Review

Epidemiology, pathogenesis, diagnosis and management of COVID-19

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ABSTRACT

The pneumonia cases occurred in Wuhan province of China in late December 2019 affected the whole world, and it was soon declared a pandemic by the World Health Organization. It was understood that a new type of coronavirus (2019-nCoV), called COVID-19, was caused by the symptoms of fever, cough, and shortness of breath. The incubation period of the pathogen transmitted by the droplets of infected patients varies between 2 and 14 days. Although the disease has a lower mortality than previous severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks, it has threatened all humanity with a serious need for intensive care and increased death reports. In particular, those with comorbidities, children, elderly, and healthcare professionals are at a great risk. The precautions have not been able to fully control the virus, since no specific treatment or vaccine has been found yet. In this review, we discuss the virology, epidemiology, clinic, diagnosis and treatment of COVID-19 in the light of literature data.

Keywords: Clinical features, coronavirus, COVID-19, epidemiology, pathogenesis, SARS-CoV-2.

In the last month of 2019, pneumonia cases were reported resembling the SARS outbreak in 2003 with an unknown etiology occurring in a seafood market in Wuhan Hubei Province, China.[1,2] This unidentified pneumonia caused more than 80,000 cases in China and was thought to be caused by a new type of coronavirus (CoV) called 2019-nCoV.[2]

On January 30th, 2020, the World Health Organization (WHO) reported that the current situation was a "public health emergency of international concern"[3] and on February 11th, 2020, this new coronavirus pneumonia was named as Coronavirus Disease-2019 (COVID-19).[4] The responsible pathogen was named as severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses.[5]

Following the first case, the virus spread within 8 to 12 weeks which overthrown the whole world. On March 11th, 2020, the WHO accepted COVID-19 infection as a global epidemic.[6] Currently, pandemic has grown rapidly in addition to China, United States of America (USA), Italy, Spain, France, Germany, United Kingdom (UK), Turkey and across the world. According to the WHO data updated on April 23rd, 2020, 2,544,792 cases were reported with a total of 175,694 deaths.[7] No doubt, by the time you read this article, the numbers will continue to increase.

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According to the growing concern associated with the SARS-CoV-2 infection, data transfer about clinical knowledge and the latest developments is extremely important for both patients and healthcare professionals. In this review, we discuss the virology, epidemiology, clinic, diagnosis and treatment of COVID-19 in the light of literature data.

VIROLOGY

The CoV family is a class of enveloped, single-stranded non-segmented ribonucleic acid (RNA) virus which causes many diseases in the respiratory tract, gastrointestinal, hepatic, and cardiovascular system.[1] The CoVs are genotypically and serologically divided into four subfamilies: α, β, γ, and δ-CoVs.[1,8] The previously known SARS coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), and SARS-CoV-2, which was first isolated from the bronchoalveolar lavage (BAL) fluid of a COVID-19 patient in Wuhan Jinyintan Hospital on December 30th, 2019 was accepted as a member of the β-CoVs.[2,8] Phylogenetic analysis shows that SARS-CoV-2 has 79.5% and 50% similar genomic structure with SARS-CoV and MERS-CoV.[2]

The SARS-CoV-2 virion is a viral RNA wrapped in a double-layer phospholipid envelope and is approximately 60-100 nm diameter and round or oval in appearance, similar to other β-CoVs (Figure 1).[5,9] The glycoprotein regulating spike (S) protein is found in all CoVs and the hemagglutinin-esterase (HE) protein is found in some CoV's viral envelopes. Membrane (M) protein and envelope (E) proteins are between the S proteins in the viral envelope.[10]

It has been found that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor to bind to human cells through molecular-level examination.[8] The ACE-2, a membrane protein mainly expressed in the upper and lower airways, heart, kidney and intestine, also helps to cleave angiotensin (Ang) I and receptor for binding of S proteins of CoVs.[11] Wan et al.[12] examined the interaction of the SARS-CoV-2 and ACE-2 receptors and studied the recognition of the new coronavirus and its receptor. They concluded that SARS-CoV-2 used the same ACE-2 receptor as the SARS virus responsible for the 2003-2004 outbreak.

