Diagnosis and treatment of coronavirus disease 2019 (COVID-19): laboratory, PCR, and chest CT imaging findings

Abstract

Since December 2019, more than 3 million cases of coronavirus disease 2019 (COVID-19) and about 200,000 deaths have been reported worldwide. The outbreak of this novel disease has become a global health emergency and speedily continues to spread around the world. Based on the clinical data, approved cases are divided into four classes including mild, moderate, severe, and critical. About 5% of cases considered critically ill and 14% were experienced the severe disease. In China, the fatality rate of this infection was about 4%. This review focuses currently available information on the etiology, clinical symptoms, diagnosis, and mechanism of action of COVID-19. Furthermore, we present an overview of diagnostic approaches and treatment of this disease according to available findings. This review paper will help the physician to diagnose and successfully treat COVID-19.

Keywords: Chloroquine, Coronavirus, Coronavirus infection, COVID-19 vaccine, Respiratory tract infections, Viral pneumonia

Introduction

Up to 1st of May 2020, more than 3,000,000 cases with COVID-19 were diagnosed and 200,000 death cases were recorded. The coronavirus disease 2019 (COVID-19) first was reported in December 2019, in Wuhan, China. It was quickly spread to other districts of this country, and a month later to the other countries across the world, impacting over 200 countries and territories. World Health Organization (WHO) declared COVID-19 outbreak as a pandemic on March 2020 and the COVID-19 has been reported a global emergency by WHO in January 2020[1]. Like other pneumonia, including the Middle East respiratory syndrome (MERS) and the severe acute respiratory syndrome (SARS), COVID-19 could also cause acute respiratory distress syndrome (ARDS)[2].

COVID-19 has been stated to be originated from wild bats and belonged to genera β-coronavirus. Although COVID-19 and SARS-associated Coronavirus (SARS-CoV) belong to the same β-coronavirus, similarity at genome level is only 70%, and the new group has been reported to display genetic differences from SARS-CoV[3].

Almost all of the earlier cases had a history of contact to the Wuhan city, and some cases present a family clustering character. The exact source of COVID-19 is still unknown; nevertheless, it is reported that the infection may have been induced by vipers or bats[4]. This novel virus exhibits high person-to-person transmissibility and typically infects animals, including mammals and birds. In patients, coronavirus usually leads to respiratory infections, like those detected in the common cold. But, some new human coronavirus infections have caused lethal endemics including MERS and SARS endemics[1]. WHO, in the first report, projected about a 4% fatality rate for COVID-19. However, among hospitalized cases, the fatality rate is about 4–15% [1, 5].

Most of the COVID-19 subjects are adults. Among 44,672 cases in China, 2.1% were below the age of twenty. About 5% of patients experienced critically ill conditions and 14% were experienced severe disease. Initial reports documented that disease severity was accompanied with age over the 60 years and a history of co-morbid condition. Rapid detection of COVID-19 is vital to guarantee timely treatment, and from a public health perspective, quick isolation of the patient is essential to discontinue the cascade of contamination[6].

Structure

Coronaviruses (CoVs) belong to the subfamily Coronavirinae in the family of Coronaviridae of the order Nidovirales, and this subfamily includes four types named as α, β, γ, and δ coronavirus[7]. The COVID-19, a β-coronavirus with positive-sense single-stranded RNA[1] is an enveloped virions that appear as oval or round, with 60-140nm diameter, often polymorphous (Fig. 1 and 2). COVID-19 is generally spread in humans and other mammals, and its genome is more distant from SARS-CoV and MERS-CoV[8].

Coronavirus recombination rates are very high due to continuously appearing transcription errors and RNA dependent RNA polymerase (RdRP) jumps[3]. With a high mutation rate of coronaviruses, they are zoonotic pathogens that are existing in humans and other mammalians with a varied range of clinical finding from asymptomatic feature to hospitalization in the intensive care unit (ICU); leading to the infections in lungs, gastrointestinal tract, liver and central nervous system[3].

Transmission and contamination with COVID-19

Besides to person-to-person close contact (less than six feet distance) and population mobility, environmental factors could influence droplet transmission and survival of viruses. Todays, subjects with COVID-19 are known as the main source of disease. Frequently, the transmission from person-to-person happens with close contact. The transmission initially occurs when a patient sneezes, coughs, or even talks, and through the respiratory droplets formed just as the spread of influenza and other respiratory viruses. Droplets can settle down in different parts of the body, such as the mouth, lungs, and eyes of subjects with inhaled air [3, 9]. This disease can be transmitted by touching a surface or an object that has the virus on it [3, 10]. Moreover, transmission may occur through fomites in the environment around the COVID-19 patients. It has been reported that COVID-19 infection may lead to gastrointestinal infection and be existent in stool. Hence, COVID-19 may transmit via fecal-oral or body fluid routes. Consequently, coronavirus transmission can occur by direct route (close contact with COVID-19 patients) and indirect route (surfaces in the immediate environment or equipment used by COVID-19 patients) (Table 1 and 2). Usually, similar other types of respiratory pathogens, it is accepted that the most contagious when subjects are most symptomatic. However, asymptomatic infections can act as a source of disease [10]. Cases that were infected from asymptomatic subjects in the prodrome phase of COVID-19 were also documented [10]. At present, based on limited findings, there is no evidence of transmission of COVID-19 from infected pregnant mother to baby [11].

