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Editorial

COVID-19 Pandemic: Emerging Issues and Future Challenges

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The coronavirus disease 2019 (COVID-19) has been spreading very rapidly, affecting 210 countries and territories around the world and two international conveyances (worldometers.info). This has raised a major global concern. The United States of America reported highest number of deaths. This disease is caused by a new virus initially named as "Novel Coronavirus 2019-nCoV," first emerged in Wuhan city (Hubei Province, China) in late December 2019 and later renamed to "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)."[1]

SARS-CoV-2 belongs to the beta-coronavirus subfamily and closely related to SARS-CoV virus. This 30 kbp, +ssRNA enveloped coronavirus has a zoonotic origin transferred to human most likely from the source/reservoir – Bats/Pangolins.[2] Human-to-human transmission occurs primarily through respiratory droplets, fomites, and aerosol [Table 1] but also has the possibility of fecal-oral.[3]

It has been observed that the genomic sequence of this virus is 96.2% identical to a bat coronavirus, about 79% to the genomes of SARS-CoV and about 50% to the MERS-CoV, but it has a similar receptor binding domain structure as that of SARS-CoV.[5] The SARS-CoV-2 genome encodes the four major structural proteins including spike (S), envelope (E), membrane protein (M), and nucleoprotein (N) [Figure 1]. Among these structural elements, S protein has a fusion peptide, which exhibits significantly higher binding affinity to the host receptors – angiotensin-converting enzyme 2 (ACE2) receptors that SARS-CoV in human.[6] Hoffmann *et al.* demonstrated that SARS-CoV-2 entry to the host cell depends on the receptor ACE2 and the serine protease TMPRSS2 for S protein priming and can be blocked by a clinically proven protease inhibitor.[7]

To know how contagious is SARS-CoV-2? The WHO has published reproductive number "R0" to be 2.0–2.5 using early information.[8] A research on the Diamond Princess Cruise ship estimated R0 of about 2.28 and proved that intense quarantine and social distancing should be taken to control the outbreak.[9] A mathematical model, by processing published data, estimated R0 of 2.3 from reservoir to person and 3.58 from person to person, implying that 3.58 people can be infected as a result of introducing a single infected individual into an otherwise susceptible population. This is higher than in MERS and SARS-CoV.[10] A study conducted on the first 425 cases, reported in Wuhan, suggests a mean incubation period of 5.2 days (95% CI, 4.1–7.0), a mean serial interval of 7.5 days (95% CI, 5.3–19), and a basic reproductive number of 2.2 (95%

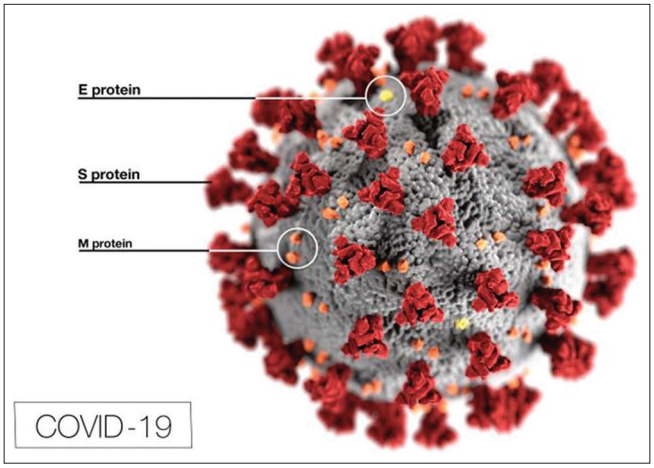

Figure 1: Schematic showing the structure of coronavirus disease 2019 – note the spikes on the out surface of the virus. (Courtesy of the US CDC Public Health Image Library, free of any copyright restrictions: https://phil.cdc.gov/Details.aspx?pid=23313).

Table 1: Viability of severe acute respiratory syndrome coronavirus 2.

