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Review Article

A Summary of Coronavirus Disease 2019: What We Should Know?

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Abstract

The emergence of Coronavirus Disease 2019 (COVID-19) has shifted the concerns of public health officials worldwide. Several previous studies have reported clinical features, methods of diagnosis and therapy approaches to combat the disease. Unfortunately, another problem arose in recognizing and distinguishing asymptomatic and presymptomatic patients who have a high risk of spreading the virus, which led health authorities to develop innovative strategies in mitigating the transmission of COVID-19. Known fever, cough, and myalgia with fatigue headache, hemoptysis, diarrhea and sometimes vomiting are the clinical features for patients confirmed with COVID-19. To confirm suspected patients, computerized tomography scan is the recommended modality since it has higher sensitivity. Several traditional approaches including antiviral, convalescent plasma therapy and monoclonal antibodies have been applied to combat the virus. Additionally, the application of several policies such as social distancing, recommendations for wearing masks and telemedicine were adopted to break the chain of the pandemic. There is much to learn from the many rapid advances in knowledge about this disease and we encourage everyone to always abide by health protocols recommended by healthcare providers so that this pandemic can end soon.

Introduction

The global pandemic Coronavirus Disease 2019 (COVID-19) has recently become the center of attention for public health officials of various countries around the world.[1] The infectious disease associated with pneumonia was first reported in December 2019 in Wuhan, China when the country's authorities first alerted the World Health Organization (WHO) to cases caused by this unknown virus. It was later discovered that the virus was a new type of Coronavirus which was temporarily named 2019-nCoV and further renamed to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses using the reference to WHO naming guidelines.[2,3] This virus is a new β-coronavirus in the Nidoviridae family that can be contracted by animals, which is suggested as the origin of the virus and also can be contracted through human-to-human transmission.[4] Since it was first identified from patients with pneumonia among workers in the Wuhan seafood market, it has quickly spread to other regions in China and to many other countries, leading the WHO to declare COVID-19 as a Public Health Emergency of International Concern on January 30, 2020 especially in countries with vulnerable health systems.[3] As of Sept 7, 2020, nearly 27 million people from more than 200 countries worldwide were confirmed infected with this virus, with over 881,000 deaths.[5] This virus can infect someone through their respiratory tract and sometimes also through the mouth or eyes. It then will target the receptors, called Angiotensin Converting Enzyme 2 (ACE2) in the body's cells.[6] Clinical manifestations of the disease are usually found in the respiratory tract because ACE2 is most highly expressed in the lungs. However, in addition to the lungs, these receptors can also be found in several places in the body such as the gastrointestinal tract, heart and kidneys, so infection from this disease will also have an impact on these organs. Many clinical manifestations have been observed in people infected with this virus.[2]

The contagion has spread rapidly and widely due to the absence of vaccines and the limited number of drugs that are available to treat this virus. Accordingly, strict therapeutic considerations are made in the context of treating this disease to reduce mortality. Apart from treatment, authorities in several countries around the world have also developed strict public policies for flattening the exponential growth curve of the infection incidence through mitigation strategies such as social distancing and face masking. In this review, we describe several clinical features,

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therapeutic approaches and strategies that can be taken to reduce the spread of this potentially lethal virus.

Clinical Features

In this review, we extracted data from a number of COVID-19 journal cases in several countries around the world including China, South Korea, Italy, and the USA. The data we collected more or less show the same results. Patients infected with this virus are generally aged 20-79 years and only a few cases are found in children and the elderly. But even so, it is the elderly patients who have a high susceptibility to death. From the data we collected, the highest percentage of deaths is in patients aged 60 years and above. This mortality pattern might be caused by their weakened immune system compared to those who are still under 60 years old. In addition, another finding is that the mortality rate in men appears to be higher than in women (Table 1). This trend is likely due to their immune response. Generally, males generate less robust immune responses and are more susceptible to a variety of infectious agents. Contrarily, females have stronger innate and adaptive immune responses and are relatively resistant to virus infections.[7] Furthermore, previous study revealed that ACE2 as a putative receptor for SARS-CoV2 is highly expressed in normal lung tissue of men, while in female receptors, current research findings suggest it could be downregulated by 17β-estradiol.[8] Some of the clinical signs and symptoms that commonly occur in these infected patients are: fever, cough, rhinorrhea, sore throat, myalgia or fatigue, headache, hemoptysis, diarrhea and sometimes vomiting.

Laboratory and Imaging Finding

Common clinical laboratory findings in COVID-19 pneumonia patients include a decrease in white blood cells count below normal levels (< $4x10^9$/mcL), lymphocytopenia (lymphocyte count <1.0 × 10^9/mcL), lower than normal platelet count (< 1.5 × 10^9/mcL), while none have a platelet count above the normal rate (Table 2). Meanwhile, another clinical finding showed the laboratory result that most of the Coronavirus positive patients had high C-reactive protein (CRP).