COVID-19 was extensively distributed on hospital floors, sickbed handrails, trash cans, and computer keyboard and mice. The positive rate was relatively high for floor swab specimens (ICU: 70%; general COVID-19 ward: 15.4%), maybe due to air flow and gravity leading most virus droplets to float to the ground. Furthermore, as health workers walk around the ward, the COVID-19 can be transferred all over the floor, as shown by the 100% positive rate from the pharmacy floor, where there were no COVID-19 patients. Moreover, 50% of the specimens from the soles of the intensive care unit (ICU) staff shoes were positive. Hence, the soles of shoes might act as potential carriers. It has been potentially proposed that staffs disinfect shoe soles before walking out of wards containing infected subjects[12].

Gender susceptibility for COVID-19 infection

While MERS-CoV regularly infects subjects aged above 50 years, SARS-CoV infects younger individuals and COVID-19 infects subjects at their middle age or above. Infected older men with co-morbid diseases are more likely to have lung disease because of severe alveolar injury, indicating men were more vulnerable than women [13]. Differences in sex hormones and immune-linked genes on the X chromosome that affect both adaptive (acquired) and innate (non-specific) immune responses, may describe the high vulnerability to the COVID-19 infection in males. More possibility of virus exposure because of occupational risk could be other participated factors in higher male infection rate [14].

Clinical manifestations of COVID-19

Understanding the clinical manifestations is vital, although these symptoms are nonspecific. Since December 2019, numerous collected subjects of "unknown viral pneumonia" have been stated, originally related to Wuhan city, China[2]. Overall, many infected subjects with COVID-19 have many clinical symptoms similar to SARS-CoV infection[14]. It is reported that clinical feature differs from simple lung infection findings to septic shock. Like MERS-CoV and SARS-CoV, the first symptoms of COVID-19 are usually explained as cough, myalgia or fatigue, shortness of breath, and fever[13, 15]. Diarrhea was rarely documented in COVID-19 infection, while intestinal symptoms existed in approximately 20-25% of the subjects with SARS-CoV and MERS-CoV infection [3]. Some cases have complained hemoptysis or headache while the others were even relatively asymptomatic[13]. Comorbidities such as underlying cardiovascular disease, hypertension, and diabetes were reported in nearly half of the patients [3]. The symptoms of acute respiratory infection appeared within the early stage of disease. In next stages septic shock, metabolic acidosis, coagulation dysfunction, and ARDS[8] can appear in severe cases [15].

The incubation period for the COVID-19, on average, is 5.2 days, but it is different among patients. Studies support a 14-day medical treatment following period for subjects exposed to the pathogen[13].

Pneumonia is a significant problem

In SARS subjects, lung injury diagnosed in the first week from the symptom onset [16]. Then, the lesions develop into peripheral/subpleural distribution, bilateral involvement, posterior part /lower lobe predilection mixed with ground-glass opacity (GGO) in the fourth week. Likewise, Pan et al.[2] in a cohort study showed 85.7% pneumonia progression including consolidation and GGO at early CT scans in COVID-19. Of note, there is asymptomatic pneumonia among some COVID-19 patients. Therefore, care must be taken for the diagnosis of such atypical subjects as these might sources of public transmission[16].

Other types of pneumonia induced by streptococcus, chlamydia and mycoplasma, and other coronavirus infections should be differentiated from COVID-19 pneumonia. It is very vital to early separate suspected subjects with fever from the others to reduce cross-infection. Respiratory symptoms in COVID-19, including breathlessness, lung failure, and constitutional symptoms such as fever, muscle ache, confusion, and headache accompanied by diffuse heterogeneous consolidation with GGO[13].

Detection of COVID-19 infection

The history of exposure or being in close contact with suspected or confirmed patients is critical evidence for the diagnosis. Nevertheless, for patients with an unknown history, clinical features and imaging appearances can show suspected COVID-19. After that, the real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) test should be done in these cases, as a reference standard[13].

According to the National Health Commission (NHC) of China, the diagnostic criteria are; 1: exposure history to cases with respiratory symptoms from Wuhan or infected cities within two weeks before the onset of disease, 2: clinical findings (fever, normal or decreased WBC count or reduced lymphocyte count and/or imaging features of pneumonia), and 3: Real-time PCR showing positive results for COVID-19. The confirmed COVID-19 pneumonia should hospitalize and isolated for therapy[2]. Based on WHO recommendations for SARS and MERS, the NHC of China proposed criteria for diagnosis and treatment of COVID-19 pneumonia [13]. A person with two clinical conditions and one contact history is regarded as a suspected patient. Without any clear contact history, suspected cases should have 3 clinical features [13]. The discharge criteria were; 1: afebrile for more than 3 days, 2: significant improvement of respiratory symptoms, and 3: improvement in the imaging abnormalities on the chest. The definitive etiology diagnosis of infection is needed, which can be more approved by PCR assay using blood or lung specimen or by viral gene sequencing. Based on the clinical findings, approved subjects are divided into different classes, including critical, severe, moderate, and mild[13].

