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Review Article

Coronavirus disease 2019 as a systemic disease: a review

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Since a cluster of pneumonia cases of unknown etiology was first reported in China in December 2019, the number of confirmed cases with coronavirus disease 2019 (COVID-19) (caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) worldwide has been increasing, and nearly two million patients are expected to have died by February 2021. Globally, COVID-19 is being considered a primary pulmonary disease, but it is more than a lung infection. This is because patients infected with SARS-CoV-2 present with a variety of clinical signs and symptoms involving many organs, ranging from fever, inflammation, myocardial injury, shock, and the development of coronary artery aneurysm. SARS-CoV-2 shows unique characteristics in its transmission, mortality, and stability in different environmental conditions. During COVID-19 pandemic, about 10 drugs have been clinically tried with none proven to be effective. With no prospect for effective drugs in the near future, there are currently possibilities of success with vaccines and convalescent plasma. Along with the prospect of vaccines and other therapeutic drugs, special precautions (isolation, testing, treating, and tracing) are strictly recommended until we return to normal situations. In this review we comprehensively analyzed the clinical presentations, characteristics, and outcomes of patients with COVID-19, and tried to assess the clinical effects of some drugs as part of the ongoing efforts to understand COVID-19 pandemic.

Key words: coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pandemic, pneumonia, systemic disease

Introduction

On December 31, 2019, a cluster of pneumonia cases of unknown etiology was first reported in Wuhan, Hubei Province, China. On January 9, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported as the novel coronavirus, the causative agent of the outbreak of coronavirus disease 2019 (COVID-19). As of early March 2020, nearly half a million cases of COVID-19 were reported worldwide across more than 150 countries [1−3]. The number of confirmed COVID-19 cases had been rapidly increasing worldwide, leading to 11,810 deaths. Clinical presentations of COVID-19 varies from no symptom (asymptomatic) to severe pneumonia. From the available data of laboratory-diagnosed COVID-19 cases, 30% were admitted and 4% had severe illness. Severe illness was noted in 15% of hospitalized cases, and death occurred in 12% of these cases, with higher case-fatality rates in older adults. Admission rates were also much higher for those aged 60 years and above. This showed that both the risk and absolute numbers of deaths rapidly increased with age for those aged 60 years and above globally.

The clinical presentation, characteristics, and outcomes of patients with COVID-19 were described in a study [4]. Among patients presenting at the hospital, the most common initial symptoms were shortness of breath (76%), fever (52%), and cough (48%). The mean onset of symptoms before presentation to the hospital was 3.5 days, and 17 (81%) out of 21 patients were admitted to the intensive care unit (ICU) less than 24 hours after hospitalization. Most (86%) of those patients had comorbidities (chronic kidney disease [47.6%], congestive heart failure [42.9%], cardiomyopathy [33%], chronic obstructive pulmonary disease [33.3%], and diabetes [33.3%]). In 20 patients (95%), chest radiograph showed abnormal findings at admission. Bilateral reticulonodular opacities

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(52%) and ground-glass opacities (48%) were the most common features on initial radiograph. Other radiographic findings include ground-glass opacities and pleural effusions on chest imaging, despite minimal respiratory symptoms. The white blood cell count was in the normal range in 14 patients (67%), and 14 patients (67%) showed an absolute lymphocyte count of less than 1,000 cells/μL. The mean white blood cell count was 9,365 μL at hospitalization. Fifteen patients (71%) were on mechanical ventilation; and acute respiratory distress syndrome (ARDS) was found in all patients requiring mechanical ventilation. Afterwards 11 patients died, 2 survived to be transferred out of the ICU, and 8 remained critically ill requiring mechanical ventilation. This study of patients with COVID-19 is a typical description of critically ill patients infected with SARS-CoV-2. These patients had a high rate of ARDS and a high risk of death. Adult patients with current or previous COVID-19 can develop a hyperinflammatory syndrome (MIS-A), which resembles multisystem inflammatory syndrome in children (MIS-C) [5]. They may present with severe cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms without severe respiratory illness while testing positive for COVID-19.

