Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Surgery 79 (2020) 143–153

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

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

Ebrahim Abbasi-Oshaghi[a,b,1,*], Fatemeh Mirzaei[a,c,1], Farhad Farahani[d], Iraj Khodadadi[e], Heidar Tayebinia[f]

[a] Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[b] Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[c] Department of Anatomical Sciences, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[d] Hearing Impairment Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[e] Nutrition Health Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[f] Department of Clinical Biochemistry, Hamadan University of Medical Sciences, Hamadan, Iran

ARTICLE INFO

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

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 continues to rapidly 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 were considered critically ill and 14% were considered to have the severe classification of the disease. In China, the fatality rate of this infection was about 4%. This review focuses on 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.

1. Introduction

Up to May 1, 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 quickly spread to other districts in the country and, a month later, to other countries across the world, impacting over 200 countries and territories. COVID-19 was reported to be a global emergency by the World Health Organization (WHO) in January 2020 and its outbreak was later declared to be a pandemic by the organization on March 2020 [1]. Like other diseases that cause pneumonia, including the Middle East respiratory syndrome (MERS) and the Severe Acute Respiratory Syndrome (SARS), COVID-19 can also cause acute respiratory distress syndrome (ARDS) [2].

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

Almost all earlier cases had a history of contact with 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. Coronaviruses usually cause respiratory infections, such as those detected in the common cold, in patients. However, 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. Around 5% of patients experienced critically ill conditions and 14% experienced severe disease. Initial reports documented that disease severity was accompanied by age over 60 years and a history of a 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

* Corresponding author. Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran.
E-mail addresses: a.oshaghi@umsha.ac.ir, 7abbasi@gmail.com (E. Abbasi-Oshaghi).
[1] Both authors contributed equally to this manuscript.

https://doi.org/10.1016/j.ijsu.2020.05.018
Received 10 March 2020; Received in revised form 5 May 2020; Accepted 6 May 2020
Available online 15 May 2020

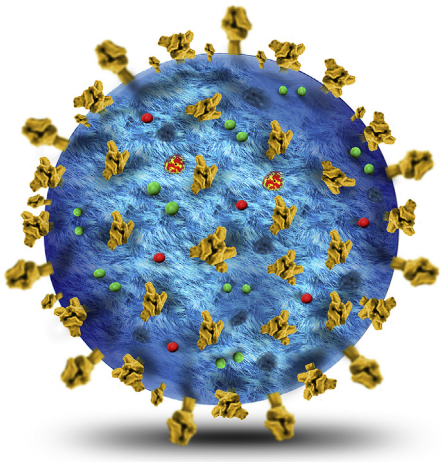

Fig. 1. A three-dimensional (3D) structure of the novel coronavirus (COVID-19).

discontinue the cascade of contamination [6].

2. 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]. COVID-19, a β-coronavirus with positive-sense single-stranded RNA [1], is an enveloped virion that appears as oval or round with 60–140 nm diameter and is often polymorphous (Figs. 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].

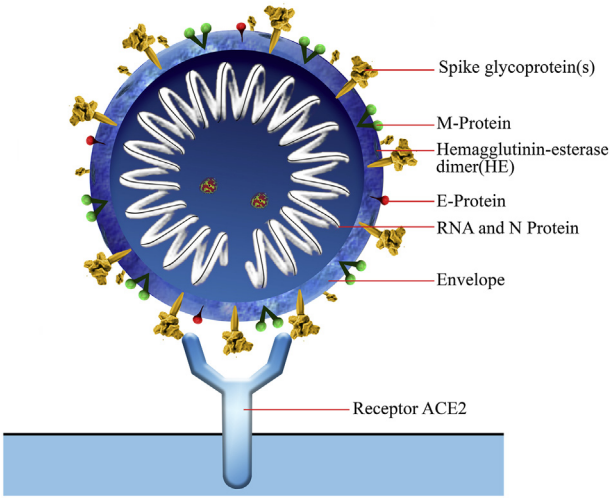

Fig. 2. Schematic diagram of the novel coronavirus structure (COVID-19). The spike protein on the membrane of the virus is necessary for entry into the cell. The spike protein can bind to the receptor, Angiotensin-converting enzyme 2 (ACE2) on the surface of human cells.