Laboratory tests

About nearly half of the patients infected with COVID-19 had a reduced WBC count and lymphopenia (reduced lymphocytes), or thrombocytopenia (low blood platelet count) with increased activated thromboplastin time. C-reactive protein (CRP) levels were increased in most patients, but procalcitonin (PCT) concentrations were normal[8]. Elevated serum ferritin levels reported in some patients[14]. All these alterations further explained that COVID-19 may exert a potential effect on lymphocytes, especially T cells. COVID-19 outbreaks and invades via lung mucosa stimulates inflammation cascades, and motivates cytokine storm, resulting in alteration in immune response such as peripheral blood leukocytes and lymphocytes. Hence, intravenous immunoglobulin was applied in most subjects with reduced WBC and lymphocyte count[8]. Augmented serum pro-inflammatory cytokine levels have also been documented, associating with the severity of the disease. Nevertheless elevated interleukin-10 levels, which is known as an anti-inflammatory cytokine, indicates a diverse pattern from that of SARS-CoV infection[14]. Some patients showed increased liver enzymes, and glucose levels and few patients exhibited abnormal muscle enzymes. Liver test abnormality of COVID-19 may not be induced by liver cell damage but by bile duct cell dysfunction and other reasons[8]. In summary, blood routine test, CRP, PCT, coagulation function, arterial blood gas, and tissue function tests (e.g. transaminases, bilirubin, myocardial enzyme, creatinine, urea nitrogen, urine volume, etc.) as tabulated in Table 3 should be monitored in patients [17]. Furthermore, subjects having upper respiratory tract symptoms and fever with leukopenia or lymphopenia should be suspected, particularly for cases with close contact or exposure history[18].

Imaging

Radiological evaluations, particularly thin slice chest computed tomography (CT) scan, has a critical role in diagnosis, management, and follow-up of COVID-19 infection [18]. Radiologists play the main role in the outbreak of COVID-19. Early diagnosis of the imaging abnormality could offer suspect pneumonia in cases at risk. Although the final detection of COVID-19 is based on RT-PCR, findings of imaging are vital for pneumonia detection[16]. CT scans are proposed in cases with suspicious lung abnormalities. Appropriate recognition of COVID-19 pneumonia could provide quick management and follow-ups. Lung imaging shows the severity of COVID-19 disease therefore physicians should be informed about radiological reports. Clinical findings from COVID-19-infected cases with a high abnormality on the CT scan who were admitted to the ICU [16] exhibited that patients on admission frequently showed subsegmental consolidation and bilateral multiple lobular, whereas CT reports from non-ICU patients showed subsegmental consolidation and bilateral ground-glass opacity (GGO) [15]. In severe infection, imaging can confirm heterogeneous consolidation with GGOs in bilateral lungs and bronchiectasis, indicating as “white lung” when most lobes of the lung are affected[19]. Furthermore, COVID-19 cases might show intralobular septal thickening and bilateral pleura along with little pleural effusion [13]. CT scan enables recognition of the initial phase of respiratory infection and provides opportunity for a quick public health care response [20]. Slice chest CT has been shown as the main evidence for approved findings. Since chest radiography is not sensitive for the diagnosis of GGO and might show normal results in the initial stage of disease[20], it is not considered as the first-line imaging method for COVID-19. Nevertheless, bilateral multifocal consolidation can be observed in severe cases, partially fused into high consolidation with minor pleural effusions and even showing with “white lung” [13]. In this respect, the thin slice chest CT test is more useful for the early diagnosis of COVID-19 pneumonia [18, 20]. High-resolution computed tomography (HRCT) will be easier to detect GGOs in the early stage[4]. A study with large sample size (3665 confirmed disease) has reported that 95.5% of cases were detected as pneumonia. The Pan et al. [2] conducted an experiment with 21 approved

COVID-19 who underwent repeated CT at about 4-day intervals and observed negative results in four cases on initial stage (0-4 days after onset of the early symptom), but repeated CT displayed abnormalities in the lung in all of these four patients.

The usual imaging features of COVID-19 pneumonia include interstitial inflammation, extensive consolidation with multifocal bilateral GGOs, bilateral involvement, noticeable peripheral or subpleural distribution, posterior part or lower lobe predilection, and multiple lesions [13]. Nevertheless, certain cases with COVID-19 pneumonia regularly revealed no respiratory distress or hypoxemia during the course of hospitalization[2]. Furthermore, since the CT scan results of COVID-19 overlap with other viral pneumonia, therefore RT-PCR assay is strongly recommended for rapid detection and treatment[4].

According to the Pan et al. report, the cases who recovered from this virus pneumonia, experienced four stages based on their CT results: (1) early stage (0-4 days) that shows small GGO distributed subpleurally in the lower part, (2) progressive stage (5-8 days) with infection quickly extended to a bilateral multi-lobe with diffused GGO, consolidation, and crazy-paving pattern, (3) peak stage (10-13 days) that shows slowly expanding of the involved part to the peak involvement, including diffused GGO, crazy-paving pattern, residual parenchymal bands, and consolidation, and finally (4) absorption stage which occurs two weeks after the onset of first symptoms and shows that the disease is managed and the consolidation is slowly absorbed (Fig. 3 and Table 4). No crazy-paving signs exist anymore. Nevertheless, in this step, widespread GGO can be observed as an indication of the consolidation absorption. According to the CT scores, the absorption step extended beyond 26 days after the onset of first symptom [2].