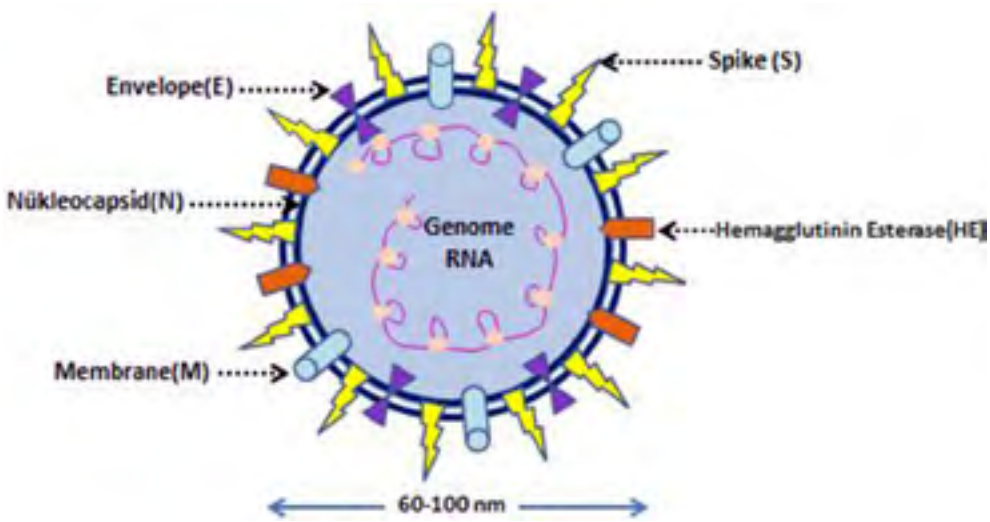

Figure 1. *Beta-coronavirus particle and genome.*
The SARS-CoV-2 virion, size 60-100, has a non-segmented positive single-stranded ribonucleic acid (RNA) genome and is surrounded by a double-layer phospholipid nucleocapsid consisting of phosphorylated nucleocapsid (N) protein. The two stratified layers regulatory glycoprotein (S) coated with the spike protein. Hemagglutinin-esterase (HE) membrane (M) and envelope (E) proteins fill these proteins in the form of pointed protrusions.

EPIDEMIOLOGY

Terminal host and intermediate host

Similar to the previous coronavirus outbreaks, there is enough evidence currently that the virus responsible for the COVID-19 pandemic has a hidden reservoir in the wild animals.[8] Paraskevis et al.[13] found that bats were the most likely natural hosts of SARS-CoV-2. In their study, SARS-CoV-2 genome showed 96.3% similarity to bat coronovirus. The virus is probably transmitted to humans by another animal host, as bat habitats are located far from human habitats; for instance, musk and camel intermediate hosts in SARS-CoV and MERS-CoV outbreaks.[5] There are many studies in the literature regarding the intermediate animal host of SARS-CoV-2. Lam et al.[14] showed that the intermediate host of SARS-CoV-2 might be pangolins due to its 99% genetic similarity with pangolin-derived CoVs; however, there might be more than one intermediate host. Of note, the terminal and intermediate hosts of such a pathogen must be recognized to prevent transmission routes.