In terms of liver function, alanine and aspartate aminotransferase were found elevated above the normal range. Furthermore, the majority of patients had elevation of creatine kinase and lactate dehydrogenase. This condition indicated that an abnormal myocardial zymogram has occurred in these patients.[9]

Abnormalities in the radiological findings of the chest have become another important part of assessing or early detection of patients with COVID-19. Chest radiography and computerized tomography (CT) scans are two modalities that can be used to assess abnormalities of a patient's chest which can also be used in early detection. Although both are reliable radiological examinations, CT scans are the considered superior in describing the condition of the chest and assisting in diagnosis.[10,11] A systematic review conducted by Salehi et al. revealed six common CT initial findings of 919 patients with COVID-19 pneumonia including bilateral involvement, peripheral distribution, posterior involvement, multilobar involvement, ground-glass opacification, and consolidation.[11] These results are closely similar to several other studies that found ground glass opacities (GGO) as the most common sign, followed by other signs including GGO with mixed consolidation, thickening of adjacent pleura, thick septal interlobular thickening, and air bronchograms, crazy paving patterns, pleural effusion, bronchiectasis, pericardial effusion, and lymphadenopathy.[10]

Furthermore, one study found early stages of the disease generally showed more GGO and a lower number of involved lobes compared to the later follow-up CT scans. This condition tended to improve after day 14 including reduction of involving lobes, resolution of crazy paving

Table 1. Demographic characteristics of patients with COVID-19

	Huang et al.[14]	Wang et al.[15]	Guan et al.[16]	Goyal et al.[17]
Age, (IQR)	44.0 (33-54)	56 (42-68)	47 (35–58)	62.2 (48.6-73.7)
Sex (%)				
Male	116 (57.4)	75 (54.3)	637 (58.1)	238 (60.6)
Female	86 (42.6)	63 (45.7)	459 (41.9)	155 (39.4)
Sign and Symptoms No. (%)				
Fever	156 (77.2)	136 (98.6)	975 (88.7)	303 (77.1)
Cough	120 (59.4)	82 (59.4)	745 (67.8)	312 (79.4)
Short breath	19 (9.4)	NA	205 (18.7)	NA
Rhinorrhea	6 (3.0)	NA	NA	NA
Sore throat	24 (11.9)	NA	153 (13.9)	NA
Diarrhea	13 (6.4)	14 (10.1)	42 (3.8)	93 (23.7)
Vomiting	4 (2.0)	5 (3.6)	55 (5.0)	75 (19.1)
Respiratory rate, median (IQR)	NA	20 (19-21)	NA	NA
MAP, median (IQR), mmHg	NA	90 (84-97)	NA	NA
Dyspnea	NA	43 (31.2)	NA	222 (56.5)
Headache	NA	9 (6.5)	150 (13.6)	NA
Heart rate median (IQR), bpm	NA	88 (78-97)	NA	NA
Myalgia or fatigue	44 (21.8)	48 (34.8) or 96 (69.6)	164 (14.9) or 164 (14.9)	107 (27.2)

Interquartile Range (IQR); Mean Arterial Pressure (MAP)

Table 2. Laboratory finding of COVID-19 patients

	Huang et al.[8]	Wang et al.[9]	Richardson et al.[18]	Xu et al.[19]
WBCs count, x109 per L	4.5 (3.8-5.7)	4.5 (3.3-6.2)	7.0 (5.2-9.5)	4.7 (3.5-5.8)
Hemoglobin (g/dL)	140(128-152)	NA	NA	137 (128.8-152.3)
Platelets (x109/L)	172(133.5-226.3)	163 (123-191)	NA	176 (135.8-215.5)
aPTT (s) (range)	NA	31.4 (29.4-33.5)	NA	NA
PT (s) (range)	12.8 (12-13.4)	13.0 (12.3-13.7)	NA	NA
Neutrophils (x109/L)	2.8 (2.1-3.8)	3.0 (2.0-4.9)	5.3 (3.7-7.7)	2.9 (2.0-3.7)
Lymphocytes (x109/L)	1.1 (0.8-1.6)	0.8 (0.6-1.1)	0.88 (0.6-1.2)	1.0 (0.8-1.5)
ALT (U/L)	25.0 (19-35)	24 (16-40)	33 (21-55)	22 (14-34)
AST (U/L)	NA	31 (24-51)	46 (31-71)	26 (20-32)
C-reactive protein mg/L	NA	NA	13.0 (6.4-26.9)	NA
Creatine kinase (U/L)	NA	92 (56-130)	171 (84-397)	69 (40.5-101)
Lactate dehydrogenase (U/L)	236.5 (175.8-370.3)	261 (182-403)	404 (300-551.5)	205 (184-260.5)
Total bilirubin (mmol/L)	9.9 (7-14)	9.8 (8.4-14.1)	NA	NA
Creatinine (μmol/L)	NA	72 (60-87)	NA	72 (61-84)

