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Analysis Of Symptoms And Severe Outcomes Of Covid-19

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Abstract- An outbreak of pneumonia, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) commonly known as COVID-19 started in Wuhan, China, in December 2019 has become a global pandemic. It has many similarities with Severe Acute Respiratory Syndrome Coronavirus(SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS).In this paper, analysis of severe complications observed in other organs is done. Comparison of immune response, various symptoms, general advisory and recovery status of patients in India is also observed.

Keywords – COVID-19, SARS-CoV-2, MERS, ACE2 receptors, Coronavirus, ARDS

I. INTRODUCTION

In December 2019, an outbreak of unfamiliar pneumonia was caused by a Corona virus infection known as COVID-19 (Corona virus disease 2019). Its high transmission rate led to a rapid increase in the number of cases and a worldwide outbreak. It was declared as a global pandemic by the WHO (World Health Organization) in March, 2020. SARS-CoV-2 (the pathogen that causes COVID-19) not only activates the antiviral immuneres ponses but can also cause uncontrolled inflammatory responses. There are many unidentified symptoms and serious implications of the virus. This paper aims to study some of the serious symptoms of COVID-19 to help understand their causes and work on treatments to curb them.

Coronaviruses

The outbreak of unidentified Pneumonia in December, 2019 was caused by a newly identified coronavirus initially termed 2019 Novel Coronavirus (COVID-19) and subsequently Severe Acute Respiratory Syndrome Coronavirus2 (SARS-CoV-2)[1]. Coronaviruses are a family of RNA viruses that primarily affect mammals and birds. But in the last few decades, they have also exhibited the ability to affect humans. Studies revealed that SARS-CoV-2 shares many similarities with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) that emerged in 2002–2003 and Middle East Respiratory Syndrome Coronavirus (MERS) that spread during 2012 - all three known to cause severe respiratory symptoms[2]. All these viruses contributed to global pandemics. SARS-CoV-2 has higher rates of transmission than SARS-CoV and MERS-CoV. Some of the main symptoms of COVID-19 are fatigue, fever, myalgia, cough, and lower respiratory signs.
Before understanding the severity of COVID-19 infection, it is important to understand the different stages/categories of COVID-19 infection:

First category- These individuals are infected by the virus, but act as carriers but may not exhibit the symptoms. These individuals are at a higher risk of spreading the virus as they might be oblivious to its presence.
Second category- Individuals with mild fever, cough, headache or possible conjunctivitis. This is due to an infection in the upper respiratory tract.

Third category- Similar to the second category, the symptoms here are more pronounced and might

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require hospitalization. Immediate treatment can help alleviate the symptoms and prevent a fatality.
Fourth category: Severe cases of COVID-19, might lead to ARDS and pneumonia. At this stage, it is fatal.

2.Dysregulation Of Immune Response In Patients With Covid-19

From the analysis of the table, the median age was 58 years (IQR (Interquartile Range), 47–67; range, 22–95 years) and 235 (52.0%) were men. When we compare the severity of infection on the basis of age, patients who had severe infection were significantly older (median age, 61 [IQR, 51–69] years vs. 53 [IQR, 41–62] years; P < .001). The percentage of men in the severe group (54.2% men) were not very different from that in non-severe group (48.2%). In the analysis, of the total 452 patients with COVID19, 201 (44.0%) patients had chronic diseases like hypertension, diabetes, chronic obstructive pulmonary disease etc.

A higher percentage in the severe cases (146 [51.0%]) is observed than in the mild cases (55 [33.1%]). The patients with severe infection were significantly more likely to have concomitant hypertension and cardiovascular diseases (36.7% vs. 18.1%; P < .001; and 8.4% vs. 1.8%; P = .004; respectively). From the table it is observed that the most common symptoms were fever (92.6%), shortness of breath (50.8%), expectoration (41.4%), fatigue (46.4%), dry cough (33.3%), and myalgia (21.4%). It is also observed that the patients with severe infection were significantly more likely to have shortness of breath and fatigue (58.4% vs. 39.2%; P < .001; and 51.4% vs. 39.2%; P = .014; respectively) as compared to the patients with non-severe infection[3].