While SARS-CoV-2 affects many organs, our study and analysis, since the pandemic began, not only covers the acute phase, but also its consequences. Therefore, we comprehensively assessed the clinical effects of COVID-19 as part of the ongoing efforts to understand the pandemic.

Systemic Effects of COVID-19

Pulmonary system

Globally, COVID-19 is considered as a primary pulmonary disease. It is characterized by diffuse alveolar damage (interstitial pneumonia), the predominant pattern of lung lesion [6]. This was evidenced by the postmortem lung tissue findings of patients who died from COVID-19 during the early pandemic period. The lungs of all patients with COVID-19 showed various macroscopic (heavy, congested, and edematous with patchy involvement) and microscopic (capillary congestion, necrosis of pneumocytes, hyaline membrane, interstitial and intraalveolar edema, and plate-fibrin thrombi) findings. However, based on the analysis of all available current data on medical, laboratory, and imaging features on COVID-19, it is certain that the clinical findings and diagnostic tests could not be explained only by impaired pulmonary ventilation. COVID-19 affects the vasculatures of the lungs and other organs. Furthermore, it has a high thrombosis tendency with acute life-threatening effect requiring adequate treatment with anticoagulants, and laboratory monitoring with appropriate imaging tests.

Recent findings suggest that respiratory failure in patients with COVID-19 is caused by thrombotic complications as well as the development of ARDS, which may have important consequences for the diagnostic and therapeutic management of these patients [7]. There is a strong correlation between D-dimer levels, disease progression, and the chest computed tomographic (CT) features suggesting venous thrombosis. Additionally, other studies in patients with COVID-19 have shown a very clear association between increased D-dimer levels, disease severity, and poor prognosis.

Imaging and pathological studies confirmed that COVID-19 involves a thrombo-inflammatory process that initially affects the lung perfusion, and consecutively affects all organs of the body. This highly thrombotic syndrome results in macro-thrombosis and embolism. Therefore, careful attention needs to be paid to the early diagnosis and management of the coagulation state that can occur in a substantial percentage of patients with COVID-19. More detailed strategies are required for the prevention of further aggravation such as thrombosis prophylaxis, close laboratory, and appropriate imaging monitoring, with early anticoagulant therapy in case of suspected venous thromboembolism. Recommendations for diagnostic and therapeutic management may include prophylactic-dose heparin, chest CT, CT angiography of pulmonary system, and routine D-dimer testing, depending on patient's symptoms and risk profiles.

Cardiovascular system

SARS-CoV-2 causes COVID-19-related pneumonia by infecting host cells through angiotensin-converting enzyme (ACE)2 receptors [8−10]. In addition, it also causes acute myocardial injury and chronic damage to the cardiovascular system. Therefore, attention should be taken particularly for the protection of the cardiovascular system during treatment of COVID-19.

It was assumed that patients with hypertension and COVID-19 on ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are more likely to have greater illness severity or increased risk of death during hospitalization for SARS-CoV-2 infection. However, according to the study investigating the association of renin-angiotensin system inhibitors with the severity of the disease or the risk of mortality in patients with hypertension and COVID-19, it was shown that ACEIs and ARBs had no effect on the severity or outcome in patients with hypertension hospitalized for COVID-19 [11]. In this study, ACEI/ARB was not shown to be associated with severity and outcomes of COVID-19 in hospitalized patients with

hypertension.

Genitourinary system

In a large prospective cohort study including 701 patients aged 50 to 71 years in China that investigated the effect of kidney disease on in-hospital mortality in patients with COVID-19 [12]. The study revealed that in-hospital mortality were higher (16%) in patients with COVID-19 and kidney diseases during hospitalization, as did patients who developed acute kidney injury (AKI). In this study, a high prevalence (over 40%) of kidney disease was found in hospitalized patients with COVID-19, with elevated serum creatinine and blood urea nitrogen (BUN) values in over 13% of the patients. On admission, the prevalence of proteinuria and hematuria was 43.9% and 26.7%, respectively. Elevated serum creatinine and BUN was seen in 14.4% and 13.1% of the patients, respectively; and estimated glomerular filtration <60 mL/min/1.73 m^2 occurred in 13.1%. During hospitalization, AKI was found in 5.1%.