RT-PCR test

The most common detection assay is RT-PCR based on the RNA isolated from respiratory specimens such as oropharyngeal swabs, sputum, nasopharyngeal aspirate, bronchoalveolar lavage, or deep tracheal aspirate[3].

At the moment, the RT-PCR method is used in clinics to confirm the COVID-19 infection. While this assay remains the reference standard to the detection of COVID-19, the high false-negative RT-PCR results [21] and inapplicability of RT-PCR in the initial phase of the disease limited the rapid diagnosis of infected subjects[13]. It has been reported that the sensitivity of chest CT was superior to that of RT-PCR (98% *vs*. 71%, respectively). The causes for the low effectiveness of viral nucleic acid measurement might include; low viral load, inappropriate sample, variation in the diagnosis rate from different kits, and undeveloped technology for detection of the nucleic acid[22]. Lower respiratory tract sample (bronchoalveolar lavage fluid, deep tracheal aspirates), and induced sputum has the highest genome fraction and viral load compared to upper respiratory tract samples, which are optimal for improving detection accuracy[3]. Nevertheless, with sample collection and transportation, as well as kit quality, the total positive rate of RT-PCR for throat swab specimens was about 60% at initial presentation in different studies (Table 5) [23, 24].

The positive rate of chest CT imaging and RT-PCR assay in Ai et al.[23] cohort study was 88%, and 59% for the detection of suspected subjects with COVID-19, respectively. They showed that chest CT imaging had higher sensitivity for the diagnosis of the COVID-19 infection as compared with initial RT-PCR from swab samples. They also reported that 42% of infected subjects exhibited improvement of follow-up chest CT scans before the RT-PCR finding turning negative[23].

Xie et al. [25], by evaluating of the 167 infected cases, showed that 3% (5/167) of patients had negative RT-PCR while they had positive chest CT. PCR procedure for COVID-19 may be falsely negative because of laboratory error, inappropriate sample, or inadequate viral load in the sample. The chest CT gives fast results, easy to do, and enables quick diagnoses of initial COVID-19 pneumonia[13].

Mechanism of action

The COVID-19 spreads and invades via the lung, stimulates inflammation, and induces cytokine storm, leading to alteration in immune cells such as WBC and lymphocytes. Accordingly, administration of intravenous immunoglobulins is being used as therapeutic strategy for most subjects with decreased levels of WBC and lymphocyte[8].

COVID-19 patients are susceptible to liver failure, since COVID-19 directly binds to angiotensin-converting enzyme-2 (ACE2) positive bile duct cells [26]. It has been shown that ACE2 is protective against several lung diseases, including ARDS, asthma, acute lung injury (ALI), chronic obstructive pulmonary disease (COPD), and pulmonary hypertension[27]. ACE2 has also been demonstrated to be the receptor for both the SARS-CoV and the human respiratory coronavirus NL63. The previous experiment established the positive correlation of ACE2 expression and the infection of SARS-CoV *in vitro* [28]. SARS-CoV significantly decreased ACE2 protein expression after infecting the host [28]. Consequently, the ACE2 expression in different organs might be vital for the vulnerability, signs, and outcome of COVID-19. An analysis of single-cell RNA-sequencing (RNA-seq) showed that Asian males might have higher ACE2 expression levels[28].

ACE2 is one of the components of the renin angiotensin system (RAS) that regulates blood pressure, systemic vascular resistance, and electrolyte balance. In the respiratory system, local lung RAS activation can influence the pathogenesis of lung damage through numerous mechanisms, including elevation of vascular permeability and changes in alveolar epithelial cells. In this cascade, renin increases angiotensinogen to produce angiotensin I (Ang I, a decapeptide hormone)[29]. The ACE hydrolyzes Ang I to angiotensin II. The angiotensins II binds to its receptors and induces vasoactive effects. ACE2 catalyzes Ang I to generate angiotensin-(1–9) and Ang II to Ang-(1–7), and antagonize several effects of Ang II. ACE2, by reducing local Ang II levels, acts as a counter-regulatory enzyme[29, 30]. ACE2 deficiency and consequent high Ang II concentration, lead to increased vascular permeability, neutrophil accumulation, pulmonary oedema, disruption of gas exchange, and exacerbation in lung function. On the other hand, active recombinant ACE2 protein alleviates ALI symptoms in ACE2 knockout animals[31]. In the lungs, RAS activity is basically high, and the activity of the ACE2 is also highly increased to control the balance of Ang II/Ang-(1–7) concentration[29, 30]. It has been shown that ACE2 participates in the severe ALI and failure that is induced by SARS, influenza A H5N1 virus, acid aspiration, sepsis, and lethal avian. Currently, ACE2 is proposed as a potential therapeutic target for the treatment of ALI in humans [32].

In animal models of ARDS, ACE2 knockout animals showed more severe symptoms, whereas the upregulation of the ACE2 has protective effects. In animals infected by SARS-CoV, both the viral spike protein and replication protein alone can decrease ACE2 but not ACE expression. Furthermore, SARS-CoV also motivates quick ACE2 downregulation from the cell surface. These findings suggest that the SARS-CoV interrupts physiological balance between ACE/ACE2 and Ang II/Ang-(1–7)[29]. Consequently, high Ang II concentration in the lung tissue aggravates acid-induced acute lung injury and causes severe lung failure. Likewise, the spike protein of COVID-19 interacts with ACE2, and probably the pathogenic mechanism might share between SARS-CoV and COVID-19 [29].