White Blood Cells (WBC); Activated Partial Thromboplastin Time (aPTT); Prothrombin Time (PT); Alanine Transaminase (ALT); Aspartate Aminotransferase (AST).

patterns and consolidative opacities.[12] Two other CT features were commonly found in Intensive Care Unit patients: bilateral multiple lobular and subsegmental areas of consolidation.[13]

Diagnosis

Early diagnosis of COVID 19 is needed to reduce mortality and mitigate transmissibility in closely confined areas of patients. Clinical characteristics were commonly used as the main consideration for diagnosis of pneumonia related to SARS-CoV2. The common clinical features include fever, cough, and myalgia or fatigue.[13] However, to confirm the patient has contracted SARS-CoV2, a sensitive modality is required. Most of the clinicians have relied on CT scans and real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) modalities in this task because of their high level of sensitivity among other modalities.[20] Although there are some findings that next generation sequencing also has a high sensitivity, but this method requires a long processing time and costs are higher than the two commonly used types of tests that only require less than 7 hours.[21,22]

Concerning molecular based diagnosis, RT-PCR relies on the principle of SARS-CoV2-specific gene amplification in COVID-19 patient samples that are usually taken from sputum (most accurate sample), nasal swabs, throat swabs (still debated) and bronchoalveolar lavage fluid (BALF). The primary genes used are those that are highly conserved in SARS-CoV2. The RNA-dependent RNA polymerase (RDRP), envelope (E) and nucleocapsid (N) genes are the primers commonly used in this technique. However, the N gene is not recommended because it has poor sensitivity that can lead to possible causes for negative results.[23]

Several published studies have demonstrated that RT-PCR has a high sensitivity in the diagnosis of patients with COVID-19. Long et al. reported that this method has a sensitivity of 83.3%.[20] Another study of 84 patients at the University of Hong Kong-Shenzhen Hospital described that the sensitivity of the technique could reach 94% and equal the results of CT scans.[24] However, this statement was challenged by many other studies' findings that RT-PCR gave many false negative results and this led to the predominate use of CT scans to diagnose patients. CT scans are non-invasive diagnostic methods that involve visualization using X-rays to produce cross-sectional images of a patient's abnormal chest condition. This method is recommended more than RT-PCR because it has a higher sensitivity. A comparative study between the two methods found a higher sensitivity of CT-scans than RT-PCR with 98% vs. 71% ($p < .001$).[25] A similar result was described in other studies conducted by Ai et al. and Long et al. that found sensitivity of 97% vs. 75% and 97.2% vs. 83.3%, respectively.[20,26] These results also underlie some programs promoted by health authorities in China that temporarily have mostly used CT scans for clinical diagnosis of the disease.[22]

Drug Therapy

There are no randomized clinical trials (RCT) that have found an effective drug against pneumonia associated COVID-19. However, some preliminary trials using the non-specific SARS-CoV2 drug approach by a number of hospitals in several countries infected with this outbreak have shown good outcomes. Some of them have included Interferon-α (IFN-α),[27] favipiravir,[28] lopinavir / ritonavir,[29] use of corticosteroid drugs,[30] convalescent plasma therapy from cured COVID-19 patients[31] or supportive therapies such as high flow nasal canula that are known to have a low risk of side effects (Table 3).[32,33] The use of aminoquinoline groups, namely chloroquine and hydroxychloroquine, also received the attention of many clinicians in this COVID-19 therapy effort because they are considered to have a good impact on patients.[34,35] Some of these therapies have varying degrees of success and a variety of side effects. Some of the therapeutic groups are generally given in a combination.[35]

Convalescent plasma therapy

Convalescent plasma (CP) is an immunotherapy with specific antibodies to SARS-CoV2 which are assumed to circulate in the plasma of patients who have recovered

Table 3. Established coronavirus drug

Drug	Drug category	Outcome	Adverse reaction	Ref.
Convalescent plasma	Immunotherapy	Improvement pulmonary image, immunological and hepatic functions, and halting viral load	No adverse reaction	31,36
Favipiravir	antiviral	Reduce the symptoms of disease and increase viral clearance	Mild and manageable side effects	28,37
Hydroxychloroquine and Chloroquine	Antimalaria and antibiotic	Improving lung imaging findings and reducing/ disappearance of viral load	None stated	34,35,38
Lopinavir/Ritonavir	Antiviral	Lowering the body temperature and restoring normal physiological mechanisms and reduced viral load from SARS CoV2 in pneumonia patients with COVID-19	No evidence of significant toxicity and side effects	39,40
Antibiotic and corticosteroid	Antibiotic and anti-inflammatory	Repaired lung lesions and successfully discharged from the hospital after 10 days of treatment from MERS CoV infection	None stated	41
Tocilizumab	Antibodic monoclonal	iImprovement of immunological and clinical function, CT finding, and prevent cytokine storm	None stated	42,43
Ramdesivir	Antiviral	Clinical improvement,	None stated	44
Arbidol	Antiviral	Reduce clinical symptoms and viral load.	None stated	45