Independent risk factors for in-hospital death after adjusting for age, sex, disease severity, comorbidity, and leukocyte count included elevated baseline serum creatinine. As the first study regarding the association between kidney disease and prognosis in patients with COVID-19, it revealed that elevated baseline serum creatinine was a risk factor of patients' admission to the ICU and need for mechanical ventilation.

Digestive system

Patients with COVID-19 present to the hospital with gastrointestinal tract symptoms as one of the chief complaints in nearly 50% of cases [13, 14]. Of 204 patients (mean age, 54.9 years) with COVID-19 (confirmed by real-time reverse transcription-polymerase chain reaction [PCR]) analyzed; the digestive system symptoms observed included anorexia (83.8%), diarrhea (29.3%), vomiting (0.8%), and abdominal pain (0.4%). The observed digestive system symptoms seemed to delay hospital admission of patients presumably due to absence of respiratory symptoms. Patients with digestive system symptoms showed a significantly longer time from onset to admission than patients without digestive system symptoms (9.0 days vs 7.3 days). As the severity of the disease increased, digestive system symptoms became worse. Patients with digestive system symptoms were less likely to recover and be discharged than patients without digestive system symptoms.

While digestive system symptoms (anorexia, diarrhea, and vomiting) may be the presenting features of COVID-19, higher index of suspicion may be necessary to pick up these cases earlier, rather than awaiting respiratory symptoms when the initial presenting features are extrapulmonary [15].

Neurologic system

ARDS due to COVID-19 is associated with neurologic dysfunction or encephalopathy, presenting as agitation and confusion, and corticospinal tract signs [16].

Post-mortem autopsy findings of brain and lung tissues taken from patients with COVID-19 have been detailed [10]. The brain tissue findings showed macroscopic atherosclerosis, and microscopic acute hypoxic injury in the cerebrum and cerebellum in all the patients. In addition, there was loss of neurons in the cerebral cortex and hippocampus, without thrombi and vasculitis. The median age of affected patients was 62 years and males were dominant. All the patients had an episode of confusion or decreased arousal from sedation induced by mechanical ventilation. The brain tissues had low viral load levels of SARS-CoV-2 on PCR in some patients. In other case series, persistent or intractable headache was the first presenting symptom of COVID-19 in a few women with a previous history of chronic and episodic migraine [17]. They presented with the typical COVID-19 symptoms and signs such as fever, cough, mild or severe muscle pain, dyspnea, nasal congestion, anosmia, diarrhea of a week duration, and tested positive for SARS-CoV-2 [16, 17]. In other patients diagnosed with COVID-19, stroke occurred as a presenting feature regardless of sex and age [18]. However, the development and severity of stroke was not necessarily related with the extent of lung involvement. These suggest that stroke, complications of COVID-19, was caused by thrombotic complications, hyper-inflammation, and tissue damage. It was concluded that COVID-19 may increase the risk of ischemic insults in the brain, even in the early stage and in mild forms of the disease, requiring further investigations along with long-term follow-up and search for more cases to assess the prognosis.

Intensive care unit

While anesthetic machines had to be used as ventilators because of insufficient ICU ventilators to meet patients' care needs during COVID-19 pandemic, the American Society of Anesthesiologists (ASA) have published guidelines on how to safely and effectively convert anesthesia machines into life-sustaining mechanical ventilators for patients.

