Open Access

SCHOLARENA

Journal of Infectious Diseases and Pathogenesis

REVIEW ARTICLE

ISSN: 2577-7939

The Epidemiology, Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19): A Review

Mouna EL Fane[1], Houda EL Fane[2], Mustapha Sodqi[3] and Imane Sellam[1]

[1]*Faculty of Medicine and Pharmacy, University Ibn zohr, Agadir, Morocco*
[2]*Faculty of Sciences, University Chouaib Doukkali, EL Jadida, Morocco*
[3]*Faculty of Medicine and Pharmacy, University Hassan, Casablanca, Morocco*

***Corresponding author:** El Fane Mouna, Faculty of Medicine and Pharmacy, University Ibn zohr, Agadir, Morocco, Tel: 212 660832362; E-mail: elfanemouna@gmail.com

Citation: Mouna EL Fane, Houda EL Fane, Mustapha Sodqi, Imane Sellam (2020) The Epidemiology, Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. J Infect Dis Pathog 3: 105

Abstract

In December 2019, a new coronavirus, named SARS-CoV-2, has emerged from China causing pneumonia outbreaks first in the Wuhan region and have now spread worldwide becoming an emergency of major international concern. The novel coronavirus SARS-CoV-2 (Covid-19) is one of the causes of respiratory infections that can spread to other people through respiratory particles, and can cause symptoms such as fever, dry cough, shortness of breath, anorexia, fatigue. In addition to the respiratory system, this virus can infect the digestive, neurological, cardiovascular and the haematological system. Diagnosis is based on the Reverse transcriptase polymerase chain reaction testing and CT scan. The imaging performance on chest CT scans from COVID-19 patients mainly manifested as bilateral ground-glass opacities in the lung periphery. Mortality is associated with older age, comorbidities, higher d-dimer, C-reactive protein concentrations and lower lymphocyte counts. Treatments, including antiviral agents, chloroquine and hydroxychloroquine, corticosteroids, immunoglobulins. This paper reviews the literature on all available information about the epidemiology, diagnosis and treatments of COVID-19.

Keywords: Coronavirus Disease 2019; COVID-19; SARS-CoV-2; Clinical Manifestation; Laboratory Examination

Introduction

Human coronavirus is an important agent causing mild to severe respiratory tract infections in humans [1]. In the past decades, two coronaviruses, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS) have caused outbreaks of severe respiratory infections in community settings around the world [1]. Since the end of 2019, a novel coronavirus with person to person transmission has spread to many other countries worldwide [2]. The novel coronavirus named 2019-novel coronavirus (2019-nCoV), and later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. The World Health Organization (WHO) named this novel coronavirus disease as COVID-19 [3]. The transmissibility is far exceeding that of SARS and MERS [2]. Therefore, the number of reported cases has been increasing rapidly since it was first detected [1]. SARS-CoV-2 is currently the world's most pressing public health threat and has a significant impact on the lives of people around the world [4].

On January 30, 2020, the WHO has declared the SARS-CoV-2 outbreakas a global health emergency of international concern. The pandemic is accelerating at an exponential rate and at risk of escalating into a global health emergency [2]. Patients with COVID-19 develop pneumonia with associated symptoms of fever, cough, and myalgia or fatigue [5]. SARS-CoV-2 can also cause enteric, hepatic, and neurologic diseases [1]. Infection often leads to severe clinical symptoms and high mortality [6]. The current diagnostic criterion for COVID-19 is the positive result of a nucleic acid test by real-time reverse transcription polymerase chain reaction RT-PCR [5]. CT imaging plays a critical role in the diagnosis and the monitoring of disease progression showing a bilateral ground-glass opacities in the lung periphery [2,5]. This review focuses on SARS-CoV-2 infection in order to provide reference for the understanding of the clinical and biological features of this infection.

Methodology

Articles were extracted, irrespective of time, using PubMed, Embase, and Google Scholar search engines, searching terms "COVID-19", "SARS-CoV-2", and "2019-nCOV" in titles, abstracts and keywords. Afterwards, clinical trials, clinical reports, case reports were briefly reviewed.

Results

Epidemiology of SARS COV-2

Current Epidemiology of SARS COV-2

The WHO was informed on December 31, 2019, about a pneumonia outbreak in Wuhan, Hubei province (China), a city with 11 million inhabitants were the largest number of confirmed cases was reported [3,7]. Outside of China, the first case of the disease in Thailand and Japan was confirmed on January 13 and 16 respectively [8]. The disease causing virus has since spread to other regions in Asia, Europe, North America, South America, Africa, and Oceania, developing into a global 2019–2020 COVID-19 pandemic by March. This infection has been subsequently span to every continent of the world except Antarctica [9]. Up to the submission date, this novel coronavirus SARS-CoV-2, has been diagnosed in more than 31 103 347 people in the world according to the WHO. SARS-CoV-2 is responsible for more than 397 388 deaths around the world [4]. China had more than 80,000 confirmed infections but has largely stemmed the surge using drastic social distancing measures. Italy had experienced some of the highest death rates worldwide [7].

Initial reports from these countries showed recent travel or close contact to patients that had traveled to China. This was followed by local spread from person to person [3,7]. To date, the original source of the viral outbreak remains unknown [10]. The first discovered place of the novel SARS-CoV 2 was reported as a wet market named Huanan Seafood Market, Wuhan, China, where there is a chance of transmission of pathogens from wild animals to humans [7, 8]. The facility is said to house many live wildlife ready to be sold for consumption [11]. The most likely natural reservoir of SARS-CoV 2 is bats, because of the close genetic similarity that SARS-CoV-2 with bat coronaviruses. In addition, pangolin is assumed to be involved as an intermediate animal reservoir for the transmission of novel virus to humans [8,11,12].

Transmission of SARS-2

SARS-Cov2 is assumed to be more contagious and more infectious than SARS-CoV and MERS-CoV with R0 varied from 2.0 to 4.01 [8,13]. Studies of familial aggregation cases infected with SARS-CoV showed that the spread of SARS-CoV occur during the diseased period, mostly in the population with a history of living together or having close contact with confirmed patients [13]. Person to person transmission of droplets is the main way the virus spreads [7]. Other possible route for transmission of COVID-19 is fomite exposure, which involves an inanimate object to carry a pathogen from one susceptible person to another during touching the surface, followed by eyes, nose, or mouth. Studies have shown the virus survives in different surfaces for days and remains viable in aerosols for hours [8,13]. The viability of the coronavirus in aerosols, plastic, stainless steel, copper and cardboardwere found to be 3, 72, 72, 4 and 24 h respectively [8,13]. Since the virus is detected in anal swabs and in the blood of patients infected with COVID-19, infected patients can spread the pathogen fecal-oral or through humor [14]. The highest transmission rates have been reported to correlate with disease severity and are particularly pronounced in hospital settings [13].

However, transmission of virus from asymptomatic patients has been reported, with high titers of viral load on pharyngeal samples of minimally symptomatic patients during the initial days of the disease [7,8]. Little is known about the seasonality of COVID-19 [15]. It was suggested that the transmission rate and stability of SARS-CoV-2 can be varied with different environmental parameters (temperature, humidity, sunlight etc). However, there is no strong evidence about decreased transmission rates of SARS-CoV-2 in temperate regions like African countries [8]. The scientists report that the new coronavirus is most likely to become a seasonal respiratory disease. It becomes more active in winter, when it enters people's bodies by droplets, and it spreads faster in cold and dry air [8]. However, there have been confirmed cases across the ocean in the southern hemisphere, suggesting that the virus is resistant. Admittedly, the seasons can affect it, but they do not necessarily make it disappear. Therefore, it is too early to say whether the new coronavirus is seasonal [11].

