



Pathogenesis, Epidemiology, and Clinical Features among SARS-CoV-2 and Associated Diseases: An Editorial

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A new human coronavirus virus emerged in Wuhan, the city of China in December 2019 named novel coronavirus (SARS-CoV-2). Currently, this coronavirus becomes a pandemic and affects most of the countries worldwide. Presently (as of 3 June 2020) 6287771 confirmed cases and 379941 deaths have been reported globally according to WHO data [1]. The clinical syndrome of coronavirus associated with SARS-CoV-2 infection; is categorized by respiratory illness ranging from upper respiratory tract from the common cold to fatal pneumonia and severe acute respiratory distress syndrome (ARDS) [2].

In this editorial, we aim to analyses the differences or character regarding theses following features (pathogenesis, epidemiology, and clinical features) among COVID-19, SARS-2, and other associated diseases.

From the total 7 coronaviruses, 4 human coronavirus produces mild symptoms, and 3 of them produce symptoms which are potentially severe in humans, caused major outbreaks of respiratory

syndrome globally in 21st century [3]. First is SARS-CoV2, β -CoV is a novel coronavirus identified as the cause of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China in late 2019 and on 31 December 2019, the outbreak found to a novel strain and later become a pandemic. Second, the MERS-CoV (Middle East respiratory syndrome) was identified in September 2012 in Saudi Arabia as the cause of (MERS) [3]. The third one is SARS-CoV was identified in 2003 as the cause of an outbreak of severe acute respiratory syndrome (SARS) that began before Asia [4].

Even though SARS-CoV-2 belongs to the same genus Betacoronavirus as the coronaviruses responsible for the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) also belongs to the same genus but (SARS-CoV and MERS-CoV, respectively), this novel coronavirus resembles to be associated with milder infections. Furthermore, SARS and MERS were viruses associated mainly with nosocomial spread, whereas SARS-CoV-2 or novel coronavirus is extensively transmitted in the community [5].

Disease	Outbreaks	Phylogenetic origin	Receptor	Case fatality rate	Deaths	Sex-ratio (M: F)	Ro
SARS-CoV-2	2019-2020	Clade I, cluster IIa	Angiotensin-converting enzyme2 (ACE2)	2.3%(5)	6545492(6)	1:6:1(8)	2 - 2.5 (10)
SARS-CoV-2	2002-2004	Claudia, cluster IIb	Angiotensin-converting enzyme2 (ACE2)	9.5%	774(7)	0:8:1(9)	1.7 - 1.9
MERS-CoV	2012, 2015, 2018	Clade 11	Dipeptidyl peptidase4 (DPP4)	34.4%	858	3:3:1	0.7

Table 1: General phylogenetic, clinical, and epidemiological features of SARS-CoV-2, SARS-CoV, and MERS-CoV.

Early initial cases of COVID-19 were found in Wuhan, China live in an animal market, suggesting that the virus was initially transmitted from animals (bats) to humans. Based on current evidence, novel coronavirus is primarily spread between people through respiratory droplets and contact routes [11] but it also occurs via contaminated surface through the transmission of small droplets.

Transmission of droplets occurs when a person is in close distance (within 1m) with a person who has respiratory symptoms (e.g., coughing or sneezing) and is, therefore, the other person mouth, nose, and eyes at higher risk of exposing to potentially infective respiratory droplets [12]. Transmission can be possible via all three cases patients' symptomatic, asymptomatic, and presymptomatic patients. As a result, the transmission of the COVID-19 virus can occur by direct contact method with infected people and indirect contact methods with surfaces in the immediate infected environment or with objects used on the infected person (e.g. table or instruments). The novel coronavirus seems more transmissible than SARS [13].

About coronavirus airborne transmission is different from droplet transmission as it shows the presence of microbes within droplet nuclei, which are generally considered to be particles size range 5 µm in diameter can sustain in the air for long periods and can also be transmitted distances over greater than 1m [13].

Many successful attempts were taken to limit the local, regional, and global spread of this pandemic. Strict steps to these measures have been successful at controlling the spread of infection in some contaminated zone. W.H.O. also emphasizes the utmost importance of frequent hand wash, respiratory etiquette, hygiene, and disinfection, as well as give the guidelines of the importance of maintaining social distances and prevention of close, unprotected contact with people with symptoms of fever or other respiratory problems.

