



Review Paper

## Coronavirus disease 2019: A clinical review

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### Abstract

*Coronavirus Disease or COVID 19 is a public health emergency caused by SARS-CoV-2. The virus is causing a pandemic with death tolls increasing at an alarming rate. It is mainly a respiratory disease that affects also affects the other systems. The disease spreads via fomites and patient presents with common symptoms of cough and cold. In this review I have reviewed the epidemiology of the disease, virus taxonomy and properties, its infectivity and transmission, risk factors, case definitions and severity of disease, clinical presentations, investigations, laboratory findings, treatment and prevention.*

**Keywords:** Coronavirus, disease.

### Introduction

The coronavirus disease (COVID 19) is caused by the novel coronavirus Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). The virus has caused a global pandemic and is a serious public health threat. Till now cases have been rising sharply and overwhelming deaths occurring all over the world. Identifying the pathophysiology of the disease and how the viral acts on the human body will not only help in finding a cure for the disease, but also prevent future pandemics as such.

### Epidemiology

The first case was detected on December 2019 as patients were getting admitted in the hospital with history of unknown cases of pneumonia in Wuhan City, Hubei, China. On January 1<sup>st</sup> 2020 the Whole sale market which was suspected to be the source of the coronavirus was suspended. On the 7<sup>th</sup> of January a virus was extracted from the patients and identified. The etiological agent was identified and named by the International Committee on Taxonomy of Viruses as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). And after that cases has been rising sharply all around the world. Strict lockdowns and public movement restrictions reduced the steep rise of cases. Still cases continue to rise. On March 11 2020 WHO declared COVID 19 as a pandemic. As of 5<sup>th</sup> August 2020 18,142,718 confirmed cases with 691,013 deaths all over the world.

Case definitions for surveillance and disease severity has been defined by the WHO, but most likely those are temporary and further modifications will be seen in the near future as further study is done on the epidemiology and pathogenesis of the disease<sup>1,2</sup>.

**The Virus: Taxonomy:** i. Realm- Riboviria, ii. Order- Nidovirales, iii. Family- Coronaviridae, iv. Subfamily- Coronavirinae, v. Genus- Betacoronavirus, vi. Subgenus- Serbecovirus, vii. Species- Severe Acute Respiratory Syndrome-related coronavirus<sup>3</sup>.

**The Virus: Properties:** The SARS-CoV-2 is a positive stranded RNA virus. It is an enveloped virus. The genome encodes four major structural proteins: the spike (S) protein, membrane (M) protein, envelope (E) protein, nucleocapsid (N) protein.

### Pathogenesis

SARS-CoV-2 like other members of the SARS like coronavirus species mainly affects the respiratory system. The pathogenicity of the virus depends on the virulence of the organism and the degree of resistance offered by the host (that is how much good is the immune response to the pathogen). The Coronavirus has certain proteins on its surface called the 'S' proteins also known as the envelope "spike protein". Its structure is quite similar to S protein in SARS-CoV, although at some points few amino sequence has been altered, but studies have shown that affinity of host receptors to S protein has not been altered much. Roujian Lu et al in his study of the COVID 19 genetic sequence of nine patients found out 99.98% similarity in their sequence. On study he found out that the genomic sequence of 2019-nCoV were similar to SARS like CoV, (namely bat-SL-CoVZC45 and bat-SL-CoVZXC21) about 88% and around 79% with SARS CoV and 50% with MERS CoV. Although 2019-nCoV is quite different from SARS CoV on genetic sequence but both have similar receptor binding domain structure<sup>4</sup>. The S protein has two parts S1 and S2. S1 is responsible for receptor binding and S2 for cell membrane fusion. Roujian Lu et al in his study found out the sequence homology between SARS-CoV and SARS-

CoV-2 and reported that SARS-CoV-2 S2 has higher degree of homology with SARS-CoV than S1 protein and has 50 Amino acid similarities with other Coronavirus mostly in S1<sup>4</sup>.

S protein of coronavirus interacts with ACE2 (Angiotensin Converting Enzyme 2) receptor present in the host cells<sup>5</sup>. ACE2 receptors are abundantly found in the lung alveolar epithelium, intestinal epithelial cells of intestine, walls of the vascular smooth muscles (both arteries and veins). ACE2 receptors are mostly abundant in type 2 pneumocytes of the lung. The virus then enters the cell after binding to ACE2 receptors. After entering the host cells it grows and multiplies there.

