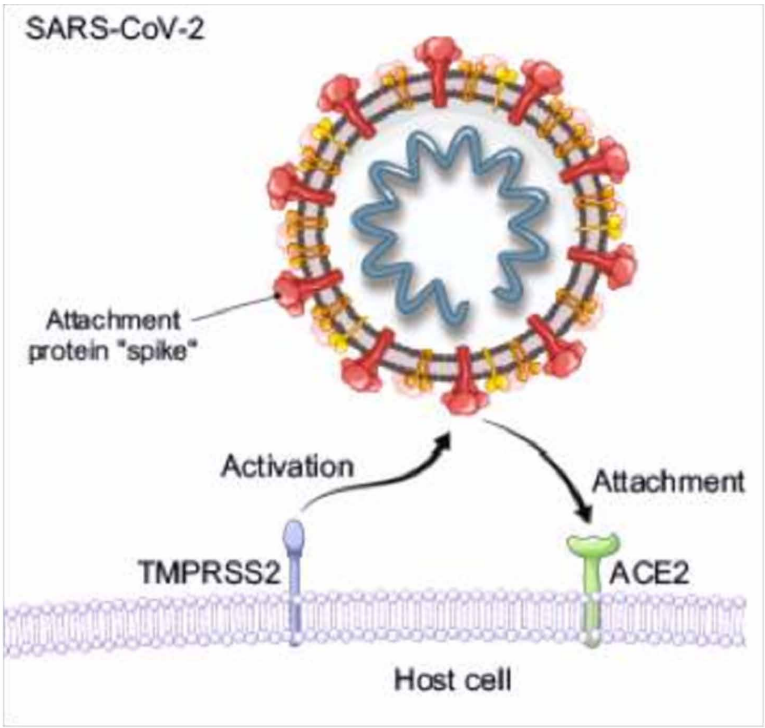
host cells and is composed of two unique subunits, S1 and S2. The S1 domain functions in virus binding to the host cell membrane, while the S2 domain is responsible for the fusion of the virus to host cell membranes to facilitate the viral genome in entering the host cell. Viral S proteins undergo proteolytic priming by the transmembrane protease, serine 2 (TMPRSS2) (Hoffmann et al., 2020). Many receptors on the human cell membrane are identified which are involved in S1 protein binding to host cells (Ashour et al., 2020). The SARS-CoV-2 may gain access to host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, with a higher affinity than reported in SARS-CoV-1 (Ashour et al., 2020; Gheblawi et al., 2020) (Fig.1). These receptors are widely expressed in the lungs (particularly type II pneumocytes and macrophages), cardiovascular system, gastrointestinal system, kidneys, neurological tissues, and the testes (Guo et al., 2020, Verdecchia et al., 2020; Fu et al., 2020). Here, the viruses replicate within the cells, releasing mature virions, which in turn infect new target cells (Margone et al., 2020).

Evidence strongly suggests human-to-human transmission through droplets spread (Guo et al, 2020; Contini et al., 2020). The median incubation period is estimated to be 5 days following exposure, with a reported range of 2–14 days (Meo et al., 2020; Park et al., 2020). The typically described presentation includes pyrexia (88%), dry cough (67%), fatigue (38.1%), productive cough (33%), dyspnea (18%), pharyngitis (13%), and headache (13%) (Guarner, 2020). The more severe cases develop pneumonia (Guo et al., 2020; Guarner, 2020). Complications include acute respiratory distress syndrome, shock, liver dysfunction, and secondary infection. Gastrointestinal symptoms, such as abdominal pain, poor appetite, nausea, vomiting, and diarrhea have also been reported (Guo et al., 2020; Trottein & Sokol, 2020). Laboratory results suggest leukopenia and lymphocytopenia (Guo et al., 2020). Although the mortality rate is reported at 2% to 3%, which is significantly lower than MERS, SARS-CoV-2 is expected to result in many more deaths due to its widespread infections (Guarner, 2020). Currently, diagnosis is based on nucleic acid identification in oropharyngeal swabs through real-time polymerase chain reaction and next-generation sequencing (Guo et al., 2020). Risk factors for hospitalization include those who are age older than 60 years, male sex, obesity, smokers, and underlying conditions including hypertension, cardiovascular disease, diabetes, and chronic respiratory diseases (Lipworth et al., 2020).

3. SARS-CoV-2 and Male Infertility: Possible Multifaceted Pathology

Surprisingly, men are reportedly more vulnerable to COVID-19 even with a higher fatality rate compared to women. Thus, it is crucial to determine whether SARS-CoV-2 infection can even affect male fertility as an immediate or long-term consequence of the disease. Among the discrete data available, an important finding is that the angiotensin-converting enzymes2 (ACE2) receptor, which aids the SARS-CoV-2 entry into host cells, is profoundly expressed in testicular cells. Besides, the endogenous androgen milieu and its receptors are associated with ACE2 activation reflecting that enhanced testosterone levels may trigger the pathogenesis of COVID-19. On the contrary, hypogonadism has also been reported in the acute phase of some COVID-19 cases. Moreover, SARS-CoV-2 infection-induced uncontrolled inflammatory responses may lead to systemic oxidative stress (OS), whose severe disruptive effects on testicular functions are well documented (Dutta & Sengupta, 2020)

Figure 1. Cellular entry mechanism. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection is mediated by the binding between viral spike proteins and angiotensin I converting enzyme 2 (ACE2) cellular receptor, and the further proteolytic cleavage and activation of spike proteins by the transmembrane protease serine 2 (TMPRSS2).



Angiotensin-Converting Enzyme-2 (Ace2) and Transmembrane Serine Protease 2 (Tmprss2) Receptors in Human Testes

Having considered these reports, it is a breakthrough revelation in male fertility research that tests show almost the highest ACE2 mRNA and protein expressions among the various body tissues (Fan et al., 2020). The four main testicular cell types showing expression of ACE2 mRNA are the seminiferous duct cells, spermatogonia, Leydig cells, and Sertoli cells (Fan et al., 2020; Shen et al., 2020). Moreover, distinctly high ACE2 expression in testicular cells, while comparatively low expression levels of ACE2 in ovarian cells (Shastri et al., 2020; Stanley et al., 2020), may also support higher vulnerability of SARS-CoV-2-mediated impairment in male gonadal functions (Figure 2).

To enter human cells, SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE2) as a key receptor. ACE2 is located in different body organs such as kidneys, heart, intestines, liver, lungs, and testes; therefore, cells that have a high expression of ACE2 could be a potential target for the virus. ACE2 is a transmembranal zinc metallopeptidase with high homology to the classic ACE. ACE isoforms are part of the renin-angiotensin-aldosterone- system (RAAS) that plays a crucial role in the regulation of blood pressure and fluid balance (Younis et al., 2020).

ACE converts Angiotensin I into Angiotensin II (Ang II), whereas ACE2 converts Angiotensin II into Angiotensin 1-7. While Ang II could have dangerous effects on the kidneys, heart, and lungs, the

Angiotensin 1-7- Mas receptor axis plays a healthy role because it has vasodilatory, anti-inflammatory, and anti-fibrotic actions (Younis et al., 2020); so even when ACE2 antagonizes the activation of the classical renin-angiotensin system modifying angiotensin II, it still provides some protection against inflammation and fibrosis. The extracellular domain of ACE2 is a cell surface receptor for the Spikes glycoproteins (S domain) on the SARS-CoV-2 envelope. To enter host cells, SARS-CoV-2 uses ACE2 and host proteases such as a transmembrane serine protease 2 (TMPRSS2) that cleaves and induces a conformational change to the viral S domain, allowing the fusion of the viral and host membranes (Hoffmann et al., 2020).

In light of these considerations, both ACE2 and TMPRSS2 have a crucial role in virus-host entering (Figure 2). TMPRSS2 is more largely expressed in human tissue than ACE2, whereas single-cell RNA sequencing (scRNA-seq) in human respiratory tissue has shown a co-expression of ACE2 and TMPRSS2 in lungs, heart, and kidneys, which would indicate that these cells are strongly susceptible to viral infection (Ding et al., 2004).

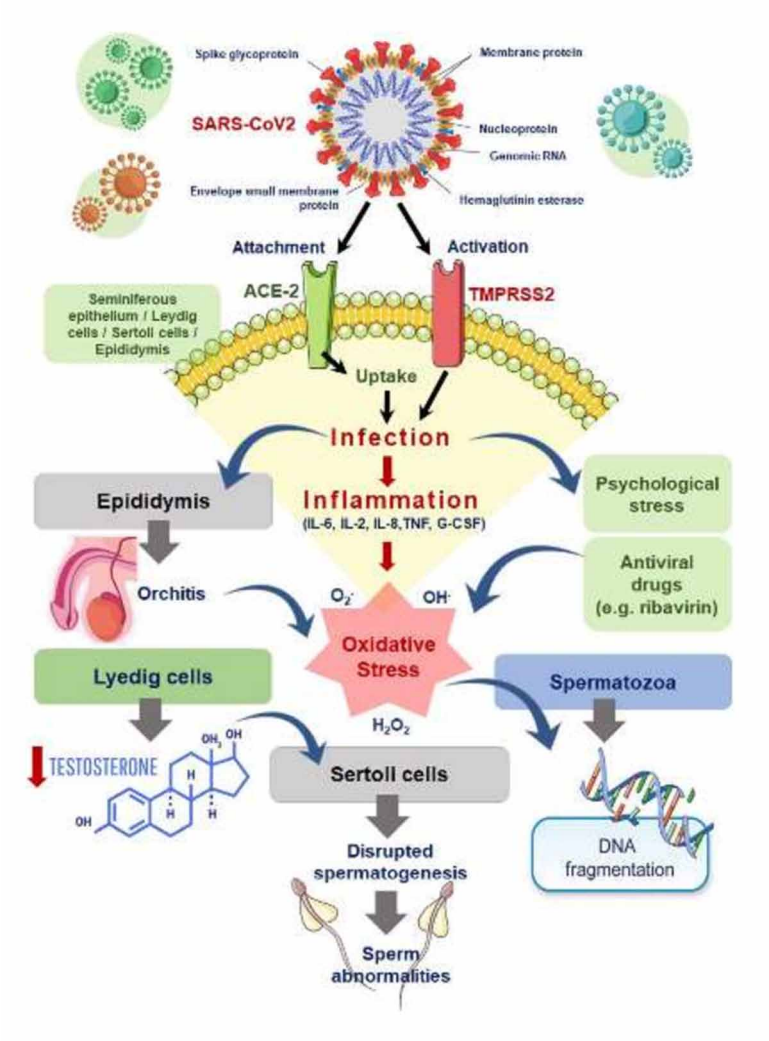
Given that clinical features of COVID-19 appear to be widely determined by the cells and tissues with co-expression of ACE2 and TMPRSS2 in their constituent cells, it is fitting to evaluate the activity of the virus on those male and female reproductive cells in which there is a co-expression of the two proteins, and if SARS-CoV-2 could consequently hurt fertility. The expression of ACE2 and TMPRSS2 has been shown in testicular cells with different interpretations (Qi et al., 2020). As ACE2 is highly expressed in human testes, it is relevant to evaluate whether COVID-19 in males, via ACE2, might damage fertility. ACE2 is expressed in the testes and epididymis, in particular in Leydig cells, Sertoli cells, and spermatogonia (Wang & Xu, 2020).

Moreover, the testicular expression of ACE2 is age-related, with a higher expression in patients aged 20 to 30, whereas as 60 year old and more patients show a reduced expression of ACE2, it could mean that young men are at higher risk of testicular damage by the virus than older patients. Although ACE2 is the key receptor for the virus, this is not enough to guarantee its entry into the host cell; the co-presence of TMPRSS2 is crucial: KE. Stanley et al. (2020) carried out an interesting study based on the evaluation of co-expression of the host-virus entry proteins on male reproductive cells.

According to this study, ACE2 is expressed in male myoid cells, spermatogonial stem cells, and Leydig cells, while TMPRSS2 expression is detected predominantly in elongated spermatids. Even though a small proportion of spermatogonial stem cells express ACE2 and TMPRSS2, finding cells that co-express both genes is extremely rare, and scRNA-seq data results suggest that spermatozoa may not be susceptible to virus infection owing to the lack of ACE2 and TMPRSS2 coexpression. Nevertheless, we have to consider that the virus could be present in the seminal fluid since this not only contains spermatozoa but also round cells (germ stem cells, leukocytes) co-expressing ACE2 and TMPRSS2. Furthermore, since semen is also formed by prostatic components, it would be appropriate to better determine which prostatic cells co-express ACE2 and TMPRSS2. For instance, it is claimed that TMPRSS2 is widely expressed in the prostate epithelial cells, including the apical plasma membrane of the prostate luminal cells, and it is also released into the seminal fluid as a component of prostasomes, organelle-like vesicles (Chen et al., 2010).

In the light of the evidence, it could be legitimate to assume that the virus via prostatic deriving components and cells could be conveyed into the seminal fluid; however, it has been demonstrated that ACE2 is not expressed on prostatic cells. Human proteome/sars-cov-2 shows in which male reproductive organs SARS-CoV-2 related proteins are simultaneously expressed, and since, in seminal vesicles,

Figure 2. Possible mechanisms of SARS-CoV-2 infection-induced impairment in male reproductive function



these proteins are simultaneously expressed, the virus could be present in the seminal fluid, and semen could be one of the pathways of viral transmission (Gordon et al., 2020).

However, there are contradicting reports stating that SARS-CoV-2 infection in males leads to acute stage hypogonadism and it is suggested that reduction in androgenic action may lead to even fatal consequences. Several studies in humans as well as in animals have linked hypogonadism with levels of increased pro-inflammatory cytokines, mainly IL- 1β, IL-6, and TNF-α (Mohamad et al., 2019; Pozzilli & Lenzi, 2020), which in turn are important inflammatory mediators in SARS-CoV-2 pathogenesis. Nevertheless, an acute critical inflammatory condition, as in the case of COVID-19, may suppress the activity of the hypothalamic-pituitary-testicular (HPT) axis, leading to reduced low luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels. But this theoretical perception does not correspond to a study conducted on 81 COVID-19 male patients, which reported lower serum tes-

tosterone levels, higher LH levels, and lower T: LH ratio in comparison to age-matched control subjects (Ma et al., 2020).

These findings may suggest direct effects of SARS-CoV-2 infection in testicular cells rather than via the HPT axis. Thus, the associations of SARS-CoV- 2 infections and modulation of sex hormones in the male are major missing links that await in-depth research interventions. SAR-CoV2 can operate via multiple possible mechanisms which may lead to disruption of male reproductive functions. It is suggested that this virus activates oxidant-sensitive pathways via inflammatory responses, thereby inducing oxidative stress (OS), which presents a common pathological mechanism to disrupt several physiological functions via oxidative damage to host tissues. OS-mediated mechanisms of male infertility are widely documented, as OS can affect semen quality and disrupt sperm functions and morphology, intracellular oxidative damage to spermatozoa by lipid peroxidation of sperm membrane, sperm DNA damage, as well as inducing apoptotic pathways in spermatozoa (Dutta et al., 2019; Sengupta & Dutta, 2020). In SARS-CoV infections, the excessive production of reactive oxygen species (ROS) may trigger mainly the nuclear factor kappa-light-chain- enhancer of activated B cells (NF-κB)-toll-like receptor (mainly TLD-4) pathways (Delgado-Roche & Mesta, 2020).

This further stimulates the release of cytokines causing an exaggeration of the inflammatory responses (Delgado-Roche & Mesta, 2020). As already discussed, this virus can potentially cause orchitis which also can lead to induction of OS. Moreover, SARS-CoV-2 infection causes psychological stress which is a major cause of systemic OS (Li et al., 2020). Besides the direct relation of SARS-CoV-2 infection and OS, treatment of COVID-19 includes antiviral drugs like ribavirin which is associated with induction of OS, reduced testosterone level, impaired spermatogenesis, and sperm abnormalities in animal studies (Almasry et al., 2017; Narayana et al., 2002).

Moreover, ribavirin treatment showed reduced sperm count (Bukhari et al, 2018) and sperm DNA fragmentation (SDF) (Anifandis et al., 2020) up to 8 months following cessation of treatment (Li et al., 2020, Pecou et al., 2009). Based on these vital reports, it can be hypothesized that the testis could be a potential target for the SARS-CoV-2 virus and testicular damage, as well as subsequent infertility after COVID-19 infection, can be theoretically explained. A direct invasion of the SARS-CoV-2 virus is caused by ACE2 receptors likely causing direct testicular damage or by affecting testicular functions by secondary immunological and inflammatory responses.

This possibility needs to be investigated through follow-up studies of the reproductive functions of reclaimed male patients. Thus, it cannot be ruled out that COVID-19 could have immediate or delayed impacts on male fertility status. So far, no definitive data is obtained to track the reproductive functions in men recovered from COVID-19. Since male infertility is already showing a global declining trend which is a major threat to humankind, it is crucial to undertake thorough research to reveal the exact impact and mechanism by which the pandemic COVID-19 might affect the male fertility parameters.

POTENTIAL INFLUENCE OF COVID-19/ACE2 ON THE FEMALE REPRODUCTIVE SYSTEM

The available evidence suggests that ACE2 is widely expressed in the ovary, uterus, vagina, and placenta. Therefore, we believe that apart from droplets and contact transmission, the possibility of mother-to-child and sexual transmission also exists. Ang II, ACE2, and Ang-(1-7) regulate follicle development and ovulation, modulate luteal angiogenesis and degeneration, and also influence the regular changes in

endometrial tissue and embryo development. Taking these functions into account, Covid-19 may disturb the female reproductive functions by regulating ACE2 (Yan et al., 2020).

Recently, cases of COVID-19 during pregnancy have been reported (Chen et al., 2020a; Zhu et al., 2020), but the influence of COVID-19 on the female reproductive system needs further investigation. In this review, we analyzed the distribution and function of ACE2, trying to predict the possible targets and transmission routes, as well as the influence on the female reproductive system, of COVID-19 (Yan et al., 2020).

ACE2 in the Ovary

ACE2 presents in the stroma and granulosa cells as well as oocytes in immature rat ovaries, the expression of which is enhanced in antral and preovulatory follicles subjected to equine CG treatment (Pereira et al., 2009). In bovine theca cells and granulosa cells, ACE2 also exists (Barreta et al., 2015; Tonellotto dos Santos et al., 2012). Notably, ACE2 mRNA transcripts were detected in ovaries from reproductive-age women and postmenopausal women (Reis et al., 2011).

We analyzed ACE2 data from the GeneCards database and found that ACE2 is the most abundantly expressed in the ovary. In the meantime, data obtained from Bgee showed that the expression level of ACE2 in oocytes is relatively high. Therefore, the ovary and oocyte might be potential targets of COVID-19. ACE2 is the key enzyme in the axis that plays a synergistic role in balancing the levels of Ang II and Ang-(1-7). Ang II induces steroid secretion (Hayashi et al., 2003; Shuttleworth et al., 2002), facilitates follicle development (Ferreira et al., 2011; Shuttleworth et al., 2002) and oocyte maturation (Giometti et al., 2005; Stefanello et al., 2006; Yoshimura et al., 1992), contributes to follicular atresia (Kotani et al., 1999; Obermuller et al., 2004; Tanaka et al., 1995), influences ovulation (Acosta et al., 2000; Ferreira et al., 2007; Guo et al., 2012; Kuji et al., 1996; Kuo et al., 1991; Miyabayashi et al., 2005; Pellicer et al., 1988; Xu et al., 2005; Xu & Stouffer, 2005; Yoshimura et al., 1992; Yoshimura et al., 1993) and maintains corpus luteum progression (Sugino et al., 2005). Ang-(1-7) promotes the production of estradiol and progesterone (Costa et al., 2003) and enhances ovulation (Muthalif et al., 1998; Tonellotto dos Santos et al., 2012; Viana et al., 2011) and the resumption of meiosis in the oocyte (Honorato-Sampaio et al., 2012). A recent study showed that the level of Ang-(1-7) is also associated with the maturation of human oocytes (Cavallo et al., 2017).

ACE2 in Uterus and Vagina

ACE2 mRNA has been identified in the uterus of humans (Vaz-Silva et al., 2009) and rats (Brosnihan et al., 2012). Vaz-Silva et al. (2009) claimed that ACE2 mRNA is more abundant in epithelial cells than in stromal cells, and higher in the secretory phase than in the proliferative phase (Vaz-Silva et al., 2009). Moreover, we confirmed the presence of ACE2 in the uterus and vagina after analyzing the data from the Human Protein Atlas and Gene Cards. Noteworthy is the report of a high infection rate among sexual partners of 35 COVID-19 positive females (Cui et al., 2020), suggesting the possibility of sexual transmission.

However, the confirmation of sexual transmission still needs extensive investigation. Ang II plays a dual role in vascular bed and endometrium regeneration and initiates menstruation through spiral artery vasoconstriction (Ahmed et al., 1995; Li and Ahmed, 1996a, 1997). The balance between Ang II and Ang-(1-7) could regulate the regeneration of the endometrium (Vaz-Silva et al., 2009) and myometrium

activity (Deliu et al., 2011; Vaz-Silva et al., 2012). Moreover, Ang II increases the proliferation of uterus epithelial and stromal cells and enhances endometrial fibrosis, an effect that can be inhibited by Ang-(1-7) (Hering et al., 2010; Shan et al., 2015; Shan et al., 2014). Notably, the normal function of Ang II in the endometrium is necessary for regular menstrual cycles, and alterations in its distribution and the level of the receptors may be related to dysfunctional uterine bleeding associated with hyperplastic endometrium (Li & Ahmed, 1996b).

Furthermore, many authors have described in the literature that intense ACE2 and Ang II expression correlates with the metastasis and prognosis of endometrial carcinoma (Delforce et al., 2017; Shibata et al., 2005; Watanabe et al., 2003), and highlighted that the increased ACE2/Ang-(1-7)/MAS/AT2R pathway activity in endometrial cancer can be an important mechanism to counteract the actions of Ang II/AT1R (Abdalla et al., 2001; Kostenis et al., 2005).

ACE2 in Pregnancy

ACE2 is widely expressed in the human placenta (Valdes et al., 2006). In placental villi, ACE2 is mainly expressed in the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of primary and secondary villi. In the maternal stroma, ACE2 is expressed in the invading and intravascular trophoblast and decidual cells. ACE2 is also found in arterial and venous endothelium and smooth muscle of the umbilical cord (Valdes et al., 2006). Of note, ACE2 reaches the highest level in early gestation (Pringle et al., 2011).

