REVIEW ARTICLE

COVID-19: A THUNDERSTORM FOR MANKIND

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Abstract

In December 2019 an outbreak of viral pneumonia occurred inWuhan, Hubei Province of People's Republic of China (PRC). Later, it was found the responsible virus was SARS-CoV-2 and WHO recognized it as a Pandemic on 11th March 2020. As of 15th July, in 213 countries, ***580,038*** *deaths have occurred among* ***13,382,020 cases.*** *Currently, many research are going on throughout the world and they are coming up with new findings and observations every day. Based on the current published literatures, this review systemically summarizes up to date information regarding structure of the causative agent, epidemiology, pathogenesis, clinical manifestations, diagnosis and treatment options of COVID-19 in the hope that it will add to the knowledge of medical professionals and formulate better plans for future.*

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Introduction

In December 2019, a pneumonia outbreak (41 cases) having clinical characteristics similar to Viral pneumonia was noticed by the health authority of Wuhan, Hubei Province, People's Republic of China (PRC). The cases had been reported since 8th December 2019 and many patients came from places around the local Huanan Seafood Wholesale Market.[1] On 31st December 2019, Chinese Health Authority alerted WHO and later Chinese Center for Disease Control and Prevention (CCDC) found that the pneumonia was caused by a novel Coronavirus, hence named the condition Novel Corona Pneumonia (NCP).[2] Subsequently, The International Committee on Taxonomy of Viruses (ICTV) named the virus, "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" on 11 February 2020, based on their genetic structure related to the coronavirus responsible for the SARS outbreak of 2003 (initially abbreviated as 2019-nCoV by WHO); while WHO officially announced the name of the disease COVID-19 in the International Classification of Disease (ICD).[3] Observing the transmission and severity of the disease on 30th January 2020, WHO declared the disease as Public Health Emergency of International Concern (PHEIC) and later on 11th March, 2020, recognized it as a Pandemic.[4] Since 12 December 2019, when the first case of COVID-19 was detected, as of 15th July 2020, worldwide 213 countries are affected, 13,382,020 cases are officially diagnosed, with 580,038 deaths.[5]

Methods:

COVID-19 has already become global public health menace and economic disaster. The genomic structure, pathophysiology and experiences fighting COVID-19 urge to be comprehensively summarized to help take optimal preventive and therapeutic measures. In addition, SARS-CoV-2 has showed marked resemblance in terms of phylogenetic analysis, pathogenesis, clinical features with SARS-CoV and MERS-CoV. Therefore, we screened PubMed, RCSB, Elsevier, EBSCO, NEJM, bioRxiv, Google Scholar database with the keywords 2019-nCoV, SARS-CoV-2, NCP, COVID-19, SARS, MERS, spike protein, reproductive number, presentations, laboratory findings, imaging modalities, therapeutic options and accessed official documents of WHO, CDC, CCDC, BSM

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(Bangladesh Society of Medicine), DGHS (Director General of Health Services) for up-to-date information. Only the articles in English were considered. This article aims to review the epidemiology, structure, pathogenesis, clinical presentation, investigation modalities, management scopes, novel therapeutic measures, and prognosis of SARS-CoV-2 in order to provide reader with updated information of this new foe to mankind.

Virology:

SARS-CoV-2 belongs to the Coronviridae family under Nidovirales order. Coronoviridae family has two sub-families: a) Coronavirinae and b) Torovirinae. Again, under Coronovirinae there are four genera: a) Alphacoronavirus, b) Betacoronavirus, c) Gamma-coronavirus and d) Deltacoronavirus. SARS-CoV-2 is an enveloped, positive sense single stranded RNA (+ssRNA) virus, which belongs to the Betacoronavirus along with SARS-CoV and MERS-CoV.[5,7] Prior to SARS-CoV-2, six CoV were known to affect human including SARS-CoV and MERS-CoV. Genome sequence analysis of SARS-CoV-2 shows complete genome sequence recognition rate of SARS-CoV and bat SARS-CoV were 79.5% and 96% respectively.[8] This suggested that the virus might originate from Bat. But Bats are unlikely to be directly responsible for transmission of the virus to humans for several reasons: a) Different non-aquatic animals (including mammals) were available for purchase in Huanan Seafood Wholesale Market but no bats were sold; b) SARS-CoV-2 and its close relatives, batSL-CoVZC45 and bat-SL-CoVZXC21, have a relatively long branch (sequence identity of less than 90%), implying those viruses are not direct ancestors of SARS-CoV-2; and c) in other coronaviruses where bat is the natural reservoir such as SARS-CoV and MERS-CoV, other animals have performed as the intermediate host (civets and possibly camels, respectively). However, bats do not necessarily need an intermediary host to transmit viruses to humans. For instance, Nipah virus in Bangladesh is transmitted through bats shedding into raw date palm sap.[6,9,10]

The most vital structural proteins of Coronavirus are spike (S) protein, membrane (M) protein, envelop (E) protein, and the nucleocapsid (N) protein. Some of the viruses such as beta Coronavirus also have hemagglutinin esterase (HE) glycoprotein. The spike protein, which is a clove shaped protein, gather in a trimeric form on the external surface of the virion, giving it the mould of a crown, which is why it is called coronavirus.[11] It plays an essential role in binding to receptors on host cells and determines host tropism. This S protein is reported to bind with angiotensin-converting enzyme 2 (ACE2), a membrane bound aminopeptidase, that is abundantly expressed in the lungs, heart, kidney, gastrointestinal tract and vast distal vasculature, the same receptor of SARS- CoV to attack host cells, whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4) as the key receptor.[12,13] The smallest structural protein of CoV, E protein has a special role in viral morphogenesis, especially during assembly and egress, while maintenance of the shape of the viral envelop is the most important role of M protein. The structure of N protein is preserved across different species of CoV family.[11] This HE enzyme, existing in the envelope of CoV, more specifically among beta coronaviridiae, is a marker of CoV and influenza virus evolution.[14]