The symptoms of COVID-19 and other acute respiratory syndromes are divided into two categories systemic and respiratory disorders. As systemic disorders are- fever, cough, fatigue, headache and muscle pain and major respiratory disorders are- rhinorrhoea, sneezing, sore throat, pneumonia, shortness of breath or difficulty breathing, chills or repeated shaking with chills, the new loss of smell or taste, vomiting and diarrhea [14]. A person having mild symptoms may not require hospitalization but the condition gets worse after 2 weeks of infection [15]. Some people become

infected but don't show any symptoms and don't feel unwell. In the case of COVID-19, respiratory disorders are more observed as compared to systemic disorders. Most people recover from the disease without getting any special treatment but it is crucial in case of older age and person suffering from chronic diseases like- heart, lung, kidney, or liver disease, diabetes, immune compromising conditions, or severe obesity (body mass index and gt; 40) which leads to multi-organ failure and death [16,17]. A person with fever, cough, and short breath or difficulty breathing should seek medical attention.

There are other several serious complications which included with COVID-19:

- Respiratory disorders like acute respiratory distress syndrome (ARDS).
- Heart disorders including arrhythmias, cardiomyopathy, and acute cardiac injury.
- Coagulation disorders like pulmonary emboli, disseminated intravascular coagulation (DIC), hemorrhage and arterial clot formation.
- Guillain-Barré syndrome (rare).
- Sepsis, shock, and multi-organ failure.

They are mentioned below:

- **Acute respiratory distress syndrome (ARDS):** When fluid filled in the alveoli of the lungs, which leads to the disturbance in the oxygen supply to the organs [18]. The fluid keeps the lungs filled with enough air that declines the transfer of oxygen in the bloodstream and also disturbs the functioning of organs. ARDS typically occurs in the people who are already suffering from critical injuries and its main symptom is shortness of the breath [19]. ARDS usually develop within 1 - 2 weeks of infection. Most people die as it damages the lungs, only a few recover completely. The seriousness of ARDS increases with age and severity of illness. ARDS is diagnosed by arterial blood gas measurement and chest x-ray.
- **Arrhythmias:** As the name "arrhythmias" it explains that disturbance in the regularity of the rhythm of the heartbeat. It means that the heartbeats either too quickly or too slow or with an irregular pattern. The heartbeats in the regular pattern because of the electrical impulses generated and spread by the myocytes. A sequence of organized myocardial contractions is triggered by unique electrical properties [20]. Various factors lead to the disturbance in the rhythm of the heartbeat

as heart disorders, such as- congenital abnormalities of structure (accessory atrioventricular connection) or function (hereditary ion channelopathies). Electrolyte abnormalities (particularly low potassium or magnesium), hypoxia (absence of enough oxygen), hormonal imbalances (hypothyroidism, hyperthyroidism), and drugs and toxins (alcohol and caffeine) are some systemic factors that cause or contribute to arrhythmia [21].

- **Cardiomyopathy:** Cardiomyopathy is an acquired or hereditary disease of the heart muscle. It is a group of diseases that cause the heart muscle to become enlarged, thick, or rigid which makes it harder for the heart to pump blood to the rest of the body [22]. The main symptoms are breathlessness, swollen legs and feet, and a bloated stomach. Cardiomyopathy can lead to heart failure. Treatment for the cardiomyopathy might include- medications, surgically implanted devices, or various cases, a heart transplant that depends on the type and seriousness of the cardiomyopathy [23].
- **Pulmonary emboli:** Pulmonary emboli occur in one of the pulmonary arteries in the lungs in which substances block

the blood flow to the lungs [24]. It can damage the lungs and other organs or decrease the oxygen levels in the blood. Substances that block the pulmonary artery travel from the other part of the body, especially from the legs [25]. Symptoms of pulmonary emboli include- shortness of the breath, chest pain particularly upon breathing in, coughing up blood, and mild fever. Pulmonary emboli can be life-threatening, while treatment greatly reduces the risk of death. Many cases can lead to passing out, abnormally low blood pressure, and sudden death [26].

- **Disseminated intravascular coagulation (DIC):** Disseminated intravascular coagulation is a condition when some tissue factors are exposed to the blood and starts the coagulation pathway. Also, the fibrinolytic pathway is involved. Cytokines stimulate the endothelial cells and these endothelial cells release the tissue plasminogen Activator (tPA) due to disturbed microvascular blood flow. This tPA and plasminogen lead to cleavage of fibrin into D-dimers and other fibrin degraded products. In excessive cases, DIC causes both thrombosis and bleeding [27].

