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A pathophysiological review on understanding multiorgan effects of COVID-19

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Abstract: COVID-19, the global pandemic affecting economic developments has been regarded as severe pulmonary dysfunction disease. The disease has caused significant mortalities all around the world. The reports suggest that major reason for patients' death are multiple organ failure, sudden cardiac arrest, severe respiratory dysfunction and body shock. These clinical conditions are majorly linked with COVID-19 comorbidities which are severely affecting disease severity. The present study describes pathophysiological findings associated with multiorgan effect of COVID-19. The study describes possible transmission route of the virus, responsible for gastro intestinal problems. The review of pathophysiological findings in COVID-19 provides a perspective to focus our therapeutic research strategies towards controlling the effect of pathogenic virus on indirectly targeted body organs. The present study will help in controlling disease morbidities as well as preventing long term effects of COVID-19.

Keywords: COVID-19, comorbidities, gastrointestinal effect, multiorgan effect, Pathophysiology.

1. INTRODUCTION:

COVID-19 has hampered our day to day lives and affected the global economy at alarming levels. Wuhan, China became epicenter of this novel, fatal pulmonary disease called coronavirus disease (COVID-19) which began in late December of 2019 [1]. Several evidences support the fact that the virus is of zoonotic capability, causing animal to human disease spread originating from wild animals trading in Hunan seafood market of Wuhan. Although specific data supporting the fact is not clear but genome sequence studies have suggested 'bats' as natural origin of the virus. After the first human case of the disease, human to human transmission is driving the spread of the disease. The major key factors involved in the transmission are based on aerosol as vehicle for transmission. The droplets released during coughing, sneezing or any mucosal contact is causing spread of the disease. It is speculated that there can be faecal to oral transmission as viral genetic material has been detected in stool samples along with progressing symptoms of gastrointestinal tract [2]. Such studies have posed the need to rethink about the course of research being followed which is mostly focused on pulmonary targets.

Although, severe form of disease is associated with deaths due to lung damage and progressive respiratory failure [3] , the virus is invading other organs as multi organ failure reports have been observed. Thus, the disease has demonstrated a spectrum of clinical observations including asymptomatic, pneumonic, respiratory dysfunction, sepsis and even multiple organ dysfunctions. However, there exists scarcity of pathological reports of COVID-19 patients due to inaccessible autopsy.

2. BACKGROUND

COVID-19 is a pulmonary disease caused by a virus named SARS-CoV-2. The disease has been characterized as pulmonary syndrome due to disease symptoms and pathological conditions observed in patients. SARS-CoV-2 is RNA virus which is member of Coronaviridae family, which is characteristically known for human infections. The family consists of four strains of low pathogenicity and two other strains which have previously caused fatal respiratory disorder SARS-CoV and middle east respiratory syndrome (MERS-CoV) [4]. The coronavirus-2019 (SARS-CoV-2) has 79% genome sequence identity with SARS-CoV and 50% genome sequence similar to MERS-CoV. The viruses also share common lung epithelial cells receptor angiotensin –converting enzyme 2 receptor (ACE-2). The receptor is also expressed in other organs such as heart, kidney, intestines, which further makes the multi organ effect of the virus technically feasible.

The disease has challenged the capacity of national health care systems. The national governments have circulated mandatory precautionary measures essential for disease prevention. The step is extremely necessary for encompassing the upcoming disease spread under the capacity of available health care. Figure 1 shows that lack of preventive measures can cause the situation to explode out of the control of health care facilities. Also, appropriate preventive measures of social distancing can help in controlling the situation. With the course of time, health care facilities are decreasing because of health workers being affected by the disease or need for their isolation due to long term exposure to disease causing situations. Further, multi-organ effect of the virus has posed additional burden on health facilities. Thus flattening of COVID-19 case curve is necessary to keep the situation under control when health care capacities are concerned.