	All Patients (N = 452)	Nonsevere (n = 166)	Severe (n = 286)	P
Characteristics				
Age, median (IQR), range, y	58 (47–67), 22–95	53 (41.25–62), 22–92	61 (51–69), 26–95	<.001
Sex				.242
Male	235 (52.0)	80 (48.2)	155 (54.2)	
Female	217 (48.0)	86 (51.8)	131 (45.8)	
Smoking	7 (1.5)	4 (2.4)	3 (1.0)	.267
Chronic medical illness				
Any	201 (44.0)	55 (33.1)	146 (51.0)	<.001
Chronic obstructive pulmonary disease	12 (2.6)	3 (1.8)	9 (3.1)	.548
Hypertension	135 (29.5)	30 (18.1)	105 (36.7)	<.001
Cardiovascular disease	27 (5.9)	3 (1.8)	24 (8.4)	.004
Cerebrovascular disease	11 (2.4)	3 (1.8)	8 (2.8)	.753
Chronic liver disease	6 (1.3)	3 (1.8)	3 (1.0)	.674
Diabetes	75 (16.4)	22 (13.3)	53 (18.5)	.152
Tuberculosis	9 (19.7)	2 (1.2)	7 (2.4)	.496
Malignant tumor	14 (3.1)	4 (2.4)	10 (3.5)	.587
Chronic kidney disease	10 (2.2)	4 (2.4)	6 (2.1)	1.000
Signs and symptoms				
Fever	423 (92.6)	152 (91.6)	271 (94.8)	.232
Dry cough	152 (33.3)	56 (33.7)	96 (33.6)	1.000
Expectoration	189 (41.4)	68 (41.0)	121 (42.3)	.843
Hemoptysis	12 (2.6)	2 (1.2)	10 (3.5)	.225
Shortness of breath	232 (50.8)	65 (39.2)	167 (58.4)	<.001
Myalgia	98 (21.4)	32 (19.3)	66 (23.1)	.407
Confusion	3 (0.7)	0 (0.0)	3 (1.0)	.301
Headache	52 (11.4)	13 (7.8)	39 (13.6)	.068
Dizziness	37 (8.1)	9 (5.4)	28 (9.8)	.112
Fatigue	212 (46.4)	65 (39.2)	147 (51.4)	.014
Rhinorrhea	8 (1.8)	2 (1.2)	6 (2.1)	.716
Pharyngalgia	22 (4.8)	10 (6.0)	12 (4.2)	.376
Anorexia	96 (21.0)	30 (18.1)	66 (23.1)	.234
Nausea and vomiting	42 (9.2)	10 (6.0)	32 (11.2)	.092
Diarrhea	122 (26.7)	44 (26.5)	78 (27.3)	.913
Abdominal pain	23 (5.0)	4 (2.4)	19 (6.6)	.073

Data are median (IQR), n (%), in which N is the total number of patients with available data. *P* values comparing severe and nonsevere cases are derived from χ^2 test, Fisher' exact test, or Mann-Whitney *U* test.
Abbreviations: COVID-19, coronavirus 2019; IQR, interquartile range.

Table 1: Characteristics observed in COVID-19 patients.

The severity of COVID-19 was judged according to the Fifth Revised Trial Version of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance [4]. Those who met the following criteria were defined as having severe-type infection: (1) respiratory distress with a respiratory rate over 30 breaths per minute, (2) oxygen saturation ≤93% in the resting state, and (3) arterial blood oxygen partial pressure (PaO2) /oxygen concentration (FiO2) ≤300 mm Hg

3.**SYMPTOMS OF COVID 19**

COVID 19 is a new virus and the symptoms experienced are different for different people. The doctors and researchers are still learning new things about the virus every day. Signs of COVID 19 may appear in 2 to 14 days, also called the incubation period (time after exposure and before developing symptoms).