Sr. No.	Disease	Symptoms	Cause	Diagnosis	Treatment
1.	ARDS (acute respiratory distress syndrome)	Severe shortness of breath, Unusually rapid breath, Low blood pressure, confusion, and extreme tiredness.	Fluid-filled in the air sacs which leaked from the smallest blood vessels.	CT scan, Chest X-ray, Oxygen level, Heart test (electrocardiogram and echocardiogram).	Supplemental oxygen, Mechanical ventilation, Medication.
2.	Arrhythmias	A fluttering in the chest, A racing heartbeat (tachycardia), A slow heartbeat (bradycardia), Chest pain, shortness of breath, Fatigue, Anxiety, Dizziness, Sweating, Fainting or near fainting.	Congenital abnormalities of structure or function, Electrolyte abnormalities, Hypoxia, High blood pressure, Hormonal imbalances, Stress, Anxiety, Drugs, and toxins.	Electrocardiogram, Echocardiogram, Holter monitor, Implantable loop recorder, Stress test, Tilt table test, Electrophysiological testing, and mapping.	Pacemaker, Vagal maneuvers, Medications, Cardioversion, Catheter ablation.
3.	Cardiomyopathy	Breathlessness, Swollen legs, and feet, A bloated stomach, fatigue, Dizziness, Fainting, Cough while lying down.	Long-term high blood pressure, Heart tissue damage from a heart attack, Obesity, Thyroid, Diabetes, Chemotherapy, Pregnancy complications, Alcohol, and drugs.	Chest X-ray, Echocardiogram, treadmill stress test, Cardiac MRI, Cardiac CT scan, Blood tests, genetic testing, and screening.	Medication, Surgically implanted devices, a Heart transplant.
4.	Pulmonary emboli	Shortness of breath, Chest pain, Cough, Rapid or irregular heartbeat, dizziness, Excessive sweating, Fever, Leg pain, or swelling.	Fat from the marrow of a broken long bone, Part of the tumor, Air bubbles, Heart disease, Cancer, Surgery, Disorders that affect clotting.	Blood test, Chest X-ray, Ultrasound, CT pulmonary angiogram, MRI.	Medications, Surgery.

In other words, DIC causes the abnormal and excessive generation of thrombin and fibrin in the circulating blood. Along with this process increase in platelet aggregation and coagulation factor consumption observed. DIC evolves in two ways, slowly or rapidly. In slow growth, it evolves over weeks or months and it causes primarily venous thrombotic and embolic manifestations and rapid growth occurs over hours and days causes primarily bleeding.

Clinical circumstances responsible for the DIC (most common)

The entry of placental tissue with tissue factor activity or is exposed to the maternal circulation, saline-induced therapeutic abortion, and amniotic fluid embolism [27]. Infection caused by gram-negative bacteria: endotoxins released by gram-negative bacteria cause formation or exposure of tissue factor activity in phagocytic, endothelial, and tissue cells. Cancer, adenocarcinomas of the prostate, and acute promyelocytic leukemia: Tumor cells express tissue factor [27]. Severe tissue damage due to head trauma, burns, frostbite, or gunshot wounds an enzyme found in certain snake venoms converts fibrinogen into fibrin and activates several coagulation factors into the blood profound intravascular hemolysis [27]. There are two types of DIC; in slow growth, it was found the occurrence of symptoms of venous thrombosis or symptoms of pulmonary embolism. Whereas In fast-growing, skin punctures sites, bleed persistently, ecchymoses form at sites of parenteral injections, and serious GI bleeding was observed [27].

Diagnosis:

- Slowly evolving DIC produces
- Mild thrombocytopenia
- Normal to minimally prolonged PT (results are typically reported as the international normalized ratio [INR]) and PTT
- Normal or moderately reduced fibrinogen level
- Increased plasma D-dimer level
- Rapidly evolving DIC results in more severe thrombocytopenia
- More prolonged PT and PTT
- Rapidly declining plasma fibrinogen level
- High plasma D-dimer level.

Guillain-Barré Syndrome (GBS) (rare)

It is very rare in the case of COVID-19 infection and also known as Acute Idiopathic Polyneuritis; Acute Inflammatory Demyelin-

ating Polyradiculoneuropathy. Guillain-Barré syndrome is considered to be acute, generally rapidly progressive but self-limited inflammatory polyneuropathy [28]. The characteristics of GBS are muscular weaknesses and mild distal sensory loss. Their causes are not fully understood yet but it is considered to be autoimmune. Some studies reveal the hostile effects of immune checkpoint inhibitors responsible for the Guillain-Barré Syndrome. There are some common pathogens included for this syndrome like *Campylobacter jejuni*, enteric viruses, Herpesviruses (including cytomegalovirus and Epstein-Barr virus), *Mycoplasma* species [28].

In most of the patients, flaccid weakness was observed, this could be considered as most dominant over other symptoms like sensory abnormalities. This weakness begins from the legs and goes unto hands and head. This type of weakness could last long for 3 - 4 weeks. In some patients, the facial or oropharyngeal muscle was also found weaken, which directly or indirectly could lead to dehydration or undernutrition. Symptoms of respiratory paralysis were also observed on the very lower side of the scale. A very unusual variant was also found which cause ophthalmoparesis, ataxia, and areflexia [28].

Diagnosis

- Clinical evaluation
- Electrodiagnostic testing
- Cerebrospinal fluid (CSF) analysis.