Virology

Coronavirus is a single- enveloped RNA virus, from the genus Betacoronavirus with a circular or elliptic shape and a diameter of 60-140 nm. It consists of four types, namely α-CoV, β-CoV, δ-CoV and γ-CoV [11]. Six species of coronavirus are known as infectious in humans, four of them, namely HKU1, NL63, 229E and OC43, are prevalent and typically cause common cold symptoms in immunocompetent individuals [1]. Coronavirus targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor, an entry receptor for SARS-CoV-2 [16]. A study, presented the crystal structure of the C-terminal domain of SARS-CoV-2 (SARS-CoV-2-CTD) S protein in complex with human ACE2, reveals a hACE2-binding mode similar overall to that observed for SARS-CoV. However, atomic details at the binding interface lead to higher affinity for receptor binding than SARS- receptor-binding domain (RBD).

Additionally, a panel of murine monoclonal antibodies and polyclonal antibodies against SARS-CoV-S1/RBD were unable to interact with the SARS-CoV-2 S protein, indicating notable differences in antigenicity between SARS-CoV and SARS-CoV-2 [17]. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembranes erine protease, TMPRSS2, facilitates cell entry via the S protein [16]. Whole genome sequencing and phylogenetic analysis reveal that the SARSCoV-2 is similar to some beta coronaviruses detected in bats, but it is distinct from SARS-Cov and MERS-CoV

[5]. Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA viaits RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles. These viral life cycles teps provide potential targets for drug therapy including viral entry and immune regulation pathways [16].

Physiopathology

Peak protein (S) is the most important means of the pathogenesis of SARS-CoV-2. It mediates entry into target cells through ACE2, which is expressed by epithelial cells in the lung, intestine, kidneys, and blood vessels [18- 20]. As a result, COVID-19 may cause multi-organ failure in extremely severe cases [8]. Expression of ACE2 is predominantly within type II alveolar cells of the lung. Patients with COVID-19 would therefore manifest a spectrum of upper and lower respiratory tract symptoms [19]. The density of ACE2 in each tissue correlates with the severity of the COVID-19 disease in that tissue. As the disease progresses, respiratory failure and consequent death may occur [8]. Histological case of a patient who died from SARS-2 infection show diffuse alveolar damage with hyaline membrane formation, consistent with severe acute respiratory distress syndrome (ARDS) [7]. Both innate and adaptive immune responses are essential to control and eliminate SARS-CoV-2 infections. SARS-CoV-2 infect macrophages and monocytes, and then macrophages present CoVs antigens to T cells, followed with T cell activation and differentiation. This process is accompanied by the production of cytokines associated with different T cell subsets leading to immune response amplification [1].

The subsequent specific T cell activation and humoral responses lead to effective viral clearance [20]. The severity of SARS-CoV-2 infection is a result of a complex interplay between the ability of inhibiting viral replication early on and possible damage induced by an overactive immune response leading to immunopathological injuries to different organs [1]. Sexual diamorphism has been suggested, but not proven. Cellular studies reveal that the expression of ACE2 is attenuated in females, in keeping with the epidemiological observation that the majority of COVID-19 infections to date have occurred in men [19]. Other studies reported that reduced susceptibility of females to viral infections might be attributed to the protection from X chromosome and sex hormones, which play an important role in innate and adaptive immunity [21].

Clinical Features

Incubation Period

The incubation period of novel coronavirus is generally between two and fourteen days, with an average of five days [8]. Onset of symptoms has been reported up to 14 days after exposure, providing basis for the length of quarantine/ self-isolation [7]. Experts suggest 14 days for quarantine [22].

Respiratory Symptoms

COVID-19 has many clinical features similar to SARS. The COVID-19 infected person may be symptomatic, presymptomatic, and asymptomatic [7, 8, 23]. Although symptoms are characterized as nonspecific, they often resemble influenza more than the common cold. Predominant respiratory symptoms include dry cough, and dyspnea [7, 23]. Pharyngodynia, nasal congestion, and rhinorrhea have been reported in patients with COVID-19 [23]. Fever could be absent in a significant part of patients at initial presentation. Mild symptoms are observed in most cases, whereas complicated and very-complicated symptoms are reported for approximately 14% and 5% respectively [8]. In more severe cases, infections could lead to ARDS and even death. The complicated symptoms include egalement sepsis and septic shock, multi organ failure, including acute kidney injury, and cardiac injury [8].

Extrarespiratory Symptoms

Although the main target cells for the virus to infect are epithelial cells and macrophages of the respiratory tract, COVID-19 RNA has been detected in the small and large intestine, lymph nodes, spleen, liver, heart, kidney, skeletal muscle, adrenal gland, and cerebrum, suggesting extra-pulmonary dissemination and virus localization in different types of tissues and fluids [22,20].

Neurological Manifestations

Neurologic manifestations ranged from fairly specific symptoms (loss of sense of smel or taste, myopathy, and stroke) to more non specific symptoms (headache, depressed level of consciousness, dizziness, orseizure). These symptoms may be non-specific manifestations of the disease or compatible with a systemic inflammatory response [24].

Olfactory Dysfunctions

A significant proportion of COVID-19 patients (20-60%) appear to have an acute loss of smell which may be an early symptom associated with COVID-19 and a screening tool for possible COVID-19 infection [23,25]. In addition, smell and/or taste loss has been noted in the absence of other known symptoms of the disease and the diagnosis of COVID-19 could be missed [26]. As a result, the patients were not isolated and the spread of the virus continued [25]. Morever, a number of high-profile studies have found an association between olfactory loss and increased 5-year mortality rates [26]. Physicians should be aware that smell, and taste

disorders could be presenting symptoms of COVID-19 [23]. They must keep in mind that olfactory disorder may appear before the rest of the complaints of cases, yielding the symptoms important for the early detection of the disease [23,26]. The pathophysiological mechanisms leading to the olfactory and gustatory dysfunctions in the COVID-19 infection are still unknown [25,26].

It could be assumed that the virus caused an inflammatory response in the nasal cavity that temporarily impedes odorants from reaching the olfactory receptor neurons [26]. However, studies observed that some patients with normal acoustic rhinometry did not recover their olfaction, suggesting that nasal inflammation and related obstruction were not the only etiological factors underlying the olfactory dysfunction in viral infection [25]. He Moreover, Multiple viruses can use the olfactory nerve as a shortcut into the central nervous systems, including influenza virus, and cause even long-term olfactory disorders in some cases suggesting a specific tropism of these viruses for structures of the olfactory sensory epithelium [27,28].

Encephalopathy

SARS-2 may exhibit neuroinvasiveness that could be associated with neurological manifestations such as febrile seizures, convulsions, change in mental status, and encephalitis. Some patients with COVID-19 may show nonspecific neurological symptoms, such as confusion, headache and stroke [7,29,30,24]. Although neurotropic and neuroinvasive capabilities of coronaviruses have been described in humans, the neuroinvasive potential of COVID-19 remains poorly understood [29,30]. The pathologic mechanism may be from the central nervous system (CNS) invasion of SARS-CoV2 [6]. The first reported case of COVID-19 infection with positive findings in CSF raises concerns regarding virus-associated neuroinvasion [30]. SARS-Cov-2 can spread from the respiratory tract to the CNS through transneuronal and hematogenous routes, causing inflammation and demyelination [29,30]. Also, the virus could even use the enteric nervous system and its sympathetic afferent neurons to reach the CNS [31]. The brain reportedly, like most other organs, expresses the h ACE2 considered to be the entry point of the SARS-CoV-2 viruses in humans and is therefore not immune to viral infection [6,31].