3. Transmission and contamination with COVID-19

Aside from person-to-person close contact (less than six feet distance) and population mobility, environmental factors could influence droplet transmission and survival of viruses. Currently, 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 through the respiratory droplets formed when a patient sneezes, coughs, or even talks, just as in 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 through inhaled air [3,9]. This disease can also 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 exist in stool. Hence, COVID-19 may also 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) (Tables 1 and 2). Usually, as with other types of respiratory pathogens, it is accepted that the most contagious time is when subjects are most symptomatic. However, asymptomatic infections can act as a source of the 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 an 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 causing most virus droplets to float to the ground. Furthermore, as health workers walk around the ward, the virus 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 proposed that staffs disinfect their shoe soles before walking out of wards containing infected subjects [12].

4. 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 were more likely to have lung disease because of severe alveolar injury, indicating that men are more vulnerable than women [13]. Differences in sex hormones and immunity-linked genes on the X chromosome that affect both adaptive (acquired) and innate (non-specific) immune responses may describe the high vulnerability to COVID-19 infection in males. Additionally, there may be a higher possibility of virus exposure because of occupational risk which could be another factor responsible for higher male infection rate [14].

5. 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 reported, originally related to Wuhan city, China [2]. Overall, many infected subjects with COVID-19 have many clinical symptoms similar to a SARS-CoV infection [14]. It is reported that the 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

Table 1
COVID-19 transmission routes.

Transmission routes	Definition
Close contact (direct or indirect)	✓ Less than 1.8 m (6 feet)
Respiratory droplets	✓ When infected patients sneezes, coughs, or talks
Airborne	✓ May 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[a]	up to 24 h
Cardboard	up to 24 h
Plastic	up to 2–3 days
Stainless Steel	up to 2–3 days
Cardboard	up to 1 day
Copper	up to 4 h

[a] The maximum transmission distance: up to 4 m.

in approximately 20–25% of the subjects with SARS-CoV and MERS-CoV infection [3]. Some cases have complained of hemoptysis or headache while others were even relatively asymptomatic [13]. Co-morbidities 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 the next stages, septic shock, metabolic acidosis, coagulation dysfunction, and ARDS [8] can appear in severe cases [15].

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

6. Pneumonia is a significant problem

In SARS subjects, lung injury is often diagnosed in the first week from the symptom onset [16]. Then, the lesions develop into peripheral/subpleural distribution, bilateral involvement, and 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 in early CT scans of patients with COVID-19. Notably, there is asymptomatic pneumonia among some COVID-19 patients. Therefore, care must be taken for the diagnosis of such atypical subjects as they might be sources of public transmission [16].

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

7. Detection of COVID-19 infection

The history of exposure or 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. history of exposure 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 case should be hospitalized and isolated for therapy [2]. Based on the 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 three 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 of the chest. The definitive etiology diagnosis of infection is needed, which can be made stronger 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].

8. 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 a 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 and are associated with the severity of the disease. Nevertheless, elevated levels of interleukin-10, which is known as an anti-inflammatory cytokine, indicate 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].

9. Imaging

Radiological evaluations, particularly thin slice chest computed tomography (CT) scan, have a critical role in diagnosis, management, and follow-up of COVID-19 infections [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, the findings of imaging are vital for pneumonia detection [16]. CT scans are proposed in cases with

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[a]	Lymphocyte count	Procalcitonin
LDH	Procalcitonin	Albumin	
ALT	Urea	WBC[b]	
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).

[a] Increased in severe cases.

[b] Patients have normal or reduced levels.

suspicious lung abnormalities. Appropriate recognition of COVID-19 pneumonia could provide quick management and follow-ups. Lung imaging shows the severity of COVID-19, therefore physicians should be informed about radiological reports. Clinical findings from COVID-19 cases with high abnormality shown in the CT scan who were admitted to the ICU [16] show that, on admission, these patients 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 scanning 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) can detect GGOs more easily in the early stage [4]. A study with a large sample size (3665 confirmed cases of the disease) has reported that 95.5% of cases were detected as pneumonia. Pan et al. [2] conducted an experiment with 21 approved COVID-19 cases who underwent repeated CT with about 4-day intervals and observed negative results in four cases in the initial stages (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