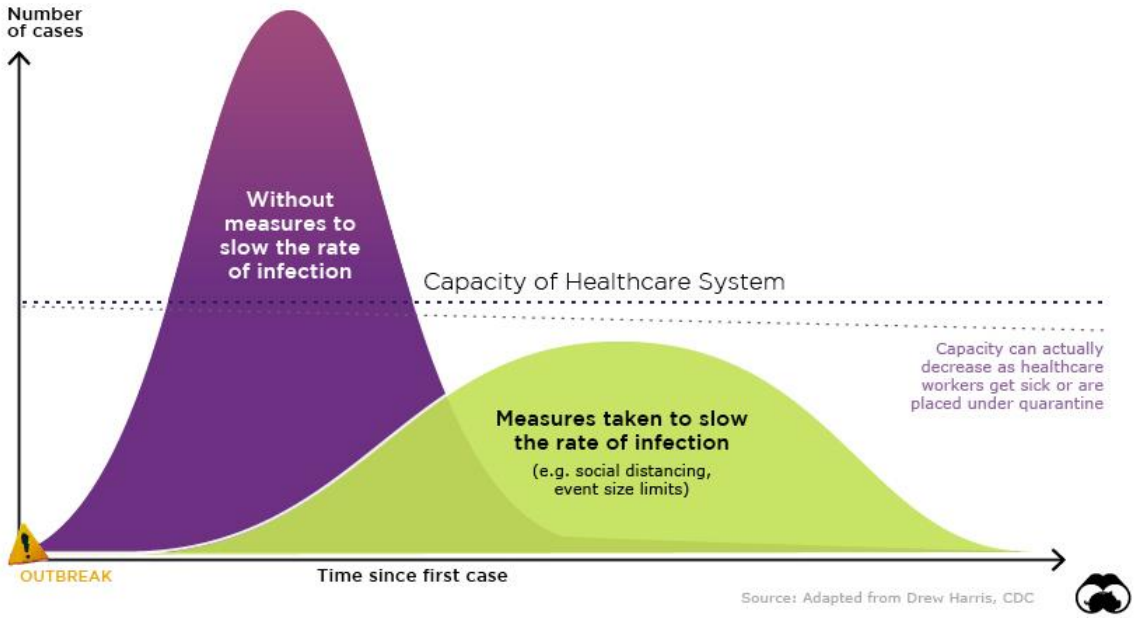

Figure 1: Importance of COVID-19 curve flattening. In order to control the disease situation, fewer burdens should be implicated on health care systems. (Adapted from Drew Harris, CDC)

3. PATHOLOGICAL VIEW OF CORONAVIRUS DISEASE – 2019

3.1 Pulmonary effect

The major symptoms of the disease are related to lungs and other pulmonary functions. The common clinical manifestation of the disease involves pneumonia characterized by flu symptoms like cough, fever, dyspnea. Further, biopsies of people who died from the severe infection have been evaluated to observe the viral effect on lungs. Zhe et al. performed postmortem biopsies and investigated pathological features of patients who died from severe infection. The person was an old age man (50 year) who complained of fever in late January 2020, with travel history to Wuhan. The disease confirmation was made on ninth day of illness. Even after medications, his fever reduced but severe cough continued. On fourteen day of illness, shortness of breath worsened and there was sudden cardiac arrest. Even after immediate ventilation, chest compression, the patient rescue was not successful.

Patient's biopsy samples were taken and histological examination revealed bilateral alveolar damage with exudates of cellular fibroid (Figure 1A, B). The right lung showed desquamation of pneumocytes and hyaline membrane formation, which are characteristics of acute respiratory distress syndrome (ARDS, Figure 1A). Pulmonary oedema was observed in left lung tissue along with hyaline membrane formation which further supports ARDS. Mononuclear inflammatory infiltrates were observed interstitially, also dominated by lymphocytes in both lungs [5]. It is reported that people who die of COVID-19 usually have at least one underlying disease apart from COVID. Several patients have shown elevated white blood counts with disease severity and lymphocytopenia was observed in all of them except the patient with leukemia [6]. According to radiographic images of chest CT scan and X-ray, all patients had bilateral pneumonia with ground-glass opacity (GGO, Figure 3). Consolidations appeared with time, specifically at disease severity.