It is currently suspected that the neuroinvasive potential of SARS-CoV2 plays a key role in the respiratory failure of COVID-19 patients [24,29]. During the epidemic period of COVID-19, when seeing patients with these neurologic manifestations, physicians should consider SARS-CoV-2 infection as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and prevention of transmission [6]. Medical imaging will certainly play an important rule to detect abnormalities in olfactory bulb, cranial nerves, and brain of COVID-19 patients [25]. Though SARS-CoV-2 is yet to be detected in cerebrospinal fluid, SARS-CoV with similar structural and functional features has been detected in the cerebrospinal fluid of patients, indicating the ability of the virus to breach the extremely rigid blood–brain barrier [31].

Neuromuscular Manifestations

There were some reports of neuromuscular complications of SARS, mainly consisting of either an axonal peripheral neuropathy or a myopathy with elevated creatinine kinase [24]. Neuromuscular complications may be directly or indirectly related to coronavirus infection [30]. Although ACE2 was identified in nervous system and skeletal muscles, there is no current evidence of direct viral invasion with inflammation and degeneration of motor neurons and peripheral nerves as seen in some viral infections (poliovirus, West Nile, herpes zoster, cytomegalovirus, etc.) [30, 32]. There have been reports of an association between Guillain–Barré syndrome (GBS) and coronavirus infections with interval between the onset of viral illness and the first symptoms of 5 to 10 days, similar to the interval seen with other infections [30, 32]. Coronavirus infections may also be associated with myopathies especially in very sick patients. A risk factor for developing critical illness myopathy is use of non-depolarizing neuromuscular blocking agents [30]. This injury could be associated with ACE2 in skeletal muscle. One other reason was the spread vasculitis seen inmany organs, including striated muscle [24]. Significantly elevated proinflammatory cytokines in serum may also cause skeletal muscle damage [6].

Gastrointestinal Symptoms

The gastrointestinal tropism of coronavirus may explain the frequent occurrence of gastrointestinal symptoms [4,33]. Among COVID-19 patients, gastrointestinal symptoms reported during disease progression varied widely [4]. Diarrhoea, decreased appetite, nausea, vomiting, abdominal pain and gastrointestinal bleeding was reported [4,33]. Different possible causes might account for digestifs features. Direct virus attack on the digestive tract could have resulted in diarrhoea [4,34]. S ACE2 receptor is highly expressed in the human small intestine, mainly inproximal and distal enterocytes, so the virus may induce diarrhea by binding to ACE2 receptor, interfering with its normal function [33,35,36]. This is supported by the detection of viral nucleocapsid protein in epithelial cells [4,34]. Furthermore, SARS-CoV-2 damages the digestive system through an inflammatory response [34]. The administration of anti-viral drugs might also have contributed since they commonly induce nausea and diarrhoea. Finally, dysbiosis of intestinal microbiota induced by antibiotics could have exacerbated digestive symptoms [4]. Diarrhoea can be one initial symptom and may even occur earlier than pyrexia or respiratory symptoms in some cases [4].

This faecal source can lead to fomite transmission, especially when infective aerosols are generated from the toilet plume [33]. Digestive symptoms are more pronounced in severe forms of the disease. One possibility is that digestive symptoms indicate viral load and replication within the gastrointestinal tract, which leads to more severe disease [34]. Another possibility is that patients with extra-pulmonary symptoms reported later for care because they did not initially have typical respiratory symptoms, and

thus presented at a later and less curable stage of disease [34]. Clinicians should be alert of the gastrointestinal symptomatology of Covid-19 [33]. Apart from gastrointestinal symptoms, patients with Covid-19 can have liver injury with raised enzymes found in blood tests [33]. Most of the liver injuries are mild and transient, although severe liver damage can occur [33]. While the mechanism of liver injury is not fully understood, the injury can be due to direct viral infection of hepatocytes, immune-related injury, or drug hepatotoxicity. There is also suggestion that the virus can invade the human body by binding to the human ACE-2 receptor, which causes liver tissue injury by upregulation of ACE-2 expression [33,34,20].

Cardiovascular Manifestations

The clinical cardiovascular manifestations of covid-19 are common [37]. They include elevation of cardiac biomarkers, cardiac arrhythmia, arterial and venous thromboembolism (VTE), and cardiogenic shock and arrest [38]. The mechanisms of cardiovascular injury from covid-19 have not been fully elucidated and are likely multifactorial. SARS- CoV-2 viral particles have been identified by RT- PCR in cardiac tissue in some cases supporting that direct cardiotoxicity may occur [38]. Although histologically unproven, SARS-CoV-2 has the potential to directly replicate within cardiomyocytes and pericytes leading to viral myocarditis [39]. Systemically elevated cytokines are also known to be cardiotoxic and have the potential to result in profound myocardial injury [39]. Furthermore, hyperinflammation with cytokine release may lead to vascular inflammation, plaque rupture and thrombus formation, myocardial inflammation, a hypercoagulable state [38]. Other systemic consequences of COVID-19 infection, including sepsis and disseminated intravascular coagulation, may also mediate cardiac injury [38].

Myocardial Injury

Acute myocardial involvement in COVID-19 is currently described as 'acute cardiac injury', defined as blood levels of cardiac biomarkers (high-sensitivity troponin I) above the 99th-percentile upper reference limit. It is described in more than 20% of patients and seems to be related to increased mortality [40]. The diagnosis is based upon clinical data, imaging and biomarkers of acute cardiac damage; the identification of the cause, either myocardial inflammation, or necrosis, is clinically relevant for the correct diagnostic and therapeutic management of patients, especially those with severe infections admitted to the intensive care unit (ICU) [40]. Patients with elevated troponin who are otherwise clinically stable do not require extensive cardiac imaging during the acute phase of COVID-19 if point of care cardiac ultrasound is not available [39]. Contrary, patients with hemodynamic instability or ventricular arrhythmias require more detailed evaluation, cardiology consultation [39].

Venous Thromboembolism (VTE)

Patients with covid-19 are at increased risk of VTE [38,15]. However, their incidence, may have been highly underestimated due to the paucity of specific imaging tests performed [41]. The available biological and clinical data raise concerns about unsuspected pulmonary embolism. Chen et al. Are clearly showed that patients with COVID-19 are at risk of acute pulmonary embolism [42]. COVID-19 is characterized by coagulation activation and endothelial dysfunction which promote the occurrence of VTE [41]. Immobilisation, sepsis are also a common cause of VTE [15,43]. It has been postulated that the high mortality observed among COVID-19 patients may be partly due to unrecognized pulmonary embolism and pulmonary in situ thrombosis [41]. Recents studies reported a positive correlation between elevated D-dimer levels on admission and in-hospital COVID-19 mortality [42]. Additionally, the conventional coagulation parameters of ICU patients were significantly higher than those of non-ICU patients [15,38]. Laboratory tests, including D-dimers, prothrombintime and platelet count should be performed to stratify patients at risk who should be given antithrombotic prophylaxis with low molecular weight heparin (LMWH) [42,15]. Furthermore, patients requiring hospital admission for COVID-19 pneumonia should receive prophylactic LMWH. Furthermore, in the case of elevated D-dimer levels on admission or sudden clinical worsening, CT pulmonary angiography should be considered [42].