During early gestation, ACE2 is expressed in the primary and secondary decidual zone and luminal and glandular epithelial cells. During late gestation, ACE2 staining is visualized in the labyrinth placenta, and amniotic and yolk sac epithelium (Ghadhanfar et al., 2017; Neves et al., 2008). Moreover, Ace2 in the placenta of rats begins to increase from mid-gestation (Vaswani et al., 2015). According to the Gene Cards, the expression of ACE2 in the placenta is greater than that detected in the lung, suggesting a possibility of viral infection of the placenta. Recently, early-onset COVID-19 infection was identified in infants whose nasopharyngeal and anal swabs were positive on day 2 and 4 of life (Zeng et al., 2020), and a neonate born to a mother with COVID-19 had elevated IgM antibodies at 2 hours after birth (Dong et al., 2020).

Given that the identification of COVID-19 in human airway epithelial cells requires at least 96 hours of culture (National Health Commission of the People's Republic of China, 2020), we speculate that intrauterine infection with COVID-19 may appear and the fetuses may be infected during gestation.

Additionally, the Human Protein Atlas and GeneCards database showed the presence of ACE2 in female breasts. Wu et al. (2020) claimed that 1 of 3 samples of breast milk was positive for COVID-19 in nucleic acid testing (Wu, 2020), indicating the chance of transmission through breastfeeding. Even if there is no virus in milk, contact transmission during breastfeeding should be taken into account. Given the weaker immune system of newborns, we advise that pregnant patients who are confirmed as positive for COVID-19 should carry out artificial feeding instead, or start breastfeeding after 14-day isolation following recovery and discharge.

Concurrently, considering its benefits in decreasing respiratory tract and gastrointestinal tract infections, sudden infant death syndrome, and diabetes of the infants (Eidelman & Schanler, 2012), breastfeeding might not be completely forbidden. Nevertheless, Ferrazzi et al. (2020) reported that when breastfed by two postpartum women diagnosed with COVID-19 and wearing no masks, the newborns tested positive (Ferrazzi et al., 2020). We strongly support that all possible precautions should be taken to avoid

spreading the virus to the infant, including washing hands before touching the infant and wearing a face mask during breastfeeding (Baud et al., 2020).

However, these precautions may not be strictly adhered to, hence increasing the risk of infection in the infants. Therefore, mothers who intend to breastfeed are encouraged to use a dedicated breast pump, and after each pumping session, the breast pump should be appropriately disinfected.

During pregnancy, Ang II, ACE2, and Ang-(1-7) function mainly through regulating blood pressure and fetus development. Meanwhile, they also interact to maintain normal uterine physiology. Ang II stimulates trophoblast invasion in rat and human cells (Hering et al., 2010). Ang-(1-7) and ACE2 may act as a local autocrine/paracrine regulator in the early (angiogenesis, apoptosis, and growth) and late (uteroplacental blood flow) events of pregnancy (Neves et al., 2008). ACE2 hydrolyzes Ang II into Ang-(1-7), and Ang I into Ang-(1-9), which is quickly converted to Ang-(1-7) and thereby controlling the blood pressure and hydro-salinity balance of pregnant women (Pringle et al., 2011). The aberrant expression of Ang II, ACE2, and Ang-(1-7) may be involved in hypertension of pregnancy, pre-eclampsia, and eclampsia (Anton et al., 2009; Anton et al., 2008; Brosnihan et al., 2004; Merrill et al., 2002; Sykes et al., 2014; Yamaleyeva et al., 2014). Brosnihan et al. (2004) described that pre-eclamptic women presented with suppressed plasma Ang-(1-7) levels when compared with normal pregnancy subjects (Brosnihan et al., 2004).

High expression of Ang II in the placental villous during pre-eclampsia causes a decreased blood flow and nutrition supply in fetuses (Anton et al., 2009; Anton et al., 2008; Shibata et al., 2006). Meanwhile, low levels of ACE2 and Ang-(1-7) in the placenta are associated with intrauterine growth restriction (Ghadhanfar et al., 2017). Ingestational Ace2-/- mice, plasma Ang-(1-7) decreases and placental Ang II increases, accompanied by abnormal placental functions (including placental hypoxia and uterine artery dysfunction) and ultimately fetal growth retardation (Bharadwaj et al., 2011; Yamaleyeva et al., 2015). Moreover, Chen et al. (2014) found that the maternal Ang-(1-7)/Ang II ratio is independently associated with gestational hypertension or pre-eclampsia, factors causing preterm birth (Chen et al., 2014). Additionally, it has been shown that the up-regulation of ACE2/Ang-(1-7)/Mas prevents premature birth (Lumbers, 2020).

It is noteworthy that premature birth and intrauterine growth restriction may predict the cardiovascular disorders that appear in adulthood (Irving et al., 2000). Bessa et al. (2019) reported that activation of the ACE2/Ang-(1-7)/ Mas axis in hypertensive pregnant rats could attenuate the cardiovascular dysfunction in adult offspring (Bessa et al., 2019), confirming the engagement of the ACE2 axis in pregnancy. COVID-19 infection poses a great threat to pregnant women and fetuses, causing premature birth (20.8%, 25/120), fetal distress (26.7%, 12/45), premature rupture of fetal membranes (13.0%, 10/77), and cesarean section (92.6%, 63/68) (Chen et al., 2020a; Chen et al., 2020b; Ferrazzi et al., 2020; Li et al., 2020; Zeng et al., 2020; Zhu et al., 2020). The considerable cesarean section rate is mainly due to the concern about COVID-19 and obstetrical indications (Chen et al., 2020b). It is worth mentioning that current data are still insufficient and some reports lack concrete details. Therefore, whether it COVID-19/ACE2 that causes the placental dysfunction remains elusive and needs further evaluation.

CONCLUSION

The pandemic due to SARS-CoV-2 has generated increasing concerns about male and female fertility and reproduction. It is argued that testicular cells expressing both ACE2 and TMPRRS2 are rare, and

this fact suggests that the virus may not harm male gametes. However, SARS-CoV-2 could indirectly compromise male gametes, testicular cells, and therefore fertility because the fever and the cytokine storm associated with COVID-19 induce sperm DNA fragmentation and reduce the male reproductive potential. COVID-19 may infect the ovary, uterus, vagina, and placenta through the ubiquitous expression of ACE2. Moreover, COVID-19 /ACE2 may disturb the female reproductive functions, resulting in infertility, menstrual disorder, and fetal distress.

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Chapter 12
Insights Into the COVID-19 Infection Related to Inherited Metabolic Diseases

Naima Fdil
Metabolic Platform, Faculty of Medicine, Cadi Ayyad University, Morocco & MoSEAR, Morocco

Es-Said Sabir
https://orcid.org/0000-0003-2246-5645
Metabolic Platform, Faculty of Medicine, Cadi Ayyad University, Morocco

Karima Lafhal
Metabolic Platform, Faculty of Medicine, Cadi Ayyad University, Morocco

Noureddine Rada
Mohammed VI Hospital University, Morocco

Redouane El Fezzazi
Faculty of Medicine, Cadi Ayyad University, Morocco

Mohamed Amine
Mohammed VI Hospital University, Morocco

Fadl Mrahib Rabou Maoulainine
Mohammed VI Hospital University, Morocco

Mohammed Bouskraoui
Mohammed VI Hospital University, Morocco

ABSTRACT

People with respiratory problems and people prone to decompensations are particularly vulnerable to COVID-19. These characteristics are often present in patients with inherited metabolic diseases (IMDs). It is therefore conceivable that patients with IMDs are at a greater risk of infection and may present a more serious form of COVID-19 disease. Currently available data about the impact of COVID-19 on

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patients suffering from IMDs are very scarce and no study has been able to confirm this hypothesis. In this chapter, the authors have tried to show that the severity of COVID-19 infection in patients with IMDs is specific to the group that the disease belongs. Indeed, lysosomal storage diseases caused by impaired degradation and accumulation of metabolites in lysosomes leads to dysfunction of lysosomal and possible impairment of the COVID-19 egress process. The fact that COVID-19 disease may be considered itself as an IMD was also discussed to highlight the interference which can exist between COVID-19 disease and IMDs in a patient.

INTRODUCTION

Inherited metabolic diseases (IMDs)also known as inborn errors of metabolism (IEMs), are a group of disorders which result from the deficiency or the abnormality of an enzyme, its cofactor or a transporter(Figure 1), resulting in accumulation of a substrate or the deficiency of the product (J V Leonard & Morris, 2000; Saudubray, Sedel, & Walter, 2006).Although IMDs are individually rare, they are collectively common, with an overall incidence of more than 1:1000(Campeau, Scriver, & Mitchell, 2008).The first description of these disorders was made by SirArchibald Garrod in 1902 (Garrod, 1902). Nowadays, there are estimated to be more than 1000 inborn errors of metabolism that have been recognized, with approximately 25% of them having manifestations in the neonatal period(Illsinger & Das, 2010; James V Leonard & Morris, 2006; Saudubray et al., 2006). The application of tandem mass spectrometry to newborn screening and prenatal diagnosis have enabled presymptomatic diagnosis for some IMDs, more than 300 "new" disorders were describedbetween 2011 and 2016, 85% presenting with predominantly neurologic manifestations(Fernandes, Saudubray, Van den Berghe, & Walter, 2006).Neonates with IMDs are usually healthy at birth with signs typically developing in hours to days after birth. The signs are usually nonspecific, and may include decreased activity, poor feeding, respiratory distress, lethargy or seizures. These signs are common to several other neonatal conditions, such as sepsis and cardiopulmonary dysfunction.Given their frequency and potential for treatment, the clinician should be aware of this group of conditions and learn to identify the typical manifestations of the different inborn errors of metabolism. The vast majority of IMDs are inherited in an autosomal recessive manner. Therefore, a history of parental consanguinity or a previously affected sibling should raise the suspicion of IMDs. Some IMDs, such as Mucopolysaccharidosis type II (MPS II), and Fabry disease, are X-linked. In X-linked disorder, typically male patients have severe diseases, whereas female patients are either asymptomatic or have milder disease due to X-chromosome inactivation.There has been significant progress for the diagnosis and treatment of IMDs especially during the last decade, early diagnosis is very important to preventmortality and morbidity in untreated cases (Raghuveer, Garg, & Graf, 2006).

Pathophysiologically, IMDs can be divided into three groups based on the substrate accumulated, the group of enzymes affected, and the organelle that has the defective pathway or the clinical presentation (Saudubray et al., 2006). The first includes IMDs causing intoxication that give rise to an acute or chronic intoxication because of defects in the intermediary metabolic pathway, resulting in the accumulation of

toxic compounds proximal to the metabolic block; (e.g., Aminoacidopathies, Organic acidurias, Defects in carbohydrate metabolism, urea cycle disorders, sugar intolerances). The second group includes IMDs resulting in energy deficiency, such as mitochondrial respiratory chain defects, defects of Krebs cycle and Fatty acid oxidation defects. The third group is IMDs resulting in defects in the synthesis or the catabolism of complex molecules in certain cellular organelles, such as lysosomal storage disorders, Peroxisomal disorders, glycosylation, and cholesterol synthesis defects.Children and adults with an IMD are particularly at higher risk of morbidity and mortality when exposed to viral or bacterial infections due to their chronic preexisting conditions and potentially vulnerable immune system (McGuire, 2020; Parvaneh, Quartier, Rostami, Casanova, & de Lonlay, 2014).

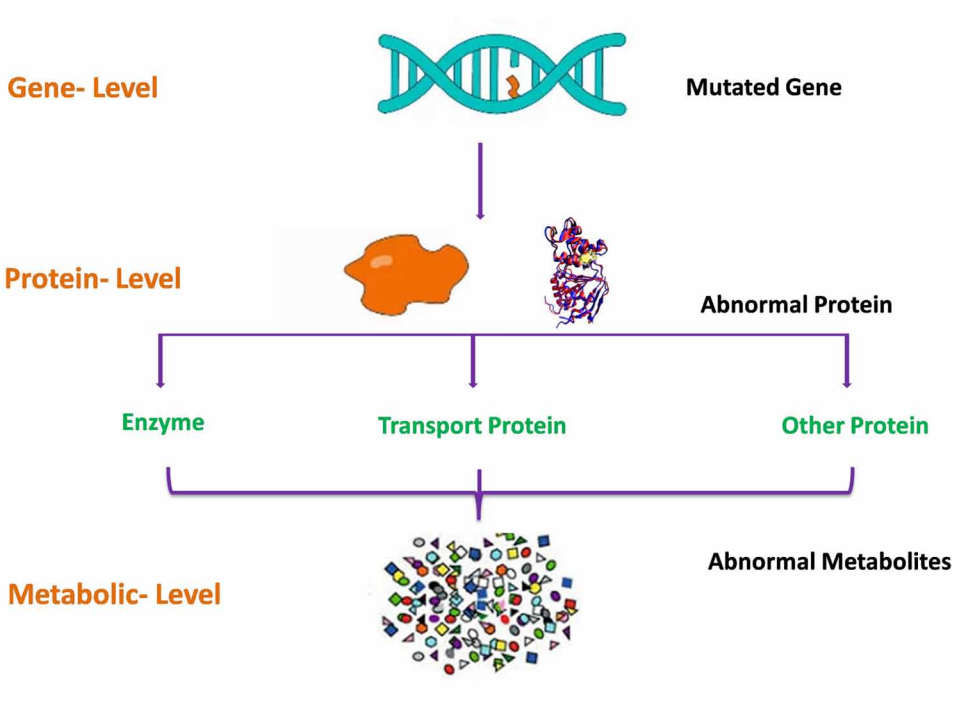
Lysosomal storage disorders (LSD) comprisemore than 50 different genetic diseases.These disorders mostly involve the dysfunction oflysosomal hydrolases, which result in impairedsubstrate degradation. The lysosome has been known as a membrane-enclosed cytoplasmic organelle responsible for the degradation of a variety of biological macromolecules, including proteins, lipids, carbohydrates and nucleic acids(Hesketh, Wartosch, Davis, Bright, & Luzio, 2018; Saftig & Klumperman, 2009). These macromolecules reach the lysosome by various routes, including the endocytic, phagocytic and autophagic pathways, to be degraded in the lysosomal lumen by more than 60 acid hydrolases for subsequent reutilization by the metabolic processes of the cell.Any disruption of lysosomal functioncan lead to the accumulation of undegraded substrate(s) in endosomes and lysosomes, eventuallycompromising cellular function(Hopwood & Brooks, 1997). Although lysosomal proteins are ubiquitously distributed, the accumulation of undegraded substrate (s) in lysosomal storage disorder patients is normally restricted to those cells, tissues, and organs in which substrate turnover is high.

At the end of December 2019, an epidemic of acute respiratory infections broke out in Wuhan, China. It is caused by a new coronavirus, later named severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The disease is highly contagious, with the ability to spread directly through interhuman transmission by the airways, and the epidemic quickly spread globally (Khanam et al., 2020).It causes a range of human respiratory tract infections varying frommild cold to severe respiratory distress syndrome(Heymann & Shindo, 2020).The World Health Organization (WHO) declared it a Public Health Emergency of International Concern on 30 January 2020, and then a Global Pandemic on 11 March 2020, less than 3 months after its appearance. At the time of writing, the Covid-19 pandemic has affected all countries and territories worldwide and has caused 3 million deaths out of a total of 127.25 million people infected. The pandemic is becoming more complex, and it is increasingly difficult to control the disease, both in terms of morbidity and mortality rate. Clinical features varied from mild illness to severe or fatal illness. The most common symptoms of Covid-19 were non-specific and mainly included fever, cough and myalgia. Other minor symptoms were sore throat, headache, chills, nausea or vomiting, diarrhea, ageusia and conjunctival congestion. TheCovid-19 was clinically classified into mild to moderate disease (non-pneumonia and pneumonia), severe disease (dyspnoea, respiratory frequency over 30/min, oxygen saturation less than 93%, PaO2/FiO2 ratio less than 300 and/or lung infiltrates more than 50% of the lung field within 24-48 hours) and critical (respiratory failure, septic shock and/or multi-organ dysfunction/failure)(Raoult, Zumla, Locatelli, Ippolito, & Kroemer, 2020; Singhal, 2020).Early diagnosis of Covid-19 is the most critical step to treat infection. The diagnostic tools are generally molecular methods, serology and viral culture. Initial laboratory investigations of hospitalized patients consist of a complete blood count, coagulation testing and serum biochemical test such as creatine kinase (CK), lactate dehydrogenase, procalcitonin, and electrolytes (Li et al., 2020).Based on laboratory tests, most

patients showed a significant decrease in total number of lymphocytes, suggesting that lymphocytes (particularly T lymphocytes) are likely target of SARS-CoV-2.

Current available data about the impact of Covid-19 on patients suffering from IMDs are very scarce. Published data concerning the pandemic are mainly reports describing expert opinions about management challenges and guidelines for IMDs disorders (Brunetti-Pierri, Fecarotta, Staiano, Strisciuglio, & Parenti, 2020; Liu et al., 2020). Case reports of IMDs patients with confirmed viral infection have also been published recently(Andrade-Campos, Escuder-Azuara, de Frutos, Serrano-Gonzalo, & Giraldo, 2020).

Figure 1. Inborn Errors of Metabolism a genetic disease



INHERITED METABOLIC DISEASES AND COVID-19 INFECTION

An increasing number of patients with IMDs are surviving to adulthood and are therefore on a par with healthy adults with respect to Covid-19 disease, information on Covid -19 infection for these patients is either obtained from reports of isolated cases or small series of cases and no single Centre is likely to have enough experience with any single condition to provide definitive guidelines for management.

This chapter highlights the impact of Covid -19 on patients with inherited metabolic diseases, focusing on the interferences between the two associated conditions, results and lessons to be learned.Two main conditions characteristic of IMD suggest that Covid-19infections will have adverse consequences in patients with IMD:

-Some patients with inherited metabolic disease are at risk of worsening (decompensation) of their metabolic condition if they develop a viral infection.

-Respiratory manifestations are frequent in patients with IMD with a wide range of pathomechanisms linked to metabolites storage inducting infiltration of pulmonary structures by abnormal cells, organomegaly and deformities.It is obvious that a Covid-19 infection will be fatal for these patients by accelerating respiratory decline.

VIRAL DECOMPENSATION

Communicable infectious diseases of childhood place children with inherited metabolic diseases at high risk of metabolic decompensation with serious consequences. Many inherited metabolic diseases, especially disorders of intermediary metabolism are complicated by episodes of decompensation due to bacterial or viral infections which often lead to death. The clinical signs vary from one patient to another but generally include abnormal behavior, drowsiness, and a glazed look. Prompt intervention is essential if death and/or long term neurological sequelae are to be avoided. We list here as examples some of these diseases like fatty acid oxidation defects, Glycogen storage disease type I, Organic acidemias, Maple syrup urine disease and Urea cycle disorders. A number of IMD also has an associated immunodeficiency(Kingsley, Varman, Chatterjee, Kingsley, & Roth, 2006).

RESPIRATORY MANIFESTATIONS IN PATIENTS WITH INHERITED METABOLIC DISEASES

Respiratory manifestations are part of the clinical picture of several inherited metabolic diseases, either at presentation or as late-onset features; sometimes it can also be the only manifestation of underlying IMD. The largest group involving the respiratory system consists of those with interstitial lung disease due to storage of complex molecules. Respiratory symptoms are frequent in patients with LSD with pathomechanisms such as infiltration of pulmonary structures by abnormal cells in Niemann-*Pick*(NPD) and Gaucher diseases (GD), airway soft tissue infiltration, accompanied by limited chest mobility in Mucchopolysaccharidoses diseases (MPSs), dyspnea, wheezing in Fabry disease (FD) with a compromised respiratory function by cardiac involvement(Magage et al., 2007). The hepatosplenomegaly and spinal deformity reduce lung volume in these diseases.

Several other inherited metabolic diseases involving nervous or neuromuscular systems, are usually progressive, and often cause chronic airway aspiration and respiratory infections. This is the case of some organic acidemias(Brandstetter, Weinhouse, Splaingard, & Tang, 1990) and several mitochondrial disorders.

In mitochondrial diseases, associated pulmonary manifestations include respiratory failure, recurrent sleep apnea, and pulmonary hypertension(Schapira, 2006). Respiratory failure may occur owing to muscle fatigue, either in the setting of exercise intolerance associated with lactic acidosis or from hypoventilation induced by events such as pneumonia. In aminoacidopathies (such as maple syrup urine disease), organic aciduria (such as methylmalonic or propionic aciduria), and urea cycle disorders (such as ornithinetranscarbamylase deficiency), respiratory symptoms are often the first, nonspecific sign of acute metabolic decompensation and tachypnea may be the presenting symptom, usually in the absence of other signs of pneumopathy.

In patients with mucoviscidosis, the chief symptom is the production of a thick, stickymucusthat clogs therespiratorytract and thegastrointestinal tract. This results in chronic respiratory infections. Chronic cough, recurrentpneumonia, and the progressive loss of lung function are the major manifestations of lung disease, which is the most common cause of death of persons with cystic fibrosis.

We will not go into more detail about the association of respiratory manifestations with IMD; other studies have focused on this axis and have described the most exemplary respiratory manifestations of inherited metabolic diseases in childhood and adulthood(Santamaria et al., 2013).

ARE IMDS PATIENTS MORE OR LESS SUSCEPTIBLE TO COVID-19 BASED ON REAL'S EXPERIENCES AND STUDIES?

Airways disease due to viral infections worsens the morbidity of many inherited metabolic disorders, leading to increased hospitalizations, mortality and overall healthcare costs. Faced with theCovid-19 pandemic, people with IMDs were categorized as high risk patients.However, based on few studies that have focused on IMDs and the Covid-19 pandemic, no studies reporting an increase in morbidity or mortality rate have been reported in these patients although they are subject to viral decompensations and suffer from respiratory complications related to their diseases as we pointed out above.Moreover, the European Reference Network for Hereditary Metabolic Diseases (MetabERN) hasshown that The COVID-19 incidence in the population of rare metabolic patients was lower than that of the general European population (72.9×100,000 vs. 117×100,000)(Lampe et al., 2020).