Computerized Tomography (CT); Middle East Respiratory Syndrome Coronavirus (MERS CoV)

from the COVID-19 outbreak. This therapy is not new in the prevention or treatment of infectious diseases. For more than two decades, this method has also been used in the treatment of MERS coronavirus epidemic, SARS, Ebola, pandemic influenza A, and avian-origin influenza A with satisfactory efficacy and safety.[31,36] A small scale study conducted by Duan et al. in 10 patients in three participating hospitals in China proved that this therapy could potentially improve the clinical outcomes in severe COVID-19 hospitalized patients. The study found an increasing of neutralizing antibodies after CP was transfused in all patients. Pulmonary image improvement was seen in a patient, one day post onset of illness. Other apparent outcomes included a decrease in CRP, increasing of lymphocyte count, and a drop of aminopherase level indicating improvement of immunological and hepatic functions. Furthermore, on the 12th day post onset of illness, the RT-PCR test confirmed that all patients tested negative for SARS-CoV2. Furthermore, the researchers did not find any serious adverse reactions during CP therapy.[31] In another case report, a patient who tested positive for COVID-19 received CP therapy at Dongguan Ninth People's Hospital, China. The treatment also obtained the same results which had previously demonstrated the potential to improve the survival rate of SARS-CoV2 infection. Despite these promising results, this study has a limitation which is the small sample size so treatment efficacy needs further clinical testing by RCTs.[36]

Contrary to these findings, an RCT of convalescent plasma therapy in China found that addition of convalescent plasma therapy in standard therapy did not result in a statistically significant improvement in time to clinical improvement within 28 days compared to standard therapy without convalescent plasma. Although, this study was stopped before reaching the planned total number of patients, namely 103 of 200, this finding could be one of the considerations in the adoption of this therapy for handling COVID-19.[46]

Chloroquine and Hydroxychloroquine

Besides being indicated for the treatment and prevention of malaria and chronic inflammation, chloroquine (CQ) and hydroxychloroquine (HCQ) are demonstrated to have anti-Coronavirus activity. They could block the receptor entry of the virus into ACE2. Furthermore, this aminoquinoline group can also inhibit viral replication by affecting the normal proteolytic processing, endosomal acidification, and also by the immunomodulatory effect through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.[30,35,47] One study conducted by Wang et al. demonstrated that the combination of chloroquine and remdesivir can inhibit the emergence of SARS-CoV2 *in vitro* suggesting it could be used for the treatment of COVID-19.[48] In clinical evidence, the combination treatment has proven to inhibit exacerbating pneumonia with COVID-19, improving lung imaging findings and reducing/disappearance of viral load.[34,40] However, the use of chloroquine as an adjuvant therapy for patients hospitalized with COVID-19 should be in low doses because of its potential safety hazard.[38] Another evidence of hydroxychloroquine published by Gautret et al. revealed that the use of hydroxychloroquine in COVID-19 treatment can increase viral clearance and even be able to halt viral load in patients when used together with azithromycin.[35]

However, a large retrospective study refuted this evidence and revealed doubts on the efficacy of HCQ in COVID-19 treatment. A systematic review and recent meta-analysis found that using HCQ alone was not associated with reduced mortality in hospitalized COVID-19 patients.[49] The same result was also found in a study conducted by Rosenberg et al.. They evaluated the results of treatments of HCQ alone, azithromycin alone, or both compared with neither drug with in-hospital mortality among 1438 patients with COVID-19 in New York. They concluded that treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital

mortality. Furthermore, the results from a study conducted by Magagnoli et al.[50] on 368 patients found that the use of HCQ alone was associated with an increased number of deaths. They found the death rate in the HCQ group were higher than negative control with 27.8% vs 11.4% (p <0.03), respectively. Meanwhile, there were no significant differences in the reduction of need for mechanical ventilation after HCQ alone or in a combination treatment with azithromycin.