Incubation period

Although there are differences between the studies regarding the incubation times of COVID-19, it takes an average of 5.1 days, according to data from the Centers for Disease Control and Prevention (CDC).[8] Lauer et al.[15] also examined 181 patients and the incubation period of COVID-19 ranged from 2.1 to 14.7 days with a mean of 5.1 days. The 14-day quarantine period as determined by the WHO also supports this data.[8] It should be also kept in mind that the latent period of COVID-19 may be shorter than the incubation period, and patients may be also contagious in the asymptomatic phase.[15]

Transmission route

The main source of infection until now is patients with infected pneumonia.[1] Droplets produced by coughing and sneezing and close direct contact are considered primary transmission routes for the virus.[5] Also, recent data indicate that there is a risk of fecal-oral transmission and that virus can be detected in the urine and feces of COVID-19 patients.[9] It raises the concern of contamination what the inanimate objects (e.g., elevator buttons, toilet faucets, etc.) can be transmitted to another person when contaminated with the virus. Van Doremalen et al.[16] found that the virus could survive as an aerosol for up to three hours in the air, up to four hours on copper, 24 hours on cardboard, and two to three days on plastic-stainless steel surface.[16] There is no clear evidence of vertical transmission from aerosols, vaginal secretions or breast milk during pregnancy and childbirth.[5] However, Zhu et al.,[17] in the report of 10 newborns born from mothers with 2019-nCoV pneumonia, the new coronavirus type might cause neonatal infection.

Numbers and ratios

The COVID-19 pandemic started in Wuhan on December 8th, 2020, and soon spread the rest of China, neighboring countries such as South Korea, Hong Kong and Singapore.[5,18] Outside of the mainland China, the first COVID-19 incident was diagnosed in Bangkok (Thailand) on January 13th,[19] and the first incident in Europe was diagnosed in Italy on January 20th, 2020.[18]

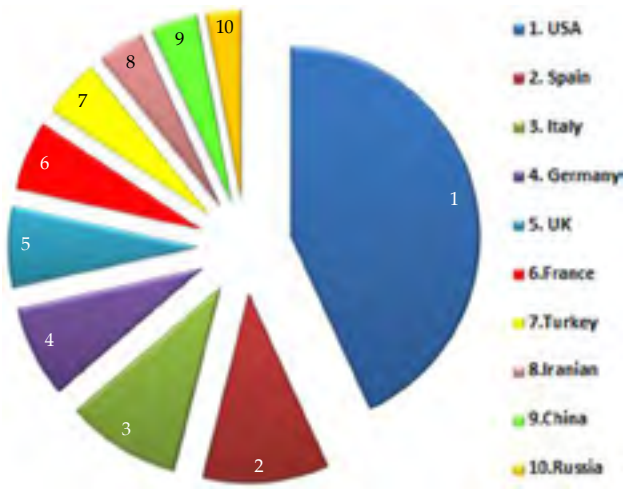

Figure 2. *Top 10 countries with the highest number of cases worldwide.*

According to the WHO data on April 23rd, 2020, the top 10 countries of COVID-19 case load are as follows: USA 44%, Spain 11%, Italy 10%, Germany 8%, UK 7%, France 6%, Turkey 5%, Iran 4%, China 4%, and Russia 3%. On the basis of all cases worldwide, other countries which do not enter the table have 26% of cases.

