Genomic Variations of SARS-CoV-2 and Effect of Various Factors on COVID-19

Anju Rani¹, Rajyavardhan Arya², Pradeep Kumar Sharma³

¹Department of Life Sciences, Graphic Era Deemed to be University, Dehradun-248002, India; ²Quality Assurance Department, Pure and Cure Healthcare Pvt. Ltd, Haridwar, India; ³Department of Environment Sciences, Graphic Era Deemed to be University, Dehradun-248002, India.

ABSTRACT

Introduction: COVID-19 (SARS-CoV-2) is a disease caused by the newly discovered novel Coronavirus. The first case of SARS-CoV-2 was reported in Wuhan, China in December 2019 which later turned out pandemic affecting large population across the world till now.

Aim: This study aimed to review morphological differences of SARS-CoV-2 with other viruses belongs to beta coronaviruses and to analyze the effect of various factors on the spread of disease.

Conclusion: SARS-CoV-2 causes a severe acute respiratory illness with morbidity rate up to 3%. Despite 79% similarity with SARS-CoV, key differences have been observed in spike glycoprotein, 2 accessory proteins and 2 non-structural proteins (nsp). High transmissibility of SARS-CoV-2 across the globe may be associated with these genetic differences. However, geographical differences in cases also suggest the influence of natural immunity, climatic conditions on disease spread. Unavailability of an effective vaccine and antiviral therapy left only social distancing and lockdown as an option to minimize disease spread. Further investigations are needed to know the mode of transmission, resistance to environmental factors. The developments of vaccine for SARS-CoV-2 in many countries are in Phase II & III of clinical trial whereas many drugs have been repurposed to check their efficacy in combating SARS-CoV-2 infections.

Key Words: SARS-COV-2, COVID-19, Spike glycoprotein, Climate, Social distancing

INTRODUCTION

Coronaviruses (CoVs) are important pathogens for human and vertebrates. They can infect the respiratory, gastrointestinal, hepatic, and central nervous system of human, livestock, birds, bat, mouse, and many other wild animals. Coronavirus has become a term everyone is well aware across the world. Coronaviruses (CoV) belong to the family Coronaviridae, order Nidovirales. The family has four genera i.e Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus. Alpha and Beta coronaviruses have gene sources from bats and rodents while Delta and Gamma Coronaviruses have from avian species. The genus Betacoronavirus is classified into four groups; Betacoronavirus group A, Betacoronavirus group B, Betacoronavirus group C and Betacoronavirus group D³. Coronaviruses are zoonotic pathogens that are present in humans and various animals. The animal host includes dogs, cats, camel, pig, cow, horse, mouse and few birds. Till now seven human coronaviruses (HCoVs) are known capable of infecting humans (Fig.1). All seven human coronaviruses (HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63, SARS- CoV, MERS- CoV and SARS-CoV-2) belong to genus Betacoronaviruses. Among seven human Coronaviruses, HCoV-229E, HCoV-NL63 belongs to Betacoronavirus group A, HCoV-OC43 and HCoV-HKU1 belongs to group B while SARS- CoV, MERS- CoV and SARS-CoV-2 (COVID-19) belongs to Group B & C. Human Coronaviruses can cause mild respiratory infections like common cold to severe life taking respiratory illness³.

Before the emergence of SARS-CoV-2 pandemic, two other human coronavirus outbreak (SARS and MERS) occurred globally in the year 2003 and 2012 respectively. Severe acute respiratory syndrome (SARS) was firstly noticed in the Guangdong State of China. The disease rapidly spread worldwide before the epidemic was restricted in 2003, after...
over 8000 cases and several 800 deaths in 29 countries with a mortality rate around 10%. The epidemiological and genetic studies suggested that SARS was a zoonotic disease and that coronavirus evolved from a coronavirus that naturally infects Himalayan palm civets.