Cutaneous Manifestations

Is not much information of cutaneous involvement in COVID-19 in the literature [44]. Few cases of rashes on patients with laboratory-confirmed Covid-19 were described [45]. Cutaneous manifestations are mainly aspecific and highly variable [46,47]. Erythematous rash, localized or widespread urticaria, seem to be the most common manifestations in acute severe cases [48, 49]. A skin rash with petechiae has also been described as a possible initial presentation of COVID-19 disease, chill burns, as well as acute hemorrhagic edema of infancy associated with coronavirus [50,51]. An "epidemic" of acute and self-healing vasculitic lesions (mottling, livedo reticularis, petechiae rash, purpura, chilblain) in asymptomatic children and adolescents was observed after the first autochthonous cases of COVID-19 reported in Italy. This vasculitis is very characteristic, it's multifocal and often asymmetric, appearing a few at a time in 2-3 days, then undergoing a different evolution from the initial erythema to infiltration or exudation or ecchymosis, and eventually self-healing in 12-20 days [52]. The pathogenesis of cutaneous manifestations remains unknown. Skin manifestations could be related with the COVID-19 viral infection or with the immune response [50].

Vasculitic lesions could be associated with a series of thrombotic events such as disseminated intravascular coagulation (DIC), hyaline thrombus formation, acral ischemia, and thrombocytopenia [47]. The cutaneous manifestations can be inaugural of the disease before fever or any respiratory symptom [45]. Therefore, clinicians should be warned that skin manifestations in the current context of the COVID-19 pandemic may be the first manifestations of this infection, even without any respiratory symptoms [49]. It is essential to take into account and promote the potential recognition among clinicians of this possible skin manifestation of covid-19, and lead to think about testing COVID-19 in these case [45,46].

Diagnosis and Imaging

Laboratory tests for Coronavirus

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) Testing

Currently, the fluorescence-based real-time RT-PCR method is the current gold standard for detecting SARS-CoV-2 from respiratory specimens [19]. RT-PCR is sensitive and can effectively confirm early SARS-CoV2 infection [53]. Current diagnostic tests include RT-PCR, real-time RT-PCR (rRT-PCR), and RT loop-mediated isothermal amplification (RT-LAMP) [22]. Real-time fluorescence quantitative RT-PCR and viral gene sequencing are the gold standard for the diagnosis of COVID-19 [22,54]. The test utilizes specific primers and probes that target the RNA-dependent RNA polymerase (RdRp), envelope and nucleocapsid genes of SARS-CoV-2, among which the RdRp assay has the highest analytical sensitivity (3.8 RNA copies/reaction at 95% detection probability) [19]. The RT-PCR results usually become positive after several days (2-8 days) [22]. Repeated sampling might be required when initial tests are negative despite suspicious clinical features [55].

However, most commercially available assays for COVID-19 provide qualitative results and false-negatives may be due to a low viral load [19]. Although at present the nucleic acids of SARS-CoV-2 cannot be quantified, it is known that the lower the RT-PCT-CT value during amplification, the higher the virus load in the specimen being examined and vice versa [13]. Currently, the nucleic acid test based on individual nasopharyngeal and throat swabs is the standard diagnostic method for COVID-19 [56]. Sampling from the lower respiratory tract with sputum and endotracheal aspirates, potentially generate aerosol and must be performed with strict airborne precautions [55]. Oropharyngeal swabs detected the COVID-19 virus less frequently than nasopharyngeal swabs and should not be used in place of nasopharyngeal swabs, particularly from day 8+ of symptom onset [13,22,57]. Despite its crucial role in identifying SARS-CoV-2 infection, the limitations of RT-PCR soon became obvious. The virus may not be present in sufficient quantity in the upper respiratory tract leading to false negative results. During a pandemic, false negative results can produce grave consequences by facilitating the circulation of contagious individuals who spread the virus [58]. Furthermore, these methods are dependent on the time-window of viral replication in the incubation period, low viral titer, and subject to incorrect sample collection [58].

Furthermore, the PCR is not useful in identifying patients who are post infection and may be immune [56,59]. In addition, the sensitivity of RT-PCR assays for the critically ill is currently unknown [55]. Lymphocyte, CD4+ T lymphocyte, and CD8+ T lymphocyte counts are significantly reduced in the severe patients, and were negatively correlated with SARS-CoV-2 RNA load, which suggested that the reduction of lymphocytes and their subpopulations directly affected by viral load was closely related to disease progress [60,61]. Simple two consecutive respiratory nucleic acid tests (sampling interval of at least 1 day) are taken as discharge criteria [54]. However, several reports showed that a small portion of such recovered patients tested positive for infection through the nucleic acid test again during a follow-up visit. These results only indicate the presence of the SARS-CoV-2 virus in the patients, not whether re-infection or recurrence has occurred. One possible solution for this is to detect the titer of IgG in these patients, as the level of IgG usually increases with re-infection of the same virus [56].

Antibody Testing

The value of combining antibody and RNA PCR testing was confirmed in some report which stated that the detection rate increased to 98.6% for combined testing compared to 51.9% for a single PCR [59]. The most widely used biomarkers for COVID-19 are IgM and IgG antibodies to spike and nucleocapsid proteins, they can be detected by a number of methods including ELISA and immunochromatographic testing [59]. IgM and IgG antibodies are produced from the second week of viral infection. IgM manifests earlier than IgG (from 10 to 30 days), but it then weakens and disappears IgM levels decrease after about a month indicating that it may be a useful marker of more recent infection. IgG appears at day 20 onwards, however can persist for a long time following infection and is associated with viral neutralizing activity, which is likely essential for recovery from COVID-19 [56,58,59,61]. The detection and profile of specific antibodies to SARS-CoV-2 will provide valuable information for rapid screening of suspects patients with negative RT–PCR results and in surveying for asymptomatic infection in close contacts [53,58,61]. Antibody testing may allow mass testing of the population and identification of individuals who have recovered from infection [59]. Furthermore, concentrated IgG antibody may be informative in vaccine development and treatment for SARS-CoV-2 [58, 61]. Antibody testing will also allow ongoing surveillance of the population to determine population immune status and will allow detection of both potentially immune and susceptible [58,59]. Antibodies have also a prognostic value. According to recently published studies, a high titer of antibodies may be associated with increased severity of patients with COVID-19, indicating strong immune response in the severe patients [59]. Although the IgM-IgG test is an important index for the diagnosis of COVID-19, limitations still exist. The variation of the methodology and antigens used in the IgM and IgG antibody detection kits are essential for the testing sensitivity and specificity [56].

Chest Computed Tomography (CT)

Chest CT has an irreplaceable role in the early diagnosis of COVID-19 [62]. It is a critical screening method for COVID-19 due to its high sensitivity and convenience [21]. For that, it have been a main clinical diagnostic criteria for the COVID-19 in China [62]. The typical chest CT imaging characteristics of COVID-19 include multiple, peripheral, bilateral, patchy, sub-segmental, or

segmental ground glass opacities and areas of consolidation, which are mostly distributed along the bronchovascular bundles and subpleural space [62]. The presence of associated interlobular septal thickening in the areas of ground glass opacity can give a crazy paving appearance [62]. Currently, chest CT is used to assess the severity of lung involvement in COVID-19 pneumonia and the severe stage patients is statistically significant [2,62]. Chest CT manifestations of COVID-19 are divided into three stages according to the time of onset and the response of body to the virus: early, advanced, and severe, based on the extent of lesion involvement [62].