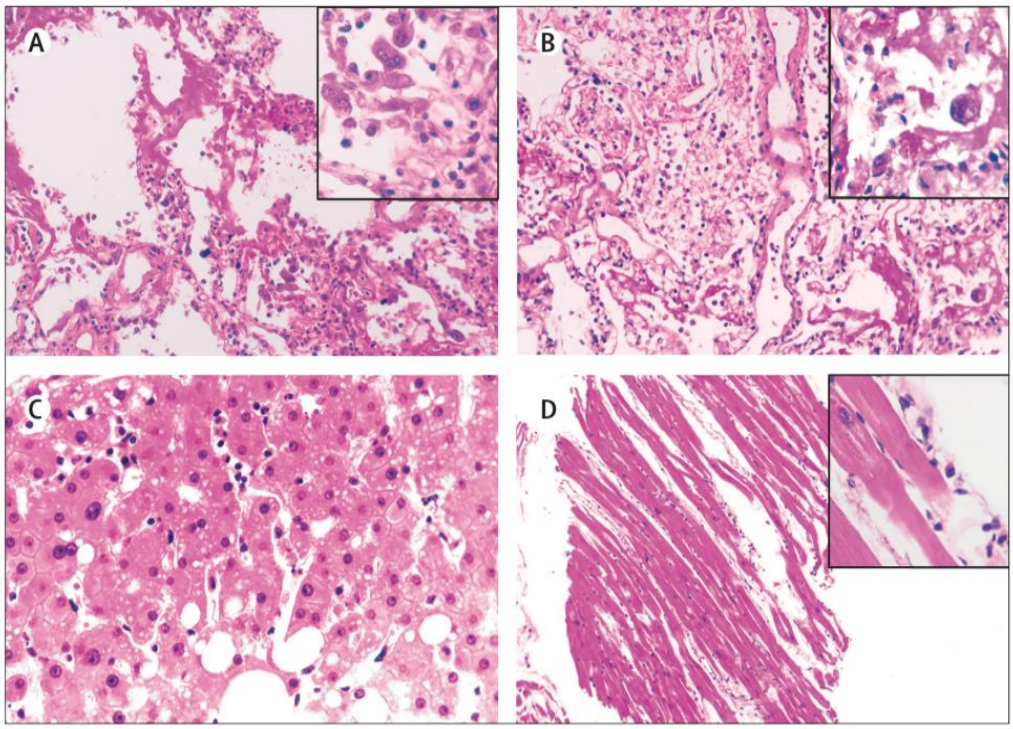

Figure 2: Pathological characteristics of A) right lung tissue B) left lung tissue C) liver tissue D) heart tissue of patient severely affected by COVID-19 [5].

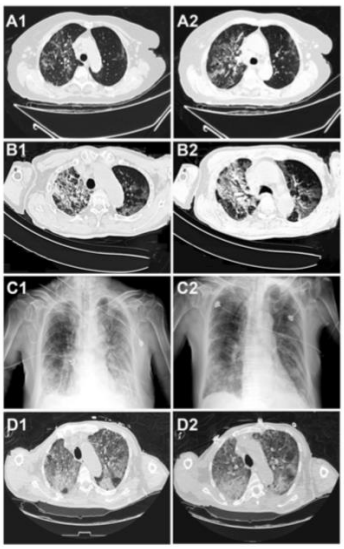

Figure 3: Radiographic image of chest CT scan and X-ray of COVID-19 patients. Left and right images show earlier and latter time points, respectively [5].

