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An Overview on Multiorgan Complications of Novelcoronavirus

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ABSTRACT

Since the outbreak and rapid spread of COVID-19 starting late December 2019, it has been apparent thatdiseaseprognosishaslargelybeeninfluencedbymultiorgancomplications.Chronicitysuchascardiovascular diseases have been the most common risk factors for severity and mortality. The directeffectsofsevereacuterespiratorysyndromeonbody-wideorgansthroughACE2hasbeenassociatedwithintricacy of the disease. Acute respiratory syndrome, heart failure, renal failure, liver damage, shock, andmultiorgan failure have the reason due to death. Acknowledging the comorbidities and potential organinjuries throughout the study of COVID-19 is therefore essential in the clinical management of patients.Thispaperaimstoaddontotheever-emerginglandscapeofmedicalknowledgeonCOVID-19,encapsulatingits multiorgan impact.

KEYWORDS: Covid-19,SARS–CoV2,Multiorganintricacy

I. INTRODUCTION

Coronaviridae is a family of enveloped, positive-strand RNA viruses which infect amphibians, birds, and mammals[1]. The group includes the subfamilies Letovirinae and Ortho coronavirinae; the members of the latter are known as coronaviruses.COVID-19 is a disease caused by a new strain of coronavirus. Formerly,this disease was referred to as 2019 novel coronavirus‘ or 2019-nCoV.‘ The COVID-19 virus is a new virus linked to the same family of viruses as Severe Acute Respiratory Syndrome (SARS) and some types of common cold.Orthocoronavirinae - sub family Coronaviridae - family.They are enveloped viruses with a positive sense single-stranded RNA genome .The name corona virus is derived from the Latin coran, meaning “crown” or “halo”, which refers to the characteristic appearance reminiscent of a crown when viewed under electron microscopy, due to the surface covering in club-shaped protein spikes[2]. Corona viruses are classified Into three groups, initially based on antigenic relationships of the spike (S), membrane (M) and nucleocapsid (N) proteins and now re-enforced by viral genetic phylogeny V[3] .

HISTORY AND EVALUATION OF CORONA VIRUSCOVID-19

Coronaviruses are a big family of different viruses. Some of them cause the common cold in people. Others infect animals, including bats, camels, and cattlethenew coronavirus that causes COVID-19. Covid-19 first detected in Wuhan, China, in late 2019[4] Experts say SARS-CoV-2 originated in batsThat‘s also how the coronaviruses behind Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) got started. SARS-CoV-2 made the jump to humans at one of Wuhan‘s openair wet markets[5].They‘re where customers buy fresh meat and fish, including animals that are killed on the spot. Some wet markets sell wild or banned species like cobras, wild boars, and raccoon dogs. Crowded conditions can let viruses from different animals swap genes. Sometimes the virus changes so much it can start to infect and spread among peopleStill, the Wuhan market didn‘t sell bats at the time of the outbreak. That‘s why early suspicion also fell on pangolins, also called scaly anteaters, which are sold illegally in some markets in China[6]. Some coronaviruses that infect pangolins are similar to SARS-CoV-2. As SARS-CoV- 2 spread both inside and outside China, it infected people who, meaning that people are unwittingly catching and passing on the

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coronavirus. This growing worldwide transmission is what is now a pandemic[7].

EPIDEMIOLOGY OF COVID-19

On 29 December 2019, the first four cases of an acute respiratory syndrome of unknown etiology were reported in Wuhan City, Hubei Province, China among people linked to a local seafood market.Research is underway to understand more about transmissibility, severity, and other features associated with COVID-19. It appears that most of the early cases had some sort of contact history with the original seafood market Soon, a secondary source of infection was found to be humantohuman transmission via close contact. There was an increase of infected people with no history of exposure to wildlife or visiting Wuhan, and multiple cases of infection were detected among medical professionals. It became clearthat the COVID-19 infection occurs throughexposure to the virus, and both the immunosuppressed and normal population appear susceptible. Some studies have reported an age distribution of adult patients between 25 and 89 years old. Most adult patients were between 35 and 55 years old and there were fewer identified cases among children and infants .A study on early transmission dynamics of the virus reported the median age of patients to be 59 years, ranging from 15 to 89 years, with the majority (59%) being male. It was suggested that the population most at risk may be people with poorimmune function such as older people and those with renal and hepatic dysfunction[8]

COVID-19 A GLOBAL PANDEMIC

The COVID-19 pandemic has claimed over 900000 lives around the world and infected over 29 million individuals.

