The Socially Distanced Social Animal – In The New Covid-19 Era

Coronaviruses are a group of single-stranded RNA (positive) viruses [Figure 1] belonging to the subfamily *Coronavirinae* (*Coronaviridae* family). Based on genomic sequencing the subfamily *Coronavirinae* is further subdivided into four genera — *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*.[1] Over the last 20 years, *betacoronavirus* genera have produced two epidemics SARS CoV (2002-03), MERS CoV (2014-16).[2] An acute respiratory illness broke out in Wuhan, China in December 2019. A novel virus belonging to the genera *betacoronavirus* found to be causing this disease Corona Virus Disease-2019 (COVID- 19)) is presently classified as severe acute respiratory syndrome CoV 2 (SARS-CoV-2) virus. On February 1, 2020, WHO declared COVID-19 as a public health emergency of international concern. On the day of writing this editorial (04/04/2020), SARS-CoV-2 has infected 1,083,211 patients worldwide and 3,108 patients were infected in India. The case fatality rate of SARS CoV is 14-15%, MERS CoV is 35% and the rate of SARS- CoV- 2 is around 2.5% suggesting that SARS- CoV- 2 is less deadly than its cousins as on date.[3]

The incubation period of SARS-CoV- 2 ranges from 1-14 days (mean incubation period: 5-6 days). SARS- CoV- 2 spreads via air-borne droplet particles/aerosols (coughing and sneezing) or direct contact with the secretions of the infected individual producing human to human transmission. The droplet particles do not travel beyond 2 meters and do not remain in the air. Thus far, there is no evidence of intrauterine transmission or transmission during delivery.[2,4,5] SARS- CoV- 2 has been extracted from stool samples however faeco-oral transmission has not been documented.[6] Basic reproduction number (R_0) indicates the ability of an organism to spread. R_0 of SARS- CoV- 2 is 2-2.5. The serial interval (SI) is the time taken for successive cases to be infected. The mean serial interval for SARS- CoV- 2 is 3.96 days (4-7 days) which much lower than 8.4 days documented for SARS CoV.[6,7] Majority of infections (approximately 81%) are mildly symptomatic, although these patients can spread the disease. R0, SI and large number of mildly symptomatic patients are epidemiologically significant and responsible for the exponential spread of the virus.

The natural reservoir of SARS CoV, MERS CoV is presumed to be bat and the intermediate hosts of SARS CoV and MERS CoV are palm civet and dromedary camel respectively. Early genomic matching studies suggest that the natural reservoir for SARS- CoV- 2 is presumed to be bat and Malayan pangolin species extensively used in China for medicinal purposes are also involved in the transmission chain.[8,9]

The receptor for entry of SARS- CoV- 2 is human angiotensin converting enzyme 2 (hACE 2) receptor present in respiratory epithelium and type II pulmonary pneumocyte which is the same as that of SARS CoV whereas MERS CoV utilizes the dipeptidyl peptidase 4 (DPP4) receptor for binding and entry.[1] The hACE 2 receptors are also expressed in the heart (cardiac myocytes, endothelium of myocardial vessels), kidney (proximal tubule, distal tubule) and major blood vessels (endothelium and smooth muscle cells). In the brain, the above receptors are seen in endothelium and smooth muscle cells of blood vessels. Animal studies (rat) have shown that the receptors are also seen in neurons.[10] Speculation that ACE inhibitors/Angiotensin receptor blockers upregulates ACE 2 receptor and increases the susceptibility to infection lacks evidence. It is advised that patients continue the ACE inhibitors/ Angiotensin receptor blockers medications [Figure 2].[11]

SARS- CoV- 2 replicates both in the upper and lower respiratory tract. This is in contrast with SARS CoV, as the latter has an affinity to the lower respiratory tract than the upper respiratory tract. The presence and multiplication of the virus in the upper respiratory tract is the reason for high infectivity than other viruses belonging to the group.[5]

81% of the infected patients are mildly symptomatic, 14% are severely symptomatic and 5% are critically ill. The most common manifestations of the infection include fever (92.8%), cough (69.8%), difficulty in breathing (34.5%), myalgia (27.7%), headache (7.2%), and diarrhoea (6.1%). The severity and complications of the disease are significantly higher in the elderly population. Age-dependent changes in the functions of T- and B- lymphocytes lead to excessive production of type 2 cytokines resulting in prolonged inflammatory response and cytokine storm that might explain the severity in the elderly. Severe manifestations of the respiratory system include pneumonia, ARDS. Other manifestations include sepsis, acute kidney injury, arrhythmia, acute cardiac injury, coagulopathy, and shock.[3,12]