Middle East Respiratory Syndrome (MERS), another fatal respiratory disease outbreak occurred in 2012, with its origin in Saudi Arabia. It affected 2494 people and caused 858 deaths with a mortality rate of 37%6,14. A similar virus came out and spread in South Korea in 2015, with infections primarily being associated with hospitals and healthcare persons. In case of MERS outbreak, dromedary camels worked as an intermediate host in the transmission of viruses to human with the bat as a reservoir host6.

Recently an outbreak of new coronavirus was reported in Wuhan, China at the end of December 2019. Studies reported that novel virus belongs to a beta group of coronaviruses and ICTV named this novel virus as SARS –CoV-2 on account of its similarity (79%) with SARS-CoV7.

**MORPHOLOGY AND GENOMIC VARIATION OF SARS-COV-2**

Coronaviruses are enveloped, positive-sense RNA (≈30Kb size) viruses ranging from 60 nm to 140 nm in diameter. The presence of glycoprotein spikes on its surface gives it a crown-like appearance and therefore it is named as a coronavirus (In Latin Coronum means crown) [Fig.2]. Coronaviruses possess characteristic club-shaped spikes composed of trimers8. Some beta coronaviruses also contain a second fringe of shorter spikes made up of hemagglutinin-esterase (HE). The genomic RNA of coronaviruses vary from 26,000 and 32,000 bases and 6 to 11 open reading frames (ORFs) [6]. The genomic RNA is 5' capped and 3' polyadenylated and is used as a template to translate polyprotein pp1a/pp1ab. The first ORF represents about 67% of the whole genome encodes non-structural proteins (nsp) while the remaining ORFs (33% of the genome) at 3′ end encode accessory proteins and four structural proteins6. The Structural proteins include spike glycoprotein (S), envelope (E), membrane (M) and nucleocapsid (N) protein.

The genome size of SARS CoV-2 is 29.8 Kb and genome annotation revealed that it has 14 ORFs that encodes 27 proteins. Similar to other beta coronaviruses, the largest gene orf1ab at 5′ end of the genome encodes pp1a and pp1lab proteins [Fig.3]. The pp1a and pp1lab proteins consist of 15 non-structural proteins, pp1a protein contains 10 nsp (nsp1 to nsp10) while pp1lab contains 5 nsp (nsp12 to nsp16). In case of SARS CoV-2, nsp3 and nsp2 showed 102 and 61 amino acid substitutions6.

The novel SARS CoV-2 stain also consists of four structural proteins i.e spike (S), envelope (E), membrane (M) and nucleocapsid (N) protein10. Among the four structural proteins, the spike surface glycoprotein plays a vital role in binding to host cell receptors and the determination of host selection and initiation of the infection cycle. Although spike protein binds to angiotensin-converting enzyme-2 (ACE-2) receptor on host cell analogous to SARS-CoV, various studies have revealed variations in SARS-CoV-2 spike protein11,12. Total 27 amino acids substitutions were observed in spike protein, which included 6 amino acid substitutions in Receptor binding domain, 6 substitution in underpinning subdomain and 4 substitutions in the C-terminal domain in RBD of S1 domain6. The S2 domain of SARS CoV-2 needed for cell membrane fusion showed approximately 93% sequence identity with bat-SL-CoVZC45 and bat-SL-CoVZXC21, bat derived viruses in comparison to only 68% similarity in S1 domain. The S protein SARS CoV-2 showed 76% similarity with SARS-CoV, whereas genome similarity was observed to be 79%7. In another study, 6 RBD amino acids are crucial for binding to ACE2 receptors and decisive for the host range of SARS-CoV-like viruses. Out of these six residues, five were found to be at variance between SARS-CoV-2 and SARS-CoV11. These amino acid substitutions in spike protein may account for higher (10-20 times) binding affinity of S protein to ACE2 receptor when compared to SARS-CoV, which in turn could be the reason of higher transmissibility of COVID-1913,14.

