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Original Article

Millennium pandemic: A review of coronavirus disease (COVID-19)

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ABSTRACT

Coronaviruses, a large family of single-stranded RNA viruses, can infect humans and animals, and can cause neurological, gastrointestinal and hepatic diseases as well as causing various lung diseases, including pneumonia, with shortness of breath, cough and fever. At the end of December 2019, a group of health authorities reported unidentified cases of pneumonia in a seafood market in Wuhan, China. The World Health Organization (WHO) used term 2019 novel coronavirus (COVID-19) to refer to a coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December and the WHO announced that the official name of the 2019 novel coronavirus was coronavirus disease (COVID-19). COVID-19 is seen in many countries around the World and has been accepted as a pandemic by WHO. It is defined as a suspicious case with fever, sore throat, cough, and people with a history of traveling to China or some parts of the country, or someone who contact with a patient who has a history of travel in China or contact with a confirmed COVID-19 infection patient. Currently, there is no proven vaccine or antiviral therapy that can be used against animal or human coronavirus. To control the outbreak, the drugs must be developed as soon as possible. Various drugs have been used in the treatment of COVID-19 and the main ones are chloroquine, remdesivir, lopinavir/ritonavir, oseltamivir, favipiravir. Since the virus affects the whole World, vaccines and/or new curative antiviral drugs are needed to end the pandemic. For this purpose, large-scale observational studies are needed.

Keywords: 2019-nCoV, COVID-19, coronavirus, epidemiology, pneumonia, treatment, pandemic.

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Introduction

Coronaviruses, a large family of single-stranded RNA viruses, can infect humans and animals, and can cause neurological, gastrointestinal and hepatic diseases as well as causing various lung diseases, including pneumonia, with shortness of breath, cough and fever [1, 2]. Four coronavirus species called HKU1, NL63, 229E, OC43 are in circulation in humans and are generally cause mild respiratory diseases [3].

In the last 20 years, 2 violent events occurred with the transition of betacoronaviruses from animals to humans. The first incident was in

2002. A new genus of beta coronavirus passed on to people using palm civet cats as hosts and bats as intermediate hosts in Guangdong province in China. This virus, called severe acute respiratory syndrome (SARS) coronavirus, affected 8422 people in China and Hong Kong and 916 people died (mortality rate was 11%) [4]. Almost 10 years later, in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV) appeared in Saudi Arabia, using dromedary camels as hosts, bats as intermediate hosts, 2494 people affected and 858 people died (mortality rate was 34%) [5].

At the end of December 2019, a group of health authorities reported unidentified cases of pneumonia in a seafood market in Wuhan, China [6]. Although most of the early infected patients were seen in the Huanan seafood market in Wuhan, China, 13 of 141 cases were not affiliated with the market [7]. Although it started in the first patient on 1 December 2019, its relationship with seafood market was not reported. There was no epidemiological link between the first case and the next ones. Probably the first virus came to the market and spread from there [8].

The World Health Organization (WHO) used term 2019 novel coronavirus (COVID-19) to refer to a coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December and the WHO announced that the official name of the 2019 novel coronavirus was coronavirus disease (COVID-19) [9]. The current reference name for the virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and at the end of December 2019, this virus was blamed as the cause of pneumonia cases occurring in Wuhan, China [6]. COVID-19 has been declared as a Public Health Emergency of International concern by the WHO [10].

COVID-19 is seen in many countries around the World and has been accepted as a pandemic by WHO. With this review, we aim to explain general information about COVID-19, its diagnosis, laboratory and radiological findings, diagnosis and treatment methods.

Clinical findings and symptoms

Examining the current epidemiological study, most individuals had a close contact history with a patient with COVID-19 or a recent travel history to Wuhan or Hubei province in China [11]. The symptoms of COVID-19 infection were not specific. The most common symptoms were fever, weakness, fatigue and dry cough. Some patients also had headache and/or muscle pain, but no upper respiratory tract symptoms [11]. Diarrhea was reported with a frequency of 10.6% in SARS and 30% in MERS [12]. More than half of the patients developed shortness of breath. The median duration of the appearance of dyspnea from the beginning of the disease was 8 days [7]. If the disease could not controlled, patients with COVID-19 may develop acute respiratory distress syndrome (ARDS), followed by septic shock, metabolic acidosis and coagulation dysfunction [11]. Although pneumonia was also seen in patients infected with COVID-19, few had pleuritic chest pain [13].