Neurological manifestations are more likely in those with severe infections.[13] The neurological manifestations may be secondary to systemic effects of the virus or directly mediated by the virus. The altered sensorium that occurs in the infection may due to hypoxia, metabolic derangements or multi-organ dysfunction. The direct viral-mediated effects, as evidenced by the presence of SARS-CoV 2 in the cerebrospinal fluid, are probably mediated through hACE2 receptors. The viral access to the CNS may be facilitated hematogenously (probably infected macrophages acting as Trojan horses) or contiguous spread through the cribriform plate.[14] These manifestations include anosmia, dysgeusia, cerebral infarct, Intracerebral hemorrhage, aseptic meningitis, seizures, acute necrotizing encephalopathy. seizure and ataxia. It may also involve the

peripheral nervous system causing Guillain Barre syndrome and muscle injury.[13,15-19] The respiratory failure may also result from virus-mediated destruction of medullary neurons.[20] These manifestations described are far from complete as our understanding of the neurotropism and neurovirulence of the virus is likely to unfurl as the pandemic progresses [Figure 3].

Laboratory findings of SARS- CoV- 2 infection include normal total blood count with lymphopenia which is the most consistent finding (reduced immunological response to the virus), reduced albumin (impaired liver function) with elevated liver enzymes and bilirubin (liver injury), elevated creatine (kidney injury), elevated lactate dehydrogenase (severe lung injury/multisystem involvement), elevated cardiac troponin (cardiac injury), elevated levels of D- dimer, prothrombin time and partial thromboplastin time and thrombocytopenia (consumption coagulopathy), elevated ferritin (severe inflammation), elevated c- reactive protein (severe viral infection) and elevated interleukin-6 (cytokine storm) and procalcitonin (secondary bacterial infection). Detection of viral nucleic acid from nasopharyngeal swab by real-time reverse transcriptase-polymerase chain reaction (r RT-PCR), is now the GOLD STANDARD for confirming a suspected COVID-19 patient is now the GOLD STANDARD for confirming a suspected COVID-19 patient (sensitivity: 50-79%). The swab specimens are collected from the following sites: nasopharynx, oropharynx, expectorated sputum, lower respiratory tract aspirate, bronchoalveolar lavage and rectal swab. Rapid IgG/IgM antibody test has been developed, which can detect the presence of antibodies from blood,

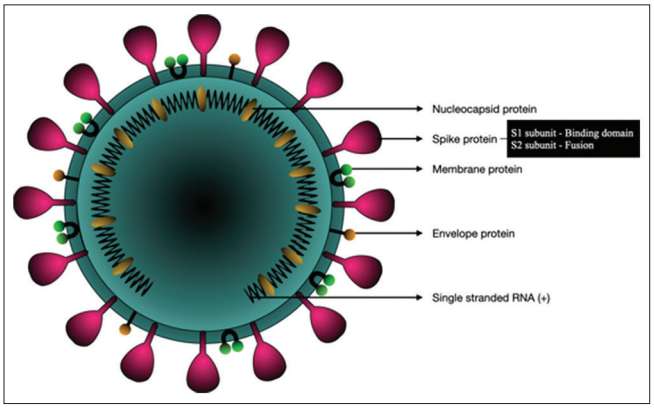

Figure 1: Structure of SARS CoV-2. The spike protein, membrane and envelope protein are located on the surface of virion. The S1 and S2 subunit of the spike protein causes binding to hACE2 receptor and fusion with the host cell membrane respectively. The core of the virion consists of nucleocapsid protein and single stranded RNA (+)