Although guidance is available from the manufacturers, the guidance may not cover all possible clinical scenarios. Anesthesia professionals will need to ensure maintenance of these machines while in use. The safe and effective use requires an understanding of the capabilities

of the machines available, the differences between anesthesia machines and ICU ventilators, and how to set anesthesia machine controls to mimic ICU-type ventilation strategies.

In the early stage of COVID-19 outbreak, an Italian group analyzed 1,591 critically ill patients admitted with COVID-19 [19]. The great majority of the patients were older men aged 56–70 years, and were male dominant (82%). Of the patients with available data, 68% had at least one comorbidity (hypertension [49%], followed by cardiovascular disorders, hypercholesterolemia, and diabetes in that order). A large proportion of the patients admitted to the ICU required mechanical ventilation with high level positive end-expiratory pressure (PEEP) because of acute hypoxemic respiratory failure; and the ICU mortality was 26%. Endotracheal intubation and invasive mechanical ventilation were needed in 88% of the patients, whereas only 11% could be managed with non-invasive ventilation.

Special Occasions with COVID-19

Pregnant women

Pregnant women admitted to hospital for delivery also needed universal laboratory testing for COVID-19 using nasopharyngeal swabs and quantitative PCR test [20]. According to some studies, there are benefits to PCR testing for COVID-19 in pregnant women, before the delivery, for the following reasons [21–23]. Firstly, SARS-CoV-2 RNA was detected in human milk of an actively breastfeeding patient with mild SARS-CoV-2 infection despite the uncertainty of the risk of infection through breast feeding [21]. There was no indication of viability of the virus. Secondly, a study compared the clinical courses and outcomes between pregnant and non-pregnant women of reproductive age, infected with SARS-CoV-2 [22]. Medical records of both groups were retrospectively reviewed for age, comorbidity, and the severity of disease, virus clearance time, and duration of hospital admission, mainly to assess the possibility of vertical transmission. There were no differences in the above variables between both groups, and the potential for vertical transmission could not be assessed although some of the pregnant women had severe pneumonia. Thirdly, contrary to the uncertainty of the vertical transmission from mothers with COVID-19 to their new-born in the preceding study, another study described clinical symptoms and outcomes of neonates with COVID-19 [23]. Among 33 newborns delivered by mothers with COVID-19, 3 babies delivered by caesarean section presented with early-onset COVID-19, manifested by lethargy, fever, vomiting, and pneumonia on chest radiograph, and were laboratory-confirmed positive. It is strongly suggested that the sources of COVID-19 in the neonates' upper respiratory tracts or anuses were maternal, considering the strict implementation of infection control and prevention procedures during the delivery. The authors noted that vertical maternal-fetal transmission cannot be ruled out in the current clinical setting.

Other issue of concern in pregnant women is that severe COVID-19 can predispose to preeclampsia-like syndrome that is differentiated from actual preeclampsia by the measurement of angiogenic factors (sFlt-1/PlGF ratio), lactate dehydrogenase (LDH) and uterine artery pulsatility index (UtAPI) [24]. These laboratory tests could help reduce misdiagnosis in pregnancies with severe COVID-19.

Neonates

While vertical maternal-fetal transmission is a subject of debate [25–27], a study showed no vertical transmission of SARS-CoV-2 and no perinatal complications in the third trimester [25]. Nineteen neonates were delivered by their mothers who had laboratory-confirmed COVID-19 in an isolation room. They were immediately separated from their mothers and isolated for at least 14 days. SARS-CoV-2 reverse transcriptase-PCR (RT-PCR) in the throat swab, urine, and feces of all neonates were negative. RT-PCR in breast milk and amniotic fluid was also negative. None of the neonates showed clinical, radiologic, hematologic, or biochemical evidence of SARS-CoV-2 infection. Consequently, delivery in isolation and immediate separation from the infected mothers and caregivers are strongly advised.