Patients were divided into 3 groups as mild, severe and critical, depending on the severity of the symptoms (Table-1). Mild patients had non-pneumonia or mild pneumonia. Severe patients had several clinical findings, including dyspnea, respiratory frequency $\geq$ 30/min, blood oxygen saturation $\leq$ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates >50% within 24 to 48 hours. Critical patients had severe conditions, such as respiratory failure, septic

shock, and/or multiple organ dysfunction or failure [14].

Table 1. Clinical symptoms associated with COVID-19.

Clinical Types	Symptoms
Mild	Nonpneumonia or mild pneumonia
Severe	Dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates >50% within 24 to 48 hours
Critical	Respiratory failure, septic shock, and/or multiple organ dysfunction or failure

Laboratory findings

Among the laboratory findings, leukopenia and lymphopenia were the most common [7, 15, 16]. Lymphopenia was the most important laboratory finding in COVID-19 infection. While lactate dehydrogenase (LDH) and creatine kinase (CPK) increased in all patients, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) was found to be high in half of the patients. In most patients, myocardial tests were abnormal, with elevated CPK and LDH. In most patients, procalcitonine was normal, while C - reactive protein (CRP) was above the normal range. D-dimer was elevated in one third of the patients [7, 13, 15, 16].

In a study investigating cytokines in the serum of COVID-19 patients. Interleukin (IL)1B, IL1RA, IL7, IL8, IL9, IL10, basic in plasma fibroblast growth factor (FGF), granulocyte colony stimulating factor (GCSF), granulocyte-macrophage colony stimulating factor (GMCSF), interferon-gamma (IFNγ), induced protein-10 (IP10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1A (MIP1A), macrophage inflammatory protein-1B (MIP1B), platelet-derived growth factor (PDGF), tumor necrotic factor alpha (TNFα) and vascular endothelial growth factor (VEGF) concentrations were higher than healthy adults. Plasma levels of IL5, IL12 p70, IL15, Eotaxin and RANTES (regulated upon activation, normal T cell expressed and secreted [also known as CCL5]) were similar to that of healthy individuals and patients. When the serum plasma of patients with and without intensive care unit is compared, IL2, IL7, IL10, GCSF, IP10, mitochondrial pyruvate carrier 1 (MPC1), MIP1A, and TNFα levels were higher in intensive care patients than in non-intensive care patients [7].

Radiological findings

Radiological images of patients infected with COVID-19 are quite diverse and can be rapidly progressed [17-19]. At least two-thirds of patients had at least two lobes affected. At least 5 lobes were effected in half of the patients. The most common manifestations in computerize tomography (CT) images are irregular ground glass opacities (GGO) and patchy consolidations, especially in the middle and outer zones of the lung [19, 20].

In one study, radiological findings was divided into 4 stages according to CT images of patients infected with COVID-19. In the early stage, unilateral or bilateral GGO in the lower lobes of the lung was the main radiological findings. In the progressive stage, diffuse and bilateral GGO and consolidation in more than 2 lobes

were the main findings. In the peak stage, diffuse GGO and consolidation began to become more evident. In the absorption stage, wide GGO could be observed and consolidation was gradually absorbed [20].

Pathological findings

Pathological findings of COVID-19 were rare. In one study, primary finding in biopsy of a 50-year-old man with cardiac arrest due to respiratory failure died after 14 days were cellular fibromyxoid exudates, and bilateral diffuse alveolar hemorrhage areas and infiltrated areas where lymphocytes predominate [21]. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were identified in the intraalveolar spaces, showing viral cytopathic-like changes. No obvious intranuclear or intracytoplasmic viral inclusions were identified. These pathological features show great similarities to SARS-CoV and MERS-CoV infection [22-24].