The membrane protein (M) being the most abundant structural protein (218-263 amino acids), contains 3 transmembrane domain and plays an important role in the regeneration of virus within the cell15. Moreover glycosylation of M proteins in Golgi apparatus16,17 is essential for fusion of virus into cell and to make protein antigenic. The presence of envelope (E) protein, a small structural protein (76-109 amino acids) is required for assembly and morphogenesis of virions and therefore plays a crucial role in viral pathogenesis18. The nucleocapsid protein (N) contains two domains (349-470 amino acids) which bind to genomic RNA. The nucleocapsid protein performs various functions like the packaging of the genome into the virion, IFN antagonist and repressor of RNA interference thus facilitate smooth replication of virus17. Studies carried out by so far have not found significant variation in M, E and N protein of SARS-CoV-2 when compared with SARS-CoV. The M, E & N protein of SARS-CoV-2 showed 90.1%, 94.7% and 90.6% similarity with SARS-CoV, while only 39.2%, 34.1% and 45.9% similarity was observed with MERS corresponding proteins respectively19.

The 3′ end of SARS-CoV-2 genome also contains eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14). Previous studies have suggested their role in modulation of host immune response and pathogenesis20,21. The open reading frame 3b and 6 functions as antagonists of innate immune by
obstructing the production of Type 1 IFN. Functions of other accessory protein have been mentioned in Table 2. In comparison with SARS-CoV, the accessory protein 3b and 8b of SARS-CoV-2 has shown variations in amino acid length (Table 1). Further accessory protein 8a was found to be absent in SARS-CoV-2 whereas it possesses orf 14 in addition.

**EFFECT OF VARIOUS FACTORS ON THE OCCURRENCE OF COVID-19 AND MORBIDITY RATE**

**Blood group**

Previous studies were conducted to find out the susceptibility of SARS-CoV disease with ABO blood group. During the SARS outbreak in 2003, staff in Hong Kong Hospital showed low incidence in O blood group individuals compared to non-O blood group individuals. In the line of this study, another cellular model study was carried out by Guillon et al. to investigate blocking of viral spike glycoprotein binding to host ACE-2 receptor by natural antibodies. The experimental findings suggested that anti-A antibodies particularly inhibited the adhesion of SARS-CoV S protein-expressing cells to ACE-2-expressing cell lines.

On the onset of novel coronavirus disease (COVID-19) in 2019, a similar study was carried out in China with 1775 patients to check out the susceptibility of disease in ABO blood group. Results showed a low risk of disease incidence with blood group O, whereas the maximum risk was associated with blood group ‘A’. The probable mechanism for the same may be due to the presence of natural anti-A antibody in the blood. The possible role of these natural antibodies may be in inhibition of S protein/ACE2-dependent adhesion, blocking virus entry followed by complement-mediated neutralization and in the generation of cytotoxic T-cell response against pathogen.

**Climate**

Although few studies have been carried out to look at the effect of weather on SARS-CoV-2, yet consensus could not be established in terms of research outcomes. The first study in this regard was carried out by Luo et al. in which effect of absolute humidity on the transmission rate of COVID-19 was studied. Findings of this study suggested that high temperature and humidity will not necessarily lead to turn down cases. A subsequent study was conducted by Bu et al. and optimum conditions for the survival of the SARS-CoV-2 was found to be 19°C temperature, 75% humidity and precipitation below 30 mm/ month. In a similar study effect of temperature and humidity was studied on the incidence of COVID-19 in China between Jan 20 and Feb 29, 2020. The daily incidence of disease was found to be lowest at -10°C while the maximum was observed at 10°C and absolute humidity (7 g/mm³). With the rise of temperature daily incidences decrease while no association was observed between humidity and incidence. One more study of China posted on 31 March revealed that increase with every 1°C in average temperature (5.04 to 8.2°C) and every 1% in average relative humidity (67% to 85.5%) led to decrease in daily confirmed cases by 36-57% and 11-22% respectively. However, these relations were not found steady throughout mainland China.