3.2 Cardiovascular effect

The infection caused by virus has been reported to cause systemic inflammation and over expression of immune system key players leading to cytokine storm, causing organ failure. Severely affected people have shown several cardiovascular injuries with a delay between disease symptoms and pathological implications on cardiac tissue. The patients with disease history of cardiovascular disease and hypertension have higher mortality rate than others [7]. The disease can cause mayocarditis, arrhythmia and heart failure even in case of acute form of the disease. The pathogenic receptor ACE2 is prevalent in heart tissue providing susceptibility to myocardial infection. The rise in cytokine levels can cause instability to atherosclerotic plaque, causing possibilities of myocardial infarction [8]. Other problems associated with the disease infection include blood pressure abnormalities, reduced ejection fraction, palpitations and heart enlargement [9]. Overall, studies suggest that cardiac problems occur due to inflammatory hyper secretions. Even the histological examination of heart tissue biopsy has shown interstitial mononuclear infiltrates present in diseased patients (Figure 2d). However, the causes behind these observations as the direct effect or indirect effect of viral infection cannot be marked out distinctively.

Table 1: Correlation between pathological manifestations observed in COVID-19 patients with severe long term cardiac problems [10].

Cardiac problems	**Pathological features of COVID-19**
Cardiac arrhythmia	Myocardial inflammation, atrial fibrillation, conduction block, ventricular tachycardia, ventricullar fibrillation
Myocardial injury and heart failure	Elevated serum creatine kinase, lactate dehydrogenase, high-sensitivity cardiac troponin
Myocarditis	myocyte necrosis and mononuclear cell infiltrates (Endomyocardial Biopsy)
Ischaemic heart disease	local microvascular inflammation, microvascular dysfunction

3.3 Renal effect of the disease

Among the symptoms of the disease COVID-19, some clinical cases have reported abrupt kidney function loss within 7 days of infection [11]. According to a study conducted by Li et al., kidney functioning was analysed in 193 COVID-19 patients, and problems of blodd urea nitrogen (31%), increased serum creatinine (22%), proteinuria (60%) and hematuria (48%) were observed [12]. Moreover it has been studied that patients with acute kidney injury have high mortality rate as compared to those without any kidney injury. Liver biopsy specimens of patients with COVID have shown microvesicular steatosis at moderate level along with portal activity, indicating that injury could be caused by the virus or drug used in COVID-19. According to another report, mild lobular infiltration by small lymphocytes and centrilobular sinusoidal dilation was observed in the liver along with patchy necrosis (Figure 2c) [6]. Figure 4 represents histological images of alterations observed in liver tissue highlighting infiltration by lymphocytes i hepatic cells, fibrosis in hepatic nodules and necrosis and hepatocytes.