All SARS-CoV-2 isolated from humans to date are genetically related to coronaviruses isolated from bat populations, specifically, the genus Rhinolophus. Wuhan Institute of Virology found 96% similarity at whole genome level with to bat coronavirus.[15] Many initial COVID-19 cases were linked to Huanan Seafood Wholesale Market indicating that SARS-CoV-2 could be transmitted from that market to humans. Environmental samples taken from this market in late December 2019 came positive for SARS-CoV-2, further suggesting it. Most of the evidence imply that the virus is not a manipulated or constructed virus.[16]

The basic reproduction number (Ro), an indicator of transmissibility, represents number of new infections likely to stem from a single case. This means that if Ro is 3, then a single infected person is estimated to infect three persons. If Ro >1, the number infected is prone to increase, and for Ro <1, transmission is expected to die out. One study found average Ro to be 3.28 and median Ro to be 2.79 which clearly exceed WHO estimation of 1.4-2.5. (17)Majumder et al, estimated Ro to be 2.0-3.3 using IDEA model.[18]

Overall, the Case Fatality Rate (CFR) of COVID-19 is 2.3%.[19] Although highly transmissible, the CFR of COVID-19 seems to be lower than that of SARS (9.5%) and MERS (34.4%), but higher than that of influenza (0.1%).[20] Bangladesh has experienced CFR of 1.36%.[21] In spite of an eventually stable CFR around 3, COVID-19 appeared to be extraordinarily devastating and deadly due to its massively affected population.

The time from moment of exposure to an infectious agent and development of symptoms and signs of that disease is called Incubation period. The longer the incubation period, the higher the chance of asymptomatic and subclinical infection. Most of the guidelines relied on the 14 days period of incubation period[22,23] but most patients become symptomatic four to five days after the exposure.[24,25]

Table-I

Epidemiology characteristics of COVID-19, SARS and MERS.(12)

	COVID-19	SARS	MERS
Original location	Wuhan, China	Guangdong, China	Jeddah, Saudi Arabia
Total cases (global)	13,382,020	8096	2229
Total deaths (global)	580,038	774	791
Reproductive number	3.28	3.0	<1.0
Incubation period (days)	4.75–6.4	4.0	4.5–5.2
Case Fatality rate (%)	3.0	9.6	35.5
CFR with comorbidities (%)	73.3	46.0	60.0

The exact mode of spread of SARS-CoV-2 is not obvious. It is believed to occur mainly via respiratory droplets, akin to the transmission of influenza. With droplet transmission, when a person with infection coughs, sneezes, or talks, virus released in the respiratory secretions can infect others if it makes direct contact with the mucous membranes; infection can also occur if a person touches a contaminated surface and then touches his or her eyes, nose, or mouth. Droplets usually do not travel more than 6 feet and do not stay in the air.[26]

Whether SARS-CoV-2 can be transmitted via the airborne route under natural conditions has been issue of controversy. A study in which SARS-CoV-2 grown in tissue culture remained viable in experimentally generated aerosols for at least three hours and was more stable on plastic and stainless steel than on copper and cardboard, and up to 72 hours after application to these surfaces viable virus was detected[27]; another study done in two of the COVID-19 dedicated Hospitals in WUHAN revealed that SARS-CoV-2 was widely dispersed in the air and on object surfaces in both the ICU and General Ward, inferring a potentially high infection risk for health care workers and other close contacts.[28] Although long-range airborne transmission of SARS-CoV-2 has not undoubtedly been documented, airborne precautions are universally recommended when aerosol-generating procedures are performed.[29]

SARS-CoV-2 has been detected in samples of tears, saliva, stool, urine, gastrointestinal tract and semen. Although it has been an issue of doubt whether feco-oral transmission occurs or not, WHO-China joint mission report suggests that it is not a significant mode of transmission.[30]

Although precise interval during which an individual with COVID-19 is infectious is still doubtful, SARS-CoV-2 can be transmitted prior to the onset of symptoms and throughout the course of illness. However, detection of viral RNA does not essentially indicate the presence of infectious virus, and thus viral RNA detection after the resolution of illness does not necessarily indicate infectiousness.[26,31,32]

Although all ages and both sexes are susceptible, elderly people especially with comorbidities are at highest risk (median age at death 75 years).[33] A study of nine pregnant women revealed that pregnancy did not worsen symptoms or prognosis of COVID-19 and also there was no evidence to suggest possible vertical intrauterine infection.[34]

Pathogenesis

Pathogenesis of SARS-CoV-2 can be divided into three phases correlating to the clinical manifestations: First phase during asymptomatic period, includes first 2-3 days of infection, when inhaled virus likely binds to the epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV-2 and SARS-CoV.[35] Virus locally propagates with a limited innate immune response. At this point, the virus can be detected by RT PCR of nasal swabs. Although the viral burden may be low, these individuals are infectious and nasal swabs might be more sensitive than throat swabs during this period. The next few days comprise the next phase of upper airway and conducting airway response. The virus proliferates and migrates down the respiratory tract along the conducting airways, and a more vigorous innate immune response is triggered. Early markers of the innate immune response along with nasal swab and

sputum RT-PCR should come positive during this period. COVID-19 is now clinically manifested. The CXCL10 level (or some other innate response cytokine) may be predictive of the subsequent clinical course. The last stage is hypoxia, ground glass infiltrates, and progression to ARDS. Unfortunately, around 20% of the infected patients will advance to stage 3 disease and will have pulmonary infiltrates and some of them will develop very severe disease. The virus now reaches the gas exchange units of the lung, especial peripheral and subpleural ones and infects alveolar type II epithelial cells. Both SARS-CoV-2 and influenza preferentially attack type II cells compared to type I cells. The virus proliferates within type II cells, large number of viral particles are released, the cells undergo apoptosis and the released particles infect type II cells in adjacent units.[36]