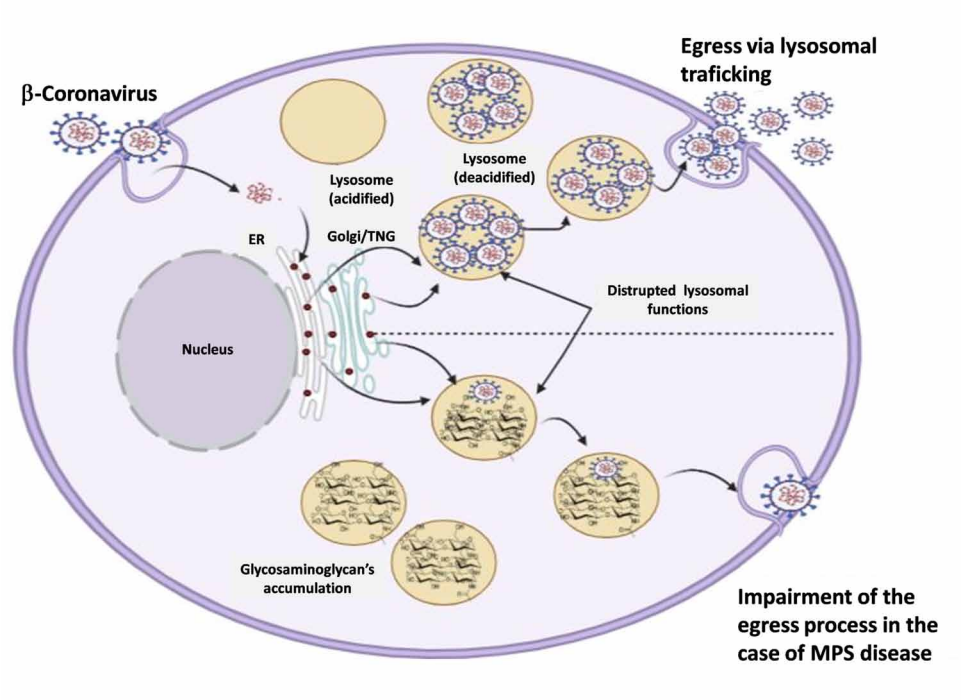
On the other side, It can be stated that some IMDs seem to prevent and moderate infection with Covid-19, in a previous article(Fdil et al., 2020), we have outlined the state of play in Morocco, particularly with patients with LSD, and we made several hypothesesto explain the absence of Covid 19 infections and/or asymptomatic infection in Moroccan patients with LSDs suchas a) proteases are partially or totally disrupted due to metabolites overload, b) compared to healthy people; LSDs patients have an "improved" immunity stimulated by overloaded metabolites, and c) the role of the gut microbiota in influencing Covid-19 disease in Fabry disease.

A study in 2009showed that the build-up of sub epiphyseal cartilage is speculated to be a direct consequence of cathepsin K inhibition by MPS I-associated GAGs which supports one of the hypotheses that we had formulated previously: proteases, which play an important role in the virus entry cell are partially or totally deactivated in patients with LSDs(Wilson et al., 2009).

In a recent study(Pierzynowska, Gaffke, & Węgrzyn, 2020), authors, using transcriptomic (RNA-seq) analyses in patients suffering from all types and subtypes of mucopolysaccharidosis, suggested that MPS cells might be less, rather than more, susceptible to Covid-19 infection by showing that four genes (GTF2F2, RAB18, TMEM97, PDE4DIP) coding for proteins potentially facilitating virus development were down-regulated, while two genes (FBN1, MFGE8), the products of which potentially interfere with virus propagation, were up-regulated in most MPS types. Moreover, Pierzynowska et al.(Pierzynowska et al., 2020), to explain the observation which reports that intact coronaviruses have been detected in lysosomal at late stages of infection(Ducatelle & Hoorens, 1984), demonstrated that β-coronaviruses egress from infected cellsis assured by tracking a path through lysosomal organelles, unlike other enveloped RNA viruses, whose egress tracks with the biosynthetic secretory pathway or directly buds out of the plasma membrane. The result of this study also confirms the low susceptibility of patients with LSD to Covid-19 infection.Indeed, lysosomal storagediseases caused by impaired degradation and resultant

accumulation of upstream substrates and intermediates in lysosomal(Figure 2), leads to dysfunction of lysosomal and possible impairment of Covid-19 egress process. This hypothesis suggests that there may also be a low susceptibility to Covid-19 infection in patients with the most common severe neurodegenerative disorders, like Alzheimer's disease, Parkinson's disease, and Huntington's diseasecaused by accumulation of misfolded protein aggregates.

Figure 2. The scheme of the possible influence of an LSD (mucopolysaccharidosis, as example) on coronavirus egress. MPS is a group of inherited metabolic diseases caused by impaired degradation and resultant accumulation of glycosaminoglycansin lysosomes. This accumulation leads to lysosome dysfunction and possible alteration of the coronavirus egress process. In both cases the lysosomal functions are disrupted, the fact that the egress virus occurs via the lysosomes may support the supposition that covid 19 itself is an inherited metabolic disease.



Keeping in mind these data and hypothesis above, it makes sense to reclassify IMDs taking the response to Covid-19 infection as a benchmark; two groups of patients should be considered in separate ways, the group of patients with LSDs, who seem to be more preserved than healthy people taking into account the assumptions above and the group of other IMD patients who are likely to be particularly fragile and at risk of life-threatening acute metabolic decompensation in case of Covid-19 infection. This category especially includes patients with defects of amino acid and organic acid metabolism, urea cycle defects, and disorders of carbohydrate and energy metabolism.

It should be noted that patients with LSDs who are under specific treatments and whose overload biomarkers are in the normal range, like Gb1, Gb3 and GAGs, in patients with Gaucher disease, Fabry

disease and MPS respectively, will be positioned as healthy people faced byCovid-19 and may show a prevalence of Covid-19 comparable with the general population

IS COVID-19 ITSELF AN INHERITED DISEASE OF THE METABOLISM?

Recent evidence suggests that susceptibility to severe respiratory distress and life threatening complications of Covid-19 could have a genetic background(David et al., n.d.; Van Der Made et al., 2020). To identify the potential genetic factors involved in the development of Covid-19 severe infection characterized by respiratory failure, a group of researchers conducted a genomewide association study involving 1980 patients with severe Covid-19 disease in Italy and Spain. They identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system(David et al., n.d.).Among the six genes at 3p21.31; SLC6A20 encodes the proline transporter SIT1.Ellinghaus et al showed that SIT1 interacts with angiotensin converting enzyme 2 (ACE2), the specific functional receptor for Covid-19(Ni et al., 2020; Vuille-dit-Bille et al., 2015).

Another team of researchers has identified, in case series of 4 young male patients with severe Covid-19, a rare putative loss-of-function variants of X-chromosomal Toll-like receptor 7*(TLR7)* that were associated with impaired type I and II IFN responses(Van Der Made et al., 2020). Such variants might affect immune function, as shown for some immune- disorders(David et al., n.d.). This result supports another study showing that some genetic variations in*TLR7*have been suspected responsible for the male sex bias in Covid-19, taking into account its localization on the X chromosome and its function in innate immunity(Scully, Haverfield, Ursin, Tannenbaum, & Klein, 2020).

Studies involving the TLR7 role in severe Covid-19 infection; were initiated and based on several studies carried out to decipher a susceptibility to severe viral infections such as influenza A(Pang, Pillai, & Iwasaki, 2013) and HIV(Oh et al., 2009) virus. In these studies, it has been shown, that the delivery of the TLR7 agonists prevented peak viral replication, bodyweight loss, airway and pulmonary inflammation, significant reduction in pro-inflammatory neutrophil chemotactic cytokines and prevented the increase in viral-induced lung dysfunction against influenza A, a virus-induced morbidity in mice, and that a functional TLR7 variant is associated with susceptibility to and a more severe clinical course of HIV-1 disease.

CONCLUSION

All these studies state that patients with severe Covid-19 infection, involving respiratory failure, have one or more genetic predispositions that can be used for screening as part of the initiation of preventive measures. Moreover, Coronavirus egress, mediated by the lysosomal exocytosis as shown in Figure 2, shows that the virus disrupts lysosomal functions just as accumulated metabolites do in a patient with lysosomal overload disease. Those, patients with lysosomal storage diseases are at lower risk of developing severe symptoms when infected with Covid-19, this data could be used to identify existing and future therapies for Covid-19 infection. Chaperone molecules and substrate reducers appear to be good candidates.

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Section 4

Management and Therapeutic Strategies of COVID-19

Chapter 13
Therapeutic Management of COVID-19 Patients: Pharmacological and Non-Pharmacological Approaches

Abdelaati El Khiat
Higher Institute of Nursing Professions and Health Techniques, Ouarzazate, Morocco & Ministry of Health, Morocco

Youssef Ait Hamdan
Interdisciplinary Laboratory in Bio-Resources, Environment, and Materials, Higher Normal School, Morocco

Lahcen Tamegart
Neuroscience, Pharmacology, and Environment Unit (ENPE), Laboratory of Clinical and Experimental Neurology, Morocco

Ahmed Draoui
Neuroscience, Pharmacology and Environment Unit (ENPE), Laboratory of Clinical and Experimental Neurology, Morocco

Abdessamad Aglagane
Laboratory of Biodiversity and Ecosystem Functioning, Faculty of Sciences, Ibn Zohr University, Morocco

Radouane El Fari
Higher Institute of Nursing Professions and Health Techniques, Dakhla, Morocco & Ministry of Health, Morocco

Halima Gamrani
Neuroscience, Pharmacology, and Environment Unit (ENPE), Laboratory of Clinical and Experimental Neurology, Morocco

ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCov-2) or COVID-19 is a pandemic that appeared in December 2019 in China and which is an RNA virus. It gave rise to a major health crisis at the start of 2020, with numerous hospitalizations. It was quickly important to understand the pathophysiology of this viral attack on the human body in order to be able to develop treatment. However, there is no vaccine or effective therapeutic agent against SARS-CoV-2. Most of the therapeutic strategies used to deal with this virus come from the work of previous epidemics of SARS, and other influenza viruses, such as antiviral therapies (chloroquine, hydroxychloroquine), adjuvant therapies by combining antivirals with drugs. Antibiotics or immunostimulants (vitamins C, Dm and Zinc, etc,) and several other therapies to be used depending on the region.

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INTRODUCTION

The Coronavirus (COVID-19) pandemic, which first appeared in December 2019 in China, is a global challenge, especially in the face of the rapid increase in the number of critically ill patients with pneumonia and the lack of effective and definitive treatment (Worldometers 2020).

However, the majority of therapeutic strategies used to deal with this virus have come from the work of previous epidemics of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS), an essential benchmark for all treatment options in patients with COVID-19 such as remdesivir (GS-5734), interferon, lopinavir / ritonavir, and convalescent plasma. In addition to these options, many other drugs are currently being used to deal with this pandemic (Nisole *et al.* 2020).

Currently, there is no effective treatment with a sufficient level of scientific evidence for SARS-CoV-2. Thus, the aim of this chapter is to focus on the most widely used therapeutic options in the world for the management of COVID-19,which aims to decrease virus replication, help the cell block the virus and / or reduce the harmful effects of the hyper-inflammatory reaction (Figure 1).

ANTIVIRAL THERAPIES

In the era of COVID-19, there is no effective antiviral treatment for SARS-CoV-2. Indeed, the majority of therapeutic strategies used to deal with this virus have come from the work of previous epidemics of SARS, and other influenza viruses, which provide an essential benchmark for all therapeutic options in patients with COVID-19. These treatment options are essentially antiviral drugs.

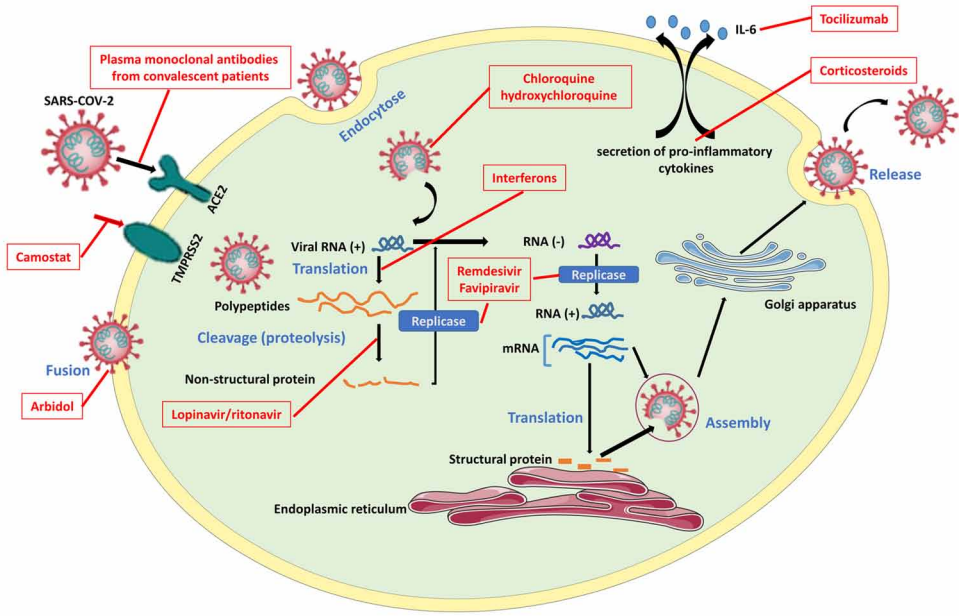
Chloroquine (CQ) and Hydroxychloroquine (HCQ)

One of the most frequently used treatment options for SARS-CoV-2 is undoubtedly chloroquine(Lecuit 2020). SARS-COV-2 has been shown to enter epithelial cells in the oral mucosa via the essential angiotensin-2 converting enzyme (ACE2) receptor by binding to the spike protein (S) virus.Therefore, it is accepted that ACE2 constitutes a functional receptor for SARS-CoV2(Wang, Cao, *et al.* 2020). Accordingly, one of the promising avenues for treating a viral infection like SARS-CoV-2 is to block this binding (Li *et al.* 2003).

Chloroquine is a molecule of the 4-aminoquinoline family used as a drug to prevent and treat malaria, but also it has effects which are qualified as antiviral. Indeed, due to its inhibitory effect on ACE2, it appears to be a potent inhibitor of SARS-COV-2 infection. In vitro, chloroquine has been shown to inhibit the fusion of ACE2 and virus at entry and post-entry stages (Wang, Cao, *et al.* 2020).Along with the antiviral activity of chloroquine, the latter has immune modulating activity in vivo and which can synergistically enhance its antiviral effect.Indeed, the results demonstrated in 100 patients with COVID-19 treated with chloroquine salts, have shown an improvement in pulmonary imaging, a shortening of the duration of the disease while inhibiting the exacerbation of pneumonia(Schrezenmeier and Dörner 2020).

Hydroxychloroquine, a derivative of chloroquine, is also an antimalarial drug. From a use point of view, hydroxychloroquine is used more than chloroquine; it is better tolerated, therefore preferable as a therapeutic option against COVID-19(Liu *et al.* 2020). It is an immunomodulatory widely used in the treatment of rheumatoid arthritis and systemic lupus erythematosus, which are rheumatic immune diseases.In vitro, it has shown an inhibitory action, which exceeds that of chloroquine against SARS-

Figure 1. SARS-CoV-2 replication cycle with the different molecules and their targets being evaluated to treat COVID-19. SARS-CoV-2 binds, via the S protein (for Spike); to the ACE2 receptor expressed on the surface of target cells, and then penetrates by endocytosis or by direct fusion to the plasma membrane. The serine protease TMPRSS2 is also involved in the entry stage of the virus, by allowing the priming of the S protein. After release of the genomic RNA in the cytoplasm, this is translated into polypeptides, which, cleaved by viral protease, make it possible to generate non-structural proteins, which form the replication / transcription complex (replicase). The genomic RNA with positive polarity (+) is then transcribed into complementary viral RNA with negative polarity (-), which serves as a template for the synthesis of genomic and subgenomic RNA, translated into structural proteins. Genomic RNA and structural proteins will then assemble in the endoplasmic reticulum. The newly formed viruses are then transported via transport vesicles to the Golgi apparatus and then to the cell surface, where they are released. Potential SARS-CoV-2 inhibitors and their known or predicted targets are indicated by rectangles at different stages of the viral cycle(Nisole et al. 2020).



COV-2. Currently, several clinical trials of hydroxychloroquine in the treatment of Covid-19 are under development and could provide important arguments on the effectiveness of hydroxychloroquine(Wang, Cao, *et al.* 2020).

Remdesivir

One of the most widely used treatment options for SARS-COV-2 is remdesivir (GS-5734). It is a new nucleoside analogue that has been recognized as a potential antiviral agent against many RNA viruses, including SARS-COV-2. In mice, remdesivir has shown significant efficacy, which results in the inhibition of RNA polymerase (RNA-dependent MERS-CoV)(Gordon, Tchesnokov, Woolner, *et al.* 2020), and in the reduction of virus replication, which leads to a decrease of the virus in lung tissue in mice infected with MERS-CoV and there is an improvement in damage to lung tissue(Sheahan *et al.* 2017).

Besides, remdesivir has good tolerance. Indeed, in the therapeutic setting of Ebola virus disease, prolonged use of remdesivir has not shown any danger for patients with Ebola virus(Gordon, Tchesnokov, Feng, *et al.* 2020). The fact that remdesivir is one of the best treatment options with better tolerance, it is the subject of more than 6 randomized, double-blind clinical trials underway to evaluate its effectiveness in hospitalized patients with COVID19 respiratory disease in different situation, mild, moderate, or severe(TRAORE *et al.* 2020).

Lopinavir/Ritonavir

Lopinavir / ritonavir complex is a frequently used protease inhibitor as a treatment option in the treatment of HIV infection(Sham *et al.* 1998). In vitro, this complex has also shown efficacy against COVID-19, by inhibiting the replication of the virus. It has been shown that the combination of lopinavir / ritonavir complex with ribavirin, compared to ribavirin alone, could be used in prophylaxis against SARS-COV-2(Chu *et al.* 2004).In adult hospitalized patients with severe COVID-19 Cao *et al.*(2020)have shown in a randomized clinical trial that lopinavir / ritonavir has no beneficial effect.In addition, treatment with lopinavir / ritonavir has many more related side effects, such as anorexia, nausea, abdominal pain, diarrhea or acute gastritis, thus, the risk of liver damage, pancreatitis, severe skin rashes and acute kidney damage(Cao *et al.* 2020).Therefore, the results of ongoing clinical trials involving treatment with lopinavir /ritonavir could help to better understand the benefits and risks of this molecule.

Umifenovir

This medicament is used for the treatment and prophylaxis of influenza and other respiratory and pulmonary infections(Pécheur *et al.* 2016). It is an indole-based antiviral agent; it has also shown inhibitory activity against hepatitis B and C viruses. In vitro, umifenovir appears to have effective antiviral activity against the pathogen of SARS, and that its derivative (arbidol mesylate) was five times greater in effect than umifenovir in decreasing the reproduction of SARS in cells. Therefore, umifenovir appears to have an effective action against SARS-COV2(Wang, Yang, et al. 2020).

Favipiravir and Ribavirin

Favipiravir and ribavirin are two nucleoside analogs, which are one of the antiviral treatment options from previous outbreaks of SARS and MERS (Furuta *et al.* 2017). These analogs have an antiviral effect through the mechanisms of lethal mutagenesis, chain termination and inhibiting nucleotide biosynthesis. The combination of favipiravir and oseltamivir in the treatment of severe influenza virus may accelerate clinical recovery more than oseltamivir alone(Wang, Yang, et al. 2020).In addition, the combination of ribavirin and interferon alpha (IFN-α) significantly reduced mortality at 14 days after treatment in critically ill patients infected with MERS(Kim *et al.* 2016).This combination is also used in the treatment of SARS, ribavirin and IFN-α. However, this combination does not seem to be a better therapeutic option for COVID-19, and in addition, the tolerance of ribavirin is much lower and therefore any uses of this option must be elucidated by clinical trials(Traore*et al.* 2020).

Other Antiviral Treatments

There are several other antiviral treatments prescribed for SARS-COV-2, including oseltamivir (Tamiflu). It is a drug used for the treatment of influenza A and B. Unfortunately, there is very little evidence for the therapeutic use of this molecule against SARSCOV-2(Tan *et al.* 2020).

ADJUSTING THERAPIES

Antibacterial Therapy

In patients with pneumonia, cross infection of bacterial pathogens like *Staphylococcus aureus* may be encountered, especially those in severe condition during medical treatment in hospital. For the diagnosis and timely intervention of bacterial infection, in patients with COVID-19, it is necessary to test the kinetics of pro-calcitonin (PCT) and protein C reactive (CRP)(Traore*et al.* 2020). So, in patients with severe viral pneumonia (extensive pneumonia, respiratory failure, hypotension and fever), in 2018, the American Society of Infectious Diseases (IDSA) has recommended the administration of antibiotics in addition to antiviral therapy. Thus, antibiotic treatment is recommended in the treatment of COVID-19 patients(Uyeki *et al.* 2019).

Azithromycin

Azithromycin is a macrolide with immunomodulatory properties used as an add-on therapy. Azithromycin is one of the most widely used antibiotics. This is because macrolides can downregulate inflammatory responses and lower the excessive production of cytokines associated with respiratory viral infections(Fiolet *et al.* 2021). These mechanisms in principle require the decrease in the accumulation of leukocytes in the lung tissue and bronchoalveoli, with the greatest reduction in the number of neutrophils.Several studies have evaluated the chloroquine/azithromycin therapeutic option in the management of Covid-19, and as we have already reported; chloroquine combined with azithromycin act at the level of receptors for the converting enzyme ‘angiotensin-2(Lagier *et al.* 2020).However, the results of these studies on the effectiveness of this therapeutic option are being evaluated to decide on this question. Thus, the tolerance of this therapeutic option must be taken into account from the point of view of the vigilance observed.

Anticoagulants

Patients withCOVID-19 have a significant risk of coagulopathy. This bleeding disorder is due to an increase in D-Dimers and is associated with an increase in mortality in patients as well.Indeed heparin, having anticoagulant and anti-inflammatory properties, may be relevant in this direction. Many studies have shown that heparin can lower the level of inflammatory biomarkers and improve the health of patients.Heparin treatment may therefore be helpful in alleviating pulmonary coagulopathy(Tagami *et al.* 2014).A meta-analysis noted that adjunct therapy with low molecular weight heparins (LMWH) may somehow decrease the risk of 7-day mortality by 48% and the risk of 28-day mortality by 37%, but also it considerably improves the PaO2 / FiO2 ratio. Therefore, heparin may prove beneficial in patients with COVID – 19(Traore*et al.* 2020).

Vitamins and Micronutrients

Vitamins C, D and zinc may play a crucial role in strengthening the immune system of patients with COVID-19. Vitamins C and D play essential roles in immunity. This is because vitamin C is involved in several aspects of immunity, including the growth, function of immune cells and the production of antibodies. However, the use of vitamin C puts the patient at risk of calcium oxalate urolithiasis in case of overdose(Urivetzky *et al.* 1992).Some studies are currently underway to assess the importance of using vitamin supplementation in COVID-19 patients(Traore*et al.* 2020).

Zinc is an essential micronutrient. It has developed effective antiviral activity with strictly regulated systemic and intracellular concentrations. Indeed, it has been approved that zinc blocks the activity of RNA polymerase (Hepatitis E virus-dependent RNA)(Kaushik *et al.* 2017).In addition, there is a blockage of coronavirus replication, in vitro, established after the use of zinc ionophores. Authors have hypothesized that effective zinc supplementation with the combination of chloroquine or hydroxychloroquine during treatment of COVID-19 may result in more effective inhibition of intracellular replication of SARS-CoV-2, thereby improving clinical outcomes of COVID-19 patients(Derwand and Scholz 2020).