Moreover, the severity of COVID-19 symptoms can range from very mild to very severe. In fact, some people may have only a few symptoms, others have no symptoms at all whereas others might experience worsened symptoms like worsened shortness of breath and pneumonia.The risk of seriousness of illness from COVID-19 increases with age. People

with existing chronic medical conditions also may have a higher risk of serious illness.

Common signs and symptoms can include: fever, cough, tiredness and early symptoms may include a loss of taste or smell[5]. Other symptoms include: shortness of breath or difficulty breathing, muscle aches, chills, sore throat, runny nose, headache, chest pain, pink eye (conjunctivitis). Some unusual symptoms include[5]:

Gastro intestinal symptoms. COVID-19 might cause mild gastrointestinal symptoms, including a loss of appetite, nausea, vomiting and diarrhoea which might only last for a day.

- **Skin changes.** Some younger people who have less severe COVID-19 might develop painful, itchy lesions on their hands and feet which is sometimes called COVID toes. This symptom typically lasts about 12 days.
- **Confusion.** COVID-19 also has been reported to cause confusion in older people, especially those with severe infections.
- **Loss of smell or taste.** COVID-19 might cause a new loss of smell or taste — without nasal congestion which lasts for nine to 14 days.
- **Eye problems.** COVID-19 may cause eye problems like enlarged, red blood vessels, swollen eyelids, excessive watering and increased discharge which are more common in people with severe infections. Older people and people with serious medical conditions are the ones to experience lingering COVID19 symptoms like: fatigue, shortness of breath, cough, joint pain, chest pain which may last for long term. Other symptoms may include: muscle pain or headache, fast or pounding heartbeat, loss of smell or taste, memory, concentration or sleep problems and even rash or hair loss.

4.Severe Outcomes In Patients With Covid-19

Although COVID-19 is primarily considered a respiratory syndrome that may cause severe hypoxemia and pneumonia, other organs including the lungs, GI tract, liver, heart and pancreas are affected.

5.1Liver Injury

Several studies have reported different intensities of liver test abnormalities,mostly in severe cases of COVID-19 [6]. Liver problems in patients with COVID-19 could be a result of viral infection of liver cells. Some COVID-19 patients (about 2-10%) have presented with diarrhoea and SARS-CoV-2 RNA has been detected in blood and stool samples[7]. It shows the possibility of viral exposure in the liver. It has been hypothesised that SARS-CoV-2 may directly enter the liver cells through ACE2 receptor, which is expressed in the bile duct and liver cells [8]. Studies have shown the presence of ACE2 receptor in cholangiocytes, indicating that ACE2 receptor may bind directly with the cholangiocytes and cause liver damage. Liver impairment could also be partly due to drug hepatotoxicity. Various drugs which are being used currently to treat COVID-19 like ribavirin and hydroxychloroquine sulfate are metabolised in the liver. They may cause hepatoxicity and induce liver damage, further impairing metabolism [6]. COVID-19-related complications such as respiratory distress syndrome, multiple organ damage, and systemic inflammatory response syndrome can induce hypoxia and shock in patients. This could lead to hypoxia-reperfusion dysfunction and hepatic ischemia [6]. Therefore, liver test markers, specificallyGGT and AST should be monitored regularly during hospitalisation.

5.2Coagulopathy

Evidence-based on numerous studies have shown that coagulation disorder is common in patients infected with COVID-19(SARS-CoV2), and its incidence is higher in severe cases[9]. Many patients are developing blood clots, including clots in small vessels, pulmonary embolisms, deep vein thromboses in the legs, and stroke-causing clots in cerebral arteries. These symptoms have been observed in patients despite putting them on blood thinners, in accordance with standard intensive care practice. Cuiet al investigated asymptomatic ICU patients for thrombosis byultrasonography and reported the incidence was 25% (20/81) [10].The incidence of thrombosis and major thromboembolic sequelaein COVID-19 ICU patients is reported to be 20% to 30% [11].