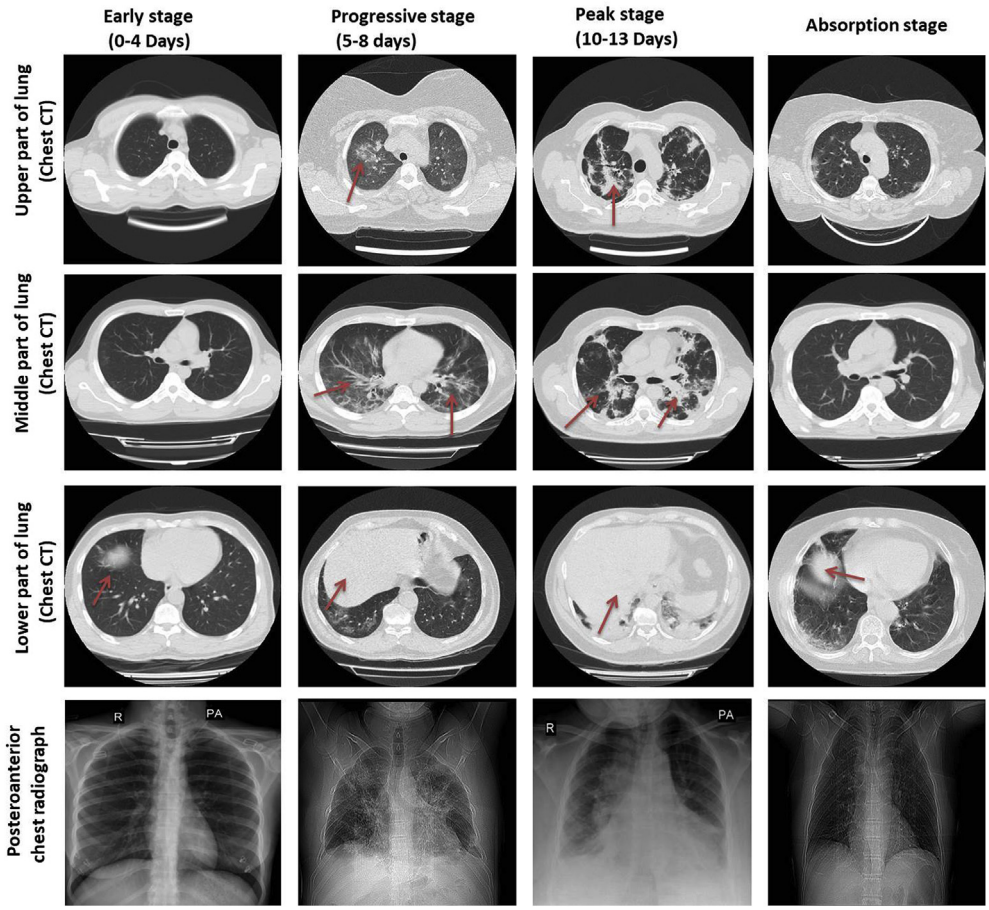

Fig. 3. Chest X-rays and computerized tomography (CT) images of COVID-19 patients. Four stages in COVID-19 patients; 1: early stage (0–4 days), 2: progressive stage (5–8 days), 3: peak stage (10–13 days), and 4: absorption stage (more detail in the text).

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 lobe 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).

[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, 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 pneumonia due to COVID-19 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 the first symptom [2].

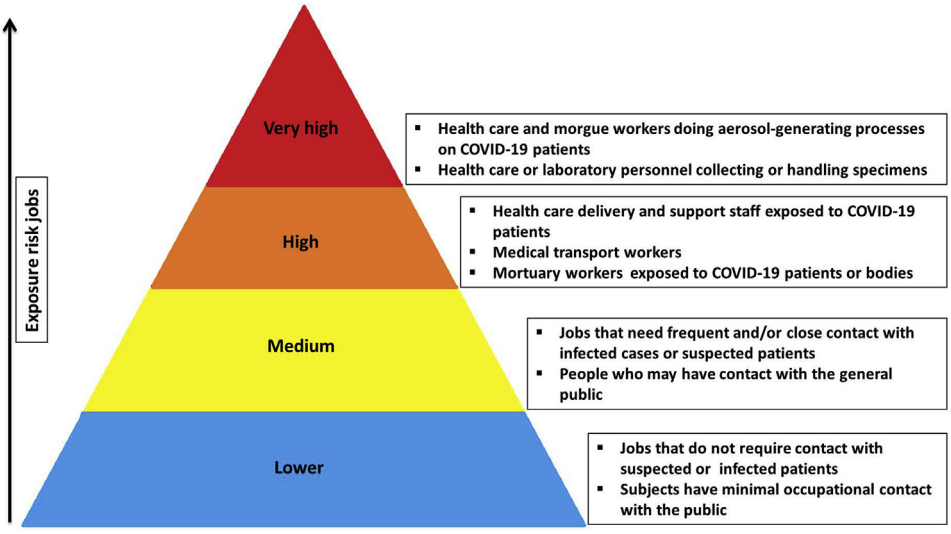

Fig. 4. Occupational risk pyramid for COVID-19 infection based on the Occupational Safety and Health Administration (OSHA) report.