S. Number	Object	Duration up to (hours)
1.	Aerosol[4]	3
2.	Plastic and stainless steel[4]	72
3.	Copper[4]	4 h
4.	Cardboard[4]	24 h

CI, 1.4–3.9), showing that this novel epidemic doubled in size every 7.4 days.[11] The data also indicated the patients' median age of 59 years (range from 15 to 89 years) with no clinical cases below the age of 15 years and no significant gender differences.[11]

The clinical spectrum of COVID-19 varies from asymptomatic forms to severe symptomatic form such as acute respiratory distress which requires mechanical ventilation and intensive care unit (ICU) support and multiple organ dysfunction syndromes. Men are more likely to test positive for SARS-Co-V2 and more likely to die from the infection; the case fatality was 2.8% for men while 1.7% for females.[12] The probable reason for this is men who are more likely to be smokers, leading to more severe COVID-19 infections. Females have a more robust immune response as compared to male.[13] Children are less likely to be affected by COVID-19 and have a better prognosis. A recent joint report by China-WHO Joint Mission Expert Group indicates that children under 18 years of age account for 2.4% of all reported cases without any mortality reported.[14] Immature immune response, immature ACE2 receptors, and more immunoglobulin level due to recurrent viral infection are the probable explanation for the reduced incidence and better prognosis in children. A study conducted on 1099 patients from 552 hospital in the mainland of China showed that the patients experienced fever (43.8% on admission and 88.7% during hospitalization), cough (67.8%), diarrhea (3.8%), ground-glass opacity on chest CT examination (56.4% on admission), and lymphocytopenia (83.2%) on admission.[12] The most commonly reported ENT symptoms were nasal congestion and rhinorrhea. However, Klopfenstein *et al*.[15] reported anosmia in 47% of patients while Lechien *et al*.[16] reported anosmia in 86% of patients. The anosmia is usually reported in European patients and exact mechanism is not known. The probable explanations were either genetic variation or ethnic specific variation in ACE 2 receptors.[16] This phenomenon is known as post-viral olfactory loss. Both these authors also reported associated dysgeusia.[16] The Centers for Disease Control and Prevention (CDC) released nationwide data that revealed >33% of COVID-19 patients are African-American, even though African-Americans make up around 13% of the population of the USA.[17]

The detection of nucleic acid of SARS-CoV-2 is the gold standard for the diagnosis of COVID-19.[18] Although upper airway specimens (nasopharyngeal swab, nasal swab, and pharyngeal swab), lower airway specimens (sputum, airway secretions, and bronchoalveolar lavage fluid), feces, urine, and blood can be collected for nucleic acid detection test, lower airway specimens have a high positivity rate and should be collected preferentially.[18] Diagnostic test sensitivity for RNA RT PCR was 67% in the 1st week; decreasing over a period of 40 day to 45% while total antibody was not that much sensitive in the 1st week (38%) but their sensitivity increased to 100% over 15–39 days following COVID-19 infection. IgG and IgM also followed a similar trend as total antibody with initial sensitivity of 29% and 19% in the 1st week and increase up to 94% and 80% over a period of 15–39 days.[19] Zhao *et al*. concluded that the antibody detection offers vital clinical information during the course of COVID-19 infection.[19] Manifestation on high-resolution computed tomography including ground-glass opacity (GGO) and crazy paving is common in COVID-19 patients.[18] The Radiological Society of North America Experts classify COVID-19 associated pneumonia into the four groups: Typical (crazy paving), indeterminate (absence of typical features, GGO), atypical (absence of atypical and indeterminate appearance, segmental consolidation without GGO, tree in bud appearance), and negative for pneumonia.[20] The CDC does not currently recommend CXR or CT to diagnose COVID-19.[21] American College of Radiology is also against the policy of using Ct for screening or as a first line test to diagnose COVID-19. ACR recommends that CT should be used sparingly and reserved for hospitalized, symptomatic patients with specific clinical indications for CT.[21] Although the risk transmission is greatest when the patients are symptomatic, several studies have documented transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic people.[22,23] The studies found no evidence