However, Wei Cao and Taisheng Li have staged COVID-19 differently into: viremia phase, acute phase (pneumonia phase) and severe or recovery phase.[14] Patients with competent immune system and without obvious risk factors may develop adequate immune responses to suppress the virus in the first or second phase without immune over-activation. On the other hand, patients with immune dysfunction may have a higher risk of worsening and becoming the severe or critical type with higher mortality. In addition, they have noticed an exceptionally high percentage of aberrant coagulation in severe and critical patients with COVID-19 featured by prolonged PT, elevated levels of D-dimer and fibrinogen, and near normal APTT. Except for some cases of severe Influenza, this was very rare for other Coronavirus infection. Few patients would finally progress to overt disseminated intravascular coagulation (DIC). They have identified several factors to contribute to the coagulation disorder in these patients: a) The persistent inflammatory condition in critical patients acts as an important trigger for the coagulation cascade. b) Certain cytokines including IL-6 could activate the coagulation cascade and suppress the fibrinolytic pathway. c) Pulmonary and peripheral endothelial injury due to direct viral attack might be a similarly important inducer of hypercoagulation. Moreover, aggressive immune-response could also be augmented by dysfunctional coagulation.[37]

Pulmonary post-mortem findings of 38 consecutive patients from two referral centres of Northern Italy has showed the lungs of all patients were heavy, congested, and oedematous, with patchy involvement. In all cases, histological examination showed characteristics corresponding to the exudative and early or intermediate proliferative phases of diffuse alveolar damage. Platelet–fibrin thrombi in small arterial vessels (<1 mm diameter) were found in 87% cases. Investigator suggested that this might explain the severe hypoxaemia that characterises ARDS in patients with COVID-19 and COVID-19 might be complicated by coagulopathy and thrombosis. Furthermore, D-dimer values of greater than 1 μg/mL had been associated with fatal outcomes in patients with COVID-19. For these reasons, the use of anticoagulants has been suggested to be potentially beneficial in patients with severe COVID-19, owing also to their anti-inflammatory properties, although their efficacy and safety are being closely monitored. Additionally, Features indicative of the fibrotic phase of diffuse alveolar damage, such as mural fibrosis and microcystic honeycombing, were observed to be focal, suggesting that none of the patients had progressed to the fibrotic phase, possibly because of the short duration of the disease.[38]

Clinical spectrum

Clinical syndromes associated with COVID-19 are: Mild illness, Pneumonia, Severe pneumonia, ARDS, Sepsis and Septic shock. Mild illness includes typical influenza like illness with some atypical symptoms in case of adults. Pneumonia class comprises of those with radiological pneumonia but with no signs of severe pneumonia which includes respiratory rate > 30 breaths/min, severe respiratory distress or SpO2 ≤ 90% on room air. ARDS is again classified depending on the PaO2/FiO2 as mild (≤300mmHg), moderate (≤200mmHg) and severe (≤100mmHg). When the patient has sign of organ dysfunction with laboratory evidences, it is considered as Sepsis and when the patient requires vasopressor to maintain MAP ≥65 mmHg and serum lactate level > 2 mmol/L, it is considered as Septic shock.[23]

According to CDC, most of the patients will experience one or more of the following symptoms: Fever (83–99%), Cough (59–82%), Fatigue (44–70%), Anorexia (40–84%), Shortness of breath (31–40%), Sputum production (28–33%) and Myalgia (11–35%). Headache, confusion, rhinorrhoea, conjunctivitis, sore throat, haemoptysis, vomiting, and diarrhoea have been reported but are less frequent (<10%).[29] Cutaneous manifestations include erythematous rash, widespread urticaria, vesicular eruptions, transient livedo reticularis among others.[39,40] A study be Wang et al, showed rather than

Table-II

Priorities for COVID-19 testing[43]

High Priority	• Hospitalized patients **with** symptoms
	• Healthcare facility workers, workers in congregate living settings, and first responders **with** symptoms
	• Residents in long-term care facilities or other congregate living settings, including prisons and shelters, **with** symptoms
Priority	• Persons **with** symptoms of potential COVID-19 infection, including fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhoea, and/or sore throat.
	• Persons **without** symptoms who are prioritized by health departments or clinicians, for any reason, including but not limited to: public health monitoring, sentinel surveillance, or screening of other asymptomatic individuals according to state and local plans.

with typical respiratory symptoms patients came with headache, languidness, unstable walking, cerebral haemorrhage, cerebral infarction; and other neurological diseases.[41]

The largest cohort of >44,000 patients of COVID-19 from China illustrated that severity of this disease can range from mild to critical: Mild to moderate (mild symptoms up to mild pneumonia): 81%; Severe (dyspnoea, hypoxia, or >50% lung involvement on imaging): 14% and Critical (respiratory failure, shock, or multiorgan system dysfunction): 5%.[19] Common complications include ARDS, AKI, Acute myocarditis, DIC, and Secondary bacterial infections.[2] Risk factors for developing severe form of disease include: age > 65 years, obesity, chronic lung disease, cardiovascular disease, CKD, CLD and immunocompromised patients.[42]

Diagnosis

To fight this war against SARS-CoV-2, there is no alternative to effective quarantine and isolation measures along with clinical management of patients; all of which require adequate screening and diagnostic tools. The standard for diagnosis of COVID-19 is the detection of viral nucleic acid (RNA). However, the detection of SARS-CoV-2 nucleic acid (RT-PCR) has high specificity and low sensitivity, therefore there may be possibility of false-negative results and the testing time could be comparatively long. For patients who meet criteria, the CDC recommends collection of specimens from the upper respiratory tract (nasopharyngeal and oropharyngeal swab) and, if possible, the lower respiratory tract too (sputum, tracheal aspirate, or bronchoalveolar lavage).