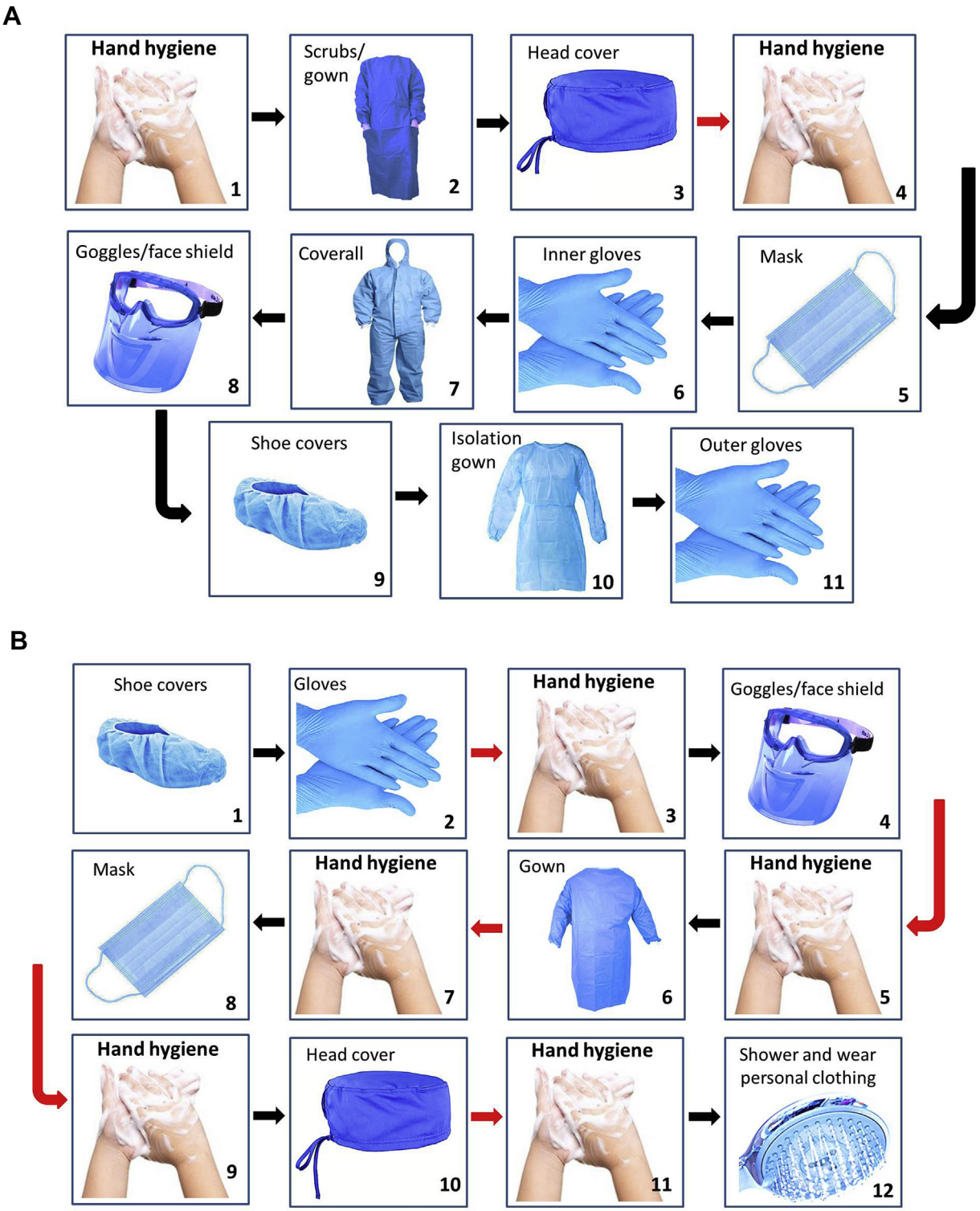

Fig. 5. Sequence for putting on (A) and removing of (B) personal protective equipment (PPE) (designed according to Chen et al. [35] paper).