Pediatric patients, including neonates, infected with SARS-CoV-2 are alleged to have mild presentation. However, enormous efforts should be made in caring for children infected with SARS-CoV-2 from two perspectives. First, infected children may persistently shed SARS-CoV-2 in stools, increasing the possibility of the virus being carried through contaminated objects [26]. However, what is more important is that children infected with SARS-CoV-2 may develop pediatric inflammatory multisystem syndrome which is characterized by a wide spectrum of presenting symptoms and signs, ranging from fever, inflammation, to myocardial injury, shock, and the development of coronary artery aneurysm [27]. This is very distinct from ordinary pediatric inflammatory conditions.

BCG vaccination and SARS-CoV-2

The World Health Organization (WHO) carried out two clinical trials for the evaluation of whether the Bacille

Calmette-Guérin vaccine (BCG) can protect from SARS-CoV-2 infection. According to the WHO, there is no evidence that the BCG protects people against infection with SARS-CoV-2 [28]. Therefore, in the absence of evidence, WHO does not recommend BCG vaccination for the prevention of SARS-CoV-2. WHO, however, recommended that BCG vaccination should be continued for neonates in countries or settings with a high incidence of tuberculosis [29, 30]. WHO also opined that BCG vaccine had no specific effects on the immune system in both animal and human studies, but these effects have not been well characterized and their clinical relevance is unknown.

Proton pump inhibitor (PPI) and COVID-19

The use of proton pump inhibitor (PPI) in patients with COVID-19 is a matter of discussion because of the recent studies linking fatal COVID-19 with PPI use [31, 32]. Currently a causal correlation is being inferred. In the last decade, PPI have been implicated for a variety of illnesses, osteoporosis, clostridium difficile colitis, liver disease, liver cancer, Alzheimer's disease, chronic kidney disease, malnutrition, early death in the elderly, and now death in COVID-19. It is estimated that one fifths of Americans struggle now with daily symptoms of heartburn, and largely due to the fact that two thirds of Americans are overweight or obese. Most people are on PPI mostly for heartburn. Additionally, obesity is a predictor of hypertension and diabetes which combined as comorbidities that may result in increased risk for severe COVID-19 and even death. These are arguably the independent contributors to increased COVID-19 mortality.

Some studies showed an increase of about three times the average person's risk of dying from COVID-19, but these studies were all retrospective, and as such are subject to confounding and the association of PPI use does not infer that the PPI caused their increased risk of death. The acid-lowering hypothesis is pure conjecture, and we know from many studies that despite PPI use to reduce stomach acid, the stomach still remains fairly acidic. Whether SARS-CoV-2 survives much more if ingested in this environment and spreads becoming fatal is inferred. Studies to confirm viral gastric survivability *in-vivo* are lacking. However, we do know that the predominant route of transmission for SARS-CoV-2 is respiratory for which a PPI should have no effect.

A more logical explanation would be that chronic PPI use is a marker of other comorbidities, namely obesity, diabetes, hypertension, and complications which have been clearly linked to COVID-19 fatalities. Therefore, until prospective randomized controlled studies are conducted to show a direct link and the understanding of the mechanism of action demonstrating how PPI increases COVID-19 fatality are available, the reasonable explanation for the PPI and COVID-19 will still be deferred until confounding is resolved.

Cancer

An analysis of a large cohort suggested that anticancer chemotherapy is not a significant contributor that may aggravate clinical outcomes of cancer patients with COVID-19 or to predict death from COVID-19 [33]. The data strongly indicated that mortality in patients with cancer and COVID-19 is mainly driven by other factors such as an advancing age and the presence of other non-cancer comorbidities. It is assumed that withholding cancer therapies from cancer patients during this pandemic poses a real risk of increasing cancer morbidity and mortality, probably much more than COVID-19 itself.

Moreover, apart from delayed cancer treatment, there were other similar studies on cancer screening during the pandemic [34]. The study describes the impact of COVID-19 pandemic on colorectal cancer screening delay. Specifically, the effect on cancer stage shift and increased mortality using a hypothetical model of the effect of delays in colorectal cancer screening colonoscopy on the stage of diagnosis of colorectal cancer and excess mortality due to colorectal cancer. Despite this study being a modeling exercise, delays in colorectal cancer screening were projected to lead to a more advanced-stage and higher risk of colorectal cancer-related death. The study emphasizes the importance of resuming colorectal cancer screening and catching up on screening and diagnostic colonoscopy efforts for those overdue.