Coronavirus Cases- 230,571,146 (global)
Deaths - 4,726,897(global)
Recovered- 207,319,635 (global)[9]

COVID-19 IN INDIA

Total Coronavirus Cases in India-33,557,583
Total Coronavirus Deaths in India- 446,025
Total recovered in India-32,802,416

COVID-19 IN KERALA

Total Coronavirus Cases in Kerala- 45,39,926
Total Coronavirus Deaths in Kerala- 23,897 [10]

MORPHOLOGY

Coronaviruses are large pleomorphic spherical particles with surface projections. The diameter of the virus particles is around 120 nm. The viral envelope consists of a lipid bilayer where the membrane (M), envelope € and spike (S) structural proteins are anchored. A subset of coronaviruses (specifically the members of betacoronavirus subgroup A) also have a shorter spikelike surface protein called hemagglutinin esterase(HE). Inside the envelope, there is the nucleocapsid, which is formed from multiple copies of the nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous beads-on-a-string type conformation. The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host cell[11]

SYMPTOMS

Signs of COVID-19 usually begin 2-14 days after a person has been infected. One study of more than 55,000 cases of

- Fever: 88%
- Dry cough: 68%
- Fatigue: 38%
- Coughing up thick phlegm from the lungs: 33%
- Shortness of breath: 19%
- Bone or joint pain: 15%
- Sore throat: 14%
- Headache: 14%
- Chills: 11%
- Nausea or vomiting: 5%
- Stuffy nose: 5%
- Diarrhea: 4%
- Coughing up blood: 1%
- Swollen eyes: 1%[12]

The VARIOUS ORGAN AFFECTED BY CORONA VIRUS ARE

- **Lungs**
- **Cardiovascular system**
- **Liver**
- **Gastrointestinal system**

1. CORONA VIRUS IMPACTS ON LUNGS

Covid-19 is a close relative of SARS. SARS is a novel type of virus that was reported in 2007 and like most SARS viruses, Covid-19 affects the respiratory tract in humans. The disease begins with mild flu influenza like indications or no manifestations and further advancement toserious side effects[13]Covid-19 primarily infects the lungs in the affected individuals and in severe cases causes death due to Acute respiratory distress syndrome and pneumonia . It is important to remember that it does not lead to ARDS and

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pneumonia in all the cases, which is an occurrence in most severe cases. COVID-19 is a respiratory disease, one that especially reaches into your respiratory tract, which includes your lungs. People who have other health conditions like heart disease, cancer, and diabetes may have more serious symptoms.

PHYSIOLOGICAL CHANGES IN LUNG STRUCTURE CAUSED BY CORONA VIRUS

When the virus gets in body, it comes into contact with the mucous membranes that linenose, mouth, and eyes. The virus enters a healthy cell and uses the cell to make new virus parts. It multiplies, and the new viruses infect nearby cells.lungs have a basic functional unit called the alveolus , the oxygen from air diffuses into the blood capillaries while the carbon dioxide from the blood diffuses into the air, to be expired subsequently[14].

A major issue with COVID-19 is with gas exchange in the alveolus. Usually, there is a very tight connection between the alveolar epithelium (type-1cells) and the capillary. COVID-19 infects angiotensin 2, kills them and floods the alveolus. In addition, there is evidence for microthrombosis which may block the vascular side. Clinically, this may appear as several conditionssevere bronchopneumonia, acute respiratory distress syndrome(ARDS) or sepsis.More severe inflammation can lead to ARDS .If a patient develops this severe of a syndrome, this can lead to longer-lasting effects on the lungs, such as fibrosis (scarring of the lung)[15].

FOUR PHASES OF COVID-19

Phase 1: Cell invasion and viral replication in the nose

Both SARS-CoV-2 and SARS-CoV gain entry via a receptor called ACE2. More commonly known for their role in controlling blood pressure and electrolytes, these receptors are also present in the lungs, back of the throat, gut, heart muscle and kidneys. Researchers from the University Medical Center Groningen in the Netherlands reported that ACE2 receptor cells were not present on the surface layer of cells in the nose and therefore, not an important site for SARS-CoV viral replication [16].Recently, an international team of researchers has found the ACE2 receptors on goblet (secretory) cells in and on ciliated (hairy) cells in the nose. More recently, scientists have found ACE2 receptors in the mouth and tongue, potentially indicating a handtomouth route of transmission. Researchers also found a plentiful supply of a protease calledTransmembrane serineprotease2(TMPRSS2) which chemically splits off the top of the coronavirus spike to allow the SARS-CoV-2 RNA to enter into the nasal cells. Once inside the cell, the virus‘s genetic material directs the cell to manufacture millions of new copies of itself. protease TMPRSS2 can act more easily to remove the top section of thecoronavirus spike because a genetic difference between SARS-CoV and SARS-CoV-2 means that there is now an easily broken section known as the furin-cleavage site. As a result , SARS-CoV-2 can bind 10 times more tightly to insert it’s RNA into the cell starting to explain COVID-19 spreads so rapidly[17]