In addition to these treatments and although not recommended by WHO, ibuprofen and indomethacin were non-steroidal anti-inflammatory drugs (NSAIDs) commonly used as adjuvant therapy in some protocols. In addition to NSAIDs, colchicine, another anti-inflammatory was also used(Deftereos *et al.* 2020).

Immunomodulators

Many types of molecules are implicated in modulation of immunity response to SARS-CoV-2 infection such as corticosteroids, Tocilizumab, Interferons, Gamma-globulin and convalescent plasma:

Corticosteroids

Different studies have discussed the use of corticosteroids in the treatment of SARS-CoV-2. Clinical study mentioned that Dexamethasone (corticosteroid) reduced the risk of death by up to 35% in patients placed on mechanical respiratory assistance, and by 20% in those who only needed oxygen (Horby *et al.* 2020). In addition, another clinical study revealed that corticosteroids like hydrocortisone, dexamethasone or methylprednisolone thanks to their potent anti-inflammatory effects which could limit the cytokine storm, and decreasing the mortality in severe and critical forms of Covid-19 (Sterne *et al.* 2020). Despite all these effects, WHO has recommended not to use corticosteroids for the treatment of viral pneumonia or SAR-CoV-2 (Mondiale de la Santé 2020).

Tocilizumab

The increased levels of cytokines such as IL-6 is one of the most important symptoms in patients with Covid-19 (Chen *et al.* 2020). Tocilizumab is a monoclonal antibody that inhibits signaling induced by IL-6 and binding to soluble IL-6 membrane receptors. IL-6 is a pro-inflammatory cytokine involved in various physiological processes such as activation of T lymphocytes, induction of immunoglobulin secretion. It is produced by lymphocytes and monocytes (Le *et al.* 2018).

Interferons

Interferon (IFNs) is a protein naturally produced by our body and more specifically by the cells of our immune system. However, the researchers noticed that the amount of interferon in the body of Covid-19 patients fell sharply. Studies revealed that type I IFNs could inhibit the replication of SARS and MERS-CoV (Morgenstern *et al.* 2005, Mustafa *et al.* 2018).

Gamma-Globulin

There is no convincing argument to recommend the intravenous gamma globulin in the treatment of Covid. In addition, studies have not found a reduction in mortality with intravenous gamma-globulin in patients with severe sepsis (Werdan *et al.* 2007, Alejandria *et al.* 2013).

Convalescent Plasma

Convalescent plasma derived from patients with antibodies against COVID-19 may be effective in reducing the death of patients with viral diseases (Marano *et al.* 2016). It turned out to have a potential effect for the treatment of MERS, SARS and Ebola virus disease (Soo *et al.* 2004, van Griensven *et al.* 2016). In addition, WHO suggested the use of plasma or convalescent serum when vaccines and antivirals were not available for an emerging virus (mondiale de la Santé 2014).

CONCLUSION

Patients with COVID-19 are receiving all standard treatment aims at maintaining vital signs. In addition, numerous scientific and clinical trials aim to improve the course of their disease while targeting the virus, cell or inflammatory reaction of the host. Currently, there is no effective treatment of any drug or specific antiviral vaccine for COVID-19 that will eliminate the virus altogether or stop the symptoms of the disease. All treatment options available today are based on experience with treating SARS, MERS, or some other previous influenza viruses. In the absence of tangible evidence of effectiveness and in the context of the epidemic emergency, some of these options were adopted. For a better understanding of this new virus, some further research should be done to obtain optimal strategies for the treatment of COVID-19.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Chapter 14
The Study of Traditional Medicine for the Treatment of COVID-19

Ranjit Barua
https://orcid.org/0000-0003-2236-3876
CHST, Indian Institute of Engineering Science And Technology, Shibpur, India

Sudipto Datta
Indian Institute of Engineering Science And Technology, Shibpur, India

Pallab Datta
National Institute of Pharmaceutical Education and Research, Kolkata, India

Amit Roy Chowdhury
Indian Institute of Engineering Science And Technology, Shibpur, India

ABSTRACT

SARS-CoV-2 is a novel virus communicable disease affected by serious acute respiratory condition coronavirus 2 (SARS-CoV-2) which goes to the family of coronavirus. December 2019, in Wuhan, China, the first case of novel coronavirus was reported, and this widespread virus globally became a pandemic. Various studies show that drug applicants are used as antivirals or immune modulators. Yet, the outcome of this examination reported the drug applicants were not ominously operative in contrast to the infection. In the interim, it's believed that taking herbal immune-modulators can avoid and/or resist COVID-19. Unluckily, definite clinical and preclinical trials to assess the special herbal immune regulators' effects have not been directed. Specific natural elements might be actual for treating COVID-19 built on universal thoughts from former tests. Though there are no exact anti-COVID-19 medicines as well as a drugs until now, the use of traditional medicine and epidemiology of novel coronavirus disease will be discussed for COVID-19 treatment.

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INTRODUCTION

After the contact of the virus with the humans in mid-December 2019 in Wuhan, China, WHO was reported officially by Chinese government the about the first case on 31st December 2019 where a patient was detected with a severe pneumonia. Later many humans were infected so drastically and rapidly as they were also suspected of the same virus on the following days which soon published online as a novel corona virus on 9thJanuary 2020. The COVID-19 emergence about 5 months' have established the quick step to the virus spread as well as the development of science. Initially the infection rate plot was flat with the rapid spread of the infection rate worldwide the curve resembled exponential curve. Maximum cases are mainly from Wuhan, central China i.e. the epicenter of the novel virus. The population of Wuhan city is approx. 11 million. The patients who were diagnosed were having symptoms like fever, dry cough, lung infiltrates on imaging and dyspnea. All the presented patient cases were found to be linked to the sea food market at Wuhan which sells many types of species of animals like snakes, marmots, poultry, bats and many more unknowns to human eating menu (Lu et al., 2020). Throat swag was used to identify the causative agent which was conducted by CCDC i.e. Chinese Centre for Disease Control on 7th Jan 2020 which was named as SARS-CoV-2 i.e. Severe Acute Respiratory Syndrome Coronavirus 2 which later named as COVID-19 by WHO (WHO, 11 Feb, 2020) as the virus was first reported on late 2019. Many other countries also reported COVID-19 cases the cases were linked to the travel history to China which helped the virus to travel to other countries within a short period of time, currently many cases are also found without travel history to China. Here in this article we shall display and highlight the known knowledge of the novel virus and we shall give a rough idea i.e. 10 key questions and the way of this novel study of the virus. The patient who are infected with this novel virus showed common symptoms like sore throat, fever and dry cough among which maximum number of cases resolved after period of time with various drug treatments but minority of cases were critical which includes septic shock, extreme pneumonia, ARDS (Chen et al., 2020) i.e. Acute Respiratory Distress Syndrome, severe pneumonia and organ failure etc. In this critical category of 54.3% of infected were male with average age of 56 years. The intensive care support was required were for old aged patients having many comorbidities like cerebrovascular, respiratory disease, endocrine, digestive and cardiovascular etc. The patients in intensive care unit mostly reported dizziness, anorexia, dyspnea and abdominal pain (Wang et al., 2020, Barua et al., 2021).

NOVEL CORONA VIRUS (COVID-19)

The novel virus resembles many specifications of the family of coronaviridae family known to human. This novel corona virus i.e. COVID-19 has single RNA strand. The meaning of "Corona" is crown which is a latin word as because the outer covering of the virus has spikes which resembles like crown. These family of virus have history of causing MERS-CoV and SARS-CoV (CCDC.,March 25, 2020). The SARS-CoV virus was first reported in 2002 which was spread in the whole world as reported by CDC i.e. Centers for Disease Control and Prevention 2020 (CCDC., March 30, 2020). The mode of transmission of this virus was by person to person through droplet. On the other hand(Hijawi et al., 2013), MERS-CoV was was first reported in September 2012 in Saudi Arabia. By doing investigation on MERS-CoV it was found the MERS was originated in Jordon, 2012 April as reported by Hijawi et al. 2013. MERS-CoV is spread by person to person through sneezing and coughing. Though, the cor-

rect mode of transmission of MERS is still not known (CCDC., March 25, 2020). RNA genome single stranded of size 30-kb are found in coronaviruses. This genome can be divided into a 3′ third and 5′ two-thirds. For the production of new virus genetic material, the first two-third genome code for the two huge polyproteins (pp1a and pp1ab from ORF1a and ORF1b) which are proteolytically slashed into the nonstructural proteins (nsp1 to -16). The remaining of the genome codes the structural proteins as well as transmits the accessory genes which generates virions as well as change the response of the host, correspondingly (de Wit et al., 2016). From the name the novel virus resembles 80% with the SARS as level of nucleotide. This close family member of the SARS-CoV is likely found in the bats which is named as RaTG13-2013 which is 96% identical. This virus emerged in the human population through bats directly of by an intermediate animal which helped the virus to pass from bats to humans (Zhou et al., 2020). More similarities are with the spikes protein which uses ACE2 for surface receptor of cells (Barua et al., 2021, Li et al., 2003) of the virus with the SARS-CoV. The virus uses these spikes to infect the ACE2 of the ciliated human lung epithelial cell which acts like a lock and key which helps the virus to attach with the specific receptor of the specific epithelial human lung cell. The virus spreads rapidly and easily in the human population. With days passes by many healthcare workers, nurses, doctors are being infected where came in close contact with the COVID-19 patients. The virus reproductive number also known as RO number is presently 3 (Liu et al., 2020), which is showing the possible for constant person to person transmission which is through potentially a fecal-oral route and respiratory droplets (Barua et al., 2021, Zhang et al., 2020).

EPIDEMIOLOGY OF COVID-19

COVID-19 the novel corona virus mainly infects the respiratory system; though other organs are also related with it. The symptoms of the lower respiratory tract infection are dry cough, dyspnea and fever which were the primary common symptoms which were reported in Wuhan, patient (Huang et al., 2020). Along with these symptoms other less common symptoms which were also reported are as follows dizziness, headache, diarrhea, vomiting and generalized weakness (Shi et al., 2020). The respiratory symptoms related to the virus are non-specific it varies from person to person the symptoms are mostly heterogeneous which varies from mild symptoms to noteworthy hypoxia along with ARDS. The incubation period i.e. the time at which the virus infected the human lung cell until the development of any symptoms and ARDS development is 9 days approx. which shows that the symptoms can progress very quickly (Huang et al., 2020). This disease can be very deadly. The number of cases growing worldwide very rapidly. The morality rate is more for older aged patients (Zhou et al., 2020) compared to younger patients which is also much lower in younger children as shown by epidemiological studies (Verdict Medical Devices, 2020,Zhonghua et al., 2020). There is not specific medicine till date for combating the virus so other antiviral drugs are mixed and applied to the patients many of which showed positive results. Various antiviral drugs like hydroxyl-chloroquine, azithromycin, remdesivir and lopinavir-ritonavir are being tested clinically (Cao et al., 2020) (Gautret et al., 2020) but neither of them are specific for the novel virus. Many countries have taken various strategies to flatten the exponential infection graph i.e. reduction of the infection rate by lockdown and social distancing. In this review article we shall discuss our present knowledge of the novel virus and study the primary method to clarify the heterogeneous symptomatology, mainly highlighting among the adult and children patients. Officially WHO declared the novel Chinese outbreak virus COVID-19 publically worldwide on January 30th,2020. WHO declared

the Public Health Emergency of International Concern posturing a high level risk to the countries with weak healthcare facilities. The breaking-up of the COVID-19 virus spreading chain can be done by isolation, robust system implementation to trace contacts, early detection and prompt treatment was stated by the emergency committee (Barua et al., 2021). Other planned aims contain the transmission extent, clinical severity ascertaining and treatment option optimizing. The mail objective is to reduce the virus economic impact as well as to stop misinformation on the worldwide scale (Zhou et al., 2020). Because of these reasons many agencies have devoted for creating articles relating to the novel coronavirus urgently accessible through open access for the support of global unified response (Huang et al., 2020). After the virus outbreak in Wuhan, China the virus spread rapidly worldwide within few months. As from the report on April 2020 the most number of infected patients is from U.S followed by various other Europian countries Spain, Italy, Germany and China. After China the most affected country with maximum number of death was Italy. The death rate like China was same in Italy for the older peoples. Case-Fatality rate was 7.2% from Italy (Onder et al., 2020) (Livingston et al., 2020) which was 3 times higher than China. Though the fatality rate of patients more than 70 years of age in Italy was more compared to the China which was almost similar in both the countries of age between 0 to 69 years of age range. This was because 23% of the patients in Italy was of age range 65 plus this was explained by the demographic characteristics. Other countries data are also available from various sources (Zhou et al., 2020) (Dong et al., 2020). In the coming days we can expect to know more from the respective countries about the virus.

TRANSMISSION OF COVID-19

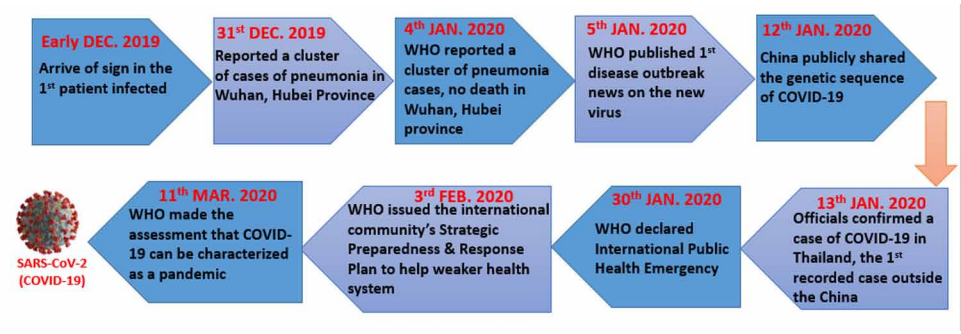
As we all know the origin of the novel virus was from the Huanan Seafood Wholesale Market of Wuhan, Seafood market so we can predict that the virus came from animal to human population through this Seafood marked. However, further cases were not linked with this mechanism of exposure. Hence, it can be concluded that the virus spread through human to human also as well as from the symptomatic patients who are also the virus transmission carrier. As the virus can spread from the asymptomatic patients i.e. before the appearance of any symptoms, isolation is the only solution to cut-off this mode of virus transmission. Like other respiratory infections like rhinovirus and flu the mode of transmission of this novel virus as also be leaved to be through respiratory droplets having particle size less than 5-10 μm in diameter by sneezing and coughing. Transmission through aerosol is also possible in case of closed space where elevated aerosol concentrations are present. For spreading of this virus close contact is necessary for transmission as data studied from China. Among these asymptomatic patients are the primary carrier of the mode of transmission upto 80% cases. This kind of virus transmission occurs between family members, close contacts and healthcare professionals who came in close contact of like 6 feet i.e. 1.8-meter approx. range of the patient. The presence of the virus on various surfaces was studies and was found out that the virus stays alive on plastics for 2-3 days, copper surface for 4 hours, cardboard surface for 1 day and on stainless steel surface for 2-3 days. From study it is also found out that the virus is found more in the ICU i.e. intensive care unit than the general wards moreover the virus can be found on pc mouse, trash cans, 4 meters' air of the patients, sickbed handrails and floor (Guo et al., 2020). From various case studies from China the incubation period of the virus was investigated by Chinese CDC i.e. Centre for Disease Control and Prevention as well as by local CDSs. From the investigation it was found out that mainly 3 to 7 days is the incubation period of the virus. Resembling to

SARS whose average incubation period was 5.1 days approx to maximum of 2 weeks as 12.5 days was the longest incubation days recorded for the novel coronavirus (Li et al., 2020). The data also showed that the double of the epidemic occurred at about 7 days while the simple reproduction number was 2.2 (R0 - R naught). We can say from the data that in average one patient can transmit the infection to almost 2.2 individuals. The 2002-2003 epidemic SARS-CoV R0 was 3 approx. (Bauch et al., 2005).

COVID-19 SYMPTOMS AND PRESENT WORLD'S CONDITIONS

On December 31, 2019, Health Commission of Hubei province initially reported about a number of patients with unknown etiology of pneumonia (Barua et al., 2021). Fig.1 shows the worldwide time line of COVID-19 outbreak. Initially 27 patients were detected with a symptoms of suspicious disease and later on the graph rose to 41 with seven severely ill patients. On 11th of January, 2020, one death was reported in the consequent report (WHO, 27th April, 2020). The Chinese administration reported to World Health Organization (WHO) that few of the patients were workingas vendors or dealers in the Huanan seafood market at Wuhan city, which was later informed to be vendingfresh live slaughtered animals (Chan et a., 2020) (Zhou et al., 2020).

Figure 1. Worldwide timeline of COVID-19



Various reports were informed about clusters of cases among families and the human to human transmission of the unknown virus was detected when the health workers were infected (Wang et al., 2020) (Phan et al., 2020). Most COVID-19 infected patients had a past history of being in connection with virus infected patients or contaminated surface orthe virus carriers. Additionally, the virus infected peoples have mutual symptoms related to common cold like cough, fever, fatigue, dizziness, and sometimes the breathing problems in vital cases. Pneumonia with respiratory problems and shocks (rarely noticed)were the most common symptoms detected in the infected patients (Du et al., 2020). The problems detected with the patients of COVID-19 are as follows:

i. Headache
ii. Dry Cough
iii. Hemoptysis
iv. Fever

v. Muscle Pain
vi. Sneezing
vii. Hemoptysis
viii. Diarrhea

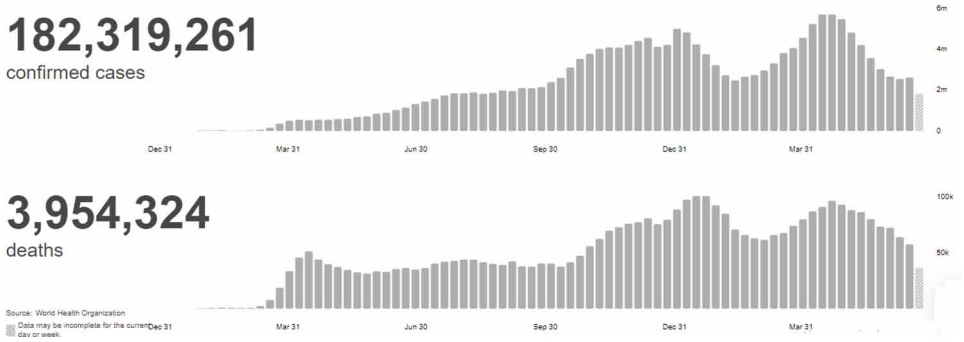
Types of COVID-19 patients are given below in Table 1.

Table 1. Types of COVID-19 patients

Serial Number	Types	Descriptions
1	Mild	Detection of digestive problems like vomiting, nausea, abdominal pain and diarrhea or infection in acute upper respiratory tract like cough, runny nose, sneezing, fever, myalgia, fatigue etc.
2	Moderate	Symptoms of pneumonia with frequent fever and cough without any hypoxemia.
3	Critical	Symptoms of pneumonia with hypoxemia and ARDS (Acute respiratory distress syndrome), heart failure, shock, myocardial injury, encephalopathy, severe kidney injury.
4	Asymptomatic	Detected COVID-19 without any clinical suspects.

Till date2nd July, 2021, there are 182,319,161confirmed COVID-19cases and 3,954,324death cases (Fig. 2). Sincein comparison of COVID-19 cases (Fig. 3), in Americas there are 72,480,288confirmed cases; in Europe 56,083,678; South-East Asia 35,037,801;Eastern Mediterranean 11,022,816; Africa 4,102,610; Western Pacific 3,591,304.

Figure 2. COVID-19 confirmed cases referred by WHO (Data last updated: 5:41pm CEST, 2 July 2021)

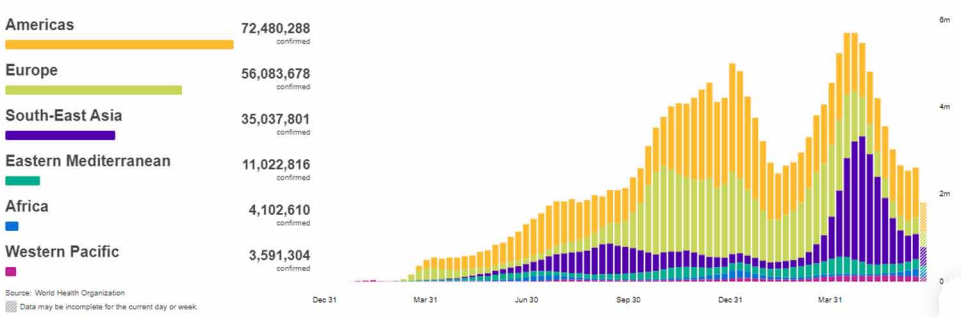


The confirm cases of the individual countries affected are given belowin descending (high to low) order (Table. 2):

Table 2. Top Five Countries name on the basis of the confirmed cases referred by WHO(5:41pm CEST, 2 July 2021)

Serial Number	Name of the Country	Number of confirmed cases till date 2nd July, 2021
1	United States of America (USA)	33,343,961
2	India	30,458,251
3	Brazil	18,557,141
4	France	5,667,087
5	Russian Federation	5,561,360

Figure 3. COVID-19 confirmed cases of different countries referred by WHO (Data last updated: 5:41pm CEST, 2 July 2021)

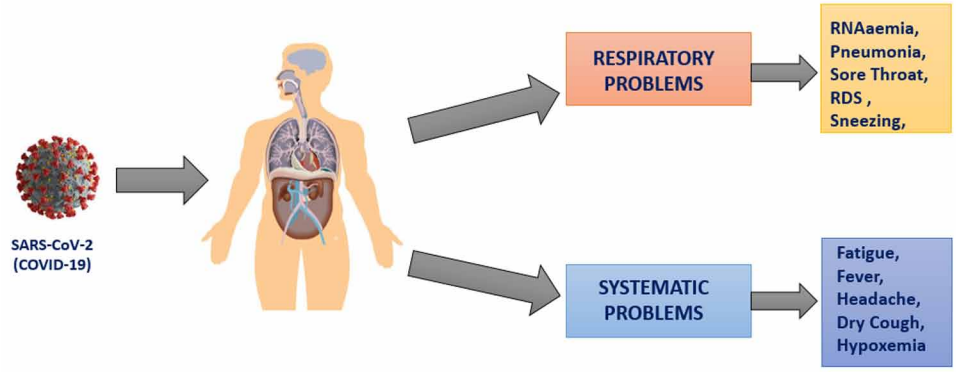


PATHOGENESIS FEATURES OF COVID-19

In case of Covid-19, all age groups are at risk. The Covid-19 virus can be transmitted by the production of large droplets of cough and sneeze of effected person; it can also be transmitted through an asymptomatic person (WHO, 22nd March, 2020).Infected person carries virus till he/she clinically recovers. The virus filled droplets can travel up to 3m and then deposit on contact area. In favorable atmospheric condition, virus can sustain for days but can be destroyed by some disinfectants like hydrogen peroxide and sodium hypochlorite.Various symptoms, for example, dry cough, fever, sneezing, muscle pain, fatigue, sore throat, dyspnea, headache and respiratory difficulties are occurreddue to COVID-19 infection (Fig. 4). The virus infection can be either occurred by coming in contact with the virus contaminated surface and then touching the eyes, nose and mouth or it can happen due to the inhalation of virus filled droplets. It is also assumed that the virus can be found in the stool, virus infectionin water source and consequentflowthroughaerosolizationorfeco-oral route (Zhou et al., 2020). The virus incubation period fluctuatesbetween 2 to 14 days (average 3–7 days). Studies have found that the virus effects the respiratory mucosathrough angiotensin receptor type 2. Various modeling studies shows the estimated reproduction rate from 2 to 6.47 (WHO, 22nd Feb, 2020) (Kampf et al., 2020). The characteristics of COVID-19fluctuates from asymptomatic phase to ARDS which is known by acute respiratory distress syndrome, also dysfunction of the multi-organ. Few of the common Covid-19symptoms are cough, sneeze, headache, fever, sore throat, myalgia, fatigue, and shortage of breath. By the end of 1st week, the

virus can proceed to pneumonia, shortage of breath and death. The advance case is related with dangerous inflammation of cytokines together with interleukin (IL) of IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A, and also tumor necrosis factor-alpha.(Cheng et al., 2020). The average time from the beginning of virus infection to progress of dyspnea was 5 days, hospitalization was 7 days, and was 8 days.The published studies show that the 15%–25% of the virus affected patients are kept in the ICU (Intensive Care Unit). Problemsinvolves ARDS (Acute Respiratory Distress Syndrome), shock, headache and acute kidney problem. In the 2nd or 3rd week, the infected person started to recover. The averagetime of staying in hospital for the people who recovered was ten days. Basically deaths are more common in elderly infected person and the person having low immunity. The casualty rate in hospitalized agedpersons was 4% to 11%. The ultimate casualty rate is approximated between 2% and 3% (WHO, 22nd Feb, 2020).