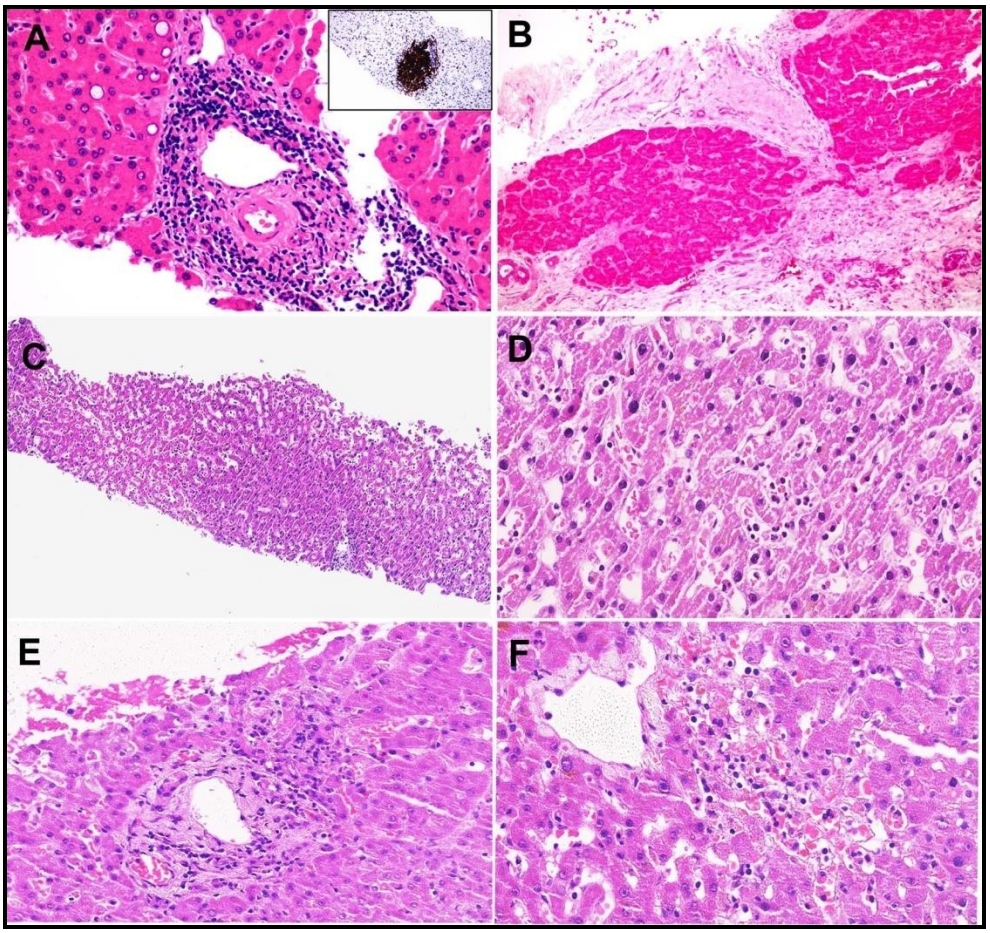

Figure 4. Histological analysis of post mortem biopsy samples of live tissue [6]. A) Lymphocytes with dense portal infiltration (insert image: CD20 immunostaining), and focal nuclei in hepatocytes B) thick fibrosis observed with cirrhotic nodules. C) & D) Normal and magnified view of sinusoidal lymphocytes. E) Focal hepatic necrosis in periportal zone. F) Focal hepatic necrosis majorly centrilobular necrosis.

3.4 Gastro intestinal effect of the disease

The presence of pathogenic virus in gastric tract can be attributed to the presence of ACE2 receptor in gastric cells. As shown in Figure 5A, ACE2 mRNA expression is very high in colon cells as compared to other cell types. This shows susceptibility of different organs to viral invasion. According to a study conducted on 204 COVID-19 patients, 50% patients reported symptoms related to their digestive system which includes diarrhea, vomiting, lack of appetite, abdomen pain. Among all the patients, six patients reported only digestive symptoms throughout the disease course [13]. The presence of SARS-CoV-2 RNA has also been reported in fecal samples of some patients. A study conducted by Wu and team observed that 55% of the patients in their study had RNA positive samples of faeces which continued for approximately 28 days, whereas RNA presence in their lungs samples was reported till 17 days [14]. These studies show that although the pathogenic virus can be cleared from pulmonary tract, it continues to sustain in gastric tract and can be transmitted through fecal excretion.