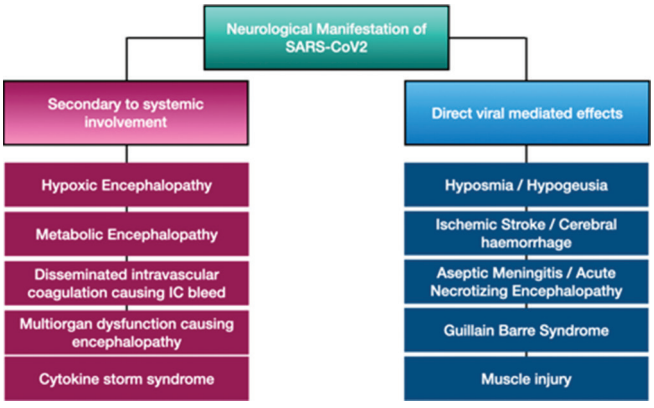

Figure 3: Neurological manifestations of SARS CoV-2

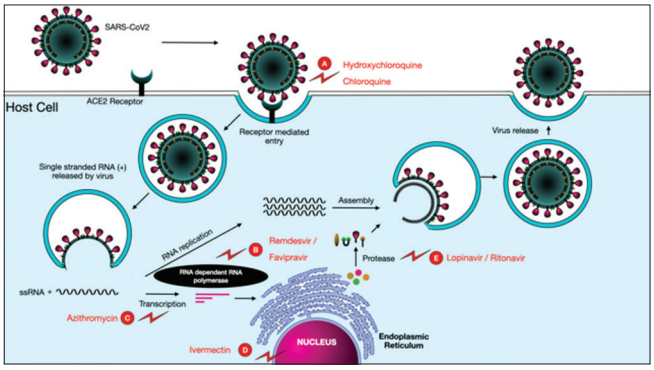

Figure 2: Replication cycle of SARS CoV-2 in the host cell. Entry of the virus into the host cell is mediated through its interaction with Angiotensin converting enzyme receptor 2. The illustration summarises the potential sites of action of various drugs that are used in COVID -19. (A) Hydroxychloroquine and chloroquine inhibits virus entry into the cell by changing the glycosylation of ACE receptor (B) Remdesivir and Favipiravir inhibit the RNA polymerase (C) Azithromycin inhibits mRNA expression and protein production, it is also immunomodulatory and decreases inflammatory response (D) Ivermectin inhibits the interaction between the viral integrase protein (IN) and the importin (IMP) $\alpha/\beta 1$ heterodimer responsible for IN nuclear import (Not shown as a part of viral replication cycle). (E) Lopinavir, Ritonavir inhibit the protease enzyme

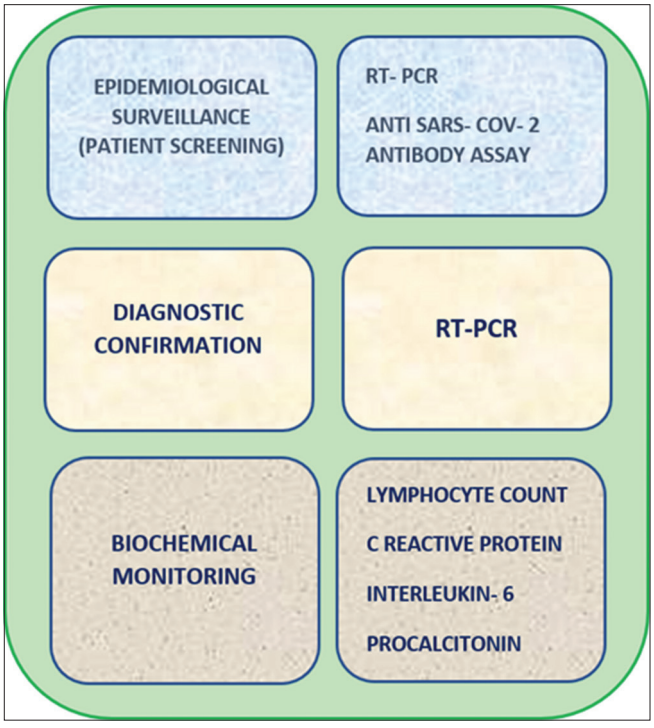

Figure 4: Laboratory monitoring in COVID- 19

serum or plasma (sensitivity: 85.6%, specificity: 91%)[21] and can serve as screening test for triage and epidemiological purposes [Figure 4]. Imaging modalities like chest X-ray shows ill defines opacities in lower zones of lung with the tendency to involve perihilar and upper lung fields in severe disease, CT chest reveals bilateral ground glass (air space) opacities in peripheral zone with predilection to involve lower zones and in some patients fine reticular opacities are also seen. USG lung revealed subpleural consolidation and B lines.[22,23]