## Interferons

Interferons are a group of signaling proteins belonging to the class of proteins known as cytokines. They are produced in the host cells when it itself gets infected by a virus, to communicate to other cells. In case of viruses type 1 Interferon (INF-1) is secreted. INF-1 stimulates Interferon Stimulated Genes (ISGs) that provides anti-viral properties to host cells.

## Immune Evasion and Cytokine Storm

SARS-CoV-2 had evolved in such a way that it has learnt ways to evade the induction of IFN-1.

Plasmacytoid dendritic cells (pDCs) get activated as a result uncontrolled activation of immune responses. Increased level of proinflammatory cytokines (TNF $\alpha$ , GSCF, MCP1, IP10, IFN- $\alpha$  and IFN- $\beta$ , IL2, IL7, IL6, IL1 $\beta$ ) and chemokines (CCL2, CCL7, CCL12)<sup>6</sup>. This uncontrolled release of cytokines is known as cytokine storm<sup>7</sup>.

## Infectivity and Transmission

The virus is considered to be highly infectious with an  $R_0$  of 2.2.  $R_0$  is the measure that determines the degree of infectivity of an individual that is how many of the susceptible individuals can be infected by an infected individual<sup>8</sup>. But Y. Liu et al studies determined its value to be 3.28<sup>9</sup>. The infection spreads from human to human via fomites from an infected individual whether symptomatic or not. When the person coughs or sneezes the virus loaded droplets are released into the air which when inhaled can cause the infection. Faeco-oral transmission is also noted among subjects. High viral load was found in the stool samples<sup>10</sup>. Vertical transmission from mother to child have been also found<sup>11</sup>. The virus was also found to be viable and alive on active surfaces. On the surface of paper it remains viable up to 3 hours, in wood up to 2 day, in cloth up to 2 days, in banknote up to 4 days and in plastic up to 7 days<sup>12</sup>.

The incubation period has been found out to be roughly 5.2 days (but it's quite variable ranging from 2 to 14 days)<sup>13,14</sup>.

**Risk Factors:** People with the following medical conditions are at an increased risk are-Male (>65years), Smokers, Cancer,

Chronic Kidney Disease, Respiratory Diseases (like-COPD, Asthma, Cystic Fibrosis), Cardiovascular Disease, Diabetes, Hypertension<sup>15</sup>.

**Clinical Manifestations:** SARS-CoV-2 is a respiratory virus just like other corona viruses. It enters the respiratory tract via oropharynx and produces the clinical symptoms like common cold. Most patients remain asymptomatic hardly producing the symptoms. Usually patients present with cough, sore throat and fever. Some patients develop rhinorrhoea, nasal blockage, anosmia, sore throat at an early stage. Later they develop other systemic responses like fever, anorexia, and muscle pain. General Manifestations patients present with are-Fever, Shivering, Lethargy, and anorexia. Respiratory symptoms noted are -cough, expectoration (not all few develop at a later stage), chest tightness, dyspnea, nasal obstruction, hyposmia or anosmia, rhinorrhea, sore throat, taste impairment.

The virus can affect the nervous system directly or indirectly via haematogenous route. Neurological symptoms include both peripheral and central nervous system. Central nervous system symptoms such as dizziness and headache. And Peripheral such as Facial Pain, Smell impairment, Taste impairment<sup>16</sup>. Musculoskeletal is also affected. Myalgia is quite a common manifestation. Gastrointestinal manifestations include -Pain Abdomen, Vomiting, Nausea, Diarrhoea. This Proves that coronavirus not only affects the respiratory system but also affects the other systems, signifying that other places must have ACE2 receptors for binding to<sup>17-24</sup>.

**Investigation:** All suspected patients should be tested for SARS-CoV-2. For this purpose swab from oropharynx or nasopharynx is preferably taken. If the result is negative but patient is under clinical suspicion expectorant is taken or in case of ventilated patient bronchoalveolar lavage or endotracheal aspirate is taken. The viral antigen is then tested by RT-PCR (Reverse Transcription Polymerase Chain Reaction)<sup>1</sup>.

Rapid Testing kits are being tested and made. FDA has currently approved one such kit<sup>25,26</sup>.