Obesity

A study determined the effect of obesity on prognosis in young people infected with COVID-19 [35–39]. Those that were overweight and infected with COVID-19, had negative outcome similar to that of the elderly in their 60s or 70s. Excess fat is suspected to be associated with a pro-inflammatory state, which could be increased by virus infection. Moreover, the ACE-2 receptor to which the SARS-CoV-2 binds is expressed in higher amounts in fat tissue than in the lungs. It is clear then that obesity can worsen any disease, including COVID-19.

Diagnosis

Universal testing in patients who are suspected or documented with COVID-19 is currently a quantitative PCR test of nasopharyngeal swabs. However, as the PCR is probably not the test of choice for monitoring the pandemic, a rapid antigen and antibody test is considered a

better combination for massive screening. The PCR positive test result is not as quickly available as the rapid antigen test for infected people, and serial negative post-exposure PCR tests have not been trusted enough by experts to minimize stay in isolation. Also, positive PCR on random samples cannot be used to conclude if the infected patients have active infections or are in the inactive phase from earlier exposure (since the PCR stays positive for weeks after the initial infection). Unlike the PCR, a positive rapid antigen test correlates well with actual infectivity and is much more reliable because of its low cost, daily repeatability, and universal acceptance by patients of the sample collection.

Increased levels of circulating endothelial cells seem to be relevant to severe forms of COVID-19 [40]. In a study of patients with COVID-19 admitted to the ICU, circulating endothelial cells were significantly higher than in patients who did not require ICU care. In addition, the degree of endothelial injury was correlated with potential markers of disease severity and inflammatory cytokines.

Treatment

In late March and early April 2020, as the case count of COVID-19 patients rapidly increased, the WHO and the Infectious Diseases Society of America (IDSA) began publishing guidelines [41] and supporting drug trials [42]. As the first trial drugs, hydroxychloroquine, Zithromax, and chloroquine were recommended in the US, where the case count was rapidly growing.

Chloroquine

In April 2020, the effect of high versus low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with COVID-19 and the link between SARS-CoV-2 viral load in sputum with risk of COVID-19 progression was tested [43]. Preliminary findings of the randomized study suggest that high doses of chloroquine diphosphate should not be used in critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir.

Hydroxychloroquine

As mentioned already, hydroxychloroquine had been used for prophylactic effects since early stage of the outbreak [44]. However, in June 2020, results of a randomized trial testing hydroxychloroquine as a prophylactic drug following exposures to SARS-CoV-2 suggested that the drug did not significantly prevent disease compatible with COVID-19 or confirmation of infection when given within 4 days after exposure [45]. The WHO, despite negative result of hydroxychloroquine, decided to continue the evaluation of hydroxychloroquine as a potential COVID-19 treatment based on a data and safety monitoring board (DSMB) decision that there was no reason to discontinue the study following a review of available data on the drug. Then, in late June 2020, the US National Institutes of Health (NIH) noted that the clinical trial to determine the safety and effectiveness of hydroxychloroquine for the hospitalized adult patients with COVID-19 had been stopped [46]. This study indicated that hydroxychloroquine had no additional benefit in comparison to placebo control group for the treatment of COVID-19 in hospitalized patients. According to the NIH, a DSMB of the NIH had determined that the study drug was very unlikely to be beneficial to hospitalized patients with COVID-19, whereas there was no harm.