Diagnosis

It is defined as a suspicious case with fever, sore throat, cough, people with a history of traveling to China or some parts of the country, or someone who contact with a patient who has a history of travel in China or contact with a confirmed COVID-19 infection patient [25].

1. Physical examination

Positive results may not be achieved in patients with mild patients. Severe patients may have shortness of breath, rales in lungs, weakened breath sounds, dullness in percussion, and increased or decreased tactile speech tumor [12, 13].

2. Laboratory tests

According to Koch's proposals, the gold standard is virus isolation in the laboratory diagnosis of the virus [26]. Viral nucleic acids can be useful in the early diagnosis of the disease, which is the most important thing. The nucleic acid in the RNA sequence of SARS-CoV-2 was aimed to be detected and the full gene sequence of SARS-CoV-2 was obtained. For this purpose, samples were taken from the upper respiratory tract (throat stick / nasopharyngeal rod / sputum sample / endotracheal sample / aspirates and bronchoalveolar lavage) and the diagnosis of SARS-CoV-2 infection was made by real-time PCR [25-27].

Other laboratory examinations are generally not specific. The white cell count is usually low or normal. There may be lymphopenia, and a lymphocyte count of < 1000 can be a sign of serious disease. Platelet count is usually low or normal. CRP and erythrocyte sedimentation rate (ESR) is generally high, but procalcitonin levels are usually normal. AST, ALT, creatinine, CPK, LDH, D-Dimer, prothrombin time may increase and these values are associated with severe disease [25].

3. CT examination

The chest X-ray usually shows infiltrated areas in the lung, but the x-ray may be normal in the early stages of the disease. CT is more sensitive and specific in demonstrating GGO, infiltrated areas and lower lobe consolidations in the lung. CT is also normal in asymptomatic patients / patients without lower respiratory tract involvement. In fact, in COVID-19 patients whose molecular tests are negative, abnormal findings can be detected in CT. Also, positivity can be detected in these patients by repeating molecular tests [25].

Treatment

Currently, there is no proven vaccine or antiviral therapy that can be used against animal or human coronaviruses. To control the

outbreak, the drugs must be developed as soon as possible. WHO stated that a vaccine for SARS-CoV-2 could be available within 18 months [28]. The most important step in the clinical management of the disease is largely symptomatic therapy. Intensive care unit may be required for severe patients and those with organ involvement [29].

Various drugs have been used in the treatment of COVID-19 and the main ones are as follows:

Chloroquine

Chloroquine is a drug with high potential to treat COVID-19 infection. Chloroquine has been used for many years in malaria treatment [30]. Several possible mechanisms for chloroquine treatment have been investigated. Chloroquine can replace intracellular pH by following the replication steps of various viruses. And with this mechanism, chloroquine can have potential positive effects in treating SARS-CoV-2 infection [31, 32]. One study found that chloroquine prevents replication of the new type of coronavirus [33]. Gao et al. found that chloroquine prevents pneumonia exacerbation, improves lung images and allows negative transformation of the virus [34].

Remdesivir

Remdesivir (GS-5734) is a 1′-cyano-substituted adenosine nucleotide analog prodrug [35]. Remdesivir has been reported to treat a first case of COVID-19 in America [36]. A study have shown that remdesivir gives good results in COVID-19 patients and treats the disease [33]. In addition, another study stated that remdesivir may be the best treatment option in COVID-19 [37].

Lopinavir/Ritonavir

Lopinavir is a protease inhibitor used in HIV treatment, with ritonavir as a booster. Lopinavir or lopinavir/ritonavir showed anti-coronavirus activity in in-vitro studies. IFN-α has broad-spectrum antiviral effect, it is an agent used in the treatment of hepatitis-B virus. IFN-α (5 million U bid inh) and lopinavir/ritonavir (400 mg/100 mg bid po) combine therapy are recommended as antiviral therapy. This treatment used to treat SARS [38]. This treatment is also recommended for SARS-CoV-2 [39].