In a recent study from Hong Kong by Chin et al., stability of SARS-CoV-2 was examined at different temperature with the initial virus concentration of 6.7 log TCID50/ml. The results showed 0.6 and 3-log unit reduction at 4°C, 22°C and 37°C on 14 days, 7days and 1 day incubation time respectively. At 56°C and 70°C temperature, no virus was detected after 30 min and 5 min respectively. Arujo and Naimi suggested that vulnerability of people for SARS-CoV-2 will be highest in warm and cold climate followed by arid climate and least in the tropical climate. According to another study, summer temperature would not reduce the size and duration of SARS-CoV-2 incidences at pandemic level, whereas differences in humidity may be important for endemic infections. The World Health Organization (WHO) also stated that virus can transmit in all areas including hot and humid weather. The debate is also going on across the globe about the mode of transmission of virus airborne versus droplet borne as this would suggest more about the effect of seasonality on virus spread and survivability. Moreover, other studies are underway and will be published soon to resolve this mystery.

**Social distancing & Lockdown**

After the emergence of covid-19 in Wuhan, China, several mitigation measures including aggressive case and contact identification, isolation and management and extreme social distancing were implemented by national Government to tackle the epidemic. Later similar measures were adopted by other countries came into the grasp of this disease. Being a novel disease and uncertainty of many factors like mode of transmission, incubation time, transmission rate, survival time outside host and fatality rate rendered policymaking difficult to alleviate the situation. Among many measures taken, social distancing proved to be an important factor in reducing transmission of the virus and thus flattening the endemic curve. A mathematical study was carried out in Wuhan, China to observe the effect of physical distancing on outbreak progression. Results predicted that restrictions on activities till April may help in delaying epidemic peak in Wuhan and early removal of restrictions may lead to second peak before time. COVID-19 spreads through direct contact between two individuals and thus transmits through population rapidly. Social distancing and lockdown strategy was aimed to reduce the size of the epidemic by limiting population mixing. Further, as per the report of WHO-China Joint
Mission on COVID-19, excessive physical distancing measures such as school and workplace shutdown, and preventing of public crowding all at once may result in increases in households cases. One study also reviewed the effectiveness of school closure in COVID-19 outbreak. Most of the affected countries implemented school closure because of the gravity of the disease. All these speculations were made based on previous pandemics of diseases like SARS, MERS and Influenza. However, according to Viner et al. modeling study, school closure would account the prevention of 2-4% of deaths only in case of COVID-19. Undoubtedly implementation of social distancing and lockdown resulted in the slow progression of disease across the globe (Fig. 4). The COVID-19 worst affected countries showed 6% to 39.6% decrease in the average daily rate of growth in cases after 3 weeks lockdown in comparison to before lockdown conditions.

**Age, Gender and underlying diseases**

Available data on COVID-19 cases suggested the lowest cases in children than elderly people. As per data from China, no morbidity has been reported under the age of 9 whereas only 0.2% fatality rate was observed in the age group of 10-19. The US States showed 0.04% of total deaths in the age group of 0-17 years. A similar pattern was observed in India also. Although lower numbers of cases have been reported in children yet it is not clear that if they are less susceptible or express mild symptoms of the disease. Moreover, the low occurrence of co-morbid diseases in children may be another factor.

The death rate was found to be augmented with increasing age as people of age group 60-80 has death rate range 23% to 47.7%. Further people with a pre-existing illness such as diabetes, cardiovascular disease, cancer, respiratory disease and hypertension put people at more risk of dying. Though men and women showed an equal number of cases, yet gender-based vulnerability was also observed in COVID-19 cases. The data of 15 countries (Fig. 5) showed mortality rate in men 1.3 to 3 times higher than women. Assumptions made for same includes higher smoking, drinking habits in men leads to co-morbid diseases, less exposure to women due to cultural, societal and work nature. A study of 331 COVID-19 patients was undertaken by Zeng et al. in Wuhan China to compare the difference of SARS-CoV-2 IgG antibody between male and female. The results evidenced a higher level of IgG antibodies in female than male patients. Further generation of IgG antibodies was found to be augmented in the early stage of disease in females.