Antiviral drug

Other preliminary data revealed that the COVID-19 associated pneumonia therapy approach using established antiviral agents has given promising results, leading to it being often prescribed in therapy related to this disease. Lopinavir/ritonavir is the most commonly prescribed treatment during this outbreak. This combination of drugs acts by inhibiting 3-chymotrypsin like protease, and was previously indicated for HIV patients who are adults or children aged more than 14 days infected with HIV.[27,30] Several studies of lopinavir/ritonavir for COVID-19 treatment found that the use of this combination treatment can reduce viral load and alleviate clinical symptoms of the disease.[39,40] Furthermore, no evidence of significant toxicity and side effects was found during the use of these drugs leading to the increased recommendations for their use in the treatment of this disease.[39] In another report, these drugs are recommended to be combined with arbidol for the treatment of patients with COVID-19 because it can improve its efficacy in alleviating clinical symptoms and accelerating the healing process.[51] However, this recommendation needs further proof, because another study revealed that no benefit was observed from the combination.[52]

Favipiravir is a product of the analogue guanine that acts on the RdRp of RNA viruses that leads to viral replication. This antivirus treatment has been approved as a novel influenza drug.[30,53] However, recently, it has also been proven to be one of the most interesting drugs against SARS-CoV2 both *in vitro* and clinically.[28,39,54] An open label study conducted by Cai et al. revealed that its combination with aerosol inhalation of Interferon-α can relieve clinical symptoms and increase viral clearance and the combination is even better than lopinavir/ritonavir.[28] Another research demonstrated that the use of favipiravir can relieve the symptoms of the disease with mild and manageable side effects.[37]

Umifenovir or customarily called as Arbidol is also a drug that is often used in COVID-19 therapy. It can interfere with the interaction of spike/ACE2 proteins and lead to inhibition of envelope viruses and host membrane fusion.[30,48] An *in vitro* study demonstrated the drug previously indicated for influenza has been effective in preliminary testing against Coronavirus suggesting it is a potential agent to combat the SARS-CoV2.[55,56] A comparative study showed treatment of pneumonia-related Coronavirus by arbidol monotherapy could reduce clinical symptoms, reduce viral load and negate SARS-CoV-2 RNA in the patient's body in a short time even faster than lopinavir/ritonavir.[54]

The last antiviral, Remdesivir (RDV) that was originally developed for the treatment of Ebola and Marburg virus diseases has the same mechanism as Favipiravir which inhibits enzymes in viral RNA replication.[30,52,57] Based on several preliminary tests both *in vitro* and clinical, this drug seems to provide promising outcomes in the treatment of diseases caused by this novel coronavirus. Gordon and colleagues claimed that it was able to directly inhibit the RdRp enzyme and halt viral replication suggesting expanded clinical use in COVID-19 patients.[30] A recent open-label clinical study described satisfactory clinical improvements of COVID-19 patients after consuming RDV. However, this study had several limitations because it was done in a small sample population, and was not double blinded and not randomized.[44] Hence, several clinical trials are currently being conducted to assess the safety and efficacy of RDV for treatment of the disease.[53,58] A recent RCT was conducted by Wang and colleagues at ten hospitals in Wuhan, but it did not meet the rigorous expectation for robust results. However, since there were some shortcomings in this study, they have suggested further studies and stricter settings.

Another study from Beigel et al.[59] reported a promising result of trial results of this drug to shorten the time to recovery in adults hospitalized with COVID-19 and lower respiratory tract infection of 1,063 patients who underwent randomization. They reported that of the 1,059 patients enrolled in the study (538 treated by remdesivir and 521 by placebo), the remdesivir group had a median recovery time of 11 days (95% confidence interval [CI]: 9 to 12), compared with the placebo group with 15 days (95% CI: 13 to 19) and result rate ratio for recovery was 1.32; 95% CI: 1.12 to 1.55; p<0.001. Furthermore, they also reported 21% vs 27% of serious adverse event in both groups of treatment remdesivir and placebo, respectively.

Monoclonal antibodies

Currently, the use of monoclonal antibodies in the treatment of pneumonia associated with COVID-19 can effectively reduce symptoms and boost immunological functions.[42] Of these options, Tocilizumab is one of the monoclonal antibodies prescribed for the treatment of patients infected with SAR-CoV2. It is an antihuman IL-6 receptor that acts to block the binding of IL-6 to its receptor and prevents cytokine storms.[57] One evidence of the drug's efficacy is the prescription of the drug for patients who are confirmed to be positive for the COVID based on RT-PCR testing in hospitals in China. Five days after treatment, improvement of immunological and clinical functions began to appear including renormalized lymphocytes count, significantly decreased of CRP and further all patients recovered at an average of 15.1 d after treatment.[42] In another finding, one case reported by Celina et al. revealed an alleviation change from CT findings in a COVID-19 pneumonia patient that was treated by this drug.[43] In accordance with the result, a

comprehensive review of Khiali et al.[60] also demonstrated that tocilizumab was effective to decrease CRP and IL-6 in serious patients with COVID-19. Accordingly, they recommended further studies concerning tocilizumab since the findings are very limited in order to confirm its efficacy and safety in patients with COVID-19 who developed ARDS.