Remdesivir

In late March 2020, the Centers for Disease Control and Prevention (CDC) released a list of drugs that were being clinically tested globally for COVID-19. The first one being tested was the investigational drug, remdesivir, which is an intravenous agent which has broad antiviral activity, inhibiting viral replication through premature termination of RNA transcription. It has *in-vitro* activity against SARS-CoV-2 and *in-vitro* and *in-vivo* activity against related beta-coronaviruses. In a cohort of patients hospitalized for COVID-19 being treated with sympathetic-use remdesivir, clinical improvement was found in 68% of the patients [47].

Convalescent plasma

In late March 2020, in a preliminary uncontrolled case series of 5 critically ill patients with laboratory-confirmed COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by accelerated clinical improvement [48]. These preliminary findings elevated the feasibility of convalescent plasma transfusion being helpful in the treatment of critically ill patients with COVID-19 and ARDS, but this approach required re-evaluation in randomized clinical trials. In April 2020, the National Convalescent Plasma Project was launched in the US for patients who have recovered from COVID-19 and want to donate plasma, and for healthcare providers who are considering this treatment for their patients [49].

Lopinavir–ritonavir

In hospitalized adult patients with COVID-19, treatment with lopinavir-ritonavir did not significantly improve clinical outcomes, decrease fatality, or diminish throat viral

RNA detectability [50]. The non-blinded randomized study recruited 199 patients aged 49 to 68 years with laboratory-confirmed SARS-CoV-2 infection to receive standard medical care plus lopinavir/ritonavir (n = 99) or standard care alone (n = 100). Nearly 14% of patients in the lopinavir-ritonavir group were unable to finish the protocol of administration, primarily due to gastrointestinal adverse events.

Dexamethasone

A preliminary report from a trial suggest that low-dose dexamethasone reduced the risk of mortality by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [51]. The study proved that dexamethasone reduced deaths in ventilated patients by one-third and in other patients receiving only oxygen by one fifth. There was no benefit for patients without ventilatory support.

Prevention/vaccine

Apart from therapeutic strategies for combating COVID-19, special precautions are also strictly required. Current accepted prevention strategies are as follows: handwashing, social distancing, changing their clothes, showering before joining family, stay in isolation, wearing masks, hygiene, limiting contact, living and sleeping separately from their family.

The Corona virus vaccine to tackle COVID-19 will soon become available presumably from certain pharmaceutical giants such as Pfizer or AstraZeneca. Pfizer Announces SARS-CoV-2 vaccine is more than 90% effective. In the global race to develop a Covid-19 vaccine, Pfizer announced on Monday that early trial results were extremely positive and encouraging. According to the *New York Times*, "Pfizer, which developed the vaccine with the German drugmaker BioNTech, released only sparse details from its clinical trial, based on the first formal review of the data by an outside panel of experts. Eleven vaccines are at the late-stage trials, including four in the US. Pfizer's progress could bode well for Moderna's vaccine, which uses similar technology. A Moderna spokesman said that it expected interim findings from its study this month. Most experts say the world will need many treatments and vaccines to bring an end to the pandemic.

Discussion

Since the first report of the novel coronavirus in December 2019, more than 10 million cases of COVID-19 have been reported, globally, and more than three million people have lost their lives during the outbreak.

SARS-CoV-2 is a highly transmissible virus that infects people and health care personnel (HCP) in health care settings. Patients infected with SARS-CoV-2 present with a variety of clinical signs and symptoms characterized by a broad spectrum of fever, inflammation, myocardial injury, shock, and the development of coronary artery aneurysm. It affects many organs, and may develop into multisystem inflammations. The clinical presentation, characteristics, and outcomes of patients with COVID-19 have been confirmed in a lot of studies. COVID-19 is regarded as a primary pulmonary disease because it shows the typical pattern of pneumonia, characterized by diffuse alveolar damage (interstitial pneumonia) as the predominant pattern of lung lesion, however, it simultaneously affects the vasculatures of the lungs and other organs. It has a high thrombosis risk, leading to life- threatening conditions requiring intensive respiratory treatment. COVID-19 also causes acute myocardial injury and chronic damage to the cardiovascular system. Great majority of COVID-19 patients who had kidney diseases were on admission to the hospital, and the in-hospital death rate was higher in those patients. This indicates the importance of close monitoring of kidney function. Patients with COVID-19 may complain of digestive symptoms, in nearly 50% of cases, earlier than pulmonary symptoms. Furthermore, the virus can stay in the gastrointestinal tracts even after clinical symptoms disappeared. So careful attention should be taken in the diagnosis, even though fecal transmission is still unclear. ARDS due to SARS-CoV-2 infection is also associated with neurologic dysfunction or encephalopathy, presenting agitation and confusion, and strokes, and this was evidenced by postmortem findings of brain tissues. In addition, SARS-CoV-2 has been implicated in various clinical circumstances. It may cause vertical transmission in neonates delivered by infected mothers. It can, moreover, have harmful impact on drugs used by complicated drug interaction.