10. 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 among 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

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

A. Preoperative recommendation
- Surgeons should check all scheduled elective programs 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 through a 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 2–3% 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 only be touched while 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 apprentices 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

Table 6 (*continued*)

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 2–3% 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 be reduced to the shortest during the coronavirus pandemic to increase the hospital capacity and reduce 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 been transferred must be carefully cleaned and disinfected
- Recovery phase should occur in the operating room, and then the patient should be transferred 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, chest imaging and a 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 of COVID-19 patients should be restricted, but if strictly essential, the number of visitors and the amount of time should be limited
- Prepare perfect protocols about how to put on and remove PPE, and ensure hand hygiene

compared to upper respiratory tract samples, which are optimal for improving detection accuracy [3]. Nevertheless, with sample collection and transportation and 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 a cohort study by Ai et al. [23] 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], evaluating 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 a laboratory error, inappropriate sample, or inadequate viral load in the sample. The chest CT gives fast results, is easy to do, and enables quick diagnoses of initial COVID-19 pneumonia [13].

11. Mechanism of action

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

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)	500 mg once, twice a day, 2 weeks	Protease inhibitors Inhibits coronavirus replication	HIV infection	Oral	Elevated risk of cardiac arrhythmias, pancreatitis, cardiac conduction abnormalities, and hepatotoxicity Caution in cases with liver disease, hemophilia, 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 Inhibits 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 as 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 Inhibits 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)	1600 mg*2/first day followed by 600 mg*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-entry	SARS, Ebola, and MERS	Intravenous infusion	Safety and efficacy not established Common side effects: increased liver enzymes (reversible), kidney injury
Interferon alpha (IFN-α) (Adjunctive/Supportive therapy)	5 million U, 2 times/day	Increase cellular immunity, Inhibits 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 be used for 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).

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) which 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 angiotensin II binds to its receptors and induces vasoactive effects. ACE2 catalyzes Ang I and Ang II to generate angiotensin-(1–9) and Ang-(1–7), respectively, and antagonizes several effects of Ang II. ACE2, by reducing local Ang II levels, acts as a counter-regulatory enzyme [29,30]. ACE2 deficiency and the 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 the 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 the pathogenic mechanism might probably be shared between SARS-CoV and COVID-19 [29].

12. Surgery in COVID-19 patients

Healthcare workers are on the front lines of battling COVID-19 which puts 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 Fig. 4. Since Covid-19 spreads quickly 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 temporarily postpone an emergency or urgent surgery on cases which 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 24 h. If the subject's condition does not allow for a 24 h 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 labeled waste bag in an anteroom. There are various levels of emergency related to COVID-19 patient needs, and assessment is required to distinguish between them. Table 6 summarizes the key recommendations for the surgeon and surgical team in different stages [33–35].

13. 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 no specific antiviral medicine or vaccine for this virus [8]. Pathogenesis of coronavirus is an extremely complex process, and much of the required details of host-pathogen interaction remain 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) raising of 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 edemas 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, which can consequently slow coronavirus entry into the cells and protect against lung injury. Remdesivir (adenosine analogue), which 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 vitro* [40]. They found that chloroquine and remdesivir are potentially effective for 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]. The use of traditional medicine to recover the physical signs of cases has also been recommended by some Chinese researchers [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 nanoparticles, due to their potential antioxidant, anti-inflammatory [47], and antiviral effects, have been found to inhibit influenza viral load and COVID-19 replication in an *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 prevention of end-organ dysfunction are suggested by the WHO for patients needing hospital admission [8,10]. Interferon-α is a wide spectrum antivirus medicine that can be used for the 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. Patients with SARS 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 four cases with mild or severe COVID-19 pneumonia. After the drug therapy, the cases showed noticeable improvement and were discharged from the hospital [39].

Some COVID-19 infected patients might have co-infections with fungi and bacteria. Chen et al. detected 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 factors involved which 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 (400 mg per time, every 8 h when required) is recommended in patients 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 the knowledge gained by treating MERS, SARS, or another family of coronavirus. Further researches are required to provide evidences of the effectiveness of these drugs.

Ethical approval

No ethical approval required.

Sources of funding

No funding received.

Author contribution

EAO and FM wrote the manuscript with support from FF, HT and IK. EAO designed the experiments, revised the manuscript. FF prepared surgery section and revised the manuscript. HT contributed to data collections and revised the manuscript. All authors read and approved the final.

Unique Identifying number (UIN)

Name of the registry:
Unique Identifying number or registration ID:
Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

Ebrahim Aabbasi-Oshaghi accepts full responsibility for this review manuscript.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

Data statement don't required for this review article.

Declaration of competing interest

The author declared no interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2020.05.018.