Surgery in COVID-19 patients

Healthcare workers are on the front lines of battling COVID-19 that put them at high risk of COVID-19 infection. Occupational Safety and Health Administration (OSHA) has separated job tasks into four risk exposure levels, as presented in Figure 4. Since Covid-19 quickly spread through respiratory droplets, head and neck surgeons who have close contact with the upper aerodigestive tract are principally at high risk. Given the high number of surgeries done worldwide, it is essential for the surgeons and surgical team to be adequately protected from coronavirus transmission. In the COVID–19 patients who need surgery, risks versus benefits of the procedure for the patient should be cautiously evaluated. The surgeon may temporary postpone an emergency or urgent surgery on cases that show coronavirus symptoms (e.g., cough, sore throat, fever). For all suspected cases that are undergoing operation, chest CT and blood tests need to be checked before admission. The surgical team can also order an in-house RT-PCR assay within 24h. If the subject's condition does not allow for a 24h wait, the patient is assumed to be COVID-19-positive. For suspected or confirmed COVID-19 cases, non-operative management is preferred. If surgery is essential in these subjects, suitable personal protective equipment (PPE) should be used (Fig. 5). Furthermore they should remove their PPE and place the PPE in a labelled waste bag in an anteroom. There are various levels of emergency related to COVID-19 patient needs, and assessment is required to distinguish among them. Table 6 summarizes the key recommendations for the surgeon and surgical team in different stages [33-35].

Treatment of COVID-19

Currently, there is no effective medicine for the treatment for COVID-19 patients, which can, in some patients, lead to lethal lung failure. Furthermore, there is not any specific antiviral or vaccine for this virus[8]. Pathogenesis of coronavirus is an extremely complex process, and much of the required details in host-pathogen interaction remained unknown. Discovering the useful medicine options for the treatment of the COVID-19 outbreak is vital [36, 37] (Table 7). There are various possible treatment approaches [29] including (i) rises in ACE2 expression by injection of soluble recombinant ACE2 protein or using therapeutic vectors expressing high levels of ACE2 which may be applicable in the future[38], (ii) using specific ACE inhibitors such as lisinopril, and (iii) inhibiting Ang II receptors. In particular, the type I Ang II receptor has been reported to promote disease by motivating oedemas and disturbing lung function[38]. Hence, a type I Ang II receptor blocker (e.g., losartan) has been successively examined for improving COVID-19 pneumonia[29]. Treatment with a soluble form of ACE2 probably acts as a competitive interceptor of coronavirus by inhibiting binding of the viral particle to the ACE2 receptor, consequently can slow coronavirus entry into the cells and protect the lung injury. Remdesivir (adenosine analogue) that is used for the treatment of the Ebola disease is incorporated in the nascent chains of viral RNA, causing premature termination. This drug is currently used for the treatment of COVID-19 infection. Randomized trial studies have reported the safety and efficacy of interferon-α (5 million U per time, twice a day) and lopinavir-ritonavir (two capsules each time, twice a day) in COVID-19 patients [39]. Wang et al. determined the efficacy of some FDA-approved drugs such as penciclovir, ribavirin, nitazoxanide, chloroquine, nafamostat, and favipiravir (T-705) for treatment of COVID-19 infection in the *in vitro*[40]. They found that chloroquine and remdesivir are potentially effective in the control of COVID-19 infection *in vitro* [40]. Chloroquine is a well-known drug that has currently been documented as a strong broad-spectrum antiviral agent for the treatment of malarial and autoimmune disease. This drug interferes with glycosylation of the cellular receptor, elevates endosomal pH needed for virus/cell fusion, and consequently reduces virus infection[41]. It has also recommended by some Chinese researchers to use traditional medicine to recover the physical signs of cases[8]. Luo et al. showed that some Chinese medicines such as *Lonicerae Japonicae Flos* (Jinyinhua), *Radix saposhnikoviae* (Fangfeng), *Radix glycyrrhizae* (Gancao), *Fructus forsythia* (Lianqiao), and *Rhizoma Atractylodis Macrocephalae* (Baizhu) are useful in the prevention of COVID-19 [42]. Some other herbal plants, through their antioxidant and anti-inflammatory activity might be considered as useful agents in the treatment of COVID-19 infection [43-46]. Furthermore, zinc nanoparticle also due to potential antioxidant, anti-inflammatory [47], and antiviral effects can inhibit influenza viral load, and COVID-19 replication in the *in vitro* experiment [48].

Isolation of infected cases and supportive cares such as fluid management, oxygen therapy, and antimicrobials agents for the treatment of secondary bacterial infections and prevent end-organ dysfunction are suggested by WHO for patients needing hospital admission [8, 10]. Interferon-α is a wide spectrum antivirus medicine that can be used to treatment of hepatitis B virus (HBV). Lopinavir is a protease inhibitor used for the treatment of human immunodeficiency viruses (HIV) with ritonavir as a booster that showed potential anti coronavirus activity. In the patient with SARS cases treated with lopinavir/ritonavir and ribavirin had a lower risk of ARDS or death as compared with ribavirin alone [49]. Beck et al. used some antiviral drugs, including arbidol, lopinavir/ritonavir, and Shufeng Jiedu

Capsule (SFJDC, herbal medicine) for the treatment of 4 cases with mild or severe COVID-19 pneumonia. After the drug therapy, cases gained noticeable improvement and discharged from the hospital[39].