## Laboratory Findings

COVID 19 patients had common laboratory findings persistent in all studies. Haematological findings were decrease in the following parameters haemoglobin percentage, eosinophil Count, platelet count, lymphocyte count, leukocyte count, crp, esr, serum ferritin. And elevated wbc count and neutrophil count.

Liver Function Test were normal initially, at a later stage they were deranged indicating liver injury. Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), Total Bilirubin were raised. Albumin is exclusively produced and synthesised in liver, so a damage in liver denotes a decrease in albumin level in blood. Here albumin levels were found to decrease.

Renal Function Test including Blood Urea Nitrogen (BUN) and Creatinine were found to be raised.

Other tests done were LDH CKMB and Creatine Kinase and Cardiac Troponin were found to be raised. Procalcitonin was also found to have been raised.

Coagulation Study found out that D-Dimer, Fibrin Degraded Product (FDP), Prothrombintime (PT), APTT are higher in patients after death compared to morbid patients. Also Fibrinogen was found to be decreased<sup>18,19,21,22,27-29</sup>.

**Prognosis:** Most patients remain asymptomatic. Of all symptomatic patients most developed fever cough and dyspnea, but progressively heal. Although among those infected few needed to be admitted in ICUs around 10-20%. And patients requiring ventilation support via intubation is 3-10%<sup>30</sup>.

And few developed conditions such as severe dyspnea, hypoxemia, pneumonia, ARDS, arrhythmia, acute cardiac injury, shock, respiratory failure and MODS. Mortality rate is 2 to 5%.

Prognosis is worsened if any of the comorbidities are present.

## Treatment

Currently no definite treatment is available for COVID 19. Symptomatic treatment is given and as per clinical case. Supportive treatment in the form of fluids, oxygen and secondary infections is the main stay of treatment.

Drugs under trial are-

**RNA polymerase inhibitors:** Remdesivir, Favipiravir, Ribavirin are currently being tested and evaluated. As structural similarities have been found out between SARS-CoV and SARS-CoV-2 so drugs that are efficient against SARS-CoV are being tested<sup>31-33</sup>.

**Antimalarial Drugs:** In vitro tests of chloroquine and hydroxychloroquine has been demonstrated to show beneficial data against SARS-CoV-2. Originally these drugs are licensed to be use in malaria treatment and in autoimmune diseases like rheumatoid arthritis. But recent studies had shown that administration of these drugs has not shown any benefits in patients<sup>34,35</sup>.

**RAS Blockers:** Renin Angiotensin System is could actually found to be protective against COVID 19<sup>36</sup>.

**Protease Inhibitors:** Protease inhibitors like Lopinavir are being tried. Various trials have found Lopinavir/Ritonavir combination to be quite useful<sup>37</sup>.

**Anti-inflammatory drugs:** Various anti-inflammatory drugs have been used to suppress the symptoms in case of cytokine storm<sup>38</sup>.

**Plasma therapy:** Passive immunization with the help convalescent sera of patients recovered from SARS-CoV-2 is being tested<sup>39</sup>.

Most of the above mentioned drugs or treatment strategies are under trial and not recommended as per WHO.

## Prevention and control

The WHO and governments all over the world are currently working and making guidelines for precautionary measures, exposure prevention, disinfection protocols for minimising the spread of the virus. A real time emphasis is being given on active and passive screening of cases and contact tracing of suspected individuals<sup>40</sup>. Testing of suspected individuals and isolation or quarantine them is the key to limit the transmission of the disease. Various measures such as maintaining social distancing, avoiding crowded places, wearing face masks, regularly hand washing with soap and water or using a alcohol based hand sanitizer, avoid touching face, eyes, nose, mouth could help to limit the spread of the disease. Vaccines are under being developed and are under clinical trial. Following rules of government regarding COVID 19 as per protocol.

## Conclusion

COVID 19 is a continuing global threat a public health emergency. In the last two decades 3 highly contagious and infective coronavirus has evolved. Each one of them having the potential to cause a pandemic. The pandemic taught us humans the importance of research and its implementation. In the long run we need to learn from mistakes and make health a priority.

Rapid advances in the understanding of the virus and its pathogenesis detection and treatment strategies are the key. All possible drugs old and new should be thought of to find quick solutions. Early detection and prompt treatment can save lives. This virus poses a serious threat to not only the health but also has devastating impacts on economy and lives in general. Post pandemic it will take a long time to get things back to pre-pandemic times. In the meantime precaution and helping the front line workers and supporting them is the only main stay of treatment.

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