On conducting analyses of lung and other clot-filled tissue from COVID-19 cases, it was observed that the clots in small blood vessels result in the deposition of immune molecules called complement proteins [12]. Complement proteins are capable of mobilizing other elements of the immune system, leading to a hyper-inflamed state. They can also injure or kill infected cells and can promote the formation of blood clots while still hindering natural clot-preventing factors in the blood [13]. So, it is possible that the virus itself may be directly setting off an immune cascade that results in clotting. On conducting research on five patients of different age

groups and symptoms, it was perceived that there is an 8-9 days interval between the first occurrence of COVID-19 symptoms in a patient and worsening of symptoms to the extent where the patient needs to be admitted [12]. In cases with mild or moderate symptoms, the patient's natural immune defenses and control mechanisms regulate the complement and coagulation responses within that 8-9 days interval. Information about coagulopathy in COVID-19 patients is still evolving. Since bleeding complication has been extremely rare in COVID-19, standard anticoagulant therapy can strongly be recommended [13].

1.3Cardiovascular:

COVID-19 infection may lead to abnormalities of the heart rhythm, weakening of the heart muscle (through inflammation or direct invasion of the heart muscle cells and lead to significant heart failure), and even cause clot formation in blood vessels. ACE2 stands for Angiotensin-converting enzyme 2. It is a membrane bound amino peptidase which has a very important role in the immune as well as cardiovascular systems[14]. Moreover, ACE2 has been identified as a functional receptor for coronaviruses[14]. SARS-CoV-2 enters by binding of the spike protein of the virus to ACE2, which issignificantly expressed in the lungs and heart. The respiratory symptoms in COVID-19 patients are a result of the invasion of SARS-CoV-2 into the alveolar epithelial cells. Acute Cardiac Injury Reports suggest that acute my ocarditis and heart failure can be caused by MERS-CoV (Middle East respiratory syndrome-related coronavirus) [15].

It has been observed that MERS-CoV and SARS-CoV-2 displays similar pathogenicity, and the myocardial damage caused by infection with these viruses increases the challenges of patient treatment. Chronic cardiovascular damage from SARS-CoV On conducting a 12 year-long follow-up survey of 25 SARS-CoV patients post recovery, it was observed that 44% of the patients developed cardiovascular system abnormalities, 60% suffered from glucose metabolism disorders and 68% had hyper lipidaemia[16]. Given that SARS- CoV and SARS-CoV-2 show structural similarity, it can be said that COVID-19 virus could also cause chronic damage to the cardiovascular system. Therefore, attention towards cardiovascular protection during treatment for COVID-19 is important. If a person gets infected with SARS-CoV-2, the chances of occurring of cardiac insufficiency are more, which leads to worsening in the condition of the patients.

5.4 Pancreatic Injury

In a study by Kaafarani et al., 74% (104/141) of the critically ill patients developed at least one gastrointestinal complication including hepatic necrosis, bowel ischemia requiring emergent surgery and bowel resection and Ogilvie-like syndrome with a very high (40%) postoperative mortality [17]. Extrapulmonary manifestations and symptoms are not well understood yet. Wang et al. earlier reported a 17% incidence of pancreatic injury among 52 patients with COVID-19 pneumonia [18]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have an affinity for the pancreas. This is because angiotensin-converting enzyme 2 (ACE2) receptor is expressed in the pancreas, both in the exocrine glands and islet cells [19]. Thus, the direct cytopathic effect of SARS-CoV-2 can lead to pancreatic injury. It is necessary to perform accurate diagnosis in COVID-19 patients for the same. Atlanta classification, which requires at least two of the given three criteria, could be used to perform diagnosis for pancreatic injury [20]:

(1) typical abdominal pain,

(2) serum amylase or lipase > 3 times the upper normal limit, and

(3) characteristic findings on diagnostic imaging

5.5 Lungs

Effect on lungs- COVID can cause lasting lung damage. This can not only lead to short term but also long-term problems. It is observed that COVID 19 primarily infects the lungs in the affected individuals and in some severe cases it can lead to various lung complication like pneumonia, ARDS and even sepsis which may even cause death[21]. In the majority of the cases i.e. 80% will exhibit mild symptoms, 14% will have pneumonia, 5% will suffer from septic shock and organ failure (mostly respiratory failure) and in 2% cases it will be fatal. ACE2 mediates SARS-CoV-2 infection Taking entry into host cells is the first step of a viral infection. A spike glycoprotein present on the viral envelope of the coronavirus can bind to specific receptors on the membrane of host cells. It has been shown through previous studies that ACE2 is a specific functional receptor for SARS-CoV[22]. Zhou et al. showed that SARS-CoV-2 can enter ACE2-expressing cells, but not cells without ACE2 or cells expressing other coronavirus receptors, confirming that ACE2 is the cell receptor for SARS-CoV-2 [24]. Further studies

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showed that the binding affinity of the SARS-CoV-2 spike glycoprotein to ACE2 is 10- to 20-fold higher than that of SARS-CoV to ACE2 [23].

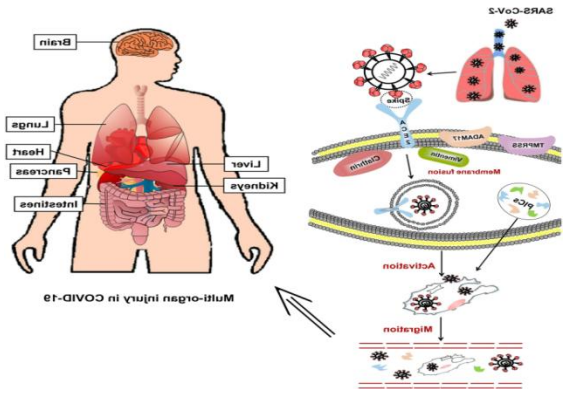

Fig1: SARS-CoV-2 enters lung cells via the ACE2 receptor. The cell-free and macrophage-phagocytosed virus can spread to other organs and infect ACE2-expressing cells at local sites, causing multi-organ injury.

Pneumonia- The sever outcomes of COVIDcan be Pneumonia [21], i.e. caused in lungs. SARS-CoV-2 enters the lungs, where the spike glycoprotein of the virus binds to ACE2 on cells, allowing the virus enter thoughalveoli (tiny air sacs). Through this, the air sacs get damaged and there is an influx of liquid leading to inflammation.This further hinders the oxygen and carbon dioxide exchange and also impairs the oxygen intake by the lungs. Hence the oxygen level in the patients gets reduced. This leads to hospitalisation of the patient and they may require oxygen and even ventilators in severe cases.

ARDS- ARDS, Acute Respiratory Distress Syndrome causes dry cough, heavy breathing, breathing difficulties and increased heart rate. Severe cases of COVID 19 infection leads to ARDS and pneumonia which shows that there is a direct correlation between COVID 19 and ARDS. In most healthy individuals it can be treated with medications and eventually the patients recover but in severe cases, where the infected person has an impaired immunity due to underlying health conditions, an infection due to COVID 19 can lead to severe ARDS. Once the patient progresses to ARDS, it eventually leads to pneumonia. ARDS can cause severe effect on lungs. The virus directly impacts the lungs and damages the alveoli. The alveolus transfers oxygen to blood vessels which carry the oxygen to the RBCs (Red blood cells) and these RBCs finally deliver the oxygen to all the internal organs. The virus damages the wall and the lining of the alveolus and capillaries, the walls thickens and the transfer of oxygen to RBC is impaired and causes breathing difficulty and hence body runs short of oxygen.