Some COVID-19 infected patients might have co-infections with fungi and bacteria. Chen et al. detect some bacteria and fungi as secondary infections, including *Klebsiella pneumonia, Acinetobacter baumannii*, *Aspergillus flavus*, *Candida albicans*, and *Candida glabrata*. They showed that *Acinetobacter baumannii* has a high drug resistance rate, causing the possibility of septic shock[50]. The host immune system is one of the main factors in secondary infections. Other involved factors that may increase mortality in COVID-19 patients are obesity, old age, diabetics, HIV infection, autoimmune disease, and pregnancy in women[50]. Therefore, early diagnosis and timely treatment of these critical patients to prevent secondary infection are necessary. Immunoglobulin injection is recommended to increase the anti-infection drug ability for severe cases [50]. Furthermore, paracetamol (400mg per time, every 8 h when required) is recommended in the patient with high temperature [9, 37].

In summary, at present, there are no vaccines and specific antiviral medicine for the treatment of COVID-19. All of the recommended drugs come from knowledge treating MERS, SARS, or another family of coronavirus. Further researches are required to provide evidences on the effectiveness of these drugs.

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Table 1. COVID-19 transmission routes.

Transmission routes	**Definition**
Close contact (direct or indirect)	✓ Less than 1.8 meters (6 feet)
Respiratory droplets	✓ When infected patients sneezes, coughs, or talks
Airborne	✓ May be occur in particular conditions in which procedures produce aerosols (e.g., bronchoscopy, nebulized treatment, manual ventilation, cardiopulmonary resuscitation, open suctioning, tracheostomy, and endotracheal intubation)
Objects and surfaces	✓ Touching an infected equipment or surface, and then touching the eyes, nose, or mouth.

Table 2. COVID-19 duration on air and object.

Objects and Surfaces	**COVID-19 duration**
Air #	up to 24 hours
Cardboard	up to 24 hours
Plastic	up to 2-3 days
Stainless Steel	up to 2-3 days
Cardboard	up to 1 day
Copper	up to 4 hours

The maximum transmission distance: up to 4 meters.

Table 3. Laboratory findings in Covid-19 patients.

Increased in most patients	**Increased in few patients**	**Decreased in most patients**	**Normal in most patients**
CRP	D-dimer*	Lymphocyte count	Procalcitonin
LDH	Procalcitonin	Albumin	
ALT	Urea	WBC#	
AST	Blood glucose		
Total bilirubin	Myohemoglobin		
Creatinine	CK		
Cardiac troponin	Ferritin		
PT			
ESR			
Cytokines (IL-6, IL-10, IL-2, IL-7)			

CRP (C-reactive protein), LDH (Lactate dehydrogenase), ALT (Alanine aminotransferase), AST(Aspartate aminotransferase), PT (Prothrombin time), ESR (Erythrocyte sedimentation rate), IL- (Interleukin-), Creatinine Kinase (CK), WBC (White blood cell).
* Increased in severe cases, #Patients have normal or reduced levels.

Table 4. Chest CT findings of COVID-19 pneumonia.

Chest CT imaging features	Definition	Severity grades
Ground glass opacities (GGO) +/- consolidation	An area of hazy elevated lung opacity	+++++
Multiple lesions	Damage or abnormal changes in a different area	++++
Bilateral distribution	Two sides distribution of GGO	++++
Posterior part / lower lobe predilection	Dorsal part/lower lob predilection	++++
Pure consolidation	Replacement of air in the alveoli by different matters (e.g., cells, blood, and pus)	++++
Peripheral / subpleural distribution	Peripherally and subpleural distributed multifocal GGOs	+++
Crazy-paving pattern	A linear pattern superimposed on a background of GGO	+++
Reticular pattern	Presence of countless lines, either due to fibrosis or thickening of the interlobular septa	++
Pleural thickening	Extensive scarring thickens the pleura	++
Bronchial wall thickening	Damage of the bronchial wall	++
Bronchiectasis	Lungs become abnormally enlarged	++
Nodules	Irregular or rounded opacity (any space-occupying lesion in single or multiple forms)	+
Pleural effusion	Fluid on the pleural cavity	+
Subpleural curvilinear line	A thin curvilinear opacity (1-3 mm), located in the subpleural area and having a parallel distribution over the pleural surface	+
Fibrosis	The alveoli become stiff and scarred	+
Mediastinal lymphadenopathy	Mediastinal lymph node enlargement	Rare
Pericardial effusion	An abnormal levels of fluid in the pericardial space	Rare
Halo sign	Pulmonary nodules surrounded by ground glass	Very rare
Cavitation	A gas-filled spaces	Absent
Calcification	Deposition of calcium salt	Absent

Finding from References: [2, 13, 19, 51]

Table 5. COVID-19 detection in various clinical samples (positive rate).

Clinical specimen	Wang et al. study[24]	Wölfel et al. study[52]
	Total cases: 1070 samples from 205 patients	Total cases: 13 samples from 4 patients
BAL fluid	93%	NT
Sputum	72%	83.33%
Nasal swabs	63%	16.66%
Brush biopsy	46%	NT
Pharyngeal swabs	32%	NT
Stool	29%	Test was not successful
Blood	1%	NT
Urine	0%	NT

Samples were prepared during the first week of symptoms. BAL (bronchoalveolar lavage), NT (Not tested).