Sepsis and septic shock

In general, sepsis is an organ dysfunction life-threatening clinical syndrome. Deregulated response to the infections could lead to sepsis. On the other hand septic shock is the failure of multiple organs, multiple organ dysfunction syndromes (MODS), like lungs, kidneys and liver. In the case of sepsis mortality rate varieties from moderate (10%) to significant (40%) [29]. It depends on the various factors like the type of various pathogens and host factors, time is taken in recognition and treatment. Sepsis shock is also a division of sepsis, where the mortality rate is increased sepsis shock mainly includes persistent hypotension. In most of the cases, sepsis shock was caused by gram-positive cocci and gram-negative bacilli in the patients suffering from immune compromise diseases and chronic diseases. In very rare cases it was found to cause by some fungi like *Candida*. Toxic shock syndrome is another unique form of this sepsis shock and it is resulted due to toxins caused by the staphylococcal and streptococcal strains [29]. Most common sites

observed for the cause of infection were lungs and the urinary, biliary and gastrointestinal tracts.

The complete mechanism of pathogenesis of septic shock is not fully resolved yet but there involved the inflammatory stimulus like bacterial toxins which cause the release of proinflammatory mediators like tumor necrosis factor (TNF) and interleukin (IL)-1 and some others like leukotrienes, lipoxygenase, histamine, bradykinin, serotonin, and IL-2 [30].

There a stage known as a warm shock that appears before the sepsis shock, it includes dilation and decreases peripheral resistance of arteries. Cardiac output increased which later on decrease with blood pressure fall. It resulted in decreased delivery of oxygen and the inability to remove the carbon dioxide and other waste and ends up on multiple organ dysfunction syndromes (MODS).

Symptoms and signs

In the early stages, there are no defined symptoms unique to sepsis. Blood pressure remains normal, maybe other signs of the infections present. Fever, the first very common sign or the early warning is the development of septic shock, blood pressure decreases, and extremities start to be pale and cold. Organ dysfunction is an additional and advanced symptom to observe.

Diagnosis

- Clinical manifestations
- Blood pressure, heart rate, oxygen monitoring.
- Complete blood count (CBC)
- Invasive central venous pressure [31].

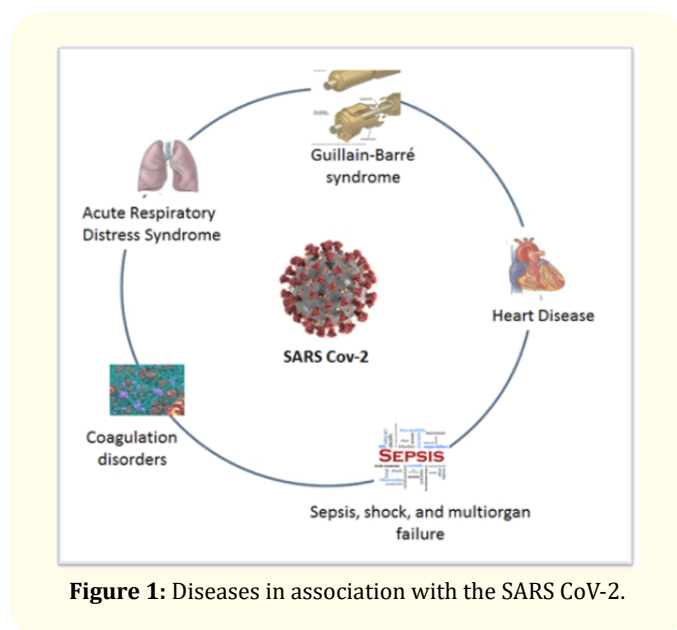


Figure 1: Diseases in association with the SARS CoV-2.

In this editorial COVID-19 characteristics, symptoms diagnosis, and treatment were discussed in detail. It was also observed that in most of the patients it is not showing any symptom at all. As it was considered a pandemic disease, we should also consider that the death rate of this disease is quite low. And the high probability of death happened due to COVID-19 of those patients who were either old or already suffering from any other disease. In this chapter, we discussed some other associated diseases with COVID-19 which was observed in patients suffering from coronavirus. Along with its infection, it makes the patient condition severe by increasing the severity of other diseases/infections discussed in this chapter. So, it can be concluded that patients with already suffering from any other disease need to be more protected. The infectious capacity of the coronavirus in a healthy body is the less and healthy immune system can treat it. So the precautions could be the one step, must be taken by an individual. Precautions like social distancing, quarantine, washing hands, and hygiene should be followed. Futuristic approach for this disease could be learning to live with most of the precautions, trying to avoid the social gathering and scientific approach is still going on towards it. Science labs worldwide are putting their efforts to develop vaccines or drugs as soon as possible.

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