Phase 2: Replication in the lung and immune system alert

The viral replication occurs in the upper respiratory tract. Seven out of nine participants listed cough among their initial symptoms.In contrast to the falling numbers of viral units in the upper respiratory tract, numbers in sputumfor most of the participants. The virus in sputum peaked at day 10-11. It was present in the sputum up to day 28 in one person. Across all participants, there was an average of 7 million units in 1 milliliter (about 35 million units in a teaspoon). This amount is about 1,000 times more than that in people with SARS [18].In the lung, the ACE2 receptor sits on top of lung cells called pneumocytes. These have an important role in producing surfactant a compound that coats the air sacs (alveoli), thus helping maintain enough surface tension to keep the sacs open for the exchange of oxygen and carbon dioxide.As soon as the body recognizes a foreign protein, it mounts the first response. One part of the body‘s immune response the lymphocytes begin to produce the first defense IgM-type antibodies and then the longer term specific neutralizing antibodies (IgG type). The viral study, 50% of the participants had IgM or IgG antibodies by day 7, and they all had these antibodies by day 14 . The amount of antibodies did not predict the clinical course of the disease80% of people with COVID-19 mild or asymptomatic disease, with common symptoms including fever, cough, and loss of sense of smell. Most will only have phase 1 or 2 physiological responses to SARS-CoV-2 infection[19] .

Phase 3: Pneumonia:

Approximately 13.8% of people with COVID-19 will have severe disease and will require hospitalization as they become short of breath. Of these individuals, 75% will have evidence of bilateral pneumonia. Pneumonia in

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COVID-19 occurs when parts of the lung consolidate and collapse. Reduced surfactant in the alveoli from the viral destruction of pneumocytes makes it difficult for the lungs to keep the alveoli open . As part of the immune response, white blood cells, such as neutrophils and macrophages, rush into the alveoli. Meanwhile, blood vessels around the air sacs become leaky in response to inflammatory chemicals that the white blood cells release. This fluid puts pressure on the alveoli from outside and, in combination with the lack of surfactant, causes them to collapse. As a result, breathing becomes difficult, and the surface area in the lung where oxygen transfer usually takes place becomes reduced, leading to breathlessness. The body attempts to heal itself by promoting inflammatory and immune responses.The evidence seems to refute this position, but this is a fast developing field, and findings are subject to change. Most patients will recover at this stage with supportive intravenous fluids and oxygen via a mask or an external positive pressure mask[20]

Phase 4: Acute respiratory distress syndrome, the cytokine storm

The critical disease is 10 days and it can come on suddenly in a small proportion of people with mild or moderate disease.In severe acute respiratory distress syndrome (ARDS), the inflammation stage gives way to the fibrosis stage. Fibrin clots form in the alveoli, and fibrin-platelet microthrombi (small blood clots) small blood vessels in the lung that are responsible for gas exchange with the alveoli.There is hope that drugs already licensed for anticlotting action in strokes could be helpful at this stage.Cytokines are chemical mediators that white blood cells such as macrophages release, and they can engulf infected cells. These cytokines which have names such as IL-1, IL-6, and TNFα have actions that include dilating the vessel walls and making them more permeable. In extreme circumstances, this can lead to a collapse of the cardiovascular system. Estrogen in mouse cells suppresses the release of cytokines from macrophages. Although animal studies often fail to translate into important findings in humans, this could be one explanation for worse outcomes from COVID-19 in males . While smaller numbers of ACE2 receptors are protective in phase 1, as there are fewer landing sites for the virus, by the time we reach phase 4, these receptors may become protective .ACE2 receptors in health play an important regulating role for the activities of angiotensin converting enzyme1(ACE1).In response to infection, ACE1 creates excess angiotensin 2 from angiotensin 1.Angiotensin 2 directly damages the lungs, causes blood vessel constriction, and makes the blood vessels leaky. Drugs that doctors typically use in the treatment of hypertension (ACE inhibitors and ARBs) may be helpful at this stage. The role of ACE2 inhibitors in treating COVID-19 is a complex one. As some authors note, on the one hand, using them may lead to a higher risk of SARS-CoV-2 infection. On the other hand, ACE inhibitors may reduce the lung damage that this infection causes[21].