**Treatment**

No effective treatment therapy has been developed for novel emerged COVID-19 disease caused by SARS-CoV-2 till now. Most of the SARS-CoV-2 critical patients have been given rescue treatment with oxygen support and convalescent plasma and immunoglobulin G therapy. Several therapeutic strategies such as plasma therapy, monoclonal antibodies, intravenous immunoglobulins, combinatorial therapy and repurposing of drugs have been explored for SARS-CoV-2 infections. Each of these therapies has some drawbacks and in some cases toxicities prevailed over benefits. Interferons (IFN) are known to plan an important role during viral infection by activation of innate immune response. Use of exogenous IFN for treatment of coronaviruses was firstly carried out in 1983. In case of SARS-CoV-2, China has carried out trials to treat patients with INF-α and ribavirin as a combination therapy. In another study dose-dependent IFNs inhibited SARS-CoV-2 in two mammalian epithelial cell lines (human Calu-3 and simian Vero E6). The results showed inhibition of SARS-CoV-1 only by IFN-alpha in these cell lines Whereas SARS-CoV-2 displayed a wider IFN sensitivity than SARS-CoV-1. For SARS-CoV-2, limited in vivo studies with IFN has been carried out so far and need further studies to conclude.

Several herbal compounds such as Glycyrrhizin, Baicalin, Escin and Resperine isolated from liquorice roots, Scutellaria baicalensis, horse chestnut and Rauwolfia spp. respectively also showed anti-coronaviral activity. Glycyrrhizin and escin showed antiviral activity against SARS-CoV. However, the mechanism of glycyrrhizin against SARS-CoV remained unclear. Baicalin (flavanoid) and risperidone (alkaloid) also showed in vitro antiviral activity against SARS-CoV. Therefore herbal medicines were tested to enhance the immunity against COVID-19. In China, a herbal formula with three herbs Scutellaria baicalensis, honeysuckle, and forsythia used to treat various diseases was also explored for the treatment of COVID-19 in a clinical trial. The preliminary results showed effectiveness yet further studies are required for validation. Further according to Unani traditional system, Jamia Hamdard, New Delhi recommended use of specific drugs/agents loban (Styrax benzoides W. G. Craib), sandroos (Hymenaea verrucosa Gaertn.), Za’fran (Crocus sativus L.), and vinegar to augment immunity. Apart from this, Indian Ayurvedic system suggested few practices such as regular intake of warm water throughout the day, practising breathing exercises & yoga, steam inhalation use of some spices (black pepper, clove, ginger, turmeric & garlic), nasally applying oil in alleviating COVID symptoms.

Various Nucleoside analogues are known for their antiviral activity. A mechanism for antiviral activity may account for interference in replication, decrease in transcription rate and fidelity etc. It has been found that only some nucleotide inhibitors were able to inhibit replication of coronaviruses. Nucleotide inhibitors such as favipiravir, Remdesivir and ribavirin, have shown in vitro inhibitory activity against SARS-CoV-2. Remdesivir (1’-cyano-substituted adenosine nucleotide) has been found to treat SARS-CoV-2 case suc-
cessfully in US\textsuperscript{69}. Another drug that has been explored for the treatment of SARS-CoV-2 infections is chloroquine/hydroxychloroquine purposed for the treatment of malaria. The mode of action of chloroquine/hydroxychloroquine against SARS-CoV-2 is not very clear and probably works by blocking viral entry into cells by inhibiting glycanss linking to host receptors, proteolytic processing, endosomal acidification and immunomodulatory effects (↓TNF-α and IL-6 production)\textsuperscript{69}. Combination of chloroquine with Remdesivir has been found effective in inhibition of SARS-CoV-2. Similarly, in a study with 6 patients’ combination of chloroquine with azithromycin showed better virus clearance (100%) than chloroquine (57%) as a single treatment drug\textsuperscript{60}. However, contradictory results have been received for use of chloroquine/hydroxychloroquine for treatment and more studies are required for establishing the relation between drug dosage and toxicity, use of the drug for prophylaxis or post infection treatment \textsuperscript{60}. It has also been observed that the use of protease inhibitors lopinavir/ritonavir decreased viral load in SARS-CoV-2 patients in Korea significantly\textsuperscript{61}. Ribavirin when used in combination of Lopinavir/Ritonavir reduced chances of acute respiratory distress syndrome in patients in addition to the low mortality rate of virus-infected patients\textsuperscript{62,63}. In an open-label trial with lopinavir/ritonavir was given as 400/100 mg orally/12 hours, no improvement has been observed in comparison to standard care\textsuperscript{64}.