References

[1] S.F. Ahmed, A.A. Quadeer, M.R. McKay, Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies, Viruses 12 (2020) 254, https://doi.org/10.3390/v12030254.
[2] F. Pan, T. Ye, P. Sun, S. Gui, B. Liang, L. Li, et al., Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia, Radiology (2020) 200370, https://doi.org/10.1148/radiol.2020200370 ([Epub ahead of print]).
[3] A.R. Sahin, A. Erdogan, P.M. Agaoglu, Y. Dineri, A.Y. Cakirci, M.E. Senel, et al., Novel Coronavirus (COVID-19) outbreak: a review of the current literature, Eur. J. Med. Oncol. 4 (2019) 1–7, https://doi.org/10.14744/ejmo.2020.12220 2020.
[4] J. Wei, H. Xu, J. Xiong, Q. Shen, B. Fan, C. Ye, et al., Novel Coronavirus (COVID-19) pneumonia: serial computed tomography findings, Korean J. Radiol. 21 (4) (2019) 501–550, https://doi.org/10.3348/kjr.2020.0112 2020.
[5] P.K. Bhatraju, B.J. Ghassemieh, M. Nichols, R. Kim, K.R. Jerome, A.K. Nalla, et al., Covid-19 in critically ill patients in the seattle region-case series, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2004500 [Epub ahead of print].
[6] The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, The Epidemiological Characteristics of Anoutbreak of 2019 Novel Coronavirus Diseases (COVID-19) – China, 2020 vol. 2, CCDCW, 2020, pp. 113–122, https://doi.org/10.46234/ccdcw2020.032.
[7] Y. Chen, Q. Liu, D. Guo, Emerging coronaviruses: genome structure, replication, and pathogenesis, J. Med. Virol. 92 (2020) 418–423, https://doi.org/10.1002/jmv.25681.
[8] J. Wu, J. Liu, X. Zhao, C. Liu, W. Wang, D. Wang, et al., Clinical characteristics of imported cases of covid-19 in jiangsu province: a multicenter descriptive study, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa199 [Epub ahead of print].
[9] C. Sohrabi, Z. Alsafi, N. O'Neill, M. Khan, A. Kerwan, A. Al-Jabir, et al., World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19), Int. J. Surg. 76 (2020) 71–76, https://doi.org/10.1016/j.ijsu.2020.02.034.
[10] Y.H. Jin, L. Cai, Z.S. Cheng, H. Cheng, T. Deng, Y.P. Fan, et al., A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version), Mil. Med. Res. 7 (2020) 4, https://doi.org/10.1186/s40779-020-0233-6.
[11] M. Karimi-Zarchi, H. Neamatzadeh, S.A. Dastgheib, H. Abbasi, S.R. Mirjalili, A. Behforouz, et al., Vertical transmission of coronavirus disease 19 (COVID-19) from infected pregnant mothers to neonates: a review, Fetal Pediatr. Pathol. (2020) 1–5, https://doi.org/10.1080/15513815.2020.1747120 [Epub ahead of print].
[12] Z.D. Guo, Z.Y. Wang, S.F. Zhang, X. Li, L. Li, C. Li, et al., Aerosol and surface distribution of severe acute respiratory syndrome coronavirus 2 in hospital wards, Wuhan, China, Emerg. Infect. Dis. 26 (2020) (2020), https://doi.org/10.3201/eid2607.200885 [Epub ahead of print].
[13] Z.Y. Zu, M.D. Jiang, P.P. Xu, W. Chen, Q.Q. Ni, G.M. Lu, et al., Coronavirus disease 2019 (COVID-19): a perspective from China, Radiology (2020) 200490, https://doi.org/10.1148/radiol.2020200490 ([Epub ahead of print]).
[14] P. Habibzadeh, E.K. Stoneman, The novel coronavirus: a bird's eye View, Int. J. Occup. Environ. Med. 11 (2020) 65, https://doi.org/10.15171/ijoem.2020.1921.
[15] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.
[16] H. Kim, Outbreak of novel coronavirus (COVID-19): what is the role of radiologists? Eur. Radiol. (2020), https://doi.org/10.1007/s00330-020-06748-2 [Epub ahead of print].
[17] R. Mardani, A. Ahmadi Vasmehjani, F. Zali, A. Gholami, S.D. Mousavi Nasab, H. Kaghazian, et al., Laboratory Parameters in detection of COVID-19 patients with positive RT-PCR; a diagnostic accuracy study, Arch. Acad. Emerg. Med. 8 (2020) e43, https://doi.org/10.22037/aaem.v8i1.632.g775.
[18] Worth Health Organization, Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (2019-nCoV) Infection Is Suspected: Interim Guidance, (28 January 2020).
[19] Y. Pan, H. Guan, Imaging changes in patients with 2019-nCov, Eur. Radiol. (2020) 2026, https://doi.org/10.1007/s00330-020-06713-z [Epub ahead of print].
[20] M.Y. Ng, E.Y. Lee, J. Yang, F. Yang, X. Li, H. Wang, et al., Imaging profile of the COVID-19 infection: radiologic findings and literature review, Radiol. Cardiothorac. Imaging 2 (2020) e200034, , https://doi.org/10.1148/ryct.2020200034.
[21] J.F.W. Chan, S. Yuan, K.-H. Kok, K.K.-W. To, H. Chu, J. Yang, et al., A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, Lancet 395 (2020) 514–523, https://doi.org/10.1016/S0140-6736(20)30154-9.
[22] Y. Fang, H. Zhang, J. Xie, M. Lin, L. Ying, P. Pang, et al., Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR, Radiology (2020) 200432, https://doi.org/10.1148/radiol.2020200432 ([Epub ahead of print]).
[23] T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, et al., Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases, Radiology (2020) 200642, https://doi.org/10.1148/radiol.