CT CHEST FINDINGS IN PATIENTS INFECTED WITH COVID- 19

Bacterial pneumonia

Bacterial pneumonia is commonly encountered in clinical practice.Pneumonia is the eighth leading cause of death and the number one cause of death from infectious disease. Bacterial pneumonias are classified into three main groups: communityacquired pneumonia, aspiration and nosocomial pneumonia and hospital acquired pneumonia. Patients typically present with fever, chills, or cough. Chest radiography is the most commonly used imaging tool in pneumonias. CT should be used in unresolved cases or when complications are suspected[22].

Viral Pneumonias

Viruses are the most common causes of respiratory tract infections and are seen more commonly in children, the elderly and the immunocompromised[23].The most common pathogen causing viral pneumonia in both immunocompetent and immunocompromised patients is influenza virus The clinical signs and symptoms of viral pneumonia are often diverse and depend on host immune status The spectrum of CT findings encountered in various pulmonary viral diseases encompasses four main ccategorie: GGO and consolidation, nodules, micronodules, and treeinbud opacities, interlobular septal thickeningand bronchial and/or bronchiolar wall thickening . Lymphadenopathy and pleural effusions may also be present. Some of the viral pneumonias can manifest as substantial GGO and include cytomegalovirus, adenovirus, herpes simplex virus, varicella zoster, measles, human meta-pneumovirus and influenza . Percentage area of lung involvement with GGOs with different viruses has been extensively described. GGOs can be seen in 50%–75% of patients with adenovirus, in more than 75% of patients with cytomegalovirus and herpes simplex virus, and in10%–25% of patients with human meta-pneumovirus and

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measles[24]

Pneumocystis Pneumonia

Pneumocystis jirovecii pneumonia (PJP) is a common opportunistic infection that causes pneumonia in immunocompromised patients and rarely, in immunocompetent individuals. It typically occurs with CD4 counts less than 200 cells per mm of PJP in a patient with HIV infection is typically subacute, characterized by a slow onset of dry cough and dyspnea. PJP in patients without HIV infection presents as an acute illness associated with severe hypoxia and results in rapid respiratory deterioration and respiratory failure .The most common highresolution CT finding of PJP is diffuse GGO, which is often greater in extent in patients without HIV infection. Lung consolidation is more common in patients without HIV infection. Unlike COVID-19, PJP predominantly affects immunosuppressed patients. Although there may be widespread GGO in PJP, in contrast to COVID-19 pneumonia it is upper lobe predominant. Nodules, cysts and spontaneous pneumothorax can also develop[25].

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is a common interstitial lung disease associated with a number of conditions such as connective tissue disorders (ie, systemic sclerosis, Sjögrensyndrome, polymyositis, dermatomyositis and systemic lupus erythematosus). In addition, it can be related to autoimmune diseases such as rheumatoid arthritis, primary biliary cirrhosis, graftversushost disease, or drug induced[26]. NSIP typically manifests in patients aged40–50 years and has a higher predilection in women. The symptoms are nonspecific and include chronic dyspnea and cough without sputum production. Pulmonary function tests show a restrictive pattern of decreased lung function and reduced gas exchange capacity. As the disease progresses, fibrotic changes develop in the form of traction bronchiectasis, volume loss, architectural distortion and subpleural irregular reticular opacity[27].

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia is a relatively rare interstitial lung disease seen more commonly in men. It can also be related to marijuana smoke inhalation, infections such as HIV, toxins or occupational exposure. Patients are predominantly middle-aged with progressively worsening shortness of breath and chronic cough. The majority of these patients are smokers. Highresolution abnormalities . Less commonly, bronchovascular nodules and bronchial wall thickening can be seen. The reverse halo sign, also called the atoll sign, is considered a hallmark feature. However, it is seen in only 20% of patients . A perilobular pattern is seen in more than half of the patients. It appears as polygonal mainly subpleural opacities surrounded by aerated lung The lung manifestations of organizing pneumonia that resemble COVID-19 disease include lower lobe, subpleural and peribronchovascular predominant GGOs and opacities with reverse halo appearance. The former opacities are migratory in 11%–24% of patients.The presence of predisposing conditions can suggest Organizing pneumonia. In contrast to COVID-19, pulmonary opacities are often migratory. Perilobular thickening, if present, is another helpful differentiating feature. Patients typically respond to steroids[28].