Few other drugs such as avermectin (antiparasitic) and dexamethasone (corticosteroids) has also shown anti SARS-CoV-2 activity\textsuperscript{65,66}. However use of steroids in COVID-19 patients was recommended only with supplemental oxygen and artificial ventilation\textsuperscript{65}. Plasma therapy is another treatment strategy employed for treatment of SARS-CoV-2. Plasma therapy was initially used for treatment of Ebola and MERS outbreak in year 2014 and 2015 respectively. Plasma therapy works as an alternative treatment when antivirals do not work for an infection. In a study with 10 critical COVID patients by Duan et al.\textsuperscript{67}, a single dose of convalescent plasma (200ml) acquired from COVID recovered patients reported neutralizing antibody titers more than 1:640 and 70% patients became free from viremia. In a study by Shen et al on 5 patients with severe COVID infections, viral load decreased within a few days on the administration of convalescent plasma\textsuperscript{68}. These studies open the possibility for the prospective use of convalescent plasma therapy for the treatment of SARS-CoV infected patients. Morphological and genomic studies of SARS-CoV-2 also reported around 66 new targets for drug development and probably will add more therapeutic agents for the treatment of SARS-CoV-2\textsuperscript{27}.

Research gaps yet to be addressed

The COVID-19 has turned out into pandemic with 31,002,904 cases and 961616 deaths till 20th Sep 2020 across the world. The rapidly spreading disease kept governments at their toes to alleviate the situation. The research community is trying hard to uncover the mystery of novel coronavirus. Because of above several studies have already been carried out for COVID-19 for virus morphology, genome structure and variations, survivability in different climatic conditions, the impact of disease in different age groups and gender vulnerability for the disease. However, various research gaps are yet to be filled to connect links. Controversy on origin and evolution is still going on and final stamping is awaited. Although research studies have almost revealed morphology, genome structure and variations in SARS-CoV-2, however, efficient therapeutics agents for treatment are still lacking. Vaccine developments are underway and reached in Phase I, II & III in many countries. The first vaccine, Sputnik V launched by Russia has shown side effects in about 14% volunteers. Till the full proof vaccine development for SARS-CoV-2, more studies should be conducted on the repurposing of existing drugs to use as preventive measure or cure. Studies carried out to check the effect of climate on COVID-19 occurrence were modelling based predictions. Results showed variations in outcomes, therefore real scale studies need to be done. The available data also indicated variations in susceptibility to COVID-19 in different blood groups, gender and age group. Limited studies have been reported to validate the results. Little is known about the factors involved (societal, cultural or physiological differences) for the lesser vulnerability of women and children to COVID-19. Uncertainty about the onset of infectiousness and the duration of the infectious period also made the situation difficult to handle. Further contact tracing of mild infection (asymptomatic) and knowing their contribution in transmissibility of disease is the utmost requirement at the moment.