Siltuximab and sarilumab are another pair of drug candidates in the anti IL-6 group which have shown some promising clinical results in patients with COVID-19. Some preliminary data found that treatment with siltuximab resulted in a significantly lower mortality rate after 30 days of treatment compared with the matched-control cohort patients (HR 0.462, 95% CI: 0.221-0.965); p=0.0399). In the study, from 30 patients who received siltuximab, 16 patients were discharged from the hospital recovered, four needed mechanical ventilation and 10 patients died.[61]

Similar to these findings, treatment using sarilumab also gave the promising endpoint in patients with COVID-19. Benucci et al.[62] demonstrated that administration of standard daily dose to patients with COVID-19 could reduce the oxygen need by 30%, and caused improvement of oxygenation expressed (increased SpO2/FiO2 ratio (Horovitz index)) by 50 or higher compared to nadir SpO2/FiO2 for at least 48 hours, while causing improvement of ultrasound aspects with transition from moderate/severe B Wet Lung pattern to modest B Wet Lung pattern at 96 hours and 7 days on 14 windows (maximum score 42), and decreasing of CRP in 24 hours (T0), 96 hours (T1), and 7 days (T2) after the first infusion. Accordingly, since the sample population in the studies were small in both drug treatments, further studies are needed with larger samples to confirm these findings concerning the efficacy and safety of these drugs.

Developing drugs

Apart from combining several drugs that have been established from antiviral and nonviral groups, the investigation of drugs for the treatment of SARS-CoV2-related pneumonia continues to be a major concern for researchers (Table 4). Some have yielded promising results both *in vivo* and *in vitro* with a range of different mechanisms. As known, the coronavirus that causes COVID pneumonia is a single-stranded RNA-enveloped virus that is supplemented by protein entry in the form of a spike protein that will bind to the host receptor, ACE2 and lead to viral endocytosis in the host cell.

The type II transmembrane serine protease (TMPRSS2) is also a host cell protein that plays an important role in the entry process where it activates post-attachment spike proteins with ACE2 which subsequently leads to endocytosis.[4] The critical roles of TMPRSS2 and Spike protein in the process of infectivity make them targets in the development of COVID-19 drugs. The use of spike inhibitors to prevent spike-host receptor attachments has suggested a new strategy in the treatment of this disease.[30,63] A newly conducted *in vivo* and *in vitro* study found EK1C4 as an agent that is highly effective against membrane fusion and infection of other human coronavirus pseudoviruses tested, including SARS-CoV and MERS-CoV, as well as SARS-CoV, and potentially inhibited the replication of live human coronaviruses, including SARS-CoV-2. Used not only as an intravenous treatment, aerosol intranasal application of the agent could also provide satisfactory results in preventing the infection in rats of exposed models.[63]

In addition, another agent developed for the treatment of patients infected during this outbreak is Camostat methysilate. This drug gives good results in combating coronavirus by targeting this protein. A satisfying result from the research of Hoffmann et. al. explained camostats can reduce SARS-CoV-2 entry by inhibiting the TMPRSS2 enzyme,[64] which is similar to the previous findings in *in vitro* and *in vivo* studies.[65,66] The novel mechanism and promising results suggest it could be used in the treatment of pneumonia-related coronavirus patients.

Once inside the cell, this virus will translate its protein to produce structural and nonstructural protein. This nonstructural protein is divided through cleavage by 3Clpro and Plpro enzymes into 16 nonstructural proteins which will be used for virus replication. For example, RNA-dependent RNA polymerase acts to synthesize RNA.[4] This stage suggests it is a potential target for drug development by an agent that could interfere with the action of claviger enzymes (3Clpro and Plpro) or RdRp inhibitors.[30,67] Chuck and colleagues successfully developed an agent that worked effectively against 3CLpro, and could inhibit 3CLpro from a broad range of coronaviruses.[67] Another research was conducted by Cho et al. that developed a papain-like protease (PLpro) inhibitor from the fruits of *Paulownia tomentosa* and Park et al. found several active compounds that showed marked inhibitory activities against the 3CLpro and PLpro that were isolated from *Salvia miltiorrhiza*.[68,69] These findings can certainly be a consideration for the development of new therapies in the absence of appropriate drugs in the face of this outbreak.