In terms of laboratory findings, common abnormalities include lymphopenia, prolonged PT, and elevated LDH. Some patients had elevated AST, creatine kinase, creatinine, and CRP. Most patients have shown normal serum procalcitonin levels. ICU-admitted patients had more laboratory abnormalities compared with non-ICU patients.[6,8,44,45]

Serological tests which detects antibodies to SARS-CoV-2 in blood, can help identify patient who had COVID-19 but less likely to give positive result in first several days of infection. Juanjuan Zhao et al, showed in their study that the seroconversion rate for Antibody, IgM and IgG was 93.1%, 82.7% and 64.7%, respectively and median seroconversion time for them were day 11, day 12 and day 14, separately.[46] While some of the COVID affected countries including USA have granted emergency authorization to use this, in Bangladesh it still has not received authorization.

Common abnormal Chest X-ray findings include consolidations and ground glass opacities (GGO), predominantly in the lower and peripheral zone. Although CT Chest is more sensitive and informative American College of Radiology (ACR) recommends not using CT scan as a screening test and using it only for hospital admitted patients if required.

Table-III

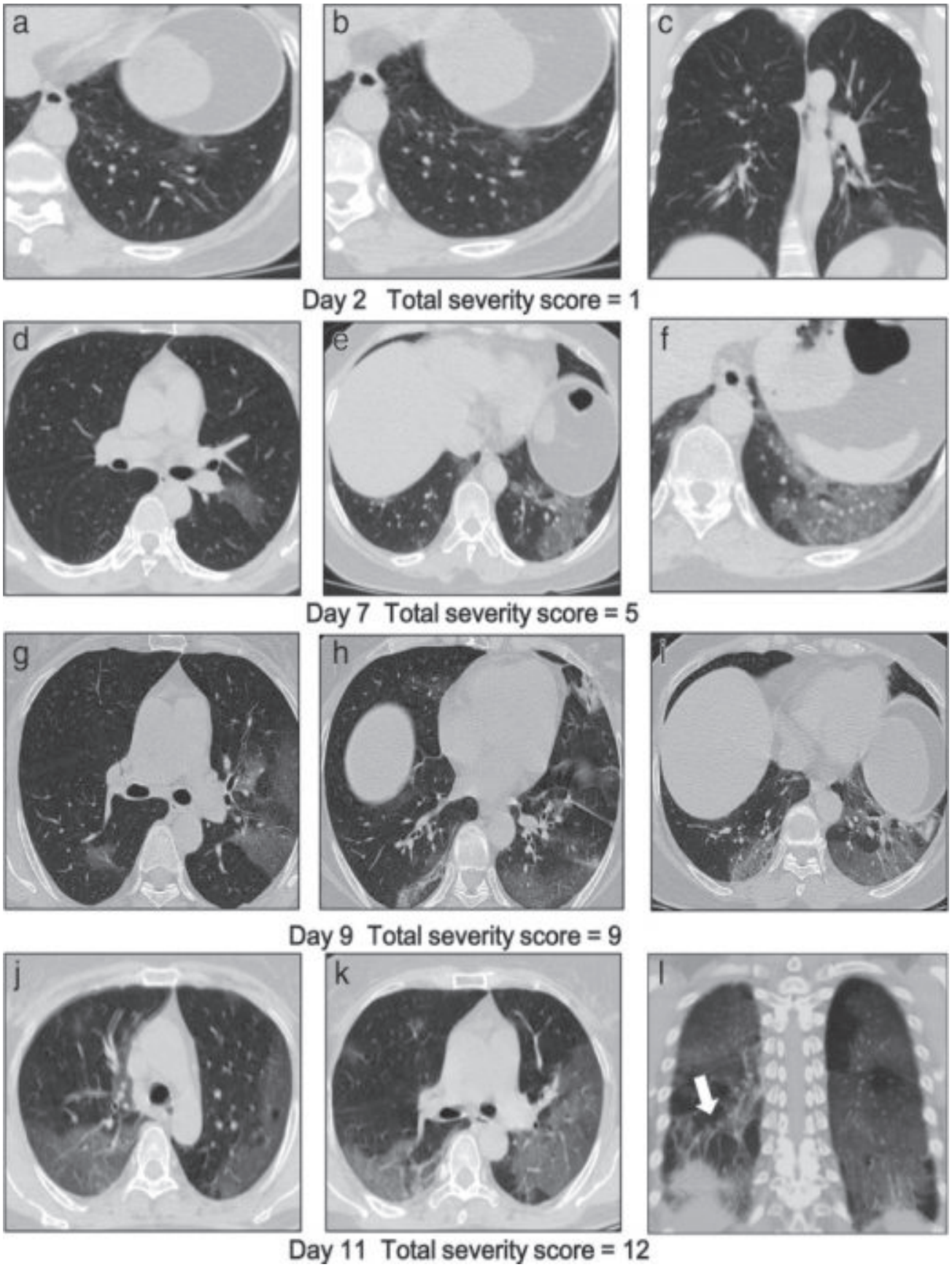
CT Scan findings in COVID-19[47,48]

COVID-19 pneumonia imaging classification	Rationale	CT findings
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia.	• Peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy-paving") • Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving") • Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)
Indeterminate appearance	Nonspecific imaging features of COVID-19 pneumonia.	• **Absence of typical features AND** • **Presence of:** • Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral. • Few very small GGO with a non-rounded and non-peripheral distribution.
Atypical appearance	Uncommonly or not reported features of COVID-19 pneumonia.	• **Absence of typical or indeterminate features AND§ Presence of:** • Isolated lobar or segmental consolidation without GGOo Discrete small nodules (centrilobular, "tree-in-bud")o Lung cavitation • Smooth interlobular septal thickening with pleural effusion
Negative for pneumonia	No features of pneumonia.	• No CT features to suggest pneumonia.