CONCLUSION

SARS Co-V-2 emerged as a novel coronavirus belongs to betacoronavirus lineage. Structural variations have been observed majorly in spike glycoprotein, and few changes in accessory and nonstructural proteins. Change in spike protein binding capacity probably accounts for its high transmissibility and thus can be targeted for development of vaccine/antiviral drugs. Characterization and functions of nonstructural proteins and accessory proteins in SARS-CoV-2 are not completely understood. Till now no treatment could be developed for COVID-19 and increasing rate of infections and morbidity is a matter of concern. Social distancing, lockdown and adoption of safety measures such as mask-wearing, use of alcohol-based sanitizers, intake of lukewarm water and vitamin C rich foods have come out a way to minimize the rate of infection and transmission. Also, lockdown provided time to national and international governments for medical preparedness. Besides social distancing and lockdown, contact tracing, number of tests carried out also played an impor-
tant role in reducing transmission and death toll. Apart from maintaining low infection level, efforts should be made to increase natural immunity, develop the culture to minimize the occurrence of forthcoming zoonotic diseases.

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Figure 1: Human Coronaviruses known till date².

Figure 2: Structure of Coronavirus¹³.
**Figure 3:** Genome organization and variations observed in non-structural protein (nsp), structural protein (S, E, M & N) and accessory proteins of SARS-CoV-2 in comparison to SARS-CoV.\(^{48}\)

**Figure 4:** Effect of three weeks lockdown on COVID-19 worst-affected countries.\(^{44}\)

**Figure 5:** Comparison of % COVID-19 cases incidence and morbidity rate between male and female in different countries.\(^{44}\)
Table 1: Comparison of structural properties of SARS-CoV, MERS-CoV and novel emergent strain SARS-CoV-2^{4,21}

| S. No. | Structural component          | SARS-CoV | MERS-CoV | SARS-CoV-2 (COVID-19) |
|-------|-------------------------------|----------|----------|----------------------|
| 1.    | Genome size                   | ~29.8 kb | ~30-31 kb| ~29.8 kb             |
| 2.    | ORFs                          | 14       | 10       | 14                   |
| 3.    | Structural proteins           |          |          |                      |
|       | *Spike surface Glycoprotein (S)* |         |          |                      |
|       | Binds to Angiotensin converting enzyme 2 (ACE2) or rarely to GD2096 as receptor | | Binds to dipeptidyl peptidase 4 (DPP4 aka CD26) receptor | Binds to Angiotensin converting enzyme 2 (ACE2) receptor |
|       | *Small Envelope protein (E)*  | Present  | Present  | Present              |
|       | *Matrix Protein (M)*          | Present  | Present  | Present              |
|       | *Nucleocapsid protein (N)*    | Present  | Present  | Present              |
| 4.    | Accessory proteins            |          |          |                      |
|       | 3a, 3b, 6, 7a, 7b, 8a, 8b, 9b | 3a, 4a, 4b, and 5 | 3b- Made up of 154 amino acids | 3b- Made up of 22 amino acids |
|       | 8b- Made up of 84 amino acids |          |          | 8a- absent 8b         |
|       | 8b- Made up of 121 amino acids|          |          |                      |
| 5.    | Non structural proteins (nsp1, nsp2, nsp3, nsp4, nsp5, nsp6, nsp7, nsp8, nsp9, nsp10, nsp11, nsp12, nsp13, nsp14, nsp15, nsp16) | 16 nsp\_s | 16 nsp\_s | 16 nsp\_s |

Table 2: Summary of SARS-CoV and SARS-CoV-2 accessory proteins and their functions (Narayanan et al., 2008; Liu et al., 2014)^{20,21}