2020200642 ([Epub ahead of print]).
[24] W. Wang, Y. Xu, R. Gao, R. Lu, K. Han, G. Wu, et al., Detection of SARS-CoV-2 in different types of clinical specimens, J. Am. Med. Assoc. (2020), https://doi.org/10.1001/jama.2020.3786 [Epub ahead of print].
[25] X. Xie, Z. Zhong, W. Zhao, C. Zheng, F. Wang, J. Liu, Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing, Radiology (2020) 200343, https://doi.org/10.1148/radiol.2020200343 ([Epub ahead of print]).
[26] Y. Wan, J. Shang, R. Graham, R.S. Baric, F. Li, Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS, J. Virol. 94 (2020), https://doi.org/10.1128/JVI.00127-20 e00127-20.
[27] H. Jia, Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease, Shock, J. Virol. 46 (2016) 239–248, https://doi.org/10.1128/JVI.00127-20.
[28] Y. Cao, L. Li, Z. Feng, S. Wan, P. Huang, X. Sun, et al., Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations, Cell Discov. 6 (2020) 1–4, https://doi.org/10.1038/s41421-020-0147-1. eCollection 2020.
[29] Y. Wu, Compensation of ACE2 function for possible clinical management of 2019-ncov-induced acute lung injury, Virol. Sin. (2020) 1–3, https://doi.org/10.1007/s12250-020-00205-6 [Epub ahead of print].
[30] J. Qiao, What are the risks of COVID-19 infection in pregnant women? Lancet 395 (2020) 760–762, https://doi.org/10.1016/S0140-6736(20)30365-2.
[31] X. Yu, Q. Lin, X. Qin, Z. Ruan, J. Zhou, Z. Lin, et al., ACE2 antagonizes VEGFa to reduce vascular permeability during acute lung injury, Cell. Physiol. Biochem. 38 (2016) 1055–1062, https://doi.org/10.1159/000443056.
[32] P. Yang, H. Gu, Z. Zhao, W. Wang, B. Cao, C. Lai, et al., Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury, Sci. Rep. 4 (2014) 7027, https://doi.org/10.1038/srep07027.
[33] F. Coccolini, G. Perrone, M. Chiarugi, F. Di Marzo, L. Ansaloni, I. Scandroglio, et al., Surgery in COVID-19 patients: operational directives, World, J. Emerg. Surg. 15 (2020) 25, https://doi.org/10.1186/s13017-020-00307-2.
[34] B. Givi, B.A. Schiff, S.B. Chinn, D. Clayburgh, N.G. Iyer, S. Jalisi, et al., Safety recommendations for evaluation and surgery of the head and neck during the COVID-19 pandemic, JAMA Otolaryngol. Head Neck Surg. (2020), https://doi.org/10.1001/jamaoto.2020.0780 [Epub ahead of print].
[35] X. Chen, Y. Liu, Y. Gong, X. Guo, M. Zuo, J. Li, et al., Perioperative Management of Patients Infected with the Novel Coronavirus: Recommendation from the Joint Task Force of the Chinese Society of Anesthesiology and the Chinese Association of Anesthesiologists, Anesthesiology, 2020, https://doi.org/10.1097/ALN.0000000000003301 ([Epub ahead of print]).
[36] L. Dong, S. Hu, J. Gao, Discovering drugs to treat coronavirus disease 2019 (COVID-19), Drug Discov. Ther. 14 (2020) 58–60, https://doi.org/10.5582/ddt.2020.01012.
[37] T. Smith, T. Prosser, COVID-19 Drug Therapy–potential options, Clinical Drug Information| Clinical Solutions, Elsevier, 2020, https://www.elsevier.com/_data/assets/pdf_file/0007/988648/COVID-19-Drug-Therapy_Mar-2020.pdf.
[38] Y. Imai, K. Kuba, S. Rao, Y. Huan, F. Guo, B. Guan, et al., Angiotensin-converting enzyme 2 protects from severe acute lung failure, Nature 436 (2005) 112–116, https://doi.org/10.1038/nature03712.