for intrauterine transmission of COVID-19 from infected pregnant mothers to their fetuses.[24,25] A retrospective multicentric cohort study in Wuhan reported the elderly age and patients with comorbidities such as hypertension (most common), diabetes, and coronary heart disease are the potential risk factors for mortality.[26] A report of 72,314 cases from the Chinese Centre for Disease Control and Prevention demonstrated an overall case fatality rate of 2.3% including 14.8% over the age of 80 years, 10.5% in cardiovascular disease, 8% between 70 and 79 years of age, 7.3% in diabetes, 6.3% in COPD, 6.0% in hypertension, and 5.6% in cancer.[27] Most of these conditions are indicative of nitric oxide (NO) deficiency and also have a high risk of developing severe acute respiratory syndrome. Older people lose the ability to make NO, which weakens immune system. NO is considered as an extremely effective antiviral agent against the SARS-CoV.[28] Dietary nitrate as found in green leafy vegetables and beetroot can help us to combat COVID-19 by inhibiting SARS-CoV replication and viral cell fusion. Evidence also suggests the role of Vitamin D supplementations in reducing the risk of COVID-19.[29]

Ma *et al*.[30] first investigated the effects of temperature, diurnal temperature range (DTR), and humidity on the deaths due to COVID-19 in Chinese population and suggested the positive association of DTR and negative association of absolute humidity with COVID-19 mortality. Another study by Wang *et al.* suggests that high temperature and high humidity reduce the transmission of influenza and SARS, and summer and rainy season in the northern hemisphere can effectively reduce the transmission of the COVID-19.[31]

SARS-CoV-2 binds to their target cells through ACE2 receptors, which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.[6] The expression of ACE2 is substantially increased in patients with diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs).[32] ACE inhibitors are associated with upregulations of receptors and facilitate the infection with SARS-CoV-2. Authors also suggest that these patients should be monitored for ACE 2 inhibitors and ARBs, or the calcium channel blockers can be considered as a suitable alternative.[33] However, the European Society of Cardiology and American Heart Association recommend that physicians should continue treatment with their usual medication, and ACE2 inhibitors (ACEIs) or ARBs should not be discontinued because of the COVID-19 infection. A recent study published by Li *et al.* concluded that ACEIs/ARBs are not associated with the severity or mortality of COVID-19 in patients with hypertension.[32] D-dimer >1 μg/mL (18.42, 2.64–128.55; P = 0·0033) on admission was found to be associated with poor prognosis.[27] Clinical recovery has been correlated with the detection of IgM and IgG antibodies and the development of immunity. Published scientific literature does not report the data on COVID-19 reinfection.

At present, no medications or vaccines have been proven to be effective for the treatment or prevention of SARS-CoV-2.[34] However, various strategies have been used to target SARS-CoV-2 such as targeting viral spike protein to inhibit membrane fusion and endocytosis, inhibiting proteolysis and RNA dependent RNA polymerase.[35] Other mechanisms such as inhibition of serine proteases and IL-6 receptor antagonist are also being explored.[35] Smith *et al*. have given a list of agents such as chloroquine, hydroxychloroquine, lopinavir, ritonavir, remdesivir, favipiravir, azithromycin, tocilizumab, leronlimab, sarilumab, COVID-19 convalescent plasma, corticosteroids, inhaled pulmonary vasodilators, NSAIDs, and bronchodilators, which are under clinical trials based on *in vitro* activity against SARS-CoV-2 or related viruses.[36] Caly *et al*.[37] reported that ivermectin, an anti-parasitic having a broad-spectrum anti-viral activity *in vitro*, is a potential inhibitor of SARS-CoV-2 into the infected cell culture. This warrants further investigation to measure the benefits in human. *In vitro* and preliminary clinical researches suggest that hydroxychloroquine alone and in combination with azithromycin could be an effective treatment for COVID-19, but increases the risk of ventricular arrhythmias.[38] Table 2 shows the mechanism of action of various repurposed or investigation agents which have shown activity against coronavirus.