Figure 4. The effects of COVID-19 infection



COVID-19 PREVENTION

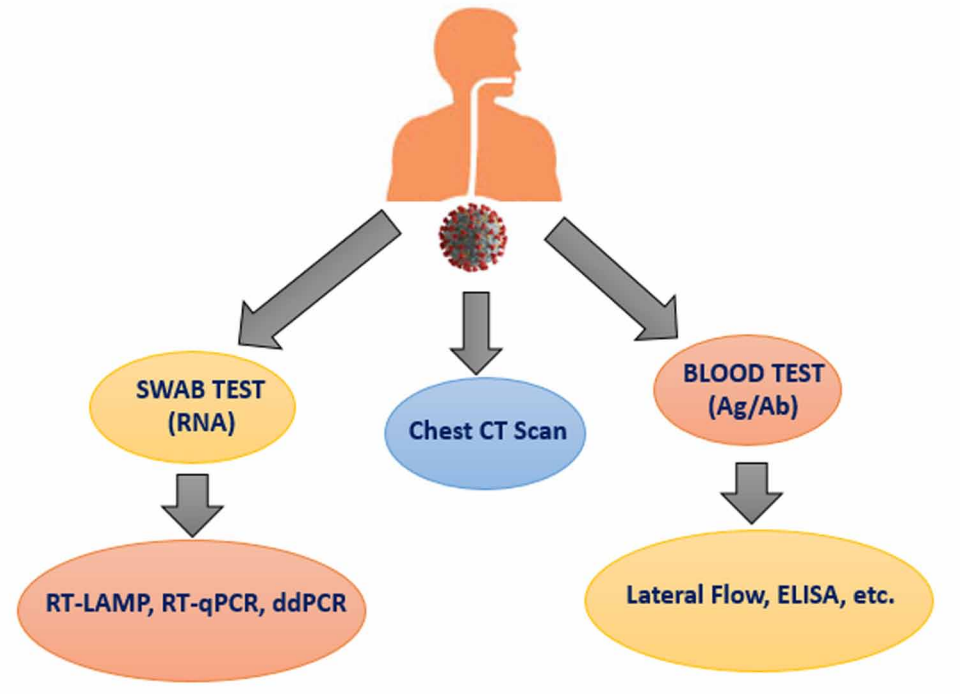
Several organizations including the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have given someguidance on avoidingadditional spread of COVID-19(WHO, 2020) (CDC, 2020). They advised to avoid highrisk zones, interaction with the infected and suspected person. It is important to maintain the hygiene by taking few measures as suggested like frequent hand wash by soap or alcohol based sanitizer, using of PPE like face masks, face guard and gloves.COVID-19 effected the normal lifestyle and other social activities like cultural program, sports, (Barua et al., 2021) etc. Bespoke Inc (Japanese company) has introduced an AI (artificial intelligence) powered chat-bot named Bebot which giveslatest information about the COVID-19 outbreak, precautions that can be taken, in addition to a symptom checker (Bespoke, 2020).

DIAGNOSIS OF COVID-19

The main characteristics of a COVID-19 suspect is fever, cough, sneeze, sore throat and shortage of breath, who have a past travel history with China or other infected areas or interaction with other persons

with same travel history or persons with infected of COVID-19.It was reported that on forty-onecomplete cases of COVID-19infection who were taken to admit at Wuhan Hospital which shows that cough (76%), fever (98%), dyspnea (55%), fatigue (44%), muscle pain which are the most existing signs and indications (Huang et al., 2020). These results were documented by another Chinese report (Chen et al., 2020). In difference to persons with typicalCorona Virus infections, some of theminfected with the Novel Corona Virus or COVID-19 had respiratory problem especiallyupper respiratory tract symptoms and indications like rhinorrhea, sore throat etc.Though, some cases can be asymptomatic case or may be without fever. Nanotechnology (Barua et al., 2020) has now been engaged in the analysis and diagnosis of COVID-19.With the help positive molecular test, confirmed case can be determined. Fig. 5 shows the several diagnostic approaches presented for the identification of COVID-19. Exact diagnosis is done by particular molecular tests on different respiratory samples like nasopharyngeal swab, oropharyngeal swab, Broncho alveolar lavage, sputum and endotracheal aspirates. Virus may also be noticed in the patients' stool and sometimes inblood (severe case).

Figure 5. Different diagnostic procedures for COVID-19 detection



Two different studies reported that the CT (computed tomography) and Chest X-ray image where it is shown that the involvement of bilateral lungis 114 (81%) of 140 assured patients (Huang et al., 2020) once morerelated to infection with typical SARS-CoV. Out of these one forty cases, sixty one cases had lymphopenia; fifty eight cases had an advancementof either AST (aspartate aminotransferase)or ALT (alanine aminotransferase) beyond the higherboundary of the reference limitwhich can also notice in typical corona virus (SARS-CoV). Between the infected patients most of the individuals' have their

normal procalcitonin levels where as the secondary infected patients were observed with elevated levels (Chen et al., 2020) Though, C-reactive protein levels and elevated serum ferritin were reported in 86% and 63% respectively. Like in diagnosis of SARS-CoV infection, rise in the plasma pro-inflammatory cytokines levels was noticed, comparing with the importanceof the illness (Wong et al., 2004). Though, rise in the interleukin 10 level is an anti-inflammatory cytokine, recommend a different pattern from the SARS-CoV infection (Neumann et al., 2019).The World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC) both have generateda guidance on clinical feature and epidemiological risk which are given in Table. 3 and 4.The suspected people should be given the facility of lab examination. Infected people may have erythrocyte sedimentation rate, elevated C-reactive protein, creatinine, lactate dehydrogenase and anelongatedprothrombin time (Wang et al., 2020).COVID-19 infection can be confirmed with the help of phylogenetic analysis and full genome sequencing on fluid from bronchoalveolar lavage (Zhu et al., 2020). Respiratory pathogens investigations should also be analyzing.

COVID-19 TREATMENT

As there is no confirmed treatment and approved vaccination available and therefore the treatment is basically symptomatic and supportive. The initial step is to keep oneself isolate from others to prevent the transmission to other non-infected people. If a person suffers from mild illness should be at home and if any danger symptom noticed, should consult a doctor. The main focus should be on maintaining

Table 3. A clinical feature comparison between World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC) (WHO, 2020) (CDC, 2020)

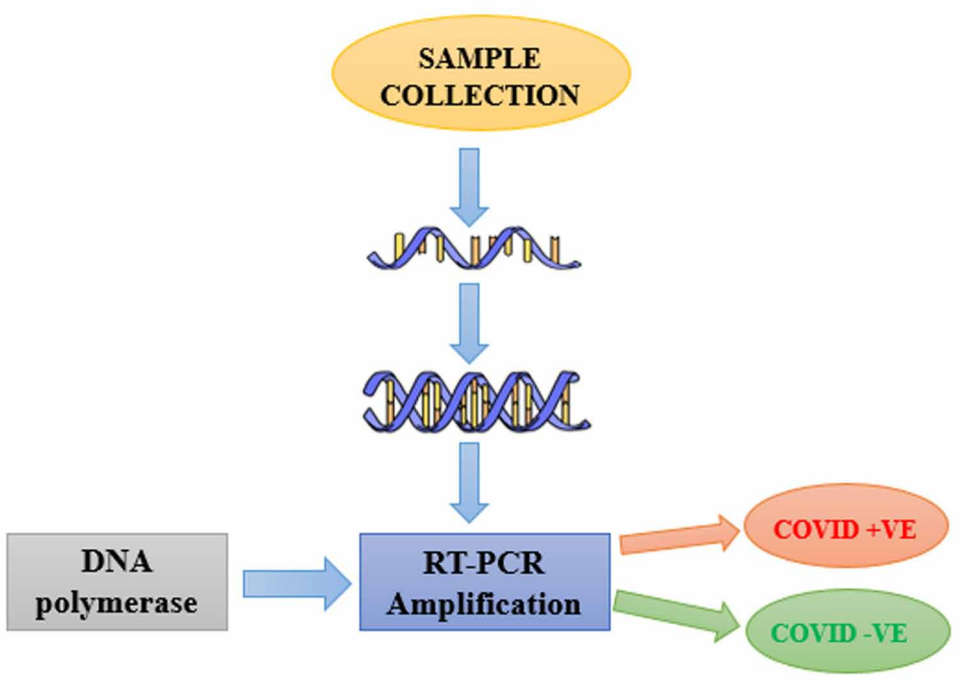
Clinical Feature (World Health Organization (WHO))	Clinical Feature (Centre for Disease Control and Prevention (CDC))
1. Fever or measured temperature ≥38C°. 2. Acute respiratory infection (ARI). 3. Cough. 4. Inception within the last ~10 days. 5. Needs to hospitalization.	1. Fever. 2. Lower respiratory tract infection.

Table 4. A comparison of "Epidemiological Risk" between World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC)(WHO, 2020) (CDC, 2020)

Epidemiological Risk (World Health Organization (WHO))	Epidemiological Risk (Centre for Disease Control and Prevention (CDC))
1. Past travel history from Wuhan, Hubei Province. 2. Healthcare and medical workers who are doing the job in asituation where patientswith ARI are being concerned. 3. Unpredicted clinical option follows despite the treatment, containing withquick deterioration. 4.Close interactionor contact in 2-3 meters for over 15 minutes with confirmed COVID-19 infection. 5. Existingwith healthcare services and facilities and hospital centers in countries where COVID-19has been informed. 6. All the above symptoms can be recognized within 14 days.	1. Past travel history from Wuhan, Hubei Province. 2. Past travel history of mainland China. 3. Close contact with infected patients within 14 days of symptom inception.

the hygiene, taking proper nutrition for better immunityand taking proper care to prevent cough and fever. Real time RT-PCR test (Fig. 6) is involved in COVID-19 test. Face mask,noninvasive ventilation or high-flow nasal cannula is important for a hypoxic patient to provide oxygen through nasal prongs. Extracorporeal membrane oxygen support and mechanical ventilation may be required. In some cases, renal replacement therapy is also required. If co-infections are doubted or confirmed, antifungals and antibiotics are needed.

Figure 6. RT-PCR test for COVID-19 detection



TRADITIONAL HERBAL TREATMENT

Several traditional fruits and herbal extracts used to heal the virus infected patients. Various traditional medicinal plants like basil, rosemary, dandelion etc. from surroundings and different places are combined to consider as the treatment of COVID-19. Research have presented that to avoid the specific cell identification and the entry of virus, a phytoagglutinin and concanavalin-A are mixed to form glycosylated membrane proteins (Greig et al., 1977). Several research shows that certain herbs extract like Lycorisradiata, Artemisia annua, Pyrrosia lingua and Lindera aggregate, are used as the resistant of COVID-19 at 2.4–88.2 μg/mL (Li et al., 2005). Few study discussed that an effective phyto-compound from lycorine can prevent COVID-19 with 15.7 Nm active concentration (Luo et al., 2020). A research study shows that the Houttuyniacordata specially an aqueous extract can prevent two effective proteins i.e. RdRp and 3CLpro in COVID-19 (Luo et al., 2020). Additionally, the extract from H. cordata can improved the cell count of CD8þ and CD4þ for in-vitro investigations in various animals displayed the immune-

stimulatory result which can reflected the significant characteristics for prevention of viral reproduction (Chiow et al., 2016). Same as, another study shows certain herbs extract like Polygonummultiflorum, Rheum officinale, emodin and also various active elements of these meditational plants were noticed to prevent the bindings of novel corona virus spike protein (S) to ACE2 through the values of IC50 within 1 to 10 μg/mL, and for the case of emodin the value is 200 μM (Ho et al., 2007). Another extract named Methanolic extract, the combination of Dioscoreabatatas and Cibotiumbarometz exhibited prevented effect against novel corona virus 3CLpro through the values of IC50 within 39 to 44 μg/mL (Wen et al., 2011). Aglaiafoveolata is an effective phyto-component has an active in-vitro cytotoxicity compared to cancer cell lines of humans. Additionally, the essential impede the mRNA HCoV-229E interpretation with the IC50 within the range 40 nM (Zhang et al., 2005). Moreover, Nigella sativa, Citrus sinensis and Anthemishyalina, extracts demonstrated the effective prevention on mouse hepatitis virus–A59 (MHV-A59) importance extract of the A. hyaline. The activities based on the raise of intracellular calcium level and decrease of TRP gene expression (Ulasliet al., 2014). Latest research data presented that alkaloids plant like cepharanthine, tetrandrine, and fangchinoline, can expressively decrease the cell death because of viral contamination in the human lung cells (MRC-5). Furthermore, various effective phyto-constituents like curcumin, five lignans, two sesquiterpenes, two sesquiterpenes, ten diterpenes, and two triterpenes, can prevent the COVID-19. Instead, a phenolic element, ferruginol, which is taken from Sequoia sempervirens (redwood), savinin, hinokinin, curcumin, and betulinic acid indicates anti-COVID reproduction act. Another inhibitor named Tylophorine which is basically drawn out from the Tylophoraindica which act as a viral imitation in the form of COVID-19 infected testicular cells (Yang et al., 2010). For the prevention and treatment of numerous widespread diseases like swine flu, plague, TCM (Chinese traditional herbal medicine) and SARS etc. has played a major part. In 2002, SARS-CoV outbreak, TCM was involved for the treatment, an inhibitor named flavone which is basically drawn out from the Scutellariabaicalensis, was applied as an anti-viral medicine. Food is characterized yang (hot) or ying (cool), as per to Chinese traditional science. It was thought that people to take yiang (cool) foods as yang (hot) body system tends to infected by SARS mostly. It was shown that Coptidis rhizome, Sophorasubprostrata Radix, Phellodendron cortex, and Cimicifuga Rhizome, could prevent appearance of N and S protein and also RNA production in COVID-19 (Kim et al., 2008). The application of traditional medicine by TCM shows effective and important remedies for A H1N1, influenza, SARS and H7N9. In novel coronavirus case, TCM believes that the characteristic of the virus relies on the environment of Wuhan. As per TCM, "Typical Treatment of COVID-19" decoction of Ma XinGan Shi along with Da Yuan Yin source can be operative to reduce the signs in patients of novel coronavirus. The decoction of Da Yun Yin and Ma XinGan Shi were estimated for the dealing of SARS-CoV (Yang et al., 2020). Indian conventional medication is one of the ancient Medicare in history and Siddha, Yoga, Ayurveda, Unani, naturopathy and homeopathy expresses a significant part for considering the numerous infections (Gomathi et al., 2020). Roughly, 2500 traditional herbs based structure is applied in Indian conventional medicine. As most of Indian traditional herbs exhibited anti-cancer, anti-oxidant and antiviral events that it may be significant to deliberate their exact accomplishments (Gomathi et al., 2020). Though, numerous medical trials must be completed to approve its function (Gomathi et al., 2020). In India, several studies about anti-COVID-19 activity applying traditional herbs. One of the articles discussed that the traditional herbs containing *Evolvulusalsinoides, Gymnemasylvestre, Indigoferatinctoria (AO), Abutilon indicum, ClerodendruminermeGaertn, Vitextrifolia, Leucasaspera, Sphaeranthusindicus*, and *Pergulariadaemi* in Tamil Nadu has anti-mouse COVID-19 activity (Vimalanathan et al., 2009). Between these, Sphaeranthusindicus, and Vitextrifolia, have seen to reduce the inflammatory cytokine level with the

help of the NF-kB conduit, which is an essential pathway in respiratory suffering in COVID-19 disease (Tiwari et al., 2009). As well, in ACR shredding, ADAM17 metalloproteinase preventer also known as *Clitoriaternatea* was seen involved. Various research article have displayed that the *Allium sativum* and *Glycyrrhizaglabra* have effective result on COVID-19 imitation, therefore they can be measured as an encouraging drug applicant for SARS-CoV2 (Keyarts et al., 2004). Furthermore, WHO identifies that traditional herbs like *Aretmisiaannua, Allium sativum L*, etc. are being deliberated as potential treatment for SARS-CoV2 and the medicinal side effects and also usefulness must be studied (Koch et al., 2020) (Clinical Trials, CDC, 2020). Table 5 enlisted some traditional herbal medicines names which are recommended for COVID-19 treatment as per TCM (Yang et al., 2020).

Table 5. Recommended traditional herbal medicines for COVID-19 treatment (Yang et al., 2020)

Serial Number	Name of Traditional Herbal Medicines by TCM	Trail Phase	Administration Procedure
1	Shuang Huang Lian	IV	Oral Liquid
2	Shen Qi Fu Zheng	IV	Injection
3	Shen Fu	IV	Injection
4	Tan Re Qing	N.A	Capsule
5	Tan Re Qing	IV	Injection
6	Ke Su Ting	IV	Capsule

CONVENTIONAL MEDICINAL TREATMENT

Several trials are going on toapply of different drugs including Oseltamivir,Hydroxy-chloroquine,Lopinavir and Ritonavir. World Health Organization (WHO) has published an extended rule for critical care management for novel corona virus (Li et al., 2020) (Chen et al., 2020). Out of ninety-nine hospitalized novel corona virus infected patientsof Wuhan, China, oxygen was providedto 76%, mechanical ventilation - 4%,noninvasive ventilation - 13%, continuous renal replacement therapy - 9%, extracorporeal membrane oxygenation - 3%, antibiotics in 71%, glucocorticoids in 19%, intravenous immunoglobulin therapy in 27% and antifungals in 15% (WHO, 20 March, 2020). Antiviral therapy involving with Ganciclovir, Oseltamivir, Ritonavir and Lopinavirwere applied to 75% infected persons. The period of noninvasive ventilation and mechanical ventilation were 4–22 days (for median 9 days) and 3–20 days (for median 17 days) respectively. All the children were cured with basic treatment and intensive care were not required (Xu et al., 2020).An anecdotal experience, a broad-spectrum anti-RNA drug, Remdesvir was used in COVID-19 (Holshue et al., 2020). But more clinical proofs are required for the usage of these drugs. The related drugs which can be used for the treatment are Arbidol which is an antiviral drug available in China and Russia, interferon, chloroquine, intravenous immunoglobulin, and also plasma of a cured COVID-19 infected patients (Zhang et al., 2020). Supportive and isolation care includes fluid management, oxygen therapy, as required for COVID-19 cases. It was reported that Sofosbuvir was aneffective inhibitor of COVID-19 RNA or RdRp (Khan et al., 2020).Also, it is recommended forCOVID-19 patientsthat AT1R or Angiotensin Receptor-1 and ACEI or Angiotensin Converting Enzyme Inhibitors can decrease the pulmonary inflammatory response (Rossignol et al., 2016). Some therapeutic mediations

like convalescent plasma (Shanmugaraj B, et al. 2020) and monoclonal antibody therapy (Sun ML, et al. 2020) are recommended for COVID-19 treatment. Table 6 enlisted some medicines names which are recommended for COVID-19 treatment.

Table 6. Recommended medicines for COVID-19 treatment(Xu et al., 2020) (Chen et al., 2020)

Serial Number	Medicines	Function
1	Hydroxy-Chloroquine	Rise in the acidic levels of endosomes, precludes the endocytosis and breaks the virus to enter in the host cell.
2	Lopinavir and ritonavir	Inhibits RNA translation progression
3	Remdesivir	From the RNA template, it prevents the RNA reproduction
4	Favipiravir	From the RNA template, it inhibits the RNA reproduction and also, prevents RNA translation progression
5	Darunavir	Stops the viral reproduction
6	Ribavarin	Inhibits mRNA capping and synthesis of viral RNA
7	Arbidol	Prevents the outer membrane synthesis of the viral outer surface
8	Oseltamivir	Prevents RNA translation progression
9	Umifenovir	Inhibits virions synthesis through endosomal membrane
10	Monoclonal antibodies	Prevents the viral infection

CONCLUSION

The pandemic by COVID-19outbreak is infecting the people globally. Different governing bodies and researchers are trying their best to come up with a vaccine which can prevent the spreading of the virus. The study of the differences in response of virus affect body of a child and an adult help to analyze immunity system. Novel corona virus or COVID-19 which originates from a viral family was thought to be benevolent in nature before the turn of the century but now it has become a worldwide emergency public health concernas per World Health Organization (WHO). For this kind of outbreaks proper health facilities and medical research work, financial stability is needed.Expectantly, the traditional medicine will have an effect on treatment of COVID-19.