Organizing Pneumonia

Organizing pneumonia present with a relatively short history of breathlessness. In addition, they have nonproductive cough, weight loss, malaise and fever. Organizing pneumonia may have unilateral or bilateral lung involvement and has myriad pulmonary manifestations. The most frequent features on highresolution CT scans include bilateral, multifocal, patchy consolidations (present in up to 90% of cases) and ground-glass abnormalities[29] . Less commonly, bronchovascular nodules and bronchial wall thickening can be seen. The reverse halo sign, also called the atoll sign, is considered a hallmark feature. However, it is seen in only 20% of patients . A perilobular pattern is seen in more than half of the patients. It appears as polygonal mainly subpleural opacities surrounded by aerated lung.The lung manifestations of organizing pneumonia that resemble COVID-19 disease include lower lobe, Subpleural and peribronchovascular predominant GGOs and opacities with reverse halo appearance. The former opacities are migratory in 11%–24% of patients. The presence of predisposing conditions can suggest organizing pneumonia. In contrast to COVID-19, pulmonary opacities are often migratory. Perilobular thickening, if present, is another helpful differentiating feature. Patients typically respond to steroids[30]

2 . CORONA VIRUS IMPACTS ON CARDIOVASCULARSYSTEM

Coronavirus disease 2019(COVID-19)attacks the cardiovascular system in multiple ways. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 and is most

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Volume 7, Issue 2 Mar-Apr 2022, pp: 708-719 www.ijprajournal.com ISSN: 2456-4494

commonly associated with being a respiratory disease. however, it also affects the cardiovascularsystem, according to the study. COVID-19 is a lung disease that causes an increased heart workload. The virus can trigger heart attacks and is associated with increased blood clots. Additionally, the virus can also directly infect the heart, which can cause muscle damage and heart failure. The most common cardiac issue in patients with COVID-19 is perhaps the cardiac injury that can be measured in the bloodstream as elevated enzymes. These patients have more complications and worse hospital outcomes.Old patients living with diabetes, hypertension, obesity or other pre-existing cardiac conditions are not only more vulnerable to COVID-19, they have worse outcomes while suffering from the disease

PATHOPHYSIOLOGY OF SARS-COV CARDIOVASCULAR INVOLVEMENT

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has emerged from China, the infection has affected many countries and led to many deaths worldwide. Like SARS- CoV, angiotensin converting enzyme (ACE)2 as a functional receptor for SARS-CoV2 is essential for the virus to make an entry in to the cell[31]. ACE2 is a part of Renin-Angiotensin-Aldosterone System, which is expressed in several organs that opposes the angiotensin (Ang) II functions by converting Ang II to Ang(1-7) , the one with vasodilation effects. The death rate of COVID-19 is estimated to be approximately 3.4%; however, some comorbid conditions like underlying cardiovascular disease, hypertension, and diabetes increase the risk of mortality. In addition, cardiovascular involvement as a complication of SARS-CoV2 could be direct through either ACE2 receptors that are expressed tremendously in the heart, or by the surge of different cytokines or by acute respiratory distress syndrome-induced hypoxia Traditional risk factors could aggravate the process of COVID-19 infection that urges the triage of these highrisk patients for SARS-CoV2. Some potential medications like chloroquine by itself or in combination with azithromycin and some protease inhibitors used for the treatment of COVID- 19 have cardiovascular adverse effects, which should be kept in mind while the patients taking these medications are being closely monitored[32].

CARDIOVASCULAR COMPLICATIONS IN COVID-19 PATIENTS

Myocardial injury

Myocardial injury can result from the associated cytokine storm manifested by elevated levels of interleukin-6 (IL-6), ferritin, lactate dehydrogenase (LDH), and D-dimer or myocardial dysfunction from the direct effect of severe acute respiratory syndrome coronavirus 2 on the heart [33].