Recovery Status Of Patients In India

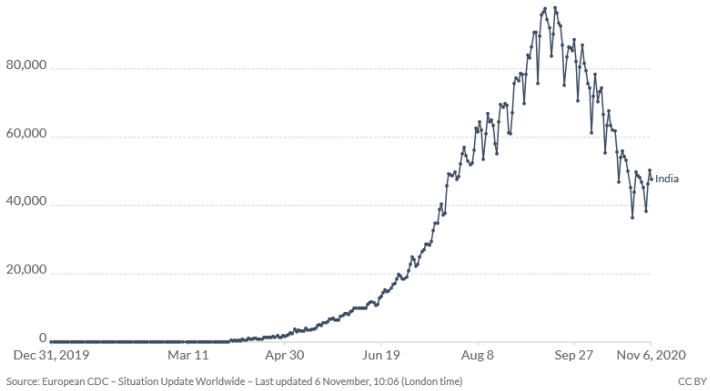

Fig. 2: COVID-19 situation in India, as of Nov 6, 2020. Source: European CDC

Almost 60 Lakhs of COVID-19 patients in India have recovered and thus the gap between the active cases & recoveries are augmenting on the daily basis. As per the Graph the India's corona virus infection situation is on a continual decline. As per the data of the health ministry, Maharashtra & Karnataka are still reporting very high numbers of active cases more than 11000 cases per day.

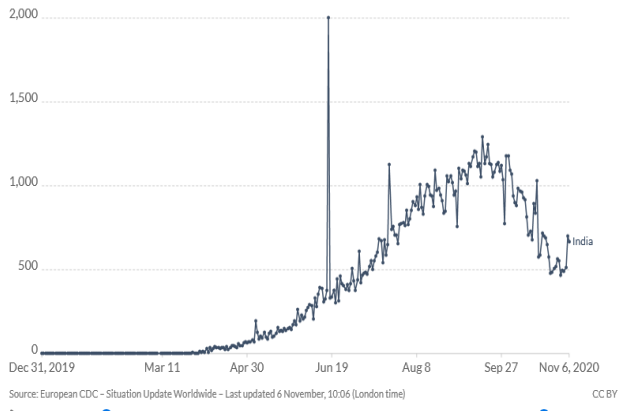

Fig. 3:Death rate inCOVID-19 patients in India, as of Nov 6, 2020. Source: European CDC

Across country 58% of the COVID-19 related deaths are reported from 25 Districts of eight states i.e. Maharashtra, Karnataka, West Bengal, Gujarat, Tamil Nadu, Punjab, UP & Andhra Pradesh. As per the reports of the National Centre for Disease Control has raised the concerns that in the winter season the

prevalence of respiratory illnesses gets multifolds and it may significantly worsen the during this season this may cause a spurt in the active cases from the state like Delhi where daily active cases may even be reported around 15000 per day. It was noted that during the Onam & Ganesh Chaturthi pandemic situation has deteriorated in states like Kerala & Maharashtra. Thus, during the upcoming festivals like Chhat, Diwali, Eid, Christmas & New year pandemic situation may become worse.

VII. GENERAL ADVISORY FOR PREVENTION OF COVID-19

1. Maintain social distancing to reduce transmission of the virus by keeping at least 1-metre distance from others.
2. Wear a mask whenever coming in contact with anyone or while at a public place.
3. Since the transmission of COVID-19 takes place through sneezing, coughing etc., it is safer to avoid public places or physical contact with anyone.
4. Maintain proper personal hygiene by washing hands properly with soap and water. While in public settings, prefer using alcohol-based hand rub.
5. Make sure to regularly disinfect or clean surfaces that are regularly in contact.
6. If any of the symptoms are observed, it is advised for the person to self-isolate. If the symptoms persist, the person should get tested.

DISCUSSIONS

So many researches have been done since the outbreak and are being done till date for the better understanding of the virus, its affects in long term to the human body, complications and scientists and researchers are working on medicines and vaccines. Although COVID-19 is a Respiratory Syndrome, it has proven to affect other organs like heart, liver and the pancreas. Our understanding of the interaction between SARS-CoV-2 and pancreas is limited at present. So, extensive research should be done for the same. It will help in formulating management strategies to deal with the current pandemic.

The severity and complication COVID-19 among older people >65 is more as compared to a healthy person and needs to be discussed. Moreover, the issues of missing data about deaths, ages and outcomes, hospitalization, ICU admission are missing for quite a percentage which can lead to underestimation of outcomes. Besides this, follow-up time needed to ascertain outcomes among active cases is equally important. Also, the data on risk factors, risk of complications with time needs to be analysed.

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