The last drug of this section is Ivermectin, an anti-malaria

Table 4. Investigational drug of coronavirus

Drug	Mechanism of action	Studies	Ref.
EK1C4	Inhibiting viral envelope and host cell membrane fusion	*In vitro* and *in vivo*	63
Camostat mesylate	Inhibiting the action of the TMPRSS2 enzyme	*In vitro* and *in vivo*	64-66
Derivate of tanshinones and Geranylated flavonoids	Inhibitor 3CLpro and Plpro enzyme	*In vitro*	68,69
EK1C4	Inhibiting viral envelope and host cell membrane fusion	*In vitro* and *in vivo*	63
Ivermectin	Inhibition of IMPα/β1 destabilization	*In vitro*	70,71

3C-like protease (3Clpro); Importin α/β1 (IMPα/β1); Papain-like protease (Plpro) Transmembrane serine protease 2 (TMPRSS2)

approved drug that is classically prescribed as the first line treatment for cutaneous migratory larvae. Some *in vitro* studies found that this drug is effective against some single strand RNA viruses such as dengue virus (DNV), Zika virus, and yellow fever virus.[70] Recently, in an *in vitro* study, Caly and colleagues found that a single dose of the drug could reduce SARS-CoV2 RNA levels for 24-48 hr. incubation periods.[71]

Mitigation of Spreading

Since it was first identified in China, COVID-19 has quickly spread throughout the world. In the initial stages, the number of new case findings has been generally comparable to infected individuals as a result of the absence of appropriate interventions and changes in the behavior of individuals in the general population.[72] Hence, the application of personal protective strategies to mitigate the outbreak spreading are suitable measures. In this regard, the WHO made seven main recommendations for the public to prevent the spread of COVID-19 including: wash hands regularly or keeping hand hygiene, maintaining at least 1 meter distance with others and avoiding crowded areas (social distancing), avoid touching the eyes, nose and mouth, practice breathing hygiene, and stay at home if you have any symptoms (cough, headache, or mild fever) or engage in self-isolation, as well as report health conditions to a qualified healthcare provider or local public health authority, and get the newest information about COVID-19 from reliable sources.

Social distancing and contact Tracking

The COVID-19 pandemic has changed the focus of public health officials throughout the world. The disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 originated in early December 2019 in China and rapidly spread to more than 100 countries in the first 2 months. In response to this global emergency, several steps have been taken by both the WHO and the authorities of vulnerable countries in developing and evaluating effective control policies to suppress the dynamic transmission.[73]

Prohibiting individuals from entering or leaving an area (lockdown) and several social distancing measures such as shutting down entire cities or communities, international banning or limiting domestic travel, conducting border control with symptom screening, and implementing isolation and quarantine are some of the policies adopted by the Chinese government and some countries that are susceptible to this virus.[73] This policy is considered effective in reducing the virus transmissibility.

In one study conducted by Pan et al., a particular Rt was determined to see the speed of the spread of SARS-CoV2 at the community level against the implementation of intervention timetable in the form of social interaction minimalization and face masking. The result was that immediately implementing these interventions could reduce the level of virus transmission and change the Rt rate from 3 to below 0.3 in the period of January 26 to March 1.[74,75]

In implementing this policy, the contact tracking and initial testing of COVID-19 were appropriate supporting steps. This approach is based on the findings of studies in Taiwan that showed people who have infections have the highest transmission power since being infected for up to 5 days after the onset of symptoms followed by presymptomatic patients and their infectivity decreases when patients suffer symptoms beyond 6 days.[73,76]

Face masking

Some recent studies found that the COVID-19 outbreak can be transmitted through direct contact and respiratory droplets. Droplets can be generated when an infected person is coughing or sneezing and anyone who is near that person will have a high risk of exposure. Mitigation measures through social distancing appear to be effective for people who have symptoms, but not for those who are asymptomatic or presymptomatic patients and who do not know that they are positive for COVID-19.[76] Asymptomatic prevalence of patients varies greatly in different regions. In Japan, Nishimura et al. evaluated 565 patients and found 41.6% (5 of every 12 confirmed cases) had no COVID-19 symptoms.[77] Meanwhile, Mao et al. reported only 2 of 78 patients were asymptomatic.[78] Recent studies found evidence that higher viral loads were detected in the nose and throat indicating that replication had started in the upper respiratory tract. This pattern of infection is certainly slightly different from previous coronaviruses.[79,80] The finding was also corroborated by the finding of high viral titration in the saliva of asymptomatic and presymptomatic people.[81]

These asymptomatic patients carry a very high risk for the spread of the virus because they will still be well received in public interactions as healthy individuals. Hence, the use of face masks in public areas is considered the solution for this dilemma, and is seen as a show of support for the seven measures recommended by WHO in suppressing the spread of this pandemic outbreak.[81] Responding to this positive aspect, a number of governments in several countries around the world released a recommendation to always use a mask in public areas. Mitigation by face mask wearing appears to be able to reduce the transmissibility of the spread and death rate due to this virus.