[39] B.R. Beck, B. Shin, Y. Choi, S. Park, K. Kang, Predicting Commercially Available Antiviral Drugs that May Act on the Novel Coronavirus (2019-nCoV), Wuhan, China through a Drug-Target Interaction Deep Learning Model, bioRxiv, 2020, https://doi.org/10.1101/2020.01.31.929547.
[40] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, et al., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (2020) 269–271, https://doi.org/10.1038/s41422-020-0282-0.
[41] M.J. Vincent, E. Bergeron, S. Benjannet, B.R. Erickson, P.E. Rollin, T.G. Ksiazek, et al., Chloroquine is a potent inhibitor of SARS coronavirus infection and spread, Virol. J. 2 (2005) 69, https://doi.org/10.1186/1743-422x-2-69.
[42] H. Luo, Q.-l. Tang, Y.-x. Shang, S.-b. Liang, M. Yang, N. Robinson, et al., Can Chinese Medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs, Chin. J. Integr. Med. (2020) 1–8, https://doi.org/10.1007/s11655-020-3192-6.
[43] S. Mehrdad Kassaee, M. Goodarzi, E. Oshaghi, Antioxidant, antiglycation and antihyperlipidemic effects of Trigonella foenum and Cinnamon in type 2 diabetic rats, Jundishapur J. Nat. Pharm. Prod. 13 (2018) e38414, , https://doi.org/10.8512/jjnpp.38414.
[44] E. Abbasi Oshaghi, M.T. Goodarzi, V. Higgins, K. Adeli, Role of resveratrol in the management of insulin resistance and related conditions: mechanism of action, Crit. Rev. Clin. Lab Sci. 54 (2017) 267–293, https://doi.org/10.1080/10408363.2017.1343274.
[45] A.P. Ravan, M. Bahmani, H.R. Ghasemi Basir, I. Salehi, E.A. Oshaghi, Hepatoprotective effects of Vaccinium arctostaphylos against CCl4-induced acute liver injury in rats, J. Basic Clin. Physiol. Pharmacol. 28 (2017) 463–471, https://doi.org/10.1515/jbcpp-2016-0181.
[46] L.T. Lin, W.C. Hsu, C.C. Lin, Antiviral natural products and herbal medicines, J. Tradit. Compl. Med. 4 (2014) 24–35, https://doi.org/10.4103/2225-4110.124335.
[47] E. Abbasi, F. Mirzaei, A. Mirzaei, Effects of ZnO nanoparticles on intestinal function and structure in normal/high fat diet-fed rats and Caco-2 cells, Nanomedicine 13 (2018) 2791–2816, https://doi.org/10.2217/nnm-2018-0202.
[48] H. Ghaffari, A. Tavakoli, A. Moradi, A. Tabarraei, F. Bokharaei-Salim, M. Zahmatkeshan, et al., Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine, J. Biomed. Sci. 26 (2019) 70, https://doi.org/10.1186/s12929-019-0563-4.
[49] Y.R. Guo, Q.D. Cao, Z.S. Hong, Y.Y. Tan, S.D. Chen, H.J. Jin, et al., The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status, Mil. Med. Res. 7 (2020) 11, https://doi.org/10.1186/s40779-020-00240-0.
[50] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.
[51] Z. Ye, Y. Zhang, Y. Wang, Z. Huang, B. Song, Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review, Eur. Radiol. (2020), https://doi.org/10.1007/s00330-020-06801-0 [Epub ahead of print].
[52] R. Wolfel, V.M. Corman, W. Guggemos, M. Seilmaier, S. Zange, M.A. Muller, et al., Virological Assessment of Hospitalized Patients with COVID-2019, Nature (2020), https://doi.org/10.1038/s41586-020-2196-x ([Epub ahead of print]).
[53] Z. Liu, Y. Zhang, X. Wang, D. Zhang, D. Diao, K. Chandramohan, Recommendations for surgery during the novel coronavirus (COVID-19) Epidemic, Indian J. Surg. 3 (2020) 133–135, https://doi.org/10.3779/j.issn.1009-3419.2020.03.01.