Table 6. Preoperative (A), operative (B) and postoperative (C) recommendation ([3, 9, 33, 53]).

A. Preoperative recommendation
• Surgeons should check all scheduled elective program and cancel, minimize, or postpone all non-urgent surgery • Surgeons must plan surgery according to the severity of the threat to the subject's life and health • In an emergency condition, cases should be located in the separated holding part and transferred to the operating room dedicated to COVID-19 patients • Transport operators should sanitize hands and wear personal protective equipment (PPE) before transfer and should minimize exposure with cases • Transfer routes of COVID-19 patients must be correctly managed and be as short as possible • The cases, wearing a surgical face mask, should be transported from the pre-defined short, direct path with minimum contact • Operators (i.e., surgeon, nurses, technicians, and anesthetist) need to be trained in the use of PPE • Operators should wash hand in a different moment, including before and after touching a patient or patient surroundings, after body fluid exposure and before engaging in clean/aseptic processes (with water and soap or 2 to 3% hydrogen peroxide solution or gel) • If oxygen is required, it can be administered by face mask over the surgical mask • Any non-intubated cases should wear a surgical mask, disposable cap, gloves, and shoe covers during transport • Operators should treat COVID-19 cases with respect, dignity, and kindness • The on-call shift can decrease the number of times surgeons move between the hospital and home • On-call surgeons should manage the initial triage arrangements and postoperative care with remote support

B. Operative recommendation

Operating room

- The operating room and entrance should be equipped with a negative pressure system
- In the hospitals without negative pressure, the positive pressure and air conditioning must be turned off
- A high frequency of air changes (25/hour) are proposed for the operating room
- The COVID-dedicated operating room must be labeled “COVID-19 infectious surgery” on the door
- The appropriate function of the laminar flow and the high-efficiency filter of the operating room must be ensured
- Once the infected cases have entered, the operating room doors must be closed
- All doors must be kept closed
- Unnecessary equipment must be moved away from an infected patient
- Minimal materials should be prepared for each operation
- Single-use material should be preferred where possible
- Use autonomous service (robots and transport system) for transfer of samples and test kits
- Clinical documentation should put outside the operating room
- Any activity that involves the pulmonary secretions, pharyngeal, nasal mucosal, and oral surfaces is recognized as a high risk to the operating room operators
- The powered devices (e.g., microdebriders, saws, drills, and ultrasonic shears) must be considered higher risk
- All electronic devices (hospital case sheets, mobile, laptop, and pagers) should be left outside the room
- Anesthetic, ultrasound machine, and computers monitor surfaces should be covered with plastic wrap to simplify cleaning
- All linen including pillowcases, crossbars, and sheets must be touched wearing PPE
- Linen can be contaminated and should hence be handled and transported carefully
- All essential material (e.g., scalpel blades, stitches, etc.) must be collected in a sterilizable steel basket
- Operating room and adjacent areas must be cleaned, sterilized, and disinfected after each operation

Staffs and patients

- All surgery should be done in a rapid and effective manner
- Reduce the total number of staff working in the operating room
- Decrease medical students and apprentice in the operating room
- Only operators that participate in direct care are permitted to enter the operating room
- All staffs should enter the operating room timely
- Staffs should not leave until the operation is finished, and once out they should not re-enter
- Prepare everything needed for operation and reduce staffs transiting in and out the operating room

- All staff in contact with the COVID-19 cases must wear PPE
- Alcoholic hand hygiene solution must continuously be available
- Double gloves are proposed to change the outer pair

C. Postoperative recommendation

- The operation room is recognized as an area with high risk of cross-infection and contamination
- Clean surface and equipment, rinse and dry, and disinfect with 2 to 3% hydrogen peroxide or 2000-5000 mg/L sodium hypochlorite solution, or 70% alcohol
- Grossly contaminated equipment should be cleaned and disinfected by 5000 g/L chlorine solution
- The hospital stay must reduce to the shortest during coronavirus pandemic to increase the hospital capacity and reduction contamination and transmission risk
- PPE must be carefully removed and disposed of in dedicated doffing areas
- Patient transfer to and from the operating room must be as rapid as possible
- Cases would be transferred while wearing a surgical mask
- All areas where COVID-19 patients have transferred must be carefully cleaned and disinfected
- Recovery phase should be occurred in the operating room, and then transfer to the ICU/general ward
- Disposable materials should be discarded through IRHW (infectious-risk health waste) containers, even if not used and should be decontaminated
- All anesthesia materials should be disinfected promptly
- For high-risk cases that have a cough with a fever after the operation, a chest imaging and PCR test should be done
- For confirmed or suspected cases, appropriate oxygen therapy should be given after operation
- The surgical team should pay attention to organ support treatment and nutritional therapy after surgery
- There is a high risk of deep vein thrombosis (DVT) and secondary lung infections in confirmed or suspected cases
- All waste in the operating room must be double-bagged and labeled “CORONAVIRUS” or “COVID-19”
- Visitors should be limited to visit COVID-19 patients, but if strictly essential, limit the number of visitors and the amount of time
- Prepare perfect protocols about how to put on and remove PPE, and do hand hygiene

Table 7. Treatment options for COVID-19.