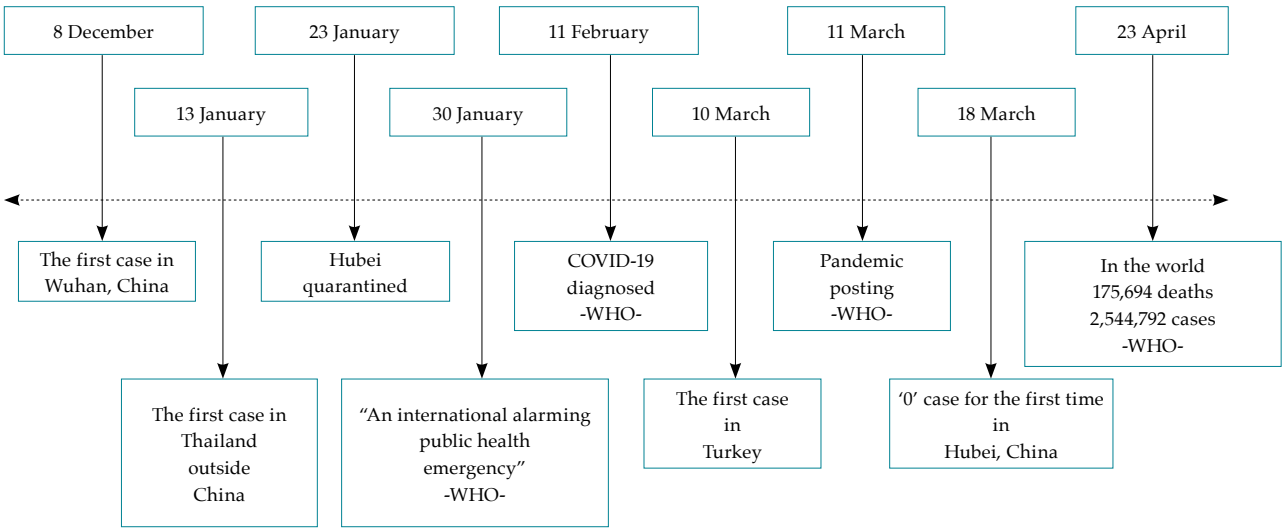

Figure 3. *The course of COVID-19 in the timeline.*
WHO: World Health Organization.

According to data from WHO on April 23rd, 2020, the top five countries with the highest number of cases and deaths were USA (800,926 cases/40,073 deaths), Spain (208,389 cases/21,717 deaths), Italy (187,327 cases/25,085 deaths), Germany (148,046 cases/5,094 deaths) and the UK (133,499 cases/18,100 deaths) (Figure 2).[7] According to the WHO assessment of the same date, the risk is very high at the global level.[7]

Recognition to up-to-date data, the mortality rate among COVID-19 patients was found to be 2%[20] in Italy and 2.3 to 2.9%[21] in China. On the other hand, SARS and MERS mortality rate was 9.6% and 34%, respectively.[22,23] Comparing COVID-19 to SARS and MERS mortality rates, it is understood that COVID-19 mortality rate is low. With aging, the risk of death increases from COVID-19 from 0.2% under 40 years of age to 3.6% over 60 years of age.[8] This rate increased to 14.8% in the population over the age of 80.[5] According to epidemiological data, it has been shown that men are more risky than women with a mortality rate of 2.8 to 1.7%.[21] Patients with concomitant comorbidities also exhibited a poorer prognosis.[5] While the case-death rate is as low as 0.9% in cases without any additional disease, it is 10.5% in cardiovascular disease, 7.3% in diabetes, 7.3%, chronic respiratory disease, 6.0% in hypertension, and 5.6% in cancer cases.[21]

After China started to apply quarantine in Hubei on January 23rd no new case reports were made for the first time in Hubei on March 18th[18], 2020.[5] Three months after the outbreak started, the Chinese government started to remove quarantine practices and slowly returned life to normal (Figure 3). However, the epidemic has

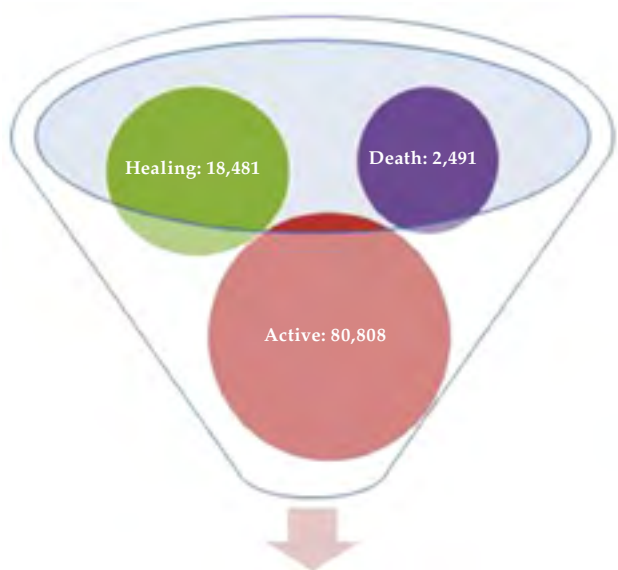

Figure 4. *On April 23rd 2020 the number of cases in Turkey.*

Table 1. Covid-19 related symptoms

Common	Rare
• Fever	• Headache
• Cough	• Rhinorrhea
• Sore throat	• Sputum
• Myalgia	• Hemoptysis
• Fatigue	• Anosmia
• Dyspnea	• Nausea
	• Vomit
	• Diarrhea

not yet been taken under control in Europe and particularly in the USA.[18]