Table-IV

Evolution of CT findings and total lung severity scores of patients with COVID-19 within 21 days after disease onset(49)

Characteristic	Time after disease onset					χ^2	*p* value
	Days 0–3 (*n* = 37)	Days 4–7 (*n* = 69)	Days 8–10 (*n* = 53)	Days 11–14 (*n* = 49)	Days 15–21 (*n* = 25)		
Pulmonary opacities							
GGO only	8 (21.6)	13 (18.8)	7 (13.2)	4 (8.2)	1 (4.0)	6.6	0.16
GGO and consolidation	12 (32.4)	26 (37.7)	8 (15.1)	5 (10.1)	1 (4.0)	22.2	< 0.01
GGO and linear opacities	2 (5.4)	2 (2.9)	4 (7.5)	2 (4.1)	2 (8.0)	1.87	0.76
Consolidation only	1 (2.8)	6 (8.7)	3 (5.7)	4 (8.2)	1 (4.0)	1.98	0.74
Consolidation and linear opacities	0 (0)	2 (2.9)	4 (7.5)	4 (8.2)	3 (12.0)	6.0	0.19
GGO, consolidation, and linear opacities	12 (32.4)	19 (27.5)	25 (47.2)	30 (61.2)	17 (68.0)	21.5	< 0.01
Negative CT	2 (5.4)	1 (1.5)	2 (3.8)	0 (0.0)	0 (0.0)	4.3	0.36
Other findings							
Discrete pulmonary nodules	4 (10.8)	4 (5.8)	3 (5.7)	1 (2.0)	0 (0)	4.8	0.36
Pleural effusion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	–
Lymphadenopathy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–	–
Cavitation	3 (8.1)	3 (4.3)	1 (1.9)	2 (4.1)	1 (4.0)	2.1	0.72
Total lung severity score							
Mean ± SD	3.9 ±2.7	4.8 ±2.9	4.9 ±2.8	5.3 ±3.3	5.2 ±2.8	–	0.29
Median (range)	4 (0–10)	5 (0–12)	5 (0–11)	5 (1–13)	5 (1–11)	–	–


a
b
c
Day 2 Total severity score = 1
d
e
f
Day 7 Total severity score = 5
g
h
i
Day 9 Total severity score = 9
j
k
l
Day 11 Total severity score = 12

Treatment: Options, Controversies and Limitations

Similar to SARS-CoV and MERS, there is still no specific treatment option for COVID-19. The treatment is essentially supportive with the first step being adequate isolation of infected person to prevent transmission. Suspected cases should wear a mask when they come to healthcare facilities for evaluation and they should be kept in a well-ventilated room approximately 2m away from other patients while waiting. If they require hospitalization, they should be kept in a single room with negative air pressure and provision for HEPA filter in the hospital for exhausted air. All health care worker should wear proper PPE and when the patient is discharge, the room should be decontaminated and disinfected following strict protocol.[29,50]

People with mild illness usually do no require hospitalization and can be managed at home with antipyretics for fever, traditional home remedies and isolation. People with risk factor can be given a pulse oximeter to monitor oxygen saturation at home.[51]

People with moderate and severe form of COVID-19, usually require hospitalization. Regular monitoring and supportive care are core to the management of these patients. Nutritional intervention prior to become infected including giving Vitamin C, Vitamin D, Zinc supplementation has been quite popular as there is no downside to speak of and there might be benefit especially for the deficit patients.

Data are limited, but bacterial superadded infection is not an usual feature of COVID-19. If sepsis is suspected, procalcitonin should be checked and broad-spectrum antibiotics should be judiciously used.

COVID-19 produces a hypercoagulable state, and the possibility of thromboembolic disease is increased in hospitalized and sometimes well-appearing individuals (some now refers to this as happy hypoxaemia). Typically, venous thromboembolism occurs but in some cases it can be arterial.[52] Most of the guidelines now suggest anticoagulant (LMWH or UFH) to be administered from the beginning of the condition.[2,23,53]

Use of glucocorticoid is not routinely recommended by WHO for viral pneumonia[54], but initially Chinese studies have supported the use of low to moderate dose of steroid in patients with COVID-19.[55,56] Later on, A clinical (Recovery) trial involving 175 NHS hospitals in UK, enrolled 11,500 patients and a total of 2104 patients were given 6mg of Dexamethasone once daily and 4321 patients were randomized for usual care. Dexamethasone lowered deaths by one-third in ventilated patients and by one fifth in other patients receiving oxygen only. There was no benefit however, among those who did not require oxygen support. Based on these facts, 1 death might be prevented by treatment with Dexamethasone of around 8 ventilated patients or 25 patients requiring oxygen alone. (57) Therefore, the updated recommendations should include dexamethasone for patients requiring oxygen therapy and later studies would reveal more about optimum dose and duration of dexamethasone to be used.

Supplemental oxygen therapy must be given to patients with respiratory distress, hypoxaemia or shock with target saturation being 94%. Once the patient is stable the target is 90% and 88% for patients with Obstructive airway disease.[54]

Although there is no definitive treatment right now, new drugs are emerging one after another. Hydroxychloroquine and Chloroquine has anti-inflammatory effects and was initially recommended in China, Bangladesh, India among several other countries for the treatment of COVID-19 but high-quality data are lacking showing its safety and efficacy.[22,23] Liu J et al, found that HCQ can efficiently inhibit SARS-CoV-2 infection in vitro perhaps by blocking endosomal transport. In combination with its anti-inflammatory function, they predicted that it had a good potential to combat the disease.[58] FDA granted emergency authorization to use this drug in hospitalized COVID-19 patients. A small randomized trial in France to provide evidence for the effectiveness of these drugs for the treatment ofCovid-19 showed better viral load clearance in COVID-19 patients and its effect reinforced by azithromycin.[59] However, Mayla Gabriela Silva Borba et al, illustrated that high dose chloroquine (600 mg twice daily for 10 days) should not be recommended due to its potential health hazards.[60] On July 4, 2020 WHO accepted the recommendation of the Solidarity Trial's International Steering Committee to discontinue the trial's hydroxychloroquine arms. The investigators found little or no reduction in mortality rate or hospital stay after administration of Hydroxychloroquine.[61]