Cytokine Storm and Heart Damage

Multiple studies reported that inflammatory markers are increased with COVID-19 infection, ranging from CRP, ferritin, interleukin-6 (IL-6), interleukin-1β (IL-1β), interferon-γ (IFN -γ), monocyte chemoattractant protein-1(MCP-1),and tumor necrosis factor-α (TNF-α) leading to cytokine storms.The cytokine storm is a complex network of severe molecular events, including a clinical phenotype of systemic inflammation, multi-organ failure, hyper-ferritinemia. It is generated by the activation of an innumerable amount of white blood cells, including B cells, T cells, NK cells, macrophages , dendritic cells, neutrophils , monocytes , and resident tissue cells, such as epithelial and endothelial cells, which release high amounts of pro-inflammatory cytokines[34]

HYPERTENSION AND COVID-19

Hypertension might be linked with up to 2.5fold more significant risk of lethal COVID-19, particularly with older individuals. In COVID-19 illness, through ACE2 receptors, the virus enters the lung and patients with hypertension have worse outcomes than those with any other underlying condition. InCOVID-19 patients, hypertension and other forms of CVD were found frequently and ACE inhibitors and angiotensin receptor blockers (ARBs) were often used for the treatment, which results in an upregulation of ACE2. There are hypotheses that ACE2 stimulating drugs used to treat hypertension can increase the risk of developing lethal COVID-19. The patients treated with ACE2elevating drugs for hypertension, diabetes or cardiac diseases are at increased risk for COVID-19 infection and should, therefore, be monitored for ACE2modulating medications, such as ACE inhibitors or ARBs [35].

Endothelial Dysfunction in COVID-19

Endothelial cell injury plays a vital role in the pathogenesis of multi-organ failure in COVID-19. The endothelium is one of the largest organs in the human body. The endothelial cells express ACE2 receptors and the viral entry causes major clinical conditions such as high blood pressure,kidney disease,cerebrovascular and neurologic disorders. The cardiovascular system is protected by the endothelial cells and the proteins they release will influence everything from blood

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clotting to the immune response. Endothelial damage leads to excessive cardiovascular impairment and causes extempore heart attacks in COVID-19. Endothelial cell damage may cause blood vessel inflammation leading to plaque rupture and heart attack . Due to the devastating immune inflammatory response and the subsequent cytokine storm, the heart status becomes exacerbated via inflammation induced heart failure[36].

3. CORONA VIRUS IMPACTS ON LIVER

In the first phase of the COVID- 19 disease, the pathogenic properties depend on binding of spike viral proteins to angiotensin converting enzyme 2 (ACE2) receptors which allow the virus to enter the target cells. ACE2 receptor expression also occurs in vascular endothelium, in the brush border of intestinal enterocytes and in cholangiocytes Thus, the symptomatic involvement of the gastrointestinal tract is possible with COVID- 19. A recent USA report describes a clinically evident gastrointestinal involvement in 61% of COVID- 19positive subjects.The presence of ACE2 receptors in the glandular cells of gastric, duodenal and distal enterocytes may result in malabsorption, unbalanced intestinal secretion and activation of the enteric nervous system, leading to gastrointestinal symptom. Liver can also become a target of COVID- 19 infection, although major liver damage is uncommon. SARS- Cov- 2 might affect the liver by direct (i.e. viral translocation from the gut to the liver) or indirect mechanisms (ie systemic inflammation, liver ischaemia and hypoxia, effects on pre- existing liver diseases, drug- related liver injury) and represents a new challenge for hepatologists. Notably, non- alcoholic fatty liver disease (NAFLD) is a chronic dysmetabolic pandemic which has become the most common liver disease in the world, with a prevalence rate of 30% in the Western population. Along with this view, the acronym NAFLD has been recently re-visited by coining the acronym MAFLD ('metabolic dysfunction- associated fatty liver disease') NAFLD/MAFLD can therefore affect the final outcome in COVID- 19- infectedpatients[37].

Mechanisms of liver injury induced by COVID-19 .

Development of liver injury in COVID-19 patients might be related to any of the following:**A direct hit from this virus.**

Corona virus binds to target cells through ACE2. Because ACE2 is expressed abundantly in the liver and in particular on biliary epithelial cells, the liver is a potential target for direct infection,which is however not yet demonstrated.

Systemic inflammation:

Immune mediated damage as a result of the severe inflammatory response following COVID- 19 infection; the inflammation biomarkers including C reactive protein (CRP), serum ferritin, LDH, D- dimer, IL- 6, IL- 2, were significant elevated in severe patients with COVID- 19.

Hepatic ischemia and hypoxia.

The hallmark of COVID- 19 is respiratory failure. Hypoxic hepatitis as a result of anoxia is therefore frequent in severe cases.

Pre-existing liver disease.