The first COVID-19 incident was diagnosed in Turkey on March 10th, 2020. According to Republic of Turkey, Ministry of Health data updated on April 23rd 2020, 791,906 tests were done and 101,790 cases were reported. A total of 2,798 patients were followed in the intensive care units due to their severity, while 2,491 patients died due to COVID-19 and 18,491 patients recovered (Figure 4).[24]

SYMPTOMATOLOGY

The clinical spectrum of SARS-CoV-2 patients varies from asymptomatic picture to mild-moderate to severe pneumonia and fulminant progressive septic shock and multiple organ dysfunction syndromes (MODS).[1] The disease is usually self-limiting and most cases with mild symptoms improve within one to two weeks.[5] There are mild-to-moderate cases with 82.1% of patients and asymptomatic individuals with a high transmission ability; however, severe cases should not be underestimated by 13.8%, critical cases by 4.7%, and death by 2.3%.[21] Wang et al.[25] reported on clinical features of 138 patients with SARS-CoV2-infected pneumonia in Wuhan and found the median duration from first symptoms to dyspnea to be five days, to hospital admission to be seven days, and to acute respiratory distress syndrome (ARDS) to be eight days.[25]

Typical symptoms which are common in COVID-19 patients are fever, dry cough, sore throat, myalgia, fatigue, and shortness of breath.[26] Rare symptoms include headache, rhinorrhea, hemoptysis, anosmia, nausea, vomiting, and diarrhea from gastrointestinal symptoms (Table 1).[20] Huang et al.[27] reported that fever (98%), cough (76%), and myalgia or fatigue (44%) were the most common symptoms in COVID-19 patients. In the aforementioned study, more than half of the patients developed dyspnea, while symptoms such as sputum (28%), headache (8%), hemoptysis (5%), and diarrhea (3%) were rarer.

In the literature, many studies are available describing the resulting clinical pathophysiological ground. It has been previously reported that the virus causes viremia by targeting ACE2 receptors in the nasal cavity, nasopharynx, oropharynx, bronchi, and gastrointestinal tract after transmission. After rapid viral replication, an excessive and complex immune reaction begins in the host. The responsible of this reaction which is called as cytokine storm is interleukin (IL)-6. Then, activation of leukocytes, reduction of B-lymphocytes, and release of chained pro-inflammatory cytokines causes epithelial and endothelial cell death and increase vascular permeability, resulting in pulmonary inflammation, edema, ARDS, and sudden death (Figure 5).[5,20,28,29]

DIAGNOSIS

Genome isolation and polymerase Chain reaction

Bacterial pneumonias such as viral and mycoplasma and chlamydia can be eliminated with serological methods. Subsequently, SARS-CoV2 isolation and viral nucleic acid detection are the gold standard for the diagnosis of COVID-19.[1,30] According to the CDC guidelines, the reverse-transcription polymerase chain reaction (RT-PCR) test has become a standard tool in the diagnosis of SARS-CoV-2.[8,26] While collecting the samples, nasopharyngeal and oropharyngeal swabs and sputum are used, as they are rapid and reliable. On the other hand, endotracheal aspirate, BAL materials, serum, urine, and feces are rarely preferred due to logistic and follow-up difficulties.[8] In a study with 866 specimens on the laboratory diagnosis of 2019-nCoV infection, the sputum sample had the highest positive rate (74.4 to 88.9%), followed by the nose swabs (53.6 to 73.3%).[31] In another study conducted on 4,880 cases in Wuhan, the positivity rate of