Lopinavir is an HIV-1 aspartate protease inhibitor, having in vitro inhibitory activity against SARS-CoV. Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450. In an open-label, randomized trial involving 199 hospitalized patients, the addition of lopinavir–ritonavir to standard care did not produce any benefit beyond standard care.[62] Therefore, most authorities including findings of Solidarity trial's investigators advise against the use of lopinavir- ritonavir for the treatment of Covid-19 and WHO has also discontinued this arm of the trial.[61]

Favipiravir, another prodrug that inhibits RNA dependant RNA polymerase, has been shown to be effective in the treatment of Influenza and Ebola. An open labelled nonrandomized controlled study highlighted the fact that Favipiravir resulted in significantly higher improvement in chest imaging and faster viral clearance. Bangladesh along with many other countries now recommend using Favipiravir for mild to moderate cases.[23] WHO still does not recommend using it outside clinical trials.[53]

Severe cases have been recommended to be managed as patient with ARDS along with administration of Remdesivir, Convalescent plasma therapy, Tocilizumab and Pulse methylprednisolone as necessary.[23]

Remdesivir, a prodrug that inhibits RNA dependant RNA polymerase, has broad spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and MERS). A study funded by Gilead sciences, producer of Remdesivir, demonstrated that out of 53 patients, 36 patients (68%) had clinical improvement in terms of oxygen saturation.[63] Bangladesh has started administrating Remdesivir in Hospitalized patients as necessary. Yet, WHO still does not recommend using Remdesivir outside clinical trials and makes caution regarding its side effects which include elevation of hepatic enzymes, GI complications, rash, renal impairment and hypotension.[53]

Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS who continued to deteriorate despite administration of all necessary medications. Moreover, several studies confirmed a shorter hospital stay and lower mortality in severe and critical cases treated with convalescent plasma than those who were not.[60] A study of five critically ill patients receiving mechanical ventilation, showed administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status.[64] Convalescent plasma is typically obtained in a blood bank by apheresis, takes approximately one to two hours by two peripheral IV lines, just like Fresh frozen plasma only in this case the donor has been affected by SARS-CoV-2 and has developed neutralizing antibody. Plasma proteins are replenished quickly, and donor can donate plasma frequently. It is administered as a standard transfusion and one or two doses are given.

Ongoing trials of the IL-6 antagonist tocilizumab, which has been shown effective against cytokine storm resulting from Chimeric Antigen Receptor (CAR)-T cell infusion against B cell ALL, may be expanded to restore T cell counts and treat severe COVID-19.[12,65] Nevertheless, WHO does not recommend its administration outside trial and remarks about its adverse effects: URTI, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions.[53]

A large population-based study in Lombardy region, Italy, found that use of ACE inhibitors and ARBs were more common in patients of COVID-19 as many of them had cardiovascular co-morbidity. Nevertheless, there was no evidence to suggest that these drugs affected the risk of COVID-19.[66]

Recently discharge criteria has been revised and now includes resolution of fever without the use of paracetamol for at least three days and significant improvement in the respiratory symptoms (e.g., cough, shortness of breath) for three days, and after discharge, can continue home or facility isolation for the duration which extends from the day of symptom onset to 21st day for hospitalized patients.[23]

Conclusion

Dengue virus was identified in 1943. Yet there is no effective vaccine. HIV, detected in eighties, even now does not have a vaccine. The fastest anti-viral vaccine to be produced till date is of Mumps, which from collecting viral samples to licensing a drug still took four years. So, where does it leave us? The good news is scientists have worked on Coronavirus vaccine before, hence there are not starting from ground zero. Still there are concerns regarding long lasting immunity, genetic stability and mutation of the virus, safety profile of the vaccine and many other issues. So, the question is: Is the virus going to stay? The response is: most probably Yes. Having a safe, effective vaccine without unwanted side effects, producing long term immunity, producing it in massive quantity to distribute in throughout the world in a short period of time is far from reality. So, the next question is: How will we live with this virus? The answer is: We will have to adapt, and life probable will not be the same, at least for a period of time. In the meantime, maintaining health hygiene, not propagating any myth, false information or panic, control source of infection, cut off route of transmission is of utmost importance. As for clinicians, they should keep themselves up to date with the recent developments regarding COVID-19 and follow local guidelines and use existing drugs while treating these patients.

References

1. Lu H, Stratton CW, Tang Y. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol [Internet]. 2020 Apr 12 [cited 2020 May 19];92(4):401-2. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25678 https://doi.org/10.1002/jmv.25678 PMid:31950516 PMCid:PMC7166628

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

3. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. World Health Organization. 2020 [cited 2020 May 16]. p. 1. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

4. WHO Timeline - COVID-19 [Internet]. [cited 2020 May 19]. Available from: https://www.who.int/news-room/detail/27-04-2020-who-timeline—covid-19

5. Coronavirus disease (COVID-19) update [Internet]. [cited 2020 May 21]. Available from: https://www.who.int/bangladesh/emergencies/coronavirus-disease-(covid-19)-update

6. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health [Internet]. 2020;13(5):667-73. Available from: https://doi.org/10.1016/j.jiph.2020.03.019 https://doi.org/10.1016/j.jiph.2020.03.019 PMid:32340833 PMCid:PMC7142680

7. Weiss SR, Navas-Martin S. Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus. Microbiol Mol Biol Rev. 2005;69(4):635-64. https://doi.org/10.1128/MMBR.69.4.635-664.2005 PMid:16339739 PMCid:PMC1306801

8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-13. https://doi.org/10.1016/S0140-6736(20)30211-7

9. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-74. https://doi.org/10.1016/S0140-6736(20)30251-8

10. Luby SP, Gurley ES, Hossain MJ. Transmission of Human Infection with Nipah Virus. Clin Infect Dis [Internet]. 2009 Dec 1 [cited 2020 May 19];49(11):1743-8. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/647951 https://doi.org/10.1086/647951. PMid:19886791 PMCid:PMC2784122