CT scan have also an important role in combination of swab tests for individuals with high clinical suspicion of COVID19 but negative RT-PCR screening wich provide a clinical challenge and suggests the critical importance to combine the two methods in the early stage of the disease to exclude the SARS-CoV-2 infection [62,21]. Chest CT has also an irreplaceable role in the monitoring the disease's clinical course for early warning of disease aggravation from COVID-19 patients, which could help clinicians to manage quickly and accurately [2,62]. Finnaly, imaging progression-free on chest CT scans was one of discharge criteria for COVID-19 patients [2]. At present stage, the long-term imaging features of COVID-19 are not yet known [2].

Clinical Forms

COVID-19 and the Older Adult

Older adults are more susceptible to COVID-19. The number of older patients infected with COVID-19 was increasing in the world and it brought a serious threat to life and health [63]. Infections in older adults often present atypically, confounding identification and management [7,63]. Usually, the infected older patients initially have fever, fatigue, dry cough, and gradually appear dyspnea, some patients may develop ARDS and septic shock, even die [63]. Fever response is often blunted in older adults, especially in those who are frail wich may increase the difficulty to identify and diagnosis COVID-19 in clinical practice if too much attention was given to fever detection. Therefore, an adjustment to a lower thre shold is recommended [7,63]. In addition, cough and shortness of breath may present as a decline in function, such as impaired mobility or falls, or confused with an exacerbation of heart failure or COPD rather than a distinct new complaint [7].

In addition, as a new disease and a new global health issue, COVID-19 infection is understandable that its emergence and spread cause anxiety and fear among the older population [63]. The COVID-19 infection is generally susceptible with a relatively high fatality rate in older patients [63]. Contributing factors for poor health outcomes include the physiologic changes of aging; multiple agerelated comorbid conditions such as heart and lung disease, diabetes, and dementia; and associated polypharmacy [7]. Management starts with diagnostics and triaging of an older adult to appropriate level of care [7].

COVID-19 in Children

The infection in neonates affecting premature infants and infants have also been reported [1]. There is a theoretical risk of vertical transmission, similar to that seen in SARS, as the ACE2 receptor is widely expressed in the placenta [19]. Additionnaly, COVID-19 infection might affect newborns who acquired the infection from the mother, suggesting a possible perinatal-peripartum transmission [64]. There continue to be conflicting data as to the role of breast feeding on transmitting neonatal-maternal infection. UNICEF recommends continuing with breast feeding, while applying necessary precautions to prevent transmission of infection [64]. In children, the incidence of SARS-CoV-2 infection is lower than that in adults [1]. However, with the spread of the epidemic, the number of children gradually increased. The transmission route in children is, similar to adults, mainly by contact and respiratory droplets [11]. At present, most of the confirmed cases of children are declared to be cluster disease, "second generation" infection, and no clear reports of children as the source of adult infection have been found [11]. As children's immune function is not mature, a lower inflammatory response to lung injuries causes milder clinical symptoms in children compared with adults [11,20,1].

In addition, the number of ACE2 receptors are significantly lower in children than in adults and more in the lungs than in other organs, which may be a reason why children have fewer clinical symptoms and organ dysfunction than adults and lung injuries even among asymptomatic children cases [20]. The median incubation period of SARS-CoV-2 infection in children is 3~7 days (range 1-14 days) [1]. Fever is present in less than half of the infected patients while asymptomatic infections have been reported to occur in at least 20% of infected children [1]. In general, pediatric patients with COVID-19 had a good prognosis and recovered within 1 to 2 weeks after disease onset, and cases of pediatric death from COVID-19 were not reported in the age range of 0 to 9 years [64]. Unlike other viral respiratory diseases in children, wheezing is not a common feature of COVID-19 in children while alveolar consolidation is the most common presentation [1]. The proportion of infected children requiring intensive care is approximately 2% [1]. Among laboratory tests, elevated LDH is more common in children than in adults ($p = 0.02$) [20]. Elevation of inflammatory markers such as C-reactive protein or procalcitonin, and lymphopenia are less common in children which suggests that inflammation caused by viral infection, is less severe in children than in adults. In addition, lung injuries are not uncommon in children and are characterized by bilateral involvement, which is similar to that of adults [20,1].

COVID-19 and Pregnancy

Pregnant women represent a high-risk population to respiratory pathogens and severe pneumonia, because of the physiologic

changes in the immune and cardiopulmonary systems, which can render them intolerant to hypoxia [19,65]. Hitherto, COVID-19 outcomes for the mother appear more promising compared to SARS and MERS [19,66]. Summarized data from small series of pregnant women diagnosed with COVID-19 during the second- and third-trimester, demonstrated that the most common symptoms at presentation were fever and cough; two-third of patients had lymphopenia and increased C-reactive protein, and 83% of cases had chest CT scan showing multiple patches of ground-glass opacity in the lungs [65]. Fetal complications of COVID-19 include miscarriage (2%), intrauterine growth restriction (10%) and pre-term birth (39%) [19]. Therefore, careful monitoring of the developmental stages of mothers who become pregnant due to COVID-19 infection is needed [11].

Risk Factors of Sever Form of Covid19

Clinical Risk Factors

Identifying the most important risk groups is essential when making decisions of anti- COVID-19 therapy for help the physicians to decide which group of patients can be managed safely at district hospitals and who needs early transfer to tertiary centers [67,68]. Previous studies have described that the presence of common comorbidities increase COVID-19 patients' risk and may lead to a poor prognosis [67]. However, the specific comorbidity by which can lead to disease progression remain unknown in COVID-19 patients [67]. The meta-analysis of retrospective studies confirms that chronic obstructive pulmonary disease (COPD) is associated with a dramatically increased risk of aggravation in patients with COVID-19. COVID19 patients with COPD had a 5.9 fold higher risk of progression than patients without COPD. Moreover, a meta-analysis identify an increased risk of aggravation in individuals who have hypertension, diabetes, cardiovascular disease, or cerebrovascular disease and no correlation between liver disease, malignant tumor or kidney disease, and COVID-19 patients' aggravation [67,37].

ACE2 expression is increased in diabetes and treatment with ACE inhibitors and Angiotensin II receptor Blockers (ARBs) increases ACE2 expression. Consequently, diabetes and hypertension treatment with ACE2-stimulating drugs will increases the risk of developing severe and fatal COVID-19 [60]. Multivariate analysis showed that selective beta-blocking agents and angiotensin II receptor blockers were independent factors associated with poor clinical and virological outcomes ($p < .05$) [69].

Biological Risk Factors

One of the independent risk factors related to morbidity of COVID-19 is neutrophil count. The increased neutrophil count may indicate progression of disease initially [37]. The other independent high-risk factors, increased blood urine nitrogen and lactate dehydrogenase related to renal failure, heart failure which may lead to fatality of COVID-19. As a gauge of inflammation, C-reactive protein showed a significant difference between death and recovery groups, so as D-Dimer [37]. D-dimer is also considered independent predictor of in-hospital death [70]. One of the best laboratory parameters inflecting heart injury for predicting mortality of COVID-19 pneumonia is cardiac troponin I [71]. Dysregulated immune cell responses and consequently immunologic abnormality are believed to play remarkable roles in the severity of virus-induced disease. When immune response is dysregulated, it would result in an excessive inflammation, even death [70].