Lei *et al.* retrospectively analyzed patients unintentionally posted for elective surgeries during the incubation period of SARS-CoV-2 infection.[48] This retrospective cohort study showed that 44.1% of patients needed ICU care, and mortality was 20.5%.[49] The case fatality rate is much higher (20.5%)[48] than reported in large series without surgeries (2.3%).[28] Elective surgeries should be postponed for a certain period (at least 14 days), or possibilities of COVID-19 infection shall be excluded before considering elective surgery during the pandemic.[48] Miller *et al*. collected data on BCG vaccination policy from 28 countries where they accessed the year of starting vaccination.[49] There was a significant positive correlation (ρ = 0.44, P = 0.02, linear correlation) between the year of starting the vaccination policy and mortality rate.[49] They found that countries with earliest vaccination policy had significantly less mortality as compared to countries started later: Iran (1974, 19.7 death/millions inhabitants), Japan (1947, 0.28 deaths/millions inhabitants), and Brazil (1920, 0.0573 deaths/million inhabitants).[49] These data suggest that BCG might confer long-lasting immunity against COVID-19. The WHO denies any role of BCG vaccine in COVID-19.[50] Therefore, randomized controlled trials using BCG are required to determine the rapidity of the response against COVID-19. Countries, where universal vaccination policy has never been

Table 2: The mechanism of the action of various repurposed and investigational agents which has shown activity toward severe acute respiratory syndrome coronavirus 2, either *in vitro, in vivo,* or in clinical trials.

Most commonly used repurposed agents	Mechanism of action	References showing use of repurposed agents, *in vitro/in vivo*/clinically
Chloroquine phosphate	Blocks viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification	[39]
Hydroxychloroquine	Blocks viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification	[40]
Lopinavir/ritonavir	Inhibition of 3-chymotryspin like protease inhibitor	[41]
Umifenovir	Targets spike protein/ACE-2 membrane fusion and thus inhibits inhibition of membrane fusion of viral envelope	[42]
Oseltamivir	Spike protein/ACE-2 membrane fusion	[43]
Remdesivir	RNA-dependent polymerase inhibitor	[44]
Favipiravir	RNA-dependent polymerase inhibitor	[35]
Nitazoxanide	Interference with the pyruvate:ferredoxin oxidoreductase enzyme-dependent electron transfer reaction	[45]
Camostat mesylate	Inhibition of serine proteases	[7]
Tocilizumab	Monoclonal antibody IL-6 receptor antagonist	[46]
Sarilumab	IL-6 receptor antagonist	[47]
Ivermectin	Causes hyperpolarization due to the activation of glutamate channel leading to the opening of chloride channel	[37]

implemented, had a high mortality rate such as Italy and the USA.

Like other coronaviruses, SARS-CoV-2 is sensitive to ultraviolet rays and heat and effectively inactivated by lipid solvents such as ether, ethanol, chlorine-containing disinfectants, peroxyacetic acid, and chloroform except chlorhexidine. Preventive measures such as catch and isolate, handwashing practice, and masks have been identified as ways and means to reduce transmission.[51-53] A summary of CDC guidelines[52] for COVID-19 is given below:

- Patients of COVID-19 may have fever, cough, and shortness breath 2–14 days after exposure
- Elderly population and people who have severe underlying medical conditions such as heart disease, lung disease, or diabetes seem to be at higher risk for developing more serious complications from COVID-19 illness
- People who develop trouble breathing, persistent pain or pressure in the chest, new confusion or inability to arouse, and bluish lips or face seek medical attention
- The best way to avoid being exposed to this virus is cleaning your hands often with soap and water at least 20 s, especially if you have been in a public place or sanitize your hand with a sanitizer that contains at least 60% of alcohol, avoid close contact by staying at home as much as possible, cover your mouth and nose with a cloth face cover when around others, and clean and disinfects frequently touched surfaces daily by a bleach solution or alcohol solution (at least 70% alcohol).

The UK's National Health Service[53] advises not to leave home in case of high temperature and/or continuous cough (meaning coughing a lot for more than an hour or 3 or more coughing episodes in 24 h). Minimizing time spent outside home and ensuring 2 m apart from anyone outside households are important measures to prevent coronavirus spread.

Given that the target organ in COVID-19 is the lung, it is important to recognize that tobacco smoke exposure also results in inflammatory processes in the lung, increased mucosal inflammation, expression of inflammatory cytokines and tumor necrosis factor α, increased permeability in epithelial cells, mucus overproduction, and impaired mucociliary clearance.[54-56] Cigarette smoking is a substantial risk factor for bacterial and viral infections, thus from the forgoing discussions, knowledge about host factors, and avoidable host factors such as smoking, may be of importance in reducing viral contamination and the severity of the disease.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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