11. Prajapat M, Sarma P, Shekhar N, Avti P, Sinha S, Kaur H, et al. Drug targets for corona virus: A systematic review. Vol. 52, Indian Journal of Pharmacology. Wolters Kluwer Medknow Publications; 2020. p. 56-65. https://doi.org/10.4103/ijp.IJP_115_20 PMid:32201449 PMCid:PMC7074424

12. Xie M, Chen Q. Insight into 2019 novel coronavirus - An updated interim review and lessons from SARS-CoV and MERS-CoV. Int J Infect Dis [Internet]. 2020;94:119-24. Available from: https://doi.org/10.1016/j.ijid.2020.03.071 https://doi.org/10.1016/j.ijid.2020.03.071. PMid:32247050 PMCid:PMC7118633

13. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe. 2020 Mar 11;27(3):325-8. https://doi.org/10.1016/j.chom.2020.02.001 PMid:32035028 PMCid:PMC7154514

14. Zeng Q, Langereis MA, Van Vliet ALW, Huizinga EG, De Groot RJ. Structure of coronavirus hemagglutinin-esterase offers insight into corona and influenza virus evolution. Proc Natl Acad Sci U S A. 2008 Jul 1;105(26):9065-9. https://doi.org/10.1073/pnas.0800502105 PMid:18550812 PMCid:PMC2 449365

15. Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar 12;579(7798):270-3.

16. WHO. Virus origin / Reducing animal-human transmission of emerging pathogens [Internet]. World Health Organization. 2020 [cited 2020 May 16]. Available from: https://www.who.int/health-topics/coronavirus/who-recommendations-to-reduce-risk-of-transmission-of-emerging-pathogens-from-animals-to-humans-in-live-animal-markets

17. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2):1-4. https://doi.org/10.1093/jtm/taaa021. PMid:32052846 PMCid:PMC7074654

18. Majumder M, Mandl KD. Early Transmissibility Assessment of a Novel Coronavirus in Wuhan, China. SSRN Electron J. 2020 Jan 28; https://doi.org/10.2139/ssrn.3524675 PMid:32714102 PMCid:PMC7366781

19. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. Vol. 323, JAMA - Journal of the American Medical Association. American Medical Association; 2020. p. 1239-42. https://doi.org/10.1001/jama.2020.2648 PMid:32091533

20. Rajgor DD, Lee H, Archuleta S, Bagdasarian N, Quek SC. The many estimates of the COVID-19 case fatality rate. Lancet Infect Dis [Internet]. 2020 [cited 2020 May 22]; Available from: https://doi.org/10.1016/S1473-3099 https://doi.org/10.1016/S1473-3099(20)30244-9.

21. (No Title) [Internet]. [cited 2020 May 22]. Available from: https://www.who.int/docs/default-source/searo/bangladesh/covid-19-who-bangladesh-situation-reports/who-ban-covid-19-update-12-20200518.pdf?sfvrsn=bdf1a911_4

22. Ministry of Health & Family Welfare - Government of India. Guidelines on Clinical Management of COVID-19. 2020;(March). Available from: https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf

23. Division DC, Welfare F. National Guidelines on Clinical Management of Coronavirus Disease 2019 (Covid-19). 2020;2019(March):0-28.

24. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. Vol. 382, New England Journal of Medicine. Massachussetts Medical Society; 2020. p. 1199-207.

25. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18). https://doi.org/10.1056/NEJMoa2002032. PMid:32109013 PMCid:PMC7092819

26. Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention - UpToDate [Internet]. [cited 2020 May 22]. Available from: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-clinical-features-diagnosis-and-prevention#H3784053209

27. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1 [Internet]. Vol. 382, The New England journal of medicine. NLM (Medline); 2020 [cited 2020 May 22]. p. 1564-7. Available from: http://www.nejm.org/doi/10.1056/NEJMc2004973. https://doi.org/10.1056/NEJMc2004973. PMid:32182409 PMCid:PMC7121658

28. Guo Z-D, Wang Z-Y, Zhang S-F, Li X, Li L, Li C, et al. Aerosol and Surface Distribution of Severe Acute Respiratory Syndrome Coronavirus 2 in Hospital Wards, Wuhan, China, 2020. Emerg Infect Dis. 2020 Jul;26(7). https://doi.org/10.3201/eid2607.200885 PMid:32275497 PMCid:PMC7323510

29. NIH Guidelines. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2020;2019.

30. (No Title) [Internet]. [cited 2020 May 22]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

31. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. Vol. 323, JAMA - Journal of the American Medical Association. American Medical Association; 2020. p. 1406-7. https://doi.org/10.1001/jama.2020.2565. PMid:32083643 PMCid:PMC7042844

32. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-NCOV infection from an asymptomatic contact in Germany. Vol. 382, New England Journal of Medicine. Massachussetts Medical Society; 2020. p. 970-1. https://doi.org/10.1056/NEJMc2001468. PMid:32003551 PMCid:PMC7120970

33. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019 nCoV) in Wuhan, China. J Med Virol [Internet]. 2020 Apr 12 [cited 2020 May 22];92(4):441-7. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25689. https://doi.org/10.1002/jmv.25689 PMid:31994742 PMCid:PMC7167192

34. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet [Internet]. 2020 [cited 2020 May 22];395(10226):809-15. Available from: https://doi.org/10.1016/ https://doi.org/10.1016/S0140-6736(20)30360-3

35. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol. 2020 Jan 29;94(7). https://doi.org/10.1128/JVI.00127-20 PMid:31996437 PMCid:PMC7081895

36. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J [Internet]. 2020 [cited 2020 May 23];55(4). Available from: https://doi.org/10.1183/13993003.00607-2020]. https://doi.org/10.1183/13993003.00607-2020 PMid:32269085 PMCid:PMC7144260