It has been shown that several cytokines and chemokines, such as interleukin-2, interleukin-7, interleukin-10, macrophage colony-stimulating factor, inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and tumor necrosis factor-α concentrations were higher in patients with severe COVID 19 pneumonia than in those with mild disease, suggesting that SARS-CoV-2 infection damages human immune system and results in systematic inflammatory response [71]. More importantly, CD3+CD8+ T cells ≤ 75 cell/μL, is a reliable predictor for mortality of patient with COVID-19 pneumonia which indicates that progressive immune-associated injury and inadequate adaptive immune responses could be possible mechanisms by which SARS-CoV-2 causes severe illness and fatal outcomes [71]. Finally, higher SARS-CoV-2 nasopharyngeal RNA loads are more common in patients with severe disease. On the one hand, high virus loads may directly damage tissues and cells; on the other hand, a strong immune response to high viral loads in the human body can also seriously damage cells and organs. Moreover, high viral loads directly influence disease progression and the time it takes for the nucleic acid test to turn negative [60].

Treatment

Options for Antiviral Therapy

Currently, definitive treatment of COVID-19 remains unknown due to the lack of the clear understanding of the pathogenesis of the disease or the nature of its causative virus [72]. No consensus or evidence-based guideline currently exists for pharmacological therapy against COVID-19 [72]. The way we can manage the patients is limited in the symptomatic treatment and the use of the drugs already in the market for treatment and clinical trials [1,73,74]. Antiviral drugs commonly used in clinical practice which may be effective for COVID-19 include remdesivir, lopinavir / ritonavir. Another researchs showed that chloroquine are highly effective in the control of COVID-19 infection [14]. However, the efficacy and safety of these drugs for COVID-19 pneumonia patients need to be assessed by clinical trials [3,14]. There are intensive efforts worldwide to develop novel treatments for COVID-19 as the pandemic continues to spread [12].

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Chloroquine phosphate is an ubiquitous antimalarial quinolone compound with broad spectrum antiviral and immunomodulating activity. Chloroquine (CQ) and (HCQ) hydroxychloroquine have along-standing history in the prevention and treatment of malaria and the treatment of chronic inflammatory diseases including systemic lupus erythematosus and rheumatoid arthritis [16]. CQ block viral entry into cells by inhibiting glycosylation of ACE, proteolytic processing, and endosomal acidification [16,19]. Moreover, CQ may also block the production of interleukin-6 and other pro- inflammatory cytokines, which are key mediators of ARDS [12]. Another potential mechanism involves the inhibition of viral release into the intracellular space [12]. The efficacy of HCQ against COVID-19 has become a very controversial issue in the medical community [69]. Several clinical studies addressing the efficacy of HCQ leading to contradictory results. Three studies showed a favourable effect. The results of treating more than 100 patients with CQ in China reported a positive signal from reportedly reducing the duration of illness, and improving COVID pneumonia and appearances on chest imaging [12]. In the republic of Korea, Kim repported that the time to viral clearance after initiation of treatment was significantly shorter with HQ plus antibiotics compared to Lopinavir/ritonavir plus antibiotics [72].

Hospital stay duration after treatment was also shortest for patients treated with HQ plus antibiotics compared to other treatment groups [72]. In France, Milliona et al reported a good clinical outcome and virological cure in 91.7% of patients treated with HQ + azithromycin (AZ) [69]. Dosing of chloroquine to treat COVID-19 has consisted of 500 mg orally once or twice daily. However, a paucity of data exists regarding the optimal dose to ensure the safety and efficacy of chloroquine [16]. CQ and HCQ are relatively well tolerated and HCQ is a more soluble and less toxic metabolite of CQ. It causes fewer side effects and is therefore considered safer than CQ [12]. However, both agents can cause rare and serious adverse effects (<10%), including QTc prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy [16]. Baseline electrocardiography to evaluate for prolonged QTc is advisable prior to and following initiation of these medications. Use of chloroquine and hydroxychloroquine in pregnancy is generally considered safe [16].

Remdesivir

Remdesivir is a prodrug of a nucleotide analogue that inhibits viral RNA polymerases wich shows broad-spectrum antiviral activity against several RNA viruses [22,74]. Remdesivir has broad spectrum activity against members of several virus families and has shown prophylactic and therapeutic efficacy in non clinical models of these coronaviruses [22,74]. The suggested mechanism for remdesivir involves the host cells' post-entry stage [2]. Currently, remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potentin vitroactivity against SARS-CoV-2 [16]. *In vitro* testing has also shown that remdesivir has activity against SARS-CoV-2. Remdesivir appears to have a favorable clinical safety profile [74]. Subsequent investigation demonstrated significant reduction of viral replication and symptoms in a mouse model infected with SARS-CoV-1 [39]. Wang *et al.* [22] presented data showing that remdesivir has superior antiviral activity to LPV and ritonavir *in vitro* [22]. In a mouse model of SARS-CoV pathogenesis, both prophylactic and therapeutic remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology [22]. Additional in vitro testing of a human cell line demonstrated markedly reduced SARS-CoV-2 activity [39]. Intravenous infusions of remdesivir between 3mg and 225 mg were well-tolerated without any evidence of liver or kidney toxicity [16].

Lopinavir/ritonavir (LPV/r)

LPV/r is a protease inhibitor that has been widely applied in the clinical treatment for HIV-1 infection. LPV/r have in vitro inhibitory activity against SARS-CoV impeding viral replication process via inhibiting protease hydrolysis [73, 57]. No published SARS-CoV-2 in vitro data exist for lopinavir/ritonavir [16]. Early reports of LPV/r for the treatment of COVID-19 are mostly case reports and small retrospective, cohort studies [16]. A randomized trial found that LPV/r treatment added to standard supportive care was not associated with clinical improvement or mortality in seriously ill patients with Covid-19 different from that associated with standard care alone [57]. Cao et al are not find that adding LPV/r treatment reduced viral RNA loads or duration of viral RNA detectability as compared with standard supportive care alone. SARS-CoV-2 RNA was still detected in 40.7% of the patients in the LPV/r group at end of the trial [57]. Furthermore, the use of lopinavir/ritonavir for severe COVID-19 was tested prospectively in 199 patients, but unfortunately did not lead to a significant reduction in viral-load or symptomatic improvement [39]. Contrary, Chu et al 12 indicated that use of LPV/r can significantly lead to the reduction of acute respiratory distress syndrome development and mortality that caused by SARS infection [73]. The most commonly used and studied LPV/r dosing regimen for COVID-19 treatment is 400mg/100mg twice daily for up to 14 days [16]. Adverse effects of LPV/r include gastrointestinal distress such as nausea and diarrhea (upto 28%) and hepatotoxicity (2%-10%) [16].