ADDITIONAL INFORMATION

The novel virus originated in Wuhan, China which is spread worldwide within a short period of time is extremely contagious respiratory disease which is better known as CoV-2 i.e. severe acute respiratory syndrome-coronavirus-2. This virus is totally different from other corona virus family; it is responsible for minor sickness like common cold in humans. It is very much important to realize the effect and the result of the pandemic. In Wuhan city of China an unknown type of pneumonia started spreading among humans in mid of December 2019. A new kind of virus emerged and entered in the family of corona virus known to human civilization which was named as COVID-2019 or simple COVID-19 by WHO

i.e. World Health Organization. Taking into account the MERS i.e. Middle East respiratory syndrome and SARS i.e. Severe acute respiratory syndrome, this novel virus which is caused by SARS-CoV-2 a beta-coronavirus which attacks the lower respiratory track cells and results into pneumonia in human beings. Regardless of severe efforts taken by various countries for quarantine, lockdown and containment the virus spreads rapidly.

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KEY TERMS AND DEFINITIONS

CDC: Centers for Disease Control and Prevention (CDC), a United States based health agency.

COVID-19: The infectious viral disease caused by SARS-CoV-2. As it is highly transmitted disease, it is the reason behind the world-wide pandemic situation.

Epidemiology: A systematic study and analysis of frequency and causes of healthcare related issues.

TCM: Traditional Chinese medicine.

Traditional Medicine: The medical treatment with different kinds of herbs, plants, minerals etc. to prevent the illness.

WHO: World Health Organization, a United Nation based organization specially deals with public health related issues.

Chapter 15
Herbal Products for Management of COVID- 19

Simran Jeet Kaur
PCTE Group of Institutes, India

ABSTRACT

COVID-19 is a human-infectious virus. The respiratory system is the primary target of the coronavirus, but it can also harm cardiac tissues and gastrointestinal organs. Many frequent circumstances, such as the medication's or medicine's purpose, the dosage/potency of the drug, and the patient's condition, can place patients in grave danger. Several cures have been reported using a variety of therapy methods. Among the various treatments, natural and synthetic medicines are the most commonly documented. Some herbal medicines, such as Tribulusterrestris, Withaniasomnifera, Curcuma longa, Ocimum sanctum, and Phyllanthusemblica, have powerful antiviral (AntiCOV-19) properties against novel coronavirus, heralding the start of a new era in herbal therapy.

INTRODUCTION

The World Health Organization, a government agency, has declared COVID a pandemic disease. Coronavirus history began in 1965 with a virus known as B814. It was first noticed in a human embryonic tracheal organ culture of an adult's respiratory tract Colds are very popular (Tyrrell DA et al 1966). The presence of an infection-causing agent was investigated by injecting the medium with Colds were observed in a large number of volunteers through the intra nasal path. Corona virus has a spherical or pleomorphic shape, single-stranded RNA that is enveloped, and a club-shaped glycoprotein covering. (Kumar, 2020) Corona viruses are divided into four types: alpha, beta, gamma, and delta. There are several serotypes of corona viruses in each subtype.

COVID-19 is a virus that infects people. Coronavirus primarily targets the respiratory system, but it can also damage myocardial tissues and gastrointestinal organs. Many common factors, such as the essence of the medication/medicine, the dosage/potency of the drug, and the patient's condition (i.e. ageing, obesity, gender, diabetes, kidney disorder, liver disease, anxiety/stress, pregnancy), can put patients at serious risk. (Farooq, 2021)There have been several reports of cures using a variety of treatment

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approaches. Natural and synthetic remedies are the most widely recorded treatments among different treatments. Other methods for inactivating pathogens, especially coronavirus infections, have been widely published, including UV A, UV C light, heat sensitivity, and octanoic acid treatment. The photodynamic and thermodynamic treatment methods include the penetration of UV light/heat into platelet fluid and the inactivation of pathogenic microorganisms and leucocytes in order to damage the nucleic acids and prevent the virus from spreading further. the severity of the treatment.(Darnell, 2006)Good evidence supports herbal medicine as possible beneficial antivirals against SARS-CoV-2 and COVID-19 preventive agents in the current literature. Researchers suggest that there are four possible ways for using nutritional therapy and herbal medicine to treat COVID-19 in future studies: use as an antiviral agent by coating on masks; use as an air-disinfectant (essential oil) to avoid aerosol transmission; and use as a surface sanitising agent to provide a disinfected atmosphere.(Panyod, 2020)

BACKGROUND

Traditional herbal remedies are gaining a lot of traction in global health discussions. India, the United States of America (USA), China, Nigeria, and the World Health Organization (WHO) have all invested heavily in traditional herbal medicine science.(Brahmbhatt, 2021) Herbal medicines are in a race to produce new drugs for therapeutic and preventive use in diseases that have less or no side effects.(Wagner, 2009) Certain natural products derived from Indian herbal medicines act by binding to the active sites of COV-19 proteases and thus inhibit viral replication.[8] Some herbal medicines, such as Tribulusterrestris, Withaniasomnifera, Curcuma longa, Ocimum sanctum, and Phyllanthusemblica, have powerful antiviral (AntiCOV-19) properties against novel coronavirus, signalling a new dawn in herbal medicine. (Brahmbhatt, 2021). Natural remedies have been identified as promising sources for the synthesis and manufacture of antiviral agents. Antibacterial, Antitumor, antifungal, anti-inflammatory and antiviral properties have been recorded. In Asian nations, Herbal plant treatments have long been used in traditional medicine.((Farooq, 2021))Herbal medicine is in a race to produce new drugs for therapeutic and preventive use in diseases that have less or no side effects. Research has identified three major types of coronavirus targets, which are as follows: 1) Coronavirus structural inhibition, 2) Coronavirus RNA synthesis and replication inhibition, and 3) Coronavirus virulence factor inhibition(Lin Ang et al, 2020) as enlisted in table 1

Table 1. Major targets of COVID-19

S.No.	Major Targets of COVID-19		
	Inhibit SARS-CoV-2 RNA synthesis and replication	**Inhibit SARS-CoV-2 at structural level**	**Inhibit virulence factor of SARS-CoV-2**
1	Papain-like protease (PLpro)	Spike Protein	Nsp 1
2	3C-like main protease (3CLpro)	E protein or N protein	Nsp3c
3	RNA-dependent RNA polymerase (RdRp)	-	ORF7
4	Helicase	-	-

HERBAL PRODUCTS AGAINST CORONAVIRUS

Certain natural products derived from Indian herbal medicines bind to the active sites of COV-19 proteases and thus inhibit viral replication. (Brahmbhatt, 2021)

Inhibition of Viral Attachment

The virus attaches to the required host cells as the first phase in viral infection. The association of viral glycoprotein with cell carbohydrate, such as sialic acid, is one of the most important mechanisms in viral attachment.

The coronavirus glycoprotein recognises the host cell, fuses with it, and kills the receptor. The operation of the receptor-destroying enzyme (RDE) is critical for virus release. The Hemagglutinin esterase (HE) glycoprotein is responsible for receptor binding and receptor-destroying activity in coronaviruses. Spike (S) glycoprotein is involved in virus-host membrane fusion and host cell recognition. (Boozari et al, 2020)SARS-CoV infection involves the renin–angiotensin system (RAS). Angiotensin converting enzyme 2 (ACE2) is active in both SARS-CoV-1 and SARS-CoV-2. ACE2 expression is elevated during SARS infection and ultimately can lead to lung failure. According to a screening method that checked interaction of S protein and ACE2 has concluded that Rheum officinale and Polygonummultiflorum can successfully inhibit ACE2. (Ho, T.-Y et al, 2007)An imbalance in the RAS between the ACE2/Ang (1–7)/Mas receptor and the ACE/Ang-II/AT1R pathway is leading to cause inflammation and extreme pneumonia. SRAR-CoV-2 binds to ACE2 and the ACE2 receptor. The ACE2/Ang (1–7)/Mas receptor pathway was inhibited, resulting in a RAS imbalance. As a result, activating the ACE2/Ang (1–7)/Mas receptor pathway in COVID-19 can reduce the pulmonary inflammatory response and mortality.(Brojakowska et al, 2020) Traditional Chinese Medicine's Sini decoction is made up of three herbs: aconite (*Aconitum carmichaelii*), licorice (*Glycyrrhizaglabra*), and ginger rhizome (*Zingiberofficinale*). By lowering inflammatory factors in lung tissue and decreasing the expression of ACE and angiotensin II type 1 receptor, sini decoction significantly reduced E. coli-induced acute lung injury (AT1R). In addition, Sini decoction has been shown to activate the ACE2-Ang-1–7-Mas pathway. As a result, Sini decoction can be useful in the treatment of COVID-19.(Liu, J et al, 2018)ACE2-Ang-(1–7)-Mas pathway was induced and Ang II-induced cell oxidative damage was reduced due to Baicalin, a glycosylated flavonoid that is derived from S. baicalensis. (Wei, X et al, 2015)

CORONAVIRUS RNA SYNTHESIS AND REPLICATION INHIBITION

3Clike protease (3CLpro) and papain-like protease (PLpro) are two essential viral protease enzymes in SARS-CoV replication. Helicase and RdRp are two other important enzymes in SARS-CoV replication. Proteolysis, viral replication and infection is considered to be done by 3CLpro enzyme (or main protease (Mpro)) that encoded in CoVs. Therefore, it also can be considered as an ideal target for antivirals. Hence, the inhibitors of these enzymes may be seen as possible COVID-19 treatments. Salvia miltiorrhiza, Angelica keiskei, Camellia sinensis, Isatisindigotica, Torreyanucifera, Juniperusformosana and many other plants have effective activity to anagonize these enzymes.

A papain-like protease (PLpro) is another CoV protease enzyme that is involved in proteolysis, innate immunity antagonist, deubiquitination, and viral replication, making it a good candidate for antiviral

drugs. Tanshinone I is the active constituent obtained from Salvia miltiorrhiza, it acts to increase effect of PLpro.

RNA-dependent RNA polymerase (RdRp) is required for positive strand RNA virus replication and transcription . Antiviral drugs that suppress the RNA polymerase are a good candidate for coronavirus therapy. As per literature, the biflavonoid skeleton is a potential RdRp inhibitor, particularly amentoflavone and robustaflavone. Dacrydiumaraucarioides yielded a sotetsuflavone with a bioflavonoid structure. (Boozari et al, 2020)

Inhibition of Helicase

For viral replication, Helicase a multifunctional protein is required. Hence, helicase inhibitors could be used as antiviral drugs in the treatment of coronaviruses. Silvestrol is a flavagline with a cyclopenta[b] benzofuran skeleton that can be isolated from Aglaia plants, especially Aglaia silvestris and Aglaia foveolata.(Pan, L et al, 2018)

Terpenoid derivatives, Polyphenols and flavonoid derivatives, Alkaloid derivatives and some miscellaneous compounds are effective against COVID.

Tribulusterrestris

The fruits of Tribulusterrestris are well-known for their use in pharmaceuticals and nutritional supplements. The papain-like protease (PLpro), an important proteolylic enzyme for defence against pathogenic virus and bacteria, was inhibited potently by a methanol extract of T. terrestris fruits. (Song Y et al, 2014)

Withaniasomnifera

The main phytochemicals of W. somnifera, withanolide-B, withanone, and withaferin-A, have predicted binding energies lower than the pharmacological inhibitor. The interaction of these phytochemicals with the main protease can delay the cleavage of pseudo-particles (PPs) into non-structural proteins (NSPs), slowing viral replication and transcription. (Maurya et al, 2020)

Glycyrrhizaglabra

Glycyrrhizaglabra (Leguminosae family) and its active component, glycyrrhizin, have antiviral activity against a variety of viruses, including hepatitis A, B, C, varicella-zoster, HIV, herpes simplex type-1, and cytomegalovirus. Researchers found that glycyrrhizin prevented SARS-associated virus replication and that it should be considered for SARS treatment. Furthermore, an in vitro study revealed that glycyrrhizin has antiviral properties against SARS infection. (Chen et al, 2004)

Curcuma Longa

Curcuma longa contains large phytoconstituents such as demethoxycurcumin, curcumin, and Diacetylcurcumin, which are the most promising inhibitors of COV-19 Main Protein (Mpro). In contrast to antimalarial medications, curcumin binds strongly to COV–19 3CL-protease and promotes essential structural changes in this viral protease, causing the enzyme to fold. Diacetylcurcumin, found in C.

longa, has been found to be more potent than Nelfinavir against COV-19 (Mpro). (Srivastava et al, 2020) However, many studies showed curcumin is an immunomodulator that may increase or decrease proinflammatory cytokines, the findings of its administration are inconclusive. This evidence raises questions about the use of curcumin as a COVID-19 treatment. CRS, also known as a cytokine storm, is a hyperinflammatory and hypercytokinaemia seen in some COVID-19 patients. Curcumin can increase the production of proinflammatory cytokines, worsening the condition of COVID-19 patients suffering from a cytokine storm. Curcumin's function in the treatment and prevention of COVID-19 requires more research. (Nugraha et al, 2020)

Ocimum Sanctum

Because of its ability to inhibit COV-19 replication, as well as its immune-modulatory and ACE II blocking properties, Ocimum sanctum extract may be used as a COVID-19 preventive measure. Tulsinol (A, B, C, D, E, F, G) and dihydrodieuginol-B from O. sanctum inhibit COV-19 Main Protease and Papain-like Protease.(Varshney et al, 2020)

Echinacea Purpurea

Because of its promising effects against viral infections, Echinacea purpurea (E. purpurea) is one of the most common herbal medicines in Europe and North America. Purple coneflower is its common name. Extracts, tinctures, teas, and sprays can all be used to make E. purpurea preparations. This form of herb is used by many Native Americans to treat respiratory infections. Chicoric and caffeic acids, alkylamides, and polysaccharides are among the bioactive compounds contained in it. (Varshney et al, 2020) Echinacea purpurea can also lead to cytokine release syndrome because the production of IL-1, IL-10, and TNF-α can be increased in COVID-19.(Sharma et al, 2009)Therefore, further investigation should be done before confirming its candidature for COVID-19 treatment.

Cinchona

Quinine sulphate acts as an antiviral agent by increasing the development of RIG-I and IFN-alpha, both will inhibit viral mRNA translation by activating PKR and degrade viral poly mRNA by activating RNAse (L). Terefore, no viral protein will be produced and it can be considered for treatment of COVID-19. However, it is not recommended that healthy people take this herbal remedy on a regular basis to avoid COVID-19 because it has the potential to cause a variety of side effects. (Varshney et al, 2020)

Xanthorrhizol

Java turmeric, also known as Curcuma xanthorrhizaRoxb (C. xanthorrhiza), is a Southeast Asian herbal plant. This plant belongs to the Curcuma genus and the Zingiberaceae family.

Because of its ability to inhibit proinflammatory cytokines, xanthorrhizol is an immunosuppressant that could be used to treat COVID-19. COVID-19 patients are vulnerable to CRS. As a result, xanthorrhizol can reduce the proinflammatory response in COVID-19 patients with or without CRS. However, since no research has been performed with xanthorrhizol in COVID-19, the administration of xanthor-

rhizol must be undertaken with caution and consideration. There is also a risk that giving xanthorrhizol to COVID-19 patients will make their condition worse. (Jantan · 2019)

Phyllanthusemblica

Phyllanthusemblica also has immunomodulatory properties, suggesting that it may help the community's health and immunity in the battle against COV-19 infection P.emblica's active constituents, phyllaemblicin-B and phyllaemblinol have a high affinity for helicase protein, which is one of COV-19's main targets. Phyllaemblicin G7 from P. (Park et al, 2012b)emblica had a high binding affinity for COVID-19's Spike Protein. The secret to P. emblica's therapeutic effect is its antioxidative and anti-inflammatory properties.

S. miltiorrhiza

S. miltiorrhiza produces tanshinones with an abietanediterpene structure. Tanshinones have a variety of biological effects, including anti-inflammatory, cardiovascular, and anti-tumor properties. These compounds inhibit the SARS-CoV 3CLpro and PLpro enzymes selectively, and their activity is dependent on the enzyme type. Different tanshinones have a stronger inhibitory effect on PLpro than others. (Park et al, 2012b)

Angelica Keiskei

Polyphenols isolated from Angelica keiskei have alkylated chalcones with a C-5 prenyl unit that display potent inhibitory activity against 3CLpro and PLpro in vitro. XanthoangelolE, xanthoangelol F (IC50: 5.6 M) are the most active alkylated chalcones against PLpro, with the most potent compounds being xanthoangelol E (IC50: 1.2 M) and xanthoangelol F (IC50: 5.6 M). Perhydroxyl group is an alkylated chalcone with more inhibitory activity, according to SAR analysis. (Park et al, 2016)

A. japonica

Hirsutenone is a diarylheptanoid isolated from A. japonica that has a strong inhibitory effect on PLpro.

Lycoris Radiate

There is presence of Antiviral activity of Lycorisradiata extract (Amaryllidaceae family) against SARS-CoV. Lycorin is the active compound in this extract, which has an alkaloid structure and has an EC50 value of 15.7 1.2 nM, indicating that it has antiviral activity. These findings showed that lycorine is a promising candidate for the production of new antiviral drugs. (Chen et al, 2005) Another study found that lycorine can inhibit the replication of coronaviruses like HCoV-OC43 (EC50: 0.15 M), MERS-CoV (EC50: 1.63 M), and HCoV-NL63 (EC50: 0.47 M) in vitro. (Shen et al, 2019)

Carapicheaipecacuanha

The key active ingredient in Carapicheaipecacuanha roots (Rubiaceae family) with anti-protozoal activity and vomiting agents is emetine, which has an alkaloid structure.One study exhibited that Emetine can

inhibit the replication of many coronaviruses in vitro, including HCoV-OC43 (EC50: 0.30 M), MERS-CoV (EC50: 0.34 M), and HCoV-NL63 (EC50: 1.43 M). Furthermore, emetine can prevent MERS-CoV from infecting host cells.(Shen et al, 2019)

Tylophoraindica

Tylopophorine and other phenanthroindolizidine alkaloid analogues isolated from Tylophoraindica (Asclepiadaceae).

Yang et al. (2010) found that tylophorine (IC50: 58 nM) and 7-methoxycryptopleurine (IC50: 20 nM) have potent inhibitory effects on coronavirus replication. Another research discovered that tylophorine at nanomolar concentrations targets viral RNA replication and cellular JAK2-mediated dominant NF-B activation, which is a natural pro-inflammatory response of host cells to viral infection in CoV. (Yang et al, 2017)

Stephaniatetrandra

The roots of Stephaniatetrandra (Menispermaceae family) contain bisbenzylisoquinoline alkaloids that have anticancer, anti-inflammatory, and antioxidant properties (Weber &Opatz, 2019). Tetrandrine (IC50: 14.51 M), fangchinoline (IC50: 12.40 M), and cepharanthine (IC50: 10.54 M) are the key active S. tetrandra alkaloids that display possible antiviral activity against HCoV-OC43 infection and viral replication suppression. (Kim et al, 2019)

Cephalotaxushainanensis

Homoharringtonine (omacetaxinemepesuccinate) is a cytotoxic alkaloid that was first discovered in the Cephalotaxushainanensis plant (Taxaceae family). The FDA has approved it as a treatment for chronic myeloid leukaemia resistance. With the lowest IC50, homoharringtonine shows strong antiviral activity against a variety of human and animal coronaviruses. (Cao et al, 2015)

Toonasinensis

In vitro, the leaf extract of Toonasinensis was found to have a significant antiviral effect against SARS-CoV, with a selectivity index of 12–17. As a result, this vegetable may be used as a new SARS-CoV antiviral medication. (Boozari et al, 2020)

Allium Sativum

Allium sativum can be an effective COVID-19 infection prevention strategy by boosting immune system cells and suppressing the synthesis and secretion of proinflammatory cytokines, as well as the proinflammatory hormone leptin derived from adipose tissue. (Donma, 2020)

Althaea Officinalis

Via anti-inflammatory and relaxing effects on the respiratory tract, Althaea officinalis preparations can suppress cough and reduce irritation. Its possible use can be in the relief of early symptoms of COVID-19, its conventional use as cold therapy in the form of upper respiratory conditions is not backed up by rigorous clinical evidence. The clinical evidence for this herbal medicine is High, and no serious problems have been identified, so it can be classified as High safe. (Silveira et al, 2020)

Andrographispaniculata

Andrographis has been shown to help with symptomatic relief of respiratory symptoms, especially in the case of uncomplicated upper respiratory tract infections. Its common use as cold therapy in the form of upper respiratory conditions is not supported by strong clinical evidence, but the evidences allow for inference of a possible use in the relief of COVID 19 early symptoms. (Silveira et al, 2020)

Commiphoramolmol

Commiphoramolmol preparations seem to have a supportive antinociceptive effect, making them useful for respiratory symptom relief. However, it takes a few weeks for its impact to become apparent, much longer than COVID-19's natural, uncomplicated evolution.

Eucalyptus Globulus

Eucalyptus globulus has a calming effect on the respiratory tract, which can help to relieve symptoms associated with upper respiratory infections. Despite the widespread use of products containing eucalyptus derivatives, more information on the effect on the respiratory tract is required. (EMA (2017a)

In the COVID-19 pandemic, a novel evidence-based herbal medicine approach plays a preventive role. Natural occurrences, Plants have a wide range of phytoconstituents. COV-19 is mainly inhibited by Tribulusterrestris, Withaniasomnifera, Curcuma longa, Ocimum sanctum, and Phyllanthusemblica. Furthermore, in-vitro and in-vivo studies are needed to determine herbal medicine efficacy. Combination treatments with allopathy and natural remedies, on the other hand, contribute to the most effective treatment choices. Many unidentified herbal medicines are still awaiting identification, purification, and medicinal testing.

FUTURE RESEARCH DIRECTIONS

It is evident that there is insufficient evidence of SARS-CoV-2-specific direct antiviral actions. To determine their significance in COVID-19 management, more research is needed into the anti-inflammatory and immunomodulatory properties, as well as the quality and safety of herbal drugs. Still there are chances that our herbal products may cause some adverse effects also. Therefore, there is need of more future research and these products may act like the major part of therapy

CONCLUSION

It is concluded that these herbal medicines may have the ability to control the production and release of proinflammatory cytokines, interfere with the virus's development in host cells, and alter certain molecular pathways relevant to the RAAS system, based on the previous description. Herbal agents may be useful in the war against COVID-19. Finally, patients should be advised that using a supplement containing one of these compounds to avoid COVID-19 or heal the disease without specific guidance or under the active supervision of a clinician is still not recommended.