37. Cao W, Li T. COVID-19: towards understanding of pathogenesis. [cited 2020 May 23]; Available from: https://doi.org/10.1038/s41422-020-0327-4. https://doi.org/10.1038/s41422-020-0327-4 PMid:32346073 PMCid:PMC7186532

38. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis [Internet]. 2020 [cited 2020 Jul 16];0(0). Available from: www.thelancet.com/infection. https://doi.org/10.1016/S1473-3099(20)30434-5

39. Manalo IF, Smith MK, Cheeley J, Jacobs R, Manalo I. A dermatologic manifestation of COVID-19: Transient livedo reticularis. 2020 [cited 2020 May 23]; Available from: https://doi.org/10.17632/kgb87k7863.1. https://doi.org/10.1016/j.jaad.2020.04.018 PMid:32283229 PMCid:PMC7146700

40. Recalcati S. Cutaneous manifestations in COVID 19: a first perspective. J Eur Acad Dermatology Venereol [Internet]. 2020 May 22 [cited 2020 May 23];34(5):e212-3. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16387 https://doi.org/10.1111/jdv.16387. PMid:32215952

41. Wang H-Y, Li X-L, Yan Z-R, Sun X-P, Han J, Zhang B-W. Potential neurological symptoms of COVID-19. Ther Adv Neurol Disord [Internet]. 2020 Jan 28 [cited 2020 May 23];13:175628642091783. Available from: http://journals.sagepub.com/doi/10.1177/1756286420917830. PMid:32284735 PMCid:PMC7119227

42. People Who Are at Higher Risk for Severe Illness | CDC [Internet]. [cited 2020 May 24]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html

43. Interim Guidance: Healthcare Professionals 2019-nCoV | CDC [Internet]. [cited 2020 May 23]. Available from: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html

44. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

45. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020 Mar 17;323(11):1061-9. https://doi.org/10.1001/jama.2020.1585 PMid:32031570 PMCid:PMC7042881

46. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020;3099(April):2019-20. https://doi.org/10.1101/2020.03.02.20030189

47. Categorization of CT findings in COVID-19 - UpToDate [Internet]. [cited 2020 May 23]. Available from: https://www.uptodate.com/contents/image?image Key=ID%2F127760&topicKey=ID%2F126981&source=see_link

48. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. Radiol Cardiothorac Imaging [Internet]. 2020 Apr 1 [cited 2020 May 23];2(2):e200152. Available from: http://pubs.rsna.org/doi/10.1148/ryct.2020200152. PMCid:PMC7233447

49. Liang T, Liu Z, Wu CC, Jin C, Zhao H, Wang Y, et al. Evolution of CT findings in patients with mild COVID-19 pneumonia. Eur Radiol [Internet]. 2020 [cited 2020 Jul 16];1. Available from: /pmc/articles/PMC7156291/?report=abstract https://doi.org/10.1007/s00330-020-06823-8. PMCid:PMC7156291

50. World Health O. Risk assessment and management of exposure of health care workers in the context of COVID-19: interim guidance, 19 March 2020. 2020;(March):2-7. Available from: https://apps.who.int/iris/handle/10665/331496

51. WHO. Home care for patients with suspected novel coronavirus (nCoV) infection presenting with mild symptoms and management of contacts. Who. 2020;(January):4-6.

52. COVID-19 anticoagulation - UpToDate [Internet]. [cited 2020 Jul 6]. Available from: https://www.uptodate.com/contents/image?image Key=HEME%2F128045 & topicKey=ID%2F127429& source=see_link

53. WHO. Clinical management of COVID-19. Interim guidance 27 May 2020. WHO Guidel. 2020;¹3(May, 27):ñ.30.

54. World Health Organization. WHO Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Who [Internet]. 2020;2019(March):12. Available from: https://www.who.int/internal-publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected%0Ahttp://apps.who.int/iris/bitstream/10665/178529/1/WHO_MERS_Clinical_15.1_eng.pdf https://doi.org/10.15557/PiMR.2020.0003

55. Li H, Yang SG, Gu L, Zhang Y, Yan XX, Liang ZA, et al. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. Influenza Other Respi Viruses. 2017 Jul 1;11(4):345-54. https://doi.org/10.1111/irv.12456 PMid:28464462 PMCid:PMC5485871

56. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Vol. 395, The Lancet. Lancet Publishing Group; 2020. p. 683-4. https://doi.org/10.1016/S0140-6736(20)30361-5

57. University of Oxford. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe - The RECOVERY Trial [Internet]. 2020 [cited 2020 Jul 6]. Available from: https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf

58. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Vol. 6, Cell Discovery. Springer Nature; 2020. p. 1-4. https://doi.org/10.1038/s41421-020-0156-0 PMid:32194981 PMCid:PMC7078228

59. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Mar;105949. https://doi.org/10.1016/j.ijantimicag.2020.105949. PMid:32205204 PMCid:PMC7102549

60. Borba MGS, Val F de A, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-

blinded, phase IIb cl. medRxiv. 2020 Apr 16;2020.04.07.20056424. https://doi.org/10.1101/2020.04.07.20056424

61. Solidarity clinical trial for COVID-19 treatments [Internet]. [cited 2020 Jul 6]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

62. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;1787-99.

63. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020;1-10.

64. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. JAMA - J Am Med Assoc. 2020 Apr 28;323(16):1582-9. https://doi.org/10.1001/jama.2020.4783 PMid:32219428 PMCid:PMC7101507

65. Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, et al. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell Induced Severe or Life Threatening Cytokine Release Syndrome. Oncologist [Internet]. 2018 Aug 6 [cited 2020 May 24];23(8):943-7. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2018-0028. https://doi.org/10.1634/theoncologist.2018-0028 PMid:29622697 PMCid:PMC6156173

66. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med [Internet]. 2020;1-10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32356627 https://doi.org/10.1056/NEJMoa2006923 PMid:32356627 PMCid:PMC7206933.