Corticosteroid Methylprednisolone

The rationale for the use of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and ARDS [22]. The use of corticosteroids in COVID-19 infection remains controversial [75]. Existing evidence is inconclusive, and even systematic reviews and meta analyses on this topic reach differing conclusions [75]. Observational studies in patients with SARS and MERS demonstrated an association with delayed viral clearance from the respiratory tract and blood [16]. A recent retrospective study of 201 patients with COVID-19 in China found that, for those who developed ARDS, treatment with methylprednisolone was associated with a decreased risk of death [16]. Furthermore, long, *et al.* [3] reported that

corticosteroid therapy is beneficial in treating COVID- 19 infection; it significantly prolongs the survival time of clinical cases [3]. However, the potential risks associated with high dose corticosteroids include secondary infections, long-term complications, and prolonged virus shedding [75]. Therefore, corticosteroids could be prescribed at the right time for the right patients. It should be used prudently in critically ill patients, patients with a chronic obstructive pulmonary disease exacerbation or refractory shock [22,75,16].

Immunotherapy

Immunotherapy is regarded as an effective method for treatment of different infectious diseases [1]. Among immunotherapy approaches to block the virus attachment or entry, monoclonal antibodies are preferred due to their specificity, purity, low risk of blood-borne pathogen contamination and safety compared to serum therapy and intravenous immunoglobulins preparations [76]. Broadly neutralizing antibodies can recognize a wide variety of glycoproteins (GPs) in virus surfaces or the protein shell of a non-enveloped virus [3]. Monoclonal antibody cocktail or the combination of different monoclonal antibodies that recognizes different epitopes on the viral surface may increase the effectiveness of virus neutralizing [76]. As both SARS-CoV and SARS-CoV-2 have the same receptor for virus entry, potential biotherapeutics to prevent SARS entry could be extrapolated to use for SARS-CoV-2 [76]. The promising results in targeting spike protein in SARS-CoV and MERS-CoV by monoclonal antibodies encourages researchers to use them in fighting against SARS-CoV-2 [76]. Trial NCT04261426 is utilizing human immunoglobulin in patients with pneumonia caused by SARS-CoV-2 [3].

Other targets in immunotherapy for COVID-19 that seem to be Promising arecytokines. Among cytokines, specificity ofIL-6 in COVID19 comes from that Elevated IL-6 is correlated with inflammatory cytokine storm severity. Therefore targeting IL-6 and its receptor (IL6R) by Siltuximab and tocilizumab monoclonal antibodies (mAb) could mitigate cytokine storm-related symptoms in severe COVID-19 patients [76]. Despite major progress in the development of monoclonal antibody based passive immunotherapy for coronavirus infection, there is no marketed monoclonal antibody. What limits the use of antibodies is that large-scale production of monoclonal antibodies for clinical application is laborious, expensive and time-consuming [76]. Clear understanding of the important early immune response in suppressing viral replication and the subsequent control of appropriate innate and adaptive immune responses are needed in order to develop more targeted treatment in different stages of COVID-19 [1].

Conclusion

The COVID-19 pandemic is a public health emergency of in ternational concern, and all countries need a coordinated international effort to fight COVID-19. Broad population screening for SARS-CoV-2 infections, isolation of confirmed cases through contact tracing and quarantine combined with social distancing, and large serological studies will be critical to slowing the spread of covid-19. It is also necessary to develop drugs and vaccines against the COVID-19 infection as soon as possible.

References

1. Lu X, Xiang Y, Du H, Kin Wong GW (2020) SARS-CoV-2 infection in children – Understanding the immune responses and controlling the pandemic. Pediatr Aller Immunol 31: 449-53.

2. Yang Z, Shi J, He Z, Ying Lu, Qingnian Xu, et al. (2020) Predictors for imaging progression on chest CT from coronavirus disease 2019 (COVID-19) patients, Aging (Albany NY). Epub 12: 6037-48.

3. Sandro G Rosa V, Santos W (2020)Clinical trials on drug repositioning for COVID-19 treatment. Rev Panam Salud Publica 44: e40.

4. Tian Y, Rong L, Nian W, Yan He (2020) Gastrointestinal features in COVID 19 and the possibility of faecal transmission. Aliment Pharmacol Ther 51: 843-51.

5. Chen X, Tang Y, Mo Y, Shengkai Li, Lin D, et al. (2020) A diagnostic model for coronavirus disease 2019 (COVID-19) based on radiological semantic and clinical features: a multi-center study. Chest 16: 1-10.

6. Mao L, Jin H, Wang M, Hu Y, Chen S, et al. (2020) Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 77: 683-90.

7. Nikolich-Zugich J, Knox K, Rios C, Natt B, Bhattacharya D, et al. (2020) SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. GeroScience 42: 505-14.

8. Acter T, Uddin N, Das J, Akhter A, Choudhury TR, et al. (2020) Evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as coronavirus disease 2019 (COVID-19) pandemic: A global health emergency. Sci Total Environ 730: 138996.

9. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Peña RV, Rivera YH, et al. (2020) Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Medicine and Infectious Disease 34: 101623.

10. Baghchechi M, Dunn J, Jaipaul N, Sharon E Jacob (2020) Art of Prevention: Life in the Time of Coronavirus. Int J Women's Dermatol 6: 137-41.

11. Huang X, Wei F, Hu L, Wen L, Chen K (2020) Epidemiology and Clinical Characteristics of COVID-19. Arch Iran Med 23: 268-71.

12. Gbinigie K, Kerstin Frie (2020) Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review. BJGP Open 4(2).

13. Wang X, Tan L, Wang X, Liu W, Lu Y, et al. (2020) Comparative accuracy of oropharyngeal and nasopharyngeal swabs for diagnosis of COVID-19. Int J Infect Dis 94: 107-9.

14. Lou J, Tian S-J, Niu S-M, Kang X-Q, H-X Lian, et al. (2020) Coronavirus disease 2019: a bibliometric. Eur Rev Med Pharmacol Sci 24: 3411-21

15. Cui S, Chen S, Li X, Lu Shi, Wang F (2019) Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost18: 1421-4.

16. Sanders M, Monogue M, Jodlowsk T, James B Cutrell (2020) Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review. JAMA 323: 1824-36.

17. Wang Q, Zhang Y, Wu L, Niu S, Song C, et al. (2020) Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. Cell 2020 181: 894-904.e9.

18. Fang L, Karakiulakis G, Roth (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Pulmonary Cell Research and Pneumology.

19. Dashraath P, Jing Lin Jeslyn W, Mei Xian Karen L, et al. (2020) Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy. American Journal of Obstetrics and Gynecology.

20. Li J, Fan J (2020) Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. J Clin Transl Hepatol 8: 13-7.

21. Dai H, Zhang X, Xia J (2020) High-resolution Chest CT Features and Clinical Characteristics of Patients Infected with COVID-19 in Jiangsu, China. International Journal of Infectious Diseases.

22. Zhai P, Ding Y, Wu X (2020) The epidemiology, diagnosis and treatment of COVID-19. International Journal of Antimicrobial Agents.

23. Lovato A, Filippis C (2020) Clinical Presentation of COVID-19: A Systematic Review Focusing on Upper Airway Symptoms. Ear, Nose & Throat J: 1-8.

24. Pleasure S, Green A, Josephson A (2020) The Spectrum of Neurologic Disease in the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic Infection. Neurologists Move to the Frontlines. JAMA Neurology.

25. Lechien J, Chiesa-Estomba CM, De Siati DR (2020) Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study Eur Arch Otorhinolaryngol 6: 1-11.

26. Soler Z, Patel Z, Turner J (2020) A primer on viral-associated olfactory loss in the era of COVID-19.

27. Beltrán-Corbellini A, Chico-García JL, Martínez-Poles (2020) Acute-onset smell and taste disorders in the context of Covid-19: a pilot multicenter PCRbased case-control study.