Drug	Proposed dose for COVID-19	Mechanism of action	Target diseases	Route of administration	Safety concerns and toxicities
Ritonavir + Lopinavir (Kaletra) (Repurposed agent)	500mg once, twice a day, 2 weeks	Protease inhibitors Inhibit coronavirus replication	HIV infection	Oral	Elevated risk of cardiac arrhythmias, pancreatitis, cardiac conduction abnormalities, and hepatotoxicity Caution in cases with liver disease, haemophilia, cardiovascular disease, and pancreatitis Potential drug interactions Common side effects: diarrhea, gastrointestinal intolerance, nausea, vomiting,
Ribavirin (Repurposed agent)	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Nucleoside inhibitor (Interfering with the synthesis of viral mRNA)	Hepatitis C, SARS, MERS	Oral or intravenous infusion	Elevated risk of anemia Is a contraindicated and teratogen in pregnancy Leads to severe dose-dependent hematologic toxicity
Chloroquine phosphate, chloroquine (Repurposed agent)	500 mg each time, 2 times/day for 5-10 days (300 mg for chloroquine)	Increasing endosomal pH Autophagy inhibitors Inhibit viral RNA polymerase Immunomodulating Probably inhibit ACE2 cellular receptor	Antimalarial agent, autoimmune disease	Oral	Elevated risk of cardiac arrhythmias, hypoglycemia, retinal damage, particularly with long time use Caution in cases with G6PD deficiency and diabetes Potential drug interactions Common side effects: Abdominal cramps, anorexia, vomiting, nausea, diarrhea
Hydroxychloroquine sulphate (Repurposed agent)	400 mg each time, 2 times/day in first day, then 200 mg 2 times/day for 4 days (Alternative dose: 400 mg daily for 5 days or 200 mg 3 times/day for 10 days)	Has same mechanism like Chloroquine	Antimalarial agent, autoimmune disease	Oral	Side effects are similar to chloroquine but less common
Arbidol (umifenovir) (Repurposed agent)	200 mg each time, 3 times/day	S protein/ACE2, membrane fusion inhibitor Inhibit the replication of coronavirus in vitro	Influenza infection	Oral	Safety and efficacy not established Common side effects: allergic reaction, gastrointestinal intolerance, increased liver enzymes
Favipiravir (T-705) (Investigational agent)	1600mg*2/first day followed by 600mg*2/day	Nucleoside analogue (RNA polymerase inhibitor)	Influenza A (H1N1), Ebola	Oral	Increased risk for embryotoxicity and teratogenicity Common side effects: diarrhea, increased liver enzymes, hyperuricemia, decreased neutrophil count
Remdesivir (GS-5734) (Investigational agent)	200 mg on day 1, then 100 mg on days 2-10	Nucleoside analogue (terminates RNA synthesis) Interfering with virus post-	SARS, Ebola, and MERS	Intravenous infusion	Safety and efficacy not established Common side effects: increased liver enzymes (reversible), kidney injury

		entry			
Interferon alpha (IFN-α) (Adjunctive/Supportive therapy)	5 million U, 2 times/day	Increase cellular immunity, Inhibit viral replication	Broad-spectrum antiviral	Oral or injectable	Failed to suppress viral replication and had some side effects when prescribe later
Tocilizumab (Actemra) (Adjunctive/Supportive therapy)	400 mg IV or 8 mg/kg × 1-2 doses Next dose 8-12 h after the first dose if insufficient response	Inhibits IL-6-mediated signaling (also reduce cytokine storm)	Rheumatoid arthritis	Intravenous infusion	Caution in patients with neutropenia a (<500 cells/µL) or thrombocytopenia (<50,000/µL) Safety in pregnancy: is unknown and may cause harm to the fetus Increased risk of URTI, hepatotoxicity, hypersensitivity reactions, infections, nasopharyngitis, hematologic effects, gastrointestinal problem Common side effects: hypertension, headache, increased AST level

Note: Most of these drugs should not use more than 10 days.
ACE2 (angiotensin-converting enzyme 2), AST (aspartate aminotransferase), G6PD (glucose-6-phosphate dehydrogenase), HIV (human immunodeficiency viruses), IL-6 (interleukin 6), IV (intravenous therapy), MERS (middle east respiratory syndrome), SARS (severe acute respiratory syndrome), URTI (upper respiratory tract infection).

Figure legends:

Fig. 1. A three-dimensional (3D) structure of the novel coronavirus (COVID-19).

Fig. 2. Schematic diagram of the novel coronavirus structure (COVID-19). The spike protein on the membrane of virus is necessary for entry into the cell. The spike protein can bind to the receptor, Angiotensin-converting enzyme 2 (ACE2) on the surface of human cells.

Fig. 3. Chest X-rays and computerized tomography (CT) images of COVID-19 patients. Four stages in COVID-19 patients; 1: early stage (0-4 days), 2: progressive stage (5-8 days), 3: peak stage (10-13 days) and 4: absorption stage (more detail in the text).

Fig. 4. Occupational risk pyramid for COVID-19 infection based on the Occupational Safety and Health Administration (OSHA) report.

Fig .5. Sequence for putting on (A) and removing of (B) personal protective equipment (PPE) (designed according to Chen et al. [35] paper).