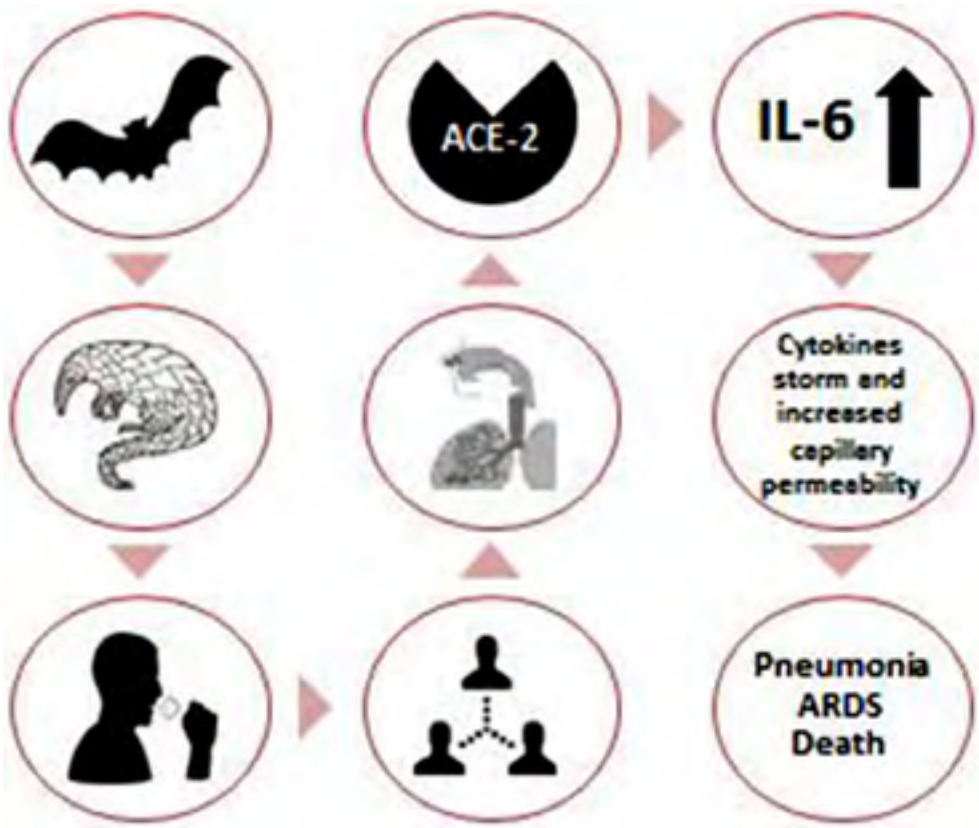

Figure 5. *Transmission and disease pathogenesis of SARS-CoV-2.*

2019-nCoV, of which the definitive host is thought to be a bat, is considered to infect the human species thanks to an intermediate host such as a pangolin. Direct and close contact after primary contamination with respiratory droplets has caused the virus to spread rapidly. It mainly forms viremia by targeting ACE-2 receptors in the upper respiratory tract. Cytokine storm, which eventually starts under the leadership of IL-6, is responsible for the entire clinical picture and death.

ACE-2: Angiotensin-converting enzyme 2; ARDS: Acute respiratory distress syndrome.

RT-PCR detection was found to be low as 38%,[32] while Fang et al.[33] reported a positivity rate of 71% in a limited series; i.e., 51 patients who received oral swabs.