According to a study investigating the viability of the virus in different environmental conditions [51], SARS-CoV-2 can be highly stable in a favorable environment, but it is also sensitive to standard disinfection. It is highly stable at the temperature of 4℃, but sensitive to heat, and shockingly, the virus was still present on the outer surface of a surgical mask on day 7 at a detectable level. Specific care activities, in particular aerosol or droplets-producing procedures, may have a higher risk of transmission. The rapid emergence and global outbreak of COVID-19 has created significant challenges even in health care facilities, particularly those with severe shor-

tages of the personal protective equipment (PPE) used to protect HCP. Evidence-based recommendations for what PPE to use in conventional, contingency, and crisis standards of care are needed. The COVID-19 pandemic has changed the way we investigate or assess patients. Some novel non-contact technologies have evolved in the provision of service to continuously monitor the patients' conditions when undergoing intensive care. Primarily, this results in increased patient surveillance, and therefore, safety.

For a time since the outbreak, more than 80% of all cases were from some specific regions although now the rate of SARS-CoV-2 infection continues to grow worldwide. Scientific evidence indicates that among diagnosed COVID-19 cases, 30% were hospitalized and 4% were in a severe state. Whereas, 15% of hospitalized cases reported with severe illness, and death occurred in 12% of those cases, with greater hospitalization and case-mortality rates for those aged 60 years and above [52]. Under these circumstances of greater fatality in the elderly, a specific marker to help predict which patients are less likely to survive, and will require intensive care, is needed. Serum cortisol concentrations in patients with COVID-19 were significantly higher than those without, indicating a cortisol stress response as in patients undergoing major surgery whose cortisol levels is probably higher [53].

Many countries have been finding solutions to increase their capability to implement the full package of measures (isolation, testing, treating, and tracing) that have turned the tide in several countries. But some countries are experiencing intense epidemics with extensive community transmission. Nevertheless, continuous efforts are required to suppress transmission in these situations. The Korea is cited globally as a standard example where the country developed an innovative testing strategy and expanded laboratory capacity. Testing and exhaustive contact tracing in selected areas were put into action, when it confronted the accelerating community transmission previously. As a result, reported infected cases in the country have been successfully declining.

Although, since the first case of COVID-19 was reported in December 2019, about 10 drugs have been tried for the treatment of SARS-CoV-2 infection, and some of them proved to be partly effective [42], there is no prospect of an effective drug(s) in the near future. WHO continues to recommend that isolation, testing, and treating every suspected case, and tracing every contact must be the mainstream strategy in the response of every country. This is the best hope of preventing further widespread community transmission.

The outlook of the pandemic seems to be bleak and almost hopeless. Fortunately, in the aspects of vaccines and therapeutic drugs (convalescent plasma), there appears to be some rays of hope, and hopefully, an end of the epidemics may be in sight. Furthermore, we need certain extreme changes in terms of public health care for combating the novel virus, and for us to return to normal situations. Such changes must include better routine disease-surveillance for the detection of early signs of an outbreak and escalating laboratory-testing capacity, intimately linked with the domestic and international public health system to enable robust monitoring and response.

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