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Chapter 16
Nutrition: A Strategy for Curtailing the Impact of COVID-19 Through Immunity Booster Foods

Muhammad Haseeb Ahmad
Government College, University Faisalabad, Pakistan

Muhammad Faizan Afzal
Government College, University Faisalabad, Pakistan

Muhammad Imran
Government College, University Faisalabad, Pakistan

Muhammad Kamran Khan
Government College, University Faisalabad, Pakistan

Nazir Ahmad
Government College, University Faisalabad, Pakistan

ABSTRACT

Nutrition is a known aspect that plays a pivotal role in the strengthening of the immune system. Populations with poor eating habits have more risk of severe COVID-19. Micronutrients such as vitamins, including vitamins A, B complex, C, D, and E; minerals including, zinc, selenium, magnesium, and copper are mainly present in plant based foods like legumes, fruits, and vegetables to build different types of immune cells that are helpful in supporting the immune system and promote the host health. Insufficient consumption of these nutrients may result to reduce the resistance to infections as well as an increasing in disease load. Garlic, black pepper, and basel leaves are known as ancient herbs which is helpful to boost the immunity. Numerous studies observed that a powerful antioxidant bioflavonoid quercetin and a glutathione may prevent the risk of COVID-19. In conclusion, foods from plant source show a vigorous role to boost the immunity for all aged groups to control COVID-19.

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INTRODUCTION

COVID-19 is a respiratory disorder officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), firstly recognized in the last month of 2019 in Wuhan, China, that is transmitted over person to person through coughing as well as sneezing and that pandemic is the main aspect that paralyzed the socioeconomic life around the world. Currently for the protection of yourself and the other people from the novel COVID-19 virus a good personal hygiene practices as well as social distancing are required because these practices play a crucial role to avoid the spreading of this pandemic. It is recommended to wash hands repeatedly with soap for 20 seconds or use ethanol based hand disinfectant. In addition to this, covering nose or mouth at the time of coughing or sneezing with disposable tissues, assume a habit of social distancing from the people who infected during this plague as well as stay home and isolate yourself if you feel unwell are certain practices that are essential for improving the immune system during this period (Hopkins, 2020).

Common cold, fever, fatigue and sore throat are some of main symptoms of COVID19 that seems within one or two weeks of virus attack. These symptoms may modified from mild to severe with the passage of time and leads to dyspnea, pneumonia, lymphopenia as well as severe respiratory syndromes and even cause death (Jiang et al., 2020). Heart, lungs as well as gastrointestinal tract are the main organs which are targeted by the SARS-CoV-2 (Chen et al., 2019). The clinical trial shows that the severity of infectious disease mostly appears in people who are obese, diabetic, and in heart as well as lungs diseased patients. The old aged people are proned to this infection due to weaken immune response because as people get older the immunity decreases, that's why in younger aged group the severity of infectious virus is low because younger aged group have stronger immune system that curtail the risk of COVID-19 (Wu et al., 2020). The influence of nutrition has been vast subject of discussion because diet can play a vital role to boost the innate as well as acquired immunity (Cooper & Ma, 2017). It is well-known that people who are malnourished have weaken immune response to tackle the pathogens that cause infections in the body (Derbyshire & Delange 2020). Immuno-nutrition is essential and plays a crucial role but not enough in the contest against possibly lethal viruses like COVID-19 because immuno-nutrients rich diet play an immune supportive response (Grimble, 2009).

This chapter delivers rationalized info about the plant based food as well as animal based food nutrients that have strong impact on COVID-19 through improving the immune response. Diet from plant source provides protection from several acute as well as chronic diseases like coronary heart disease, diabetes mellitus, hypertension and obesity, also plays a vital role in the development of immune system (Orlich & Fraser, 2014; Wright et al., 2017). COVID-19 had spread all over the world because the rate of transmission of SARS-CoV-2 is very high amongst individuals. At that time of pandemic, when the globe is enclosing by this infectious virus, nutrition must be the first priority to curb the effect of novel corona virus by strengthening the immunity because the immune system is only barrier that deal virus. In this chapter, the role of micronutrients for curtailing the effect of COVID-19 by improving immune system has been briefly discussed.

NUTRITION AND IMMUNE SYSTEM

The immune system has ability to protect the functional responses of the host as well as aid to fight against the attack of microbes, virus, pathogens and other harmful substances. Innate as well as adaptive (acquired) immunity are two main kinds of our immune system.

The innate immune system is more invariant or faster molecular motifs but non-specific. Innate immunity produces cells of physiological as well as structural barriers. Physiological barriers include pH and oxygen level well in structural barriers, skin as well as mucous membranes are included. Basophils, dendritic cells, eosinophils, macrophages, mast cells, neutrophils and natural killer cells are those cells that are produced by innate immune system (Bonham et al., 2002; Sokol & Luster, 2015).

The adaptive immune system takes more time to be activated but it is more specific than innate immunity. The adaptive immunity is responsible for synthesizing of B-cells, T lymphocytes as well as antibodies that that may used for protecting against pathogens. Major histocompatibility complex (MHC) are carried by B-cells that are characterized as an immunoglobulin. Helper T-cells are made up by T-cells which identify specific antigens that are similar with cytotoxic and MHC class II antigens as well as T-cells which identify the antigens that are correlated with major histocompatibility complex (MHC) class I molecules (Bonham et al., 2002).

All over the world malnutrition and infection both are main obstacles for development, health as well as for survival (Keusch, 2003). Immune responses like afinity, cytokine production, cell-mediated immunity and secretory antibody response are usually impaired due to nutritional deficiencies (Chandra, 1991). For the optimal response of immune system appropriate ingestion and absorption of micronutrients are necessary (Keusch, 2003). When the immune system is impaired, it becomes rapt and crier serious infections that may cause death (Ibrahim & El-Sayed, 2016). According to several scientific literatures, it has been observed that immunodeficiency arises mostly during the period of ageing and the major reason behind is malnutrition as well as due to environmental factors. Ample amount of nutrients are needed for the strengthening of immune system because the activity of immune system may have stimulated by infections which faster the metabolism, demanding energy sources, a substrate for the sake of biosynthesis as well as regulatory molecules that are mainly found in diet (Calder et al., 2020).

Evidence proves that malnutrition may impaired the both humoral as well as cell-arbitrated immune functioning (Nieman et al., 1995). Therefore, people may protect by adopting healthy nutrition during the period of COVID-19. The clinical trial of COVID-19 infection predicted that low level of pre-albumin may cause respiratory failure as well as mechanical ventilation (Caccialanza et al.,2020).

Macronutrients include protein and omega 3 fatty acids whereas micronutrient are minerals and vitamins. The various vitamins such as A, B complex (folic acid and biotin), ascorbic acid (vitamin C), D as well as vitamin E, and minerals like copper iron, selenium and zinc play vital role for immunocompetence specially during the era of COVID-19 epidemic (Ibrahim & El-Sayed, 2016; Cena & Chieppa, 2020). Therefore, to fight against the infection of COVID-19, healthy nutrition plays a key role and protect people from this pandemic.

PLANT AND ANIMAL BASED FOODS FOR STRENGTHENING THE IMMUNE SYSTEM

Now a day's large amount of scientifically authorized functional foods such as micronutrient supplements and functional yogurt full of probiotics which contain immunity boosting characteristics are easily accessible (Lopez-Varela et al., 2002). The compounds described as immunity booster should be food components or whole food. Several research and studies are working to discover the plant compounds that are involved in the immunity boosting by targeting the particular cellular functions and add to the body upon the exposure of well know allergen like air pollution and grain pollen etc. (Coleman et al., 2016). However, studies resulted that the use of functional foods aids the immune system by protecting the effect of air pollution due their useful biological activities (Nyanhanda et al., 2014).

Immune Boosting Food Constituents

Flavonoids, micronutrients and probiotics have been stated to deliver a benefit to immune system (Table 1). Probiotics or friendly bacteria help to strengthen the immune system by stimulating the production of cytokine and hence enhance gut functioning. For example, intake of 1 or 2 cups of low fat yogurt that contain probiotic or friendly bacteria may enhance the granulocytes activity, which improves natural immunity (Marteau et al., 2001).

Micronutrients such as vitamins, including vitamins A, B complex, C, D, and E; minerals including, zinc, selenium, magnesium, copper etc. are essential nutrients that play a pivotal role in the body, these nutrients are needed in relatively low amount on daily bases for proper functioning of body (Opara, 2002).Selenium (Se) deficiency leads to weaken the immune system (Lopez-Varela et al., 2002), therefore a noticeable immuno-stimulant effect has been detected by taking selenium (Se) supplementation. It may improve the activated T cells proliferation (Kiremidjian-Schumacher & Roy, 1998). Tissue injury caused by free radicals in the body is an actual risk for the weaken the functioning of immune system, subsequently phagocyte cells generate oxygen reactive species as chunk of the body's protector against illness. So, for the avoidance of immune cells injury, an ample amount of deactivating antioxidants are needed (Lopez-Varela et al., 2002). Vitamin C and E have the antioxidant activity and these nutrients are obtained directly through the diet. Several studies, indicated that Vitamin A, C, D as well as vitamin E provide immune boosting properties. According to a study taking vitamin C in a high dose may lessen the period of signs linked with common cold (Hemilä & Chalker, 2013).

Vitamin A

Vitamin A is a fat-soluble vitamin. It is necessary to improve the growth, eye vision as well as known as immunity booster (Huang et al., 2018). Vitamin A contains bioactive components like retinal, retinol and retinoic acid. Some carotenoid specially β-carotene is known as pro vitamin A which are absorbed in the human body in the form of retinol. The bioactive component of vitamin A particularly the retinoic acid can increase the production of anti-inflammatory cytokines and antibodies which are immunity booster against viral infections (Mullin, 2011). Vitamin A deficiency leads to the more inflammation as well as enhance the viral infection. The depletion of retinoic acid leads to the cause of viral infection like coronavirus by reducing the immunity (Liang et al. 2020).

Vitamin C

Vitamin C belongs to water soluble family of vitamins, naturally found in citrus fruits, also known as strong antioxidant which help to eradicate the free radicals in the body and endorse the immune response in the body. Some scientific studies reported that intake of vitamin C enhance resistance against several bacteria as well as viruses' infections (Dobrange et al., 2019). Patients who are suffering with lung infections may improve their condition by taking mega dose of ascorbic acid (12 g per day) (Kakodkar et al., 2020). Likewise, flu or common cold can be treated by using high dose of ascorbic acid (Banerjee & Kaul, 2010). A 15-g intake of vitamin C per day may reduce death rate in COVID-19 patients (Carr, 2020). Ascorbic acid also performed role as a reducing agent and also offered antiviral properties (Siegel & Morton, 1977). Vitamin C scarcity in body may cause frail collagen formation, weak the immune system, and leads to infections susceptibility as well as delayed the process of wound healing during injury (Wintergerst et al., 2006).

Vitamin D

There are two types of vitamin D including vitamin D2 and vitamin D3. Vitamin D2 is generally known as ergocalciferol whereas Vitamin D3 is called cholecalciferol. The common source of vitamin D is sunlight as well as small amount of it taken from some food sources like eggs of hen, fish liver oils etc. (Kraemer, 2012). Vitamin D deficiency leads to the increase infections rates apart from the rickets in children as well as Osteomalcia in women and other bone disorders (Aslam et al., 2017). Vitamin D3 is produced by human cells by the exposure of ultraviolet radiations from the sunlight but the Vitamin D2 is not synthesized in the human body (Bikle 2009). Vitamin D3 imparts a significant role to boost up the immunity (Mora et al., 2008). Vitamin D plays a chief role for the expression of some genes which produce protein that are lethal to foreign pathogens.

Vitamin E

Vitamin E or tocopherols is fat-soluble vitamin naturally found in broccoli, peanuts, spinach, sunflower, tomato and wheat germ (Aslam et al., 2017), also known as potent antioxidant as well as immunoregulator due to its ability to strengthen the immunity (Maslova et al., 2014). Vitamin E help to regulate the normal immune response by inhibiting as well as by inactivating the free radical in cellular membranes (Maggini et al., 2007). Similarly, for the treatment of influenza virus some antioxidants are tested and vitamin E has shown the better efficacy as compare to other antioxidants to tackle the influenza virus (Mitchell et al., 2017). Due to antiviral property of vitamin E, it is viable option for treating viruses especially for curing children who suffer in hepatitis B. It can also play major role to reduce the replication of virus and improve the immunity against infections (Wu et al., 2016). The deficiency of vitamin E may cause ataxia, weak immune function, retinopathy as well as peripheral neuropathy (Aslam et al., 2017).

Selenium (Se)

Selenium acts as a main aspect in biological processes including improve immune system, enhances free-radical scavenging and aids from oxidative stress as well as preserve antibodies levels. Oxygen reactive species are produced by the oxidative stress that damaging the cells (Guillin et al., 2019). Thio-

redoxin reductase, glutathione peroxidase as well as glutathione reductase are selenoprotein enzymes in which selenium plays a crucial role. Similarly, It reduce the oxidation due to its antioxidant activity (Kieliszek, 2019).Therefore, 200 µg/day intake of selenium supplementation shows viricidal response against viral infections (Gombart et al., 2020). Selenium supplementation is a valuable source against hepatitis, influenza A as well as HIV viruses (Steinbrenner et al., 2015).

Iron (Fe)

Iron plays a pivotal role in strengthening the immune system, essential for both repair as well as for synthesis of DNA and protein, lymphocytes maturation, proliferation of cell and cellular respiration (Gupta et al., 2019). Lactoferrin is an iron bounding protein that serve as a first defensive line against attacking microbes (Kumar & Choudhry, 2010). The over dosage of blood serum iron is injurious to health because it linked with the replication of hepatitis B virus (Zou & Sun, 2017). For the defusing of viruses, iron chelates can be used for eliminating the unbound iron as well as regulate the cellular-iron levels through controlling gene expression (Luo et al., 2020). Beef, Cashew, chicken breast, mushroom, Oysters, pork, peas, pumpkin seeds, sunflower seeds and spanish are the main source of iron(Gombart et al., 2020).

Table 1. Immunity enhancer food constituents

Food constituent	Sources	Immunity enhancing properties	Reference
Vitamin A, C, D,E	• Milk and cheese, eggs, liver, green vegetables and dark orange (broccoli, carrots, pumpkin, spinach), orange fruits (mango, melon, peach, papaya, cantaloupe) (Vitamin A) • Broccoli, blackcurrants, citrus fruits, guava, kiwi, orange, pineapple, red pepper, strawberries, kiwi, tomato (Vitamin C) • Sunflower oil, vegetable oils, peanuts, nuts and seeds, wheat germ, eggs and salmon (Vitamin E)	Avoid to damaging immune cells (antioxidant) • Protect against oxidative stress • Proliferative responses by enhancing T and B-cells in body • Enhance immunity and fight against infection (Vitamin A) • Anti-inflammatory and aids in immune responses on antibody production as well as pulmonary (Vitamin C) • Enhance immune functions that regulate host protection against infections. • Antioxidant (Vitamin E)	(Arshad et al., 2020; Calder et al., 2020; Jayawardena et al., 2020; Mishra et al., 2020).
Selenium Iron	• Cereals, eggs, fish, meat, nuts, sunflower seeds, and tofu • Green leafy vegetables, pomegranate	Immuno-stimulant Properties • Increase propagation of activated T cells	(Charan et al., 2012; Mishra et al., 2020)
Flavonoids	• Green leafy vegetables and fruits	Regulate the immune system • Antioxidant • Anti-inflammation	(Arshad et al., 2020)
Probiotics	Fermented dairy products • Yogurt • Curd	Improve the immune function • Enhance gut functioning • Stimulate hypersensitivity responses	(François et al., 2020).

Flavonoids

Flavonoids are polyphenolic compounds that are mainly found in plant based diet such as fruits, vegetables especially in green leafy vegetables as well as in nuts. Proanthocyanidins is a group of flavonoids that is mainly reported in fruits, catechins and gallocatechins are monomer units of proanthocyanidins that act as a natural substrate of polyphenol oxidases. Numerous studies stated that flavonoids provide the immune-stimulatory properties including antioxidant as well as anti-inflammation properties (González-Gallego et al., 2010; Cho et al., 2016).

Carotenoids

Plants as well as microorganisms are major source for producing carotenoids. In plants, carotenoids are found as a micro-constituent that provide red, orange as well as yellow colors (Rao & Rao, 2007). In our diet, fruits and vegetables are considered as a main source of carotenoids. Fruits and vegetables constitute the major sources of carotenoid in the human diet (Agarwal & Rao, 2000). Cryptoxanthin, α-carotene, β-carotene, lutein and lycopene are kinds of carotenoids that accounts almost 90% in the human diet (Gerster, 1997).

NATURAL IMMUNITY ENHANCING FOODS

In human beings, glutathione is a potent antioxidant. It is very useful for scratching out the injurious free radicals as well as helpful for tissue repair, production of chemicals and proteins which are involved in the immunity. Glutathione is generally produced by N-Acetylcysteine (NAC) which is taken as supplement. Several surveys in animal studies of viral illness shows that N-Acetylcysteine (NAC) act as antioxidant by reducing the intensity and duration of sign by enhancing the cellular resistance and restoration. The orally recommended amount of NAC is 500-600 mg but it might be 400-2400 mg with the prescription of doctor.

Quercetin is a well-known bioflavonoid commonly present in fruits and vegetables. Several studies involving animal and laboratories shows that quercetin can prevent a variety of viral infections particularly the COVID-19 due to its antioxidants characteristics as well as helpful in the lung tissue repair. The Bromelain is a supplement and quercetin is used as supplement with combination of vitamin C. The daily recommend amount of quercetin is approximately 500 to 1000 mg. It is mostly found in apples, black tea, chili pepper, fennel leaf, grapes, green tea, red onion, oregano and green leafy vegetables (Arshad et al., 2020).

Flavonoids and carotenoids are also known as dietary antioxidants that are very helpful in immunity. Those foods including fruits and vegetables in which these compounds are rich in amount known as natural immunity boosting foods. Flavonoids and carotenoids are naturally occurring compounds that behave as anti-inflammatory agent, antioxidant and antiproliferation agent in human being which enhanced the immunity (Kaur & Kapoor, 2001). The daily intake of fruits and vegetables is beneficial for health as well as it boosts up the immunity. The major source of flavonoids related to fruits involves berry fruits like blackcurrants, blueberries, cranberries, raspberries and blackberries. Carotenoids present in a variety of fruits and vegetables with respect to its concentration. But the dark green vegetables and orange, yellow or red color plants parts are known as the main source of carotenoids (Britton &

Khachik, 2009). The natural foods including blueberries, cherries, cocoa, cranberries, broccoli, carrots, mango, spinach, sweet potatoes, raspberries, and tomatoes contain antioxidants, and play vital role the enhancement of the immunity to combat various health disorders.

THE ROLE OF DAIRY PRODUCTS FOR IMMUNITY ENHANCING

Fermented dairy products play a key role in fermenting plant fiber that are indigestible and changing them into chemicals that enter into the circulation and aid to support the immune system. Such foods also aid in reducing high blood pressure as well as help to rise growth of useful microbes that lower the risk of allergic reactions, diarrhea, malignant tumors, and gastrointestinal ulcer. Similarly, such foods contain hypochlectrolemic properties that ultimaltely helpful in decreasing the risk of cardiovascular disease. Yogurt and cheese are fermented products that are excellent sources for probitiocs (Conlon & Bird, 2015). A cup of skimmed yogurt consumption per meal is essential because it provide useful microbes, especially during illness or at the period of rehabilitation after surgery. So, take at least one or more cups of skimmed yogurt per day (Balch, 2006; Hunter, 2008).

PROBIOTICS ROLE IN STRENGTHENING THE IMMUNE FUNCTION

Probiotics are kinds of bacteria that is present in gut, particularly in the colon, these bacteria do not cause the infections but act as a defensiveasset against the illnesses. These microbes are approximately more than hundred trillion microbial cells in numbers and that is equal almost 10 times of body cells, and due to numerous benefits of these bacteria including fight against disease, these bacteria called probiotics or friendly bacteria. Probiotic bacteria are also known as a workshop that produce variousvital vitamins for the body like vitamin K. *Bifidobacterium lactis,* is one of friendly bacteria that aids to boost up cellular immunity (Ali et al., 2019). Many pathogenic microorganisms attack on digestive tract and causes bacterial contagion leading to illnesses in the digestive tract, like abdominal pain, bloating, vomit as well as cause fever, these microbes are main source of ulcerative colitis but probiotic bacteria present in the gut act as a protective guard and fight against these pathogenic microbes. Fermented dairy products are main source of these friendly bacteria or probiotics that shows a significant role in strengthening the digestive immunity as well as also beneficial for evading the colon cancer (Arunachalam et al., 2000; Gill et al. 2000; Jacobson et al., 1991).

ROLE OF DRINKING WATER IN STRENGTHENING THE IMMUNITY

Drinking one to two glasses in early morning aid to remove toxins from the body and similarly, superfluous intake of water throughout the day helps to enhance muscle strength. Additionally, a cup of water aids to lower blood pressure when take it before going to bath as well as drinking water before 30 minutes eating a meal is helpful for digestion and also aids to avoids heart attack if taken before going to sleep. More intake of water helps to protect and strengthen lining of mucous membrane in the respiratory tract, that assist the formation of white blood cells and antibodies which areresponsible to boost the immunity performance (Petraccia et al., 2006; Popkin et al., 2010).

IMMUNE SYSTEM AND VOLATILE OILS

Volatile oils like lavender oils and coconut oil are known as immunity booster that aids to boost-up the skin immunity by using as ointments also deliberate as defensive constituents that protect the body against infection (Kushi et al., 2012).

ROLE OF BALANCE HEALTHY DIET IN STRENGTHENING THE IMMUNE FUNCTION

Health balance diet an all most a complete diet that comprises all the macronutrients such as protein, fat, carbohydrates as well as micronutrients like vitamins and minerals in a balanced amount, that may be vibrant elements which help to sustain our immunity. By adopting healthy eating habits, we can endure our immune system, such as the more consumption of fresh fruits as well as vegetables of all sorts especially in a raw form is better because valuable nutrients are present in fresh fruits and vegetables that help to strengthen our immune system (Ali et al., 2019). Similarly, fish contain zinc that works to enhance male fertility as well as help to produce new blood cells which aids to fight against infections, yogurt is best source of healthy bacteria that provide health benefits in human and improve gut functioning. Likewise, protein content, omega 3 fatty acids and other micronutrients like magnesium are present in nuts as well as olive oil, mushrooms, fiber and garlic hold antioxidants that aid to destroy free radicals. It is compulsory to evade consumption of saturated fats, hydrogenated oils and starches in larger amount, specially potato chips, high fat meat, fast foods, fat dairy products as well as puddings like cake, jellies, cacao and oriental sweets because these are products contain more saturated fat, also lessening the consumption of sugars, carbonated drinks and juices because these foods have been exposed to decrease the action of white blood cells against attacking microbes and diminish the proficiency of the immune system in elder, also reduce the consumption of refined foods (White flour, and white sugars) and not use white flour but use whole flour that is better from white flour. Avoid smoking is essential because cigarette smoke contains several chemical substances and the nicotine is one of the most persuasive substance because it disturbs the central nervous system, more adrenaline secretion as well as blood pressure, fasten the metabolic processes and heartbeat, also disturbs the immune system since cigarette smoke encompasses more nitrogen dioxide ozone compound, that rusts antioxidant vitamins then causes breakdown of DNA, that is turned to accelerates weaken immunity and aging so avoid smoking because it cause production of free radicals which clang the immune cells in our body. Eating balanced healthy diet escorted by a simple exercise, walking 25-30 minutes per day with contact to indirect sunlight which also supports to form vitamin D which is also aids to boost and recover our immune system (Donsbach, 1985; Krause et al., 1999; Hodkinson et al., 2007; Munkyong et al., 2012).