A previously RCT conducted by Suess et al. demonstrated that disciplinary face mask wearing and implementation of hand hygiene could reduce transmission of influenza viruses.[82] Furthermore, other similar evidence was presented by HKBU COVID-19 Modeling Group. They developed a transmission model to see the effect of wearing masks on reducing SARS-CoV2 transmission with the basic reproduction number (R_0) parameter. In the results, they found that this intervention was able to reduce R_0.[81] The result is similar with a conservative study that was conducted by Ferguson et al. The implementation of face masking in the general population could halt virus growth entirely and change R_0 2.4 to R_0 <1. Even if this intervention was only applied by 50% of the population,

it could decrease R_0 from 2.4 to 1.35. If described in a population of 100 infected people in a population, the spread rate that is expected to 31,280 (R_0 = 2.4) cases can be reduced to only 584 cases (R_0 = 1.35) in a month through this intervention.[83]

Internet-based health services: telemedicine

High infectivity of SARS-CoV2 has led to an increase in hospitalized COVID-19 pneumonia cases and deaths in various countries of the world. Additionally, some studies describe that there are very negative co-morbidities correlated with poor prognosis and high mortality in the disease.[84] This pattern is certainly worrisome for those who must routinely check their health with follow-ups to the hospital. Several other concerns are also felt by health care providers when they have to provide services directly to patients. The main concern of health care providers refers to asymptomatic patients who come to consult for health services.[78]

In response to this dilemma, many health authorities in vulnerable regions have made or adopted various strategies to mitigate the disease that have been declared essential to combat the characteristics of this pandemic. Telehealth and telemedicine platforms are among those strategies adopted by several countries that are vulnerable to this virus. This use of technology is an ideal form of healthcare management in the midst of this pandemic especially for more remote or isolated/lock-downed areas that may be quarantined.[85]

For example, in South Korea, telemedicine has been applied to provide health care for patients in areas that are difficult to reach by virtual visits by doctors and nurses. The Korea Herald reported that the southeastern city of Daegu and surrounding North Gyeongsang Province health authorities opened 16 community centers that can admit up to 3,800 patients in the areas.[86] Besides South Korea, there are a number of other countries that have adopted this strategy to reduce the spread of the virus including Taiwan, US, Vietnam, Singapore, India, United Kingdom, Italy and China.[87] Telemedicine can be very helpful in reducing risks to both health care providers and patients because of fewer contacts with patients[88] and patients can still access routine health services without the risk of exposure to viruses when crammed together in the waiting room in hospitals or other health care units.[89]

However, to encourage the adoption of the telemedicine approach in a region or country, large support from the government is needed especially for the provision of platforms, supporting facilities and financing. In response to this need for support, in several countries such as the US, federal and state authorities have renewed their mitigation efforts by including the expansion of telemedicine services reimbursement, relaxation of technology requirements, implementation of novel approaches to licensing and credentialing, and relaxation of supervision laws related to nonphysician providers.[85] In addition, reforms related to regulations, and forms of support for telemedicine were also demonstrated through the development of several online resources, including education about the importance and how to use telemedicine, reimbursement for physicians that visit patients by telemedicine methods, and minimization of cost to access telemedicine.[89]

In its application in the US and UK, telemedicine has been proven effective in reducing the risk of transmissibility of the virus that causes pneumonia. This is not a coincidental result, since previously this strategy has also succeeded in provided satisfactory results when applied to other outbreak epidemics including SARS-CoV, MERS-CoV, or PHEICs related to Ebola and Zika viruses. A systematic review and meta-analysis by Larson and colleagues found that telemedicine intervention is effective in improving the quality of life of patients in a way that is comparable with direct healthcare.[90] Several other studies have also found that implementing telemedicine in healthcare systems can reduce ambulance transports, increase Emergency Medical Services unit productivity, and lower the frequency of non-essential air medical transports that can subsequently lead to reduced costs of healthcare services.[91]

Conclusion

In conclusion, we underline a number of aspects related to the findings in our review. Clinical features are a consideration for diagnosis of pneumonia related to SARS-CoV2. The most common clinical features that appear in people with these diseases include: fever, cough and myalgia with fatigue or a combination of features, which are usually accompanied by diarrhea. This is because the receptors of this virus are also localized in the digestive track. However, often these signs do not appear, and while some patients are asymptomatic, they become the people with high potential to spread the virus. Hence, contact tracking and early diagnosis using tools with high sensitivity are direly needed to reduce mortality and prevent the spread of this disease. Although there is no specific drug or COVID-19 vaccine established, therapeutic approaches use existing drugs, e.g. antivirals which are able to provide some solutions to these challenging problems and reduce the risk of mortality. These preventive steps also continue to be supported by the presence of several global appeals and recommendations from regional health authorities in the form of reducing social contact and wearing masks to break the chain of transmission of the virus.

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Conflict of Interest

The authors declare they have no conflict of interest.

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