Computed tomography (CT) Imaging

Considering the negativity of RT-PCR such as low positivity and late results, it has also made CT a more preferred diagnostic tool, as it is an easily accessible method and yields rapid results.[8] Although imaging findings may alter with age, comorbidity, and severity of pneumonia, they appear to be similar to those reported with SARS and MERS.[1]

In a series of 1,014 patients, Ai et al.[34] found 71% positive RT-PCR results and the CT findings indicated positivity in 98% patients. In this study, typical CT findings of COVID-19 pneumonia were reported as areas of bilateral ground-glass opacification and consolidation sites, particularly the lower lobes, showing peripheral distribution (Figure 6). Chung et al.[35] also reported that 86% of positive patients had bilateral ground-glass opacification, although no lung cavitation, lymphadenopathy, pleural thickening, or effusion were observed. Despite its high sensitivity, however, chest CT cannot always diagnose or exclude COVID-19.[20]

Laboratory

Although the blood picture changes in COVID-19 patients, the most common laboratory findings are normal/low lymphocyte amount, unbalanced coagulation, and elevation of

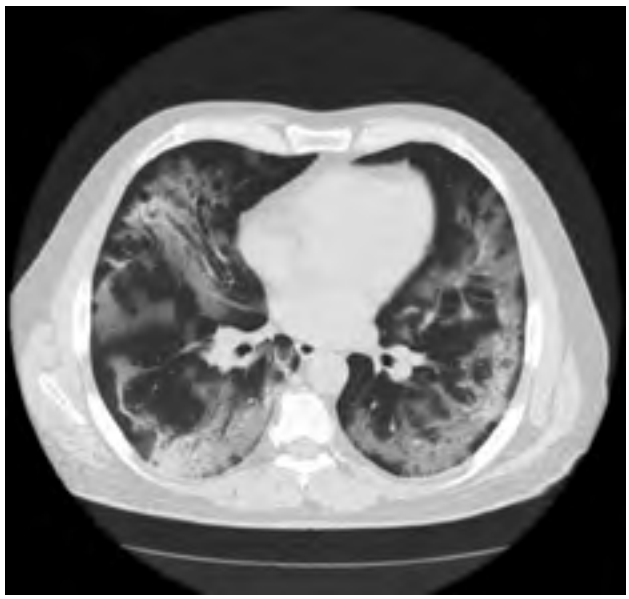

Figure 6. *Evaluation of COVID-19 patient in axial section by high resolution computed tomography imaging.*

In the bilateral lung parenchyma, there are infiltration areas and accompanying interlobular septal thickening in the lower lobe basal segments, high-density ground-glass density with a peripheral distribution, and there is "crazy-paving" pattern. These radiological findings support severe viral pneumonia.

C-reactive protein, lactate dehydrogenase, aminotransferase, and ferritin. In a series of 1,099 patients in the study of Guan et al.,[36] lymphocytopenia was the most common finding in 82.1% of patients. In a retrospective study, Zhou et al.[37] found a relation of D-dimer, troponin I, ferritin, lactate dehydrogenase, and IL-6 elevation and low basal lymphocyte count with poor prognosis in 191 patients.

TREATMENT

Patients younger than 50 years old who do not have any comorbid disease should be followed at home in accordance with the recommendations of the relevant authorities.[38] However, it should be known that the risk of developing severe disease is higher in the second week of the disease and patients should be followed closely.[38] Currently, there is no specific treatment proven to be reliable for COVID-19.[38] Oseltamivir, hydroxychloroquine, favipravir, and azithromycin have been attempted to be used in the treatment protocols based on the SARS epidemic and viral pneumonia experiences.

Oseltamivir should be given in patients with clinical findings compatible with influenza, influenza which cannot be excluded according to season and other factors, or influenza positivity based on the diagnostic test.[38] The current scientific data do not strongly support the treatment of hydroxychloroquine in individuals who are asymptomatic and in whom the PCR test for COVID-19 is positive.[38]

In the light of current data, the combination of hydroxychloroquine and azithromycin is recommended in uncomplicated mild course patients.[38] In severe cases, the combination of hydroxychloroquine, favipravir, and azithromycin is recommended.[38] It is known that macrophage activation syndrome (MAS) may also develop in the course of COVID-19 disease; however, there is no high level of evidence data regarding its incidence and definitive treatment.[38] Although randomized-controlled clinical trials are still lacking, tocilizumab, an anti-IL, and anakinra, an anti-IL-1, are recommended in patients who develop MAS.[38]

Declaration of conflicting interests

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