DIET DURING COVID-19 PANDAMIC

In the stir of the COVID-19 epidemic, immunity strengthening considers an important duty in keeping up ideal health. As a familiar proverb “prevention is better than cure”. The nutrition plays a crucial role in determining usually health as well as immunity. Carbohydrates are rich source of sugar and energy; one gram of carbs provide 4 calories. more energy or sugar consumption may increase the risk

of diabetes as well as cause obesity and as we known that obesity play a crucial role in major disease, like hypertension, diabetes and cardiovascular diseases. So, eat carbohydrates in moderate amount and this will aid to control high sugar level as well as blood pressure and alleviate diabetes. For fitness and muscle development emphasis on protein rich diet it also helpful for improving immune system. Frequently consume fresh vegetables and natural products rich in Ascorbic acid, β-carotene and other vital nutrients (Mishra et al., 2020).

Some food items such as chime pepper, mushrooms, garlic, tomato as well as green leafy vegetables such as broccoli and spinach are also satisfactory source to provide flexibility against diseases in the body (Hopkins, 2020). Avoid high fat food or fast foods and use foods from plant source can aid to provide the boost energy for immunity enhancer. Our immune system is act as a first defense line by producing antibodies in the body against the infections that caused by several viruses as well as microbes. Literature indicates that, that people that consume plant based diet have been seemed to have better white blood cells (WBCs) as compared to those who do not consume diet from plant source, because plant based foods provide sufficient amount of nutrients that needed on regular based, as well as vegetarians consume diet low in fat.

Moderate consumption of fatty foods may also be defensive against infections because several studies, showed that function of WBCs may be impaired by the consumption of fat and oils as well as diet high in fat may also interrupt functioning of gut microbiota that supports immune system (Malter et al.,1989). Sustaining an ideal weight may helpful for strengthening the immune system. Obesity has been associated to prolonged risk for diabetes, heart attack and influenza as well as many other infections (Craddock et al., 2019). For weight loss diet from plant source are very effective because plant based diet are enrich in fiber, that provide mouthful feeling without deprived of additional calories. Body mass index (BMI) may regulated by fiber, that is linked to strengthen the immune system (Rinninella et al., 2019). Diet from plant source such as fruits, vegetables, legumes as well as whole grains are well known biomarkers to reduce inflammation (Soldati et al., 2018).

RECOMMENDATIONS

- Must evaluate the nutritional status of all the patients in hospital that are infected by COVID-19.
- Implement a good personal hygiene as well as maintain at least 5 feet distancing from other people.
- Use ethanol based hand sanitizer and facemasks.
- Improve protein intake, 1.5-gram protein per kg of body weight on daily base as well as ensure consumption of micronutrients (vitamins and minerals) rich foods.

CONCLUSION

Nutrition plays significant role for good health as well as for normal body functioning. It is the main pillar for both strengthening the immune system and protecting from microbial infections such as COVID-19. The immunomodulatory properties of nutrients found in diet can support the immunity through modulating the macrophages function against infections. Healthy balance diet is almost complete diet that can provide all the nutrients either they are macronutrients or micronutrients that are needed for proper functioning of immunity. The immunity mostly negotiated at the time of diseases or infections.

So, it is necessary to increase the consumption of raw as well as cooked fruits and green leafy vegetables, also enhance the intake of foods that are rich in antioxidants, evade junk and processed foods because these foods produce free radicals account in the body that provide benefit for viral infection. Adequate intake of vitamins and minerals are required on daily base because these are mandatory for better immune function. In the biological systems immunity is natural defensive system that tackle infectious microbes in the body.

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About the Contributors

Omar El Hiba is a Professor of Physiopathology, Neuroscience and Histology, Faculty of Sciences at Chouaib Doukkali University. He was born on September 12, 1985 in Marrakech-Safi state (Morocco) andgraduated in 2007 from Cadi Ayyad University (Morocco) with a bachelor's degree in Biology. In 2009, he graduated from the same university with a Master's degree in Life and Health Sciences. He started his PhD in Neuroscience and Animal Physiology and received his PhD in 2015 on the "Physiopathology of Hepatic Encephalopathy" from Cadi Ayyad University. Since 2016, Mr.El Hiba has held the position of Professor in the Department of Biology at the Faculty of Science, Chouaib Doukkali University (Morocco). He is a member of the Nutritional Physiopathologies Team and Associate Investigator in the Laboratory of Clinical and Experimental Neurosciences and Environment, Faculty of Medicine and Pharmacy, Cadi Ayyad University. Pr. EL Hiba is currently supervising several PhD projects on the physiopathology of hepatic encephalopathy and Parkinson's disease, and, since 2014, has been a member of the International Parkinson's and Movement Disorders Society (MDS), USA and the vice-president of the Moroccan Society of Ethics and Animal Research (MoSEAR). His research works, involving several other collaborators from USA, Spain, France and other countries, have been subjected to more than 60 publications as well as an edited book. Pr. EL Hiba has more than 38 international communications in several international congresses and symposia (Egypt, France, Canada, India, Sweden, Denmark, Germany, USA). He is also a member of editorial boardsofnumerous international peer reviewed journals, where he reviewed several papers with more than 18 international awards, grants and scholarships (IBRO, MDS, CNRST, ISHEN, NeuroMed, GDRI). (Arumugam Jayakumar - Editor) Arumugam Jayakumar is missing a biography.

Jayakumar Radhakrishnan is currently an Associate Professor/Scientist at the Neuropathology Unit, SFVAFRE, VA Medical Center in Miami, USA, as well as a Scientist at the Obstetrics, Gynaecology and Reproductive Sciences at the University of Miami Miller School of Medicine, Miami, Fl. He graduated from the Postgraduate Institute of Basic Medical Sciences, University of Madras, Chennai, India in 1998. He discovered the effect of the ammonia-detoxicating action of L-Arginine on experimentally induced convulsions in rats. He then continued his research as Research Associate in Bio-Organic Laboratory and created a Neurochemistry Laboratory at the Central Leather Research Institute, Adayar, Chennai, India. Later, from 2000-2004, he was a Post-doctoral Fellow at the Division of Neuropathology, Department of Pathology, University of Miami School of Medicine, Miami, FL, Research Assistant Professor until2012. His research area mainly focused on the understanding of the physiopathology of Hepatic Encephalopathy, especially the role of ammonia, gliopathy, neuroinflammation and brain edema in different animal models of acute and hepatic liver failures, as well as in chronic traumatic encephalopathy

(CTE). Dr. Jayakumar was honored with many international and national awards, including the American Association for the study of Liver diseases and American Liver Foundation Award, Stanley J. Glaser Award for outstanding scientists from the Stanley J. Glaser foundation, Florida, Distinguished Basic Science Research award, Miami VA. With over of 100 publications and 50 international communications, Dr.Jayakumaris considered as one of the eminent specialists in hepatic encephalopathy worldwide. His research area has gained particular scientific interest and was funded through over 10 international and national funded projects. He is currently investigating the mechanisms of SARS-CoV-2 infection in humans, as well as in experimental models of COVID-19. He recently discovered novel drugs to prevent COVID-19. He is currently an Editor in many journals including Current Issues in Molecular Biology, Frontiers in Neurosciences, BioMed Research International etc., and also acts as an Editorial Board member in more than a dozen international journals.

Tiziano Balzano is currently Postdoctoral research fellow at the HM CINAC, Hospital Universitario HM Puerta del Sur (Madrid, Spain). He completed his PhD in Neuroscience in the Laboratory of Neurobiology at the Príncipe Felipe Research Center (Valencia, Spain) on hepatic encephalopathy in September 2017. His PhD thesis was focused on the underlying mechanisms by which neuroinflammation produces cognitive and motor alterations in liver diseases. Now he holds the position of Postdoctoral research fellow and his works focus on the role of neuroinflammation and neurovascular unit in the pathogenesis of Parkinson's disease. Dr. Balzano has published over than 30 international articles, book chapters and conference papers in well recognized peer reviewed journals and international scientific meetings.

Faical Isbaine was born in Beni Mellal in the middle atlas mountains of Morocco, in 1986, and studied in the little town of Tiznit in the southern part of Morocco up to the age of 18. He moved to Marrakech in 2004 to pursue his college studies at the Cadi Ayyad University of Marrakech, where he obtained an MS in "Life Sciences and Health". He obtained his PhD degree in Neurosciences at the Aix-Marseille University, 2009-2015 (Marseille, France), after which he started a postdoctoral cursus at the Cleveland Clinic (Cleveland, Ohio) between May and August 2015. The Pr. Isbaine relocated to join the Neurosurgery Department at the Emory University Hospital (Atlanta, Georgia) and was part of the Movement Disorders Team clinic. Between 2016 and 2019, Faical was involved in Deep Brain Stimulation (DBS) surgeries at the EUH - from planning surgeries, intra-operative neurophysiological recording and stimulation, and postoperative lead localization and quality assessment, creating a tight link between the neurosurgery and neurology team. Attracted by the humanitarian, clinical and scientific impact of the DBS field, he trained to become an intraoperative neurophysiologist, actively participating in a few hundred surgical implantations. In July 2019, he was promoted to the position of Assistant Professor. Since then, and with the evolution of the clinical practice at the EUH, hehas supported all intraoperative neurophysiology and research related to it. His scientific interest evolved over time, from the social neurosciences and neural basis of human interactions; a field he cherished and strove to reengage in, to the fast evolving field of Deep Brain Stimulation in general and DBS for movement disorders especially, where the mechanisms and subtle neurophysiological signatures are still being investigated. Pr. Isbainehad the privilege of working with great mentors and collaborators, including Dr. Boussaoud (PhD advisor) and Dr. Gale (Post-Doc advisor), as mentors during key periods of his scientific cursus as well as others such as Drs. Gross, Willie, Boulis, Au Yong Great (EUH, Neurosurgery), Drs. Delong, Wichmann and Miocinovic (EUH, Neurology).

* * *

Aimrane Abdelmohcine is a researcher on human health and the environment. He graduated from the university Abdelmalik Essâadi, with a master's degree in Neuroscience and biotechnology in 2013. After graduation, he worked as a high school teacher in Essaouira. He is currently working on a Ph.D. in biological sciences and human health at Chouaib Doukali University. He has conducted and supervised bachelor students in the same university since 2015. Abdelmohcine Aimrane is a reader by morning, an experimentalist by day, and a writer by night

Muhammad Faizan Afzal is the author of "Nutrition: A Strategy for Curtailing the Impact of COVID-19 Through Immunity Booster Foods" in the book "Pathophysiology and Strategies for the Management of COVID-19". He received his BS(hons) in Human Nutrition and Dietetics from Government College University, Faisalabad and MS in Food Science and Technology studies from Government College University, Faisalabad. He is a Dietitian by profession.

Muhammad Haseeb Ahmad is currently working as an assistant professor in Department of Food Science, Government College University Faisalabad, Pakistan. He has also served as an assistant professor for one year in National Institute of Food Science and Technology, University of Agriculture Faisalabad, Pakistan. He received his doctoral degree from Hohenheim University, Stuttgart, Germany in 2016. During his stay, there he also work as a research associate in various research project relevant to various food discipline. Dr. Ahmad is an author of about 25 research publications along with 8 book chapters. He has also presented his research work in various national and international conferences. His area of research is food science with special expertise in process analytics and data mining.

Nazir Ahmad has been working as assistant professor and researcher since February 2013 in department of Nutritional Sciences. I hold PhD degree in Nutrition and Biotechnology processes. He has the experience of working with international scientists during his master and doctoral studies in France where he did his master in "immunological response to of milk proteins" from International French Institute for Agriculture (INRA), Nantes, France and PhD degree on "postprandial lipemia and hepatic function" from University of Lorraine, Nancy, France. His research output has significant application in real-world and more than 40 research papers published in well reputed impacted international journals with impact factor of 53.728. He has also published many book chapters and presented his work in conferences, seminars and trainings at both national and international levels His research interests are explore the techno-functional characteristics of processed nutrients and biological evaluation of bioactive molecules in food.

Lhoussaine Ammouta is a PhD student, Faculty of Sciences and Techniques (FST), Beni Mellal, Morocco.

Ranjit Barua is a Senior Researcher at Centre for Healthcare Science and Technology, IIEST-SHIBPUR. Core research area Bio-Mechanical System, 3D Bioprinting, Tissue Engineering.

Mostafa Bentahir holds a PhD in biological sciences since Mai 2000. He joined afterwards much known academic research institutions in KULeuven and UGent where he managed several scientific

research projects in the field of infectious diseases and contributed significantly in their success. Within CTM/DLD-BIO infrastructure, Dr. Mostafa Bentahir is currently using his background and expertise acquired during the last ten years to generate bacterial and viral models mimicking biological warfare pathogens. These models are mandatory to study and simulate security break that could arise from intentional release of a biological warfare agent in the nature.

Samia Boussaa is currently Professor in ISPITS (Institut Supérieur des Professions Infirmières et des Techniques de Santé) of Ministry of Health in Marrakesh (Morocco). She obtained her PhD, in Ecology and Epidemiology, at Cadi Ayyad University (Morocco) and at Strasbourg University (France) in 2008. Her research is focused on Medical Entomology, Vector Borne Disease and especially on Epidemiology of leishmaniasis in Morocco.

Hicham Chatoui was born in Beni Mellal (Tagzirt), Morocco, in 1984. He is PhD in neurosciences & physiology, laboratory of environment, neurosciences and pharmacology at the faculty of sciences of semlalia (FSSM), Cadi Ayyad University (UCA). He obtained a master's degree in research in life sciences and health, option: Anthropobiology, FSSM, UCA, Morocco. He was a temporary teacher from 2009 until 2014 at the same university. He is pedagogical director and teacher-researcher at the school of engineering of health and biomedical engineering and agribusiness engineering at the Private University of Marrakech (UPM) since 2015. His current research focuses on the neurobehavioral and neurophysiological effects of water stress and work stress, neurotransmitters: serotonin, dopamine, GABA, vasopressin; glial markers and ependymocytes; behavior; anxiety; locomotor activity; motivation; stress, biomedical engineering, health engineering, kidney function, nutrition, food safety, neurotoxicity, immunology, environment and climate change.

Karima Chgoura is an MD from the Faculty of Medicine and Pharmacy, Cadi Ayyad University, Morocco.

Pallab Datta is an assistant professor of National Institute of Pharmaceutical Education and Research (NIPER) Kolkata. Research area modern medicine, drug delivery.

Ahmed Draoui was born in Marrakech, Morocco, in 1986. He is PhD in neurosciences & physiology, laboratory of environment, neurosciences and pharmacology at the faculty of sciences of semlalia (FSSM), Cadi Ayyad University (UCA). He obtained a master's degree specializing in natural science education (SVT), ENS, UCA, Morocco. His current research focuses on the prodromal phase and non-motor symptoms of Parkinson's disease.

Mohamed Echchakery is a Professor of Infectious Biology & Laboratory Quality at the Higher Institute of Health Sciences, Hassan 1st University of Settat, Morocco. He held a doctorate in Ecology- Epidemiology - Parasitology & Molecular Biology (2018), from the Faculty of Sciences, Semlalia Marrakech, University Cadi Ayyad, Morocco. He worked on different epidemiological aspects namely virological, parasitological, bacteriological, etc. He has published several scientific publications in infectious biology (epidemiology, parasitology, bacteriology, virology.).

Souad El Amine is a Master's student in Cadi Ayyad University, Marrakesh, Morocco.

Soraia El Baz graduated PhD in 2015 from Faculty of Sciences Semlalia, Cadi Ayyad University, specialty "Microbiology and Environmental Toxicology" with more than 15 articles, book and book chapters in numerous international journals as well as being reviewer for several scientific papers.

Moulay Abdelmonaim El Hidan was born in 1985 in Marrakech-Safi state (Morocco). In 2004 he obtained his baccalaureate, option; "Experimental Sciences". Later he continued his university studies and was graduated in 2007 from Cadi Ayyad University (Morocco) with a bachelor degree in Biology. 2 years later, Pr. El Hidan was graduated from the same university with Master's degree. From 2011 to 2018, Pr. EL Hidan held the position of high school professor of Biology. At the same time he completed his PhD project and was graduated PhD in 2016, from Cadi Ayyad University, specialty Ecophysiology and epidemiology. Since 2018, Mr. EL Hidan was nominated as professor in the Ibn Zohr University (Morocco) and associate investigator in Cadi Ayyad University. Pr. EL Hidan is currently supervising several PhD and Master's projects with different research interests aiming the scorpion venom toxicology and climate change effects on Vector-Borne diseases spread with more than 20 papers and book chapters in numerous international journals as well as being reviewer for several scientific papers in addition to around 40 communications in prestigious international congresses and symposiums.

Souad El Mouahid is a professor in Health Department in Higher Institute of Nursing Professions and Health Techniques, Health Department of Marrakech-Safi.

Halima Gamrani is a professor of neuroscience, head of the laboratory of Neuroscience, Pharmacology and Environment, FSSM, UCAM.

Muhammad Imran is Assistant Professor in the Department of Food Science, Faculty of Life Sciences, Government College University, Faisalabad–Pakistan since September 03, 2012. Dr. Muhammad Imran completed his Doctorate (Food Technology) from National Institute of Food Science and Technology, University of Agriculture, Faisalabad. He won the Indigenous and IRSIP (Department of Food Science and Human Nutrition, Michigan State University, East Lansing, USA) Fellowships for completion of doctorate research funded by HEC, Islamabad, Pakistan. Dr. Muhammad Imran has expertise in extrusion technology, microencapsulation, lipids chemistry, sensory evaluation and food process engineering. Until today, Dr. Muhammad Imran has authored 70 publications (International & National) in various Impact Journals of Scientific repute and written 10 Book Chapters as principal author and co-author. Dr. Muhammad Imran has attended several International Conferences (held nationally and locally) as Invited and Keynote Speaker and also participated as organizing member to conduct International Conferences, Seminar and Workshops etc. Dr. Muhammad Imran is the Life Time Member of PSFST.

Simran Kaur is a keen researcher working on research in various fields of pharmacy and pharmacology domain including neuroscience, behavioural sciences, cancer research and many more. Currently working with Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Ludhiana.

Raymond Klevor is a resident with the Department of Neurology, Ar-Razi Hospital, Mohammed VI University Medical Center, Marrakesh.

Karima Lafhal is a PhD student at Metabolic Platform, Biochemistry Laboratory, Faculty of Medicine, Cadi Ayyad University, Marrakech, Morocco.

Asmae Lamrani Hanchi is an assistant professor in microbiology since October 2019 in the Faculty of Medicine of Marrakech, Morocco. Specialist in biological analysis since 2016.

Natalia López González del Rey graduated in Biology at the Universidad Autónoma de Madrid in 2014. She spent her third year of her degree in Albert-Ludwigs Universität in Freiburg, Germany. In 2015, while she was doing a master in Neuroscience, she joined CINAC to work on her Master thesis about the diversity of striatal interneurons in parkinsonian models. Since 2017 she is doing her doctoral thesis studying different compensatory mechanisms in several parkinsonian models, to elucidate the ethiopathology and progression of Parkinson Disease. In the beginning of 2019, she spent six months in Universidad Austral de Chile working in the field of nanobodies against parkinsonian hallmarks in order to develop molecular tracers useful for immunohistochemistry and neuroimaging techniques.

Aaron Pambu Lelo is a Junior Lecturer Assistant at the faculty of Science, Department of Biology, University of Kinshasa, DR Congo and Researcher at National Institute of Biomedical research, Kinshasa, DR Congo. He has a Master degree from Northeast Normal University, Changchun, Jilin Province, China. currently he is a PhD student at the University of Kinshasa.

Hanane Rais is a professor of higher education at the Faculty of Medicine and Pharmacy of Marrakech. Specialty: Pathological anatomy. Master's Degree: Biopathology, Epidemiology, Public Health and Biomedical Research.

Es-Said Sabir is a PhD student at Metabolic Platform, Biochemistry Laboratory, Faculty of Medicine, Cadi Ayyad University, Marrakech, Morocco.

Lahcen Tamegart currently works at the Department of Biology, Cadi Ayyad University. Lahcen does research in animal physiology, Neuroscience and Neuropharmacology. Works on the effects of lead exposure on central nervous system of meriones shawi and neuroprotective effect of some medicinal plants.

Amira Zaky is Professor of Biochemistry at Faculty of Science in Alexandria University-Egypt. Her research line focuses mainly in investigating novel signalling pathways that contribute to the initiation events and eventually lead to neurological disorders progression. She is specifically interested in studying the role of oxidative stress and its associated modulation in the activity of the redox sensor protein Apurinic/Apyrimidinic Endonuclease 1/Redox Factor-1 (APE1/Ref-1) as a Pleiotropic pro-survival protein. Dr. Zaky is an African regional committee member of the governing council of the international brain research organization (IBRO) since 2016 and a member of the Mediterranean neuroscience society (MNS) since 2017.

Abdellah Zinedine is a Permanent Professor at the Chouaib Doukkali University, El Jadida, Morocco. He is a former Scientist at the National Institute of Hygiene (INH) of Morocco and co-founder and General Secretary of The Moroccan Society for Mycotoxicolgy (MSM) since 2011. He has served as an Expert member at the The Centre National pour la Recherche Scientifique et Technique (CNRST)

of Morocco from 2011-2014. He is a member of the Executive Committee of the Safe Mediterranean Food Network (SAMEFOOD) network (IAMZ-Zaragoza-Spain) since 2014. He has published book chapters and more than 50 international scientific papers. Prof Zinedine has coordinated National projects and have been involved in collaborative projects at an international level especially with European and African research teams. His research is mainly focused on Food Microbiology and Toxicology, Food contaminants, Risk assessment, with a special interest to mycotoxins.

Nadia Zouhairi is a PhD in Neurosciences, University Cadi Ayyad, Marrakech Biology High School teacher, Ministry of National Education.

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