Oseltamivir

Oseltamivir is a neuraminidase enzyme inhibitor and is used to treat influenza [40]. In a 42-year old male patient, COVID-19 pneumonia was detected in January 2020 in Wuhan province, China. CT images were improved after treatment with ganciclovir and oseltamivir [41]. In many studies, oseltamivir was used in combination with various antiviral drugs in patients infected with COVID-19, no positive results have been encountered [7, 13, 16].

Favipiravir

Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor. In addition to its anti-influenza virus activity, favipiravir is capable of blocking the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses [42]. A study conducted in China in February 2020 provided positive results about favipiravir. One group was given favipiravir and the other group was given lopinavir/ritonavir. The third group was the control group. Compared to the groups, better antiviral efficacy was observed in the group treated with favipiravir, and no significant adverse effects were observed in this group. Significantly more negative effects were encountered in the group treated with lopinavir/ritonavir [43].

In another study, in COVID-19 patients who did not receive antiviral therapy before, favipiravir was found to be an effective treatment when anti-viral side effects were excluded, since it provided improvement in the

clinic in 7 days, effectively reducing fever and cough [44].

Comments

As a result, 2019 novel coronavirus is a new virus and its mechanism and treatment is not fully known. Since the disease especially affects the airways and lungs, patients complained of cough and shortness of breath and some patients died from the ARDS. Although the disease occurs in China, it affects the whole world, the pandemic table is heavy in many countries, and people, countries are negatively affected both socially and economically and their health policies are insufficient. In studies conducted, patients with older age, chronic diseases such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), cancer, kidney failure, heart failure were evaluated as risk groups [45-47]. That's why people over 65 years old, people with chronic diseases such as diabetes mellitus, hypertension, cancer, heart failure, kidney failure and those who use immunosuppressive drugs need to protect themselves more.

As of 29.03.2020, the number of cases worldwide has reached 665.616, the number of deaths has reached 30.857, and the number of patients recovering from the disease has reached 141.746. The number of cases in China has reached 82.061, the number of dead has reached 3182. The number of cases in Italy has reached 92.472 and the number of dead has reached 10.023. The number of cases in United States has reached 124.686 and the number of dead has reached 2.192. The number of cases in Spain has reached 73.235 and the number of dead has reached 5.982. The number of cases in Turkey has reached 7402 and the number of dead has reached 108 people [48]. According to these data, as of 29 March 2020 date, SARS-CoV-2 mortality is 4.63% all over the World, %4.03 in China, 10.84% in Italy, 8.17% in Spain, 1.76% in United States and 1.46% in Turkey (Table 2). Although the virus first appeared in China [7] Italy has become the new center of the virus due to the dramatic increase in the number of cases and deaths in Italy.

Table 2. As of March 29, 2020, SARS-CoV-2 confirmed cases, number of deaths, mortality rate (%) in some countries.

Countries	Confirmed cases	Number of deaths	Death rate (%)
Italy	92,472	10,023	10.84
Indonesia	1,155	102	8.83
Spain	73,235	5,982	8.17
Iran	35,408	2,517	7.11
Netherlands	9,819	639	6.51
Philippines	1,075	68	6.33
France	38,105	2,314	6.07
United Kingdom	17,312	1,019	5.89
China	82,061	3,304	4.03
Belgium	9,134	353	3.86
Japan	1,693	52	3.07
Sweden	3,447	105	3.05
Brazil	3,904	114	2.92
Denmark	2,366	65	2.75
Ecuador	1,823	48	2.63
Romania	1,452	37	2.55
Portugal	5,170	100	1.93
Switzerland	14,076	264	1.88
United States	124,686	2,192	1.76
South Korea	9,583	152	1.59
Ireland	2,415	36	1.49
Turkey	7,402	108	1.46
Malaysia	2,320	27	1.16
Poland	1,638	18	1.1
Canada	5,655	61	1.08

In conclusion, since the virus affects the whole World, vaccines and/or new curative antiviral drugs are needed to end the pandemic. For this purpose, large-scale observational studies are needed.

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