28. Ollarves-Carrero MF, Rodriguez-Morales AG, Bonilla-Aldana DK (2020) Anosmia in a healthcare worker with COVID-19 in Madrid, Spain, Travel Medicine and Infectious Disease.

29. Asadi-Pooya A, Simani L (2019) Central nervous system manifestations of COVID-19: A systematic review, Journal of the Neurological Sciences.

30. Guidon A, Amato A (2019) COVID-19 and neuromuscular disorders NEUROLOGY.

31. Das G, Mukherjee N, Ghosh S (2020) Neurological Insights of COVID-19 Pandemic. ACS Chem Neurosci. 2020 Apr 22: acschemneuro.0c00201.

32. Gianpaolo Toscano G, Pavia M-F, Ravaglia S, Ruiz L, Azienda Ospedaliera A, et al. Guillain–Barré Syndrome Associated with SARS-CoV-2 The new england journal of medicine N ENGL J MED NEJM.ORG DOI: 10.1056/NEJMc2009191

33. Wong S-H, Lui R, Sung JY (2020) Covid-19 and the Digestive System.

34. Pan L, Mu M, Yang P (2020) Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study, Am J Gastroenterol.

35. Yang X, Zhao J, Yan Q (2020) A case of COVID-19 patient with the diarrhea as initial symptom and literature review. Clin Res Hepatol Gastroenterol.

36. Henry B, Santos de Oliveira MH, Benoit J (2019) Gastrointestinal symptoms associated with severity of coronavirus disease 2019 (COVID-19): a pooled analysis Intern Emerg Med.

37. Li L, Chen X (2020) Critical patients with coronavirus disease 2019: Risk factors and outcome nomogram. Journal of Infection.

38. Kang Y, Chen T, Mui D (2020) Heart Cardiovascular manifestations and treatment considerations in covid-19. 2020 Apr: heartjnl-2020-317056.

39. Hendren N, Drazne M, Bozkurt B (2020) Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome.

40. Tavazzi G, Pellegrini G, Maurelli M (2020) Myocardial localization of coronavirus in COVID 19 cardiogenic shock. Eur J Heart Fail 22: 911–5.

41. Lodigiani C, Iapichino G, Carenzo L (2020) Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thrombosis Research.

42. DC Rotzinger, C Beigelman-Aubry, C von Garnier, SD (2020) Pulmonary embolism in patients with COVID-19: Time to change the paradigm of computed tomography,. Qanadli Thromb Res 190: 58–9.

43. Asadollahi-Amin A, Hasibi M, Ghadimi F, (2020) Lung Involvement Found on Chest CT Scan in a Pre-Symptomatic Person with SARS-CoV-2 Infection: A Case Report. Trop Med Infect Dis 5: 56.

44. Tammaro A, Adebanjo GAR, F.R. Parisella FR (2020) Cutaneous manifestations in COVID 19: the experiences of Barcelona and Rome J Eur Acad Dermatol Venereol.

45. Henry D, Ackerman M, Sancelme E (2020) Urticarial eruption in COVID 19 infection. J Eur Acad Dermatol Venereol.

46. Hedou M, Carsuzaa F, Chary E (2020) Comment on "Cutaneous manifestations in COVID-19: a first perspective" by Recalcati S. Eur Acad Dermatol Venereol.

47. Tang K, Wang Y, Zhang H, Zheng Q (2020) Cutaneous manifestations of the Coronavirus Disease 2019 (COVID-19): A brief review. Dermatol Ther.

48. Estébanez A, Pérez Santiago L, Silva E (2020) Cutaneous manifestations in COVID 19: a new contribution J Eur Acad Dermatol Venereol.

49. Van Damme C, Berlingin E, Saussez S (2020) Acute urticaria with pyrexia as the first manifestations of a COVID 19 infection. J Eur Acad Dermatol Venereol.

50. Estébanez A, Pérez-Santiago L, Silva E (2020) Cutaneous manifestations in COVID-19: a new contribution. J Eur Acad Dermatol Venereol.

51. Cevik M, Bamford CG, Ho A (2020) COVID-19 pandemic a focused review for clinicians Clin Microbiol Infect.

52. Mazzotta F, Troccoli T, Bonifazi E (2020) A new vasculitis at the time of covid-19. Dermatologia Pediatrica, Bari, Italy.

53. Long Q-X, Liu B-Z, Deng H-J (2020) Antibody responses to SARS-CoV-2 in patients with COVID-19.

54. Wu J, Liu J, Li S (2020) Detection and analysis of nucleic acid in various biological samples of COVID-19 patients, Travel Medicine and Infectious Disease.

55. Phua J, Weng L, Ling L (2019) Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations for the Asian Critical Care Clinical Trials Group.

56. Xie J, Ding C, Jing L (2020) Characteristics of patients with coronavirus disease (COVID-19) confirmed using an IgM IgG antibody test. J Med Virol.

57. Bin Cao B, Yeming Wang Y, Danning Wen D (2020) A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med.

58. Infantino M, Grossi V, Lari B (2020) Diagnostic accuracy of an automated chemiluminescent immunoassay for anti SARS CoV 2 IgM and IgG antibodies: an Italian experience. J Med Virol.

59. Xiao A-T, Gao C, Zhang S (2020) Profile of Specific Antibodies to SARS-CoV-2: The First Report, Journal of Infection.

60. Liu Y, Liao W, Wan L (2020) Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. Viral immunology.

61. Whitman JD, Hiatt J, Mowery CT, Shy BR (2020) Test performance evaluation of SARS-CoV-2 serological assays.

62. Yang W, Sirajuddin A, Zhang X (2020) The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). Eur Radiol 15: 1–9.

63. Niu S, Tian S, Lou J (2020) Clinical Characteristics of Older Patients Infected with COVID-19: A Descriptive Study, Archives of Gerontology and Geriatrics.

64. Castagnoli R, Votto M, Licari A (2019) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents. A Systematic Review.

65. Yan J, Guo J, Fan C (2020) Coronavirus disease 2019 (COVID-19) in pregnant women: A report based on 116 cases. American Journal of Obstetrics and Gynecology.

66. Yang H, Sun G, Tang F (2020) Clinical Features and Outcomes of Pregnant Women Suspected of Coronavirus Disease 2019. Journal of Infection.

67. Wang B, Li R, Lu Z (2020) Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Yan Huang Aging 12: 6049–57.

68. Dong J, Zhang D, Xu J, Chen Z (2020) Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score. Clin Infect Dis.

69. Million M, Lagier JC, Gautret P (2020) Early treatment of COVID19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis.

70. Liu Y, Du X, Chen J (2020) Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. Journal of Infection.

71. Du RH, Liang LR, Yang CQ (2020) Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study. Eur Respir J.

72. Seo Kim M, Jang S-W, Park Y-K (2020) Treatment Response to Hydroxychloroquine, Lopinavir–Ritonavir, and Antibiotics for Moderate COVID-19: A First Report on the Pharmacological Outcomes from South Korea.

73. Ye X, Luo L, Xia S (2020) Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. European Review for Medical and Pharmacological Sciences 24: 3390-6.

74. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E (2020) Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J.

75. Xiang Y, Li W, Zhang Q (2020) On the use of corticosteroids for 2019-n CoV pneumonia 30361-5.

76. Jafaria A, Ghasemib S (2020) The possible of immunotherapy for COVID-19: A systematic review. International Immunopharmacology 83: 106455.