Treatment options for COVID-19 include chloroquine/ hydroxychloroquine (inhibits virus entry into the cell by changing the glycosylation of hACE 2 receptor), remdesivir (RNA polymerase inhibitor), favipiravir (RNA polymerase inhibitor), lopinavir-ritonavir (protease inhibitors), tocilizumab (IL-6 receptor monoclonal antibody and preventing the effects of cytokine storm), ivermectin (inhibits the interaction between the viral integrase protein (IN) and the importin (IMP) α/β1 heterodimer responsible for IN nuclear import) and azithromycin (probable mechanism- inhibits mRNA expression and protein production, it is also immunomodulatory and decreases inflammatory response) [Figure 2].

Convalescent plasma from cured patients, Intravenous immunoglobulin has also been tried. The vaccine for COVID-19 is underway. Mechanical ventilation (invasive ventilation preferred over non-invasive ventilation) with low tidal volume and high PEEP setting, renal replacement therapy in acute kidney injury and other supportive treatment modalities are utilized in critically ill patients. The usage of corticosteroids in patients with severe ARDS is controversial and should be judiciously used.[24-27]

American heart association/American stroke association has proposed guidelines in the management of stroke patients during this pandemic insisting the judicious use of emergency services during this period, strictly following the suggested protocol.[28] National multiple sclerosis society also has made recommendations regarding the initiation/continuation/ modifications of disease modifying therapies in multiple sclerosis patients during the pandemic. Immunomodulators that do not increase the risk of infection include glatiramer acetate, interferons and natalizumab. Immunomodulators that increase the risk of infection include dimethyl fumarate, fingolimod, siponimod and teriflunomide. Immunosuppressants increasing the risk of infection include alemtuzumab, ocrelizumab, rituximab, mitoxantrone and cladribine.[29]

With the help, many novel methods like affinity purification-mass spectrometry, 29 viral proteins of SARS- CoV- 2 making 332 high confidence human protein-protein interactions are identified. These protein-protein interactome studies along with a combination of a systematic chemoinformatic drug search with a pathway centric analysis around 70 drugs that can be utilized to treat SARS-CoV- 2 have been identified and these compounds are now being tested for their efficacy against the virus.[30]

This present pandemic since the Spanish flu of 1918 has seen rapid spread across geographies mainly due to extensive air travel and globalisation. It has also exposed the inadequacies of the global supply chain which has been largely a case of all eggs in one basket. Further, the rapid dissemination of information, true and otherwise, as seen an infodemic in the era of social media, which has resulted in unprecedented awareness of the disease in a short period of time. The downside has been the confusion and anxiety in the lay public caused by the torrent of information.

The absence of a specific curative drug and a vaccine has necessitated behavioural strategies to contain spread. The high infectivity and the presence of mildly symptomatic spreaders have resulted in an inability to quickly isolate infected patients. This has necessitated an unprecedented method of social distancing, a form of target population isolation with nearly one third of humanity under lockdown at the time of writing.

However, the number of patients who acutely require intensive care in a short period of time has overwhelmed the capacity of intensive care systems around the world.

Containment strategies such as social distancing have been attempted to flatten the curve so as to stretch the epidemic over a larger period of time allowing for healthcare systems to cope with the patient load.

Aggressive contact tracing and isolation in the earlier local transmission stage of the disease and surveillance once the epidemic has abated is required until the development of herd immunity or a vaccine.

Unprecedented fast tracking of vaccine development and strategies to develop mRNA vaccines as well as viral antigen preparations are in the pipeline. Since the description of the SARS CoV-2 genome in January 2020, vaccines like mRNA1273, a RNA printer a portable mRNA printing facility, INO -4800 a DNA Vaccine, monoclonal antibodies like sarilumab (IL-6 receptor antagonist), RNA interference oligonucleotides therapies (RNAi) like siRNA (small interfering RNA) and India based electroporated DNA vaccine are all in the race.[31]

The epidemiological behaviour of the virus remains to be observed including the possibility of seasonality and endemicity like influenza or a protracted spread over the medium term.

This will in turn necessitate population intervention strategies such as identification and containment of outbreaks and resumption of economic activities within the ambit of social distancing.

The pandemic shall entail medium to long term behavioural changes that will impact supply chains, economic models and sociocultural interactions.

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