| Accessory Protein | SARS- CoV | SARS- CoV-2 | Functions in SARS CoV |
|-------------------|-----------|-------------|-----------------------|
| 3a                | present   | present     | • Interacts with caveolin-1 during virus uptake and release  |
|                   |           |             | • Activates PERK pathway in the UPR  |
|                   |           |             | • Activates p38 kinase, NF-κB, JNK and IL-8 production  |
|                   |           |             | • Induces RANTES  |
|                   |           |             | • Induction of apoptosis and cell cycle arrest  |
| 3b                | present   | present     | • Inhibition of Type I IFN production  |
|                   |           |             | • Inhibition of Mitochondrial antiviral response  |
|                   |           |             | • Inhibition of signalling  |
|                   |           |             | • Induction of apoptosis  |
|                   |           |             | • Cell cycle arrest  |
| p6                | present   | present     | • Stimulates DNA synthesis  |
|                   |           |             | • Suppresses the expression of co-transfected plasmids  |
|                   |           |             | • Type I IFN production and signaling inhibition.  |
| 7a                | present   | present     | • Host translation inhibition  |
|                   |           |             | • Apoptosis induction and cell cycle arrest.  |
|                   |           |             | • Activates NF-κB and JNK for IL-8 and RANTES production  |
|                   |           |             | • Activates p38 and inhibits translation of cellular proteins  |
| 7b                | present   | present     | • Function not characterized fully probably helps in replication  |
| 8a                | present   | -           | • Induces caspase-dependent apoptosis  |
| 8b                | present   | present     | • Stimulates cellular DNA synthesis  |
| 9b                | present   | present     | • Undergo ubiquitination.  |
| orf14             | -         | present     | • Function not known  |
### Table 3: Summary of drugs experimented for treatment of SARS-CoV-2

| Drugs                        | Mechanism of action                                                                 | Dose used in clinical trials                                                                 | References |
|------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------|
| **Antiviral Agents**         |                                                                                     |                                                                                             |            |
| Lopinavir/Ritonavir          | 3 CL protease                                                                        | (400/100 mg orally every 12 hours for 14 days)                                               | 59,69, 70, 71 |
| Remdesivir                   | RNA polymerase inhibitor                                                              | 200 mg/dose OD IV for 1 day followed by 100 mg/dose OD IV for the next 4–9 days              | 72         |
| Favipiravir                  | RNA polymerase inhibitor                                                              | 1600 mg/per dose (orally) twice in a day for day 1, followed by 600 mg/dose (orally) twice in a day until the end of the trial | 73         |
| Oseltamivir*                 | Neuraminidase inhibitor                                                               | 300 mg orally daily, 75 mg orally once or twice daily, and 4–6 mg/kg orally (frequency not specified). | 74         |
| **Immunomodulatory drugs**  |                                                                                     |                                                                                             |            |
| Chloroquine phosphate        | Inhibition of of viral entry by preventing glycosylation of host receptors, proteolytic cleavage, and endosomal acidification. Modulation of immunogenic response by inhibiting cytokine production. In addition inhibition of autophagy followed by lysosomal activity in host cell occurs | 200 mg/dose (orally) thrice in a day for 5 days                                               | 76, 77, 78 |
| Hydroxychloroquine sulfate   | Mechanism same as of Chloroquine mechanism of action as chloroquine                  | Hydroxychloroquine: 200 mg (orally) thrice in a day for 10 days; Azithromycin: 500 mg (orally) for day 1; 250 mg daily for next 4 days | 79         |
| Chloroquine+ Azithromycin    | In addition to effect of chloroquine, azithromycin probably alleviate inflammation and modulate the immune system | Hydroxychloroquine: 200 mg (orally) thrice in a day for 10 days; Azithromycin: 500 mg (orally) for day 1; 250 mg daily for next 4 days | 79         |
| **Antiinflammatory drugs**   |                                                                                     |                                                                                             |            |
| Tocilizumab                  | IL-6 receptor Inhibition                                                              | 4–8 mg/kg intravenous diluted in normal saline (single dose)                                 | 81, 82     |
| Sarilumab                    | IL-6 receptor Inhibition                                                              | Single dose Intravenous                                                                     | 83         |
| **Immunoglobulins**          |                                                                                     |                                                                                             |            |
| Immune Globulinn (IGIV, IVIG, γ-globulin) | Provide passive immunity, suppress the virus and modulate the immune response to COVID-19 infection | 0.3–0.5 g/kg daily for 3–5 days                                                              | 84         |