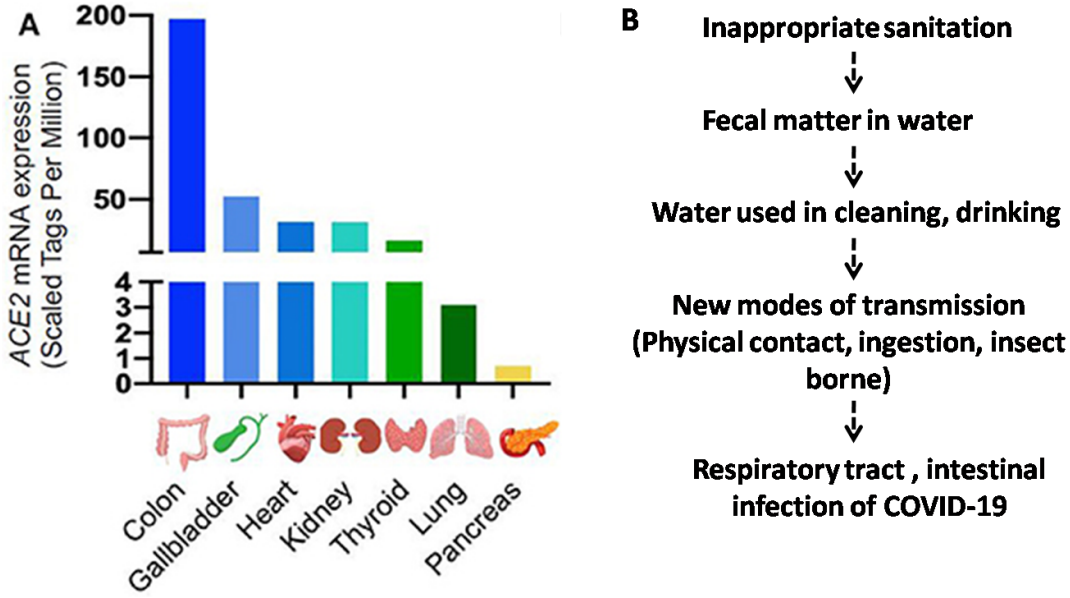

Figure 5: A) Expression of viral receptor angiotensin converting enzyme (ACE2) in different cell types. B) Possible process flow of coronavirus fecal to human transmission.

4. COMORBIDITIES AND DOUBLE EDGED HOST RESPONSE IN COVID-19

Disease symptoms observed in patients have been minimal at early phases which progress to severe respiratory failure and eventually multiple organ failure. The virus targets Angiotensin converting enzyme receptor (ACE2). This functional receptor for virus was actively expressed in lungs, heart, kidney and bladder [6] [15]. High expression of ACE2 on apical lung epithelial cells of alveolar space seems to be responsible for pulmonary ground glass opacification [16]. The virus infected lung epithelial cells produced IL-8 in addition to IL-6 as host response. IL-8 in turn attracts neutrophils and T-cells through chemical stimulus. That is why infiltration of inflammatory cells has been observed in lungs from severe COVID-19 patients, and groups of innate immune cells and adaptive immune cells exist in these inflammatory cells [17]. The majority of cells expected among innate immunity are Neutrophils. Neutrophils can affect the patient's body in positive as well as negative ways as it can induce injuries in different body organs [18].

The multi-organ effect of coronavirus has been deteriorating the disease condition in several patients. Along with symptoms of pneumonia, the mortality has been linked with

multiple organ failure, shock, sudden respiratory distress and renal failure [19]. Therefore it is required to pay attention towards comorbidities in treatment of COVID-19. Especially in old age patients, it is necessary to locate additional body comorbidities along with pneumonia. The patients should ideally be grouped on the basis of pre-existing diseases, COVID-19 comorbidities and drug treatments should be provided accordingly. Moreover, it is necessary that the research should be focus on the spectrum of multi organ injuries that can occur in COVID-19.

5. CONCLUSION

COVID-19 pandemic is a live issue affecting everyone's life worldwide. There are pathological findings in literature but without fundamental therapeutic interventions, the complexity of the disease cannot be tracked down to effective treatments. There is a growing need for targeted therapies based on understanding of pathological response. The mortality rate of disease is focus of concern. According to reports, disease mortality has been related to multiple organs dysfunction and multiorgan injuries observed in COVID-19 patients. The patients' death is mostly associated with sudden cardiac arrest, respiratory failure or shock. The present study describes pathophysiological findings associated with multiorgan effect of COVID-19. The study provides multiorgan based research perspective to control hyper inflammation effect on body organs. The study describes possible transmission route of the virus, responsible for gastro intestinal problems. Overall, it is time to focus our therapeutic research strategies towards controlling the effect of pathogenic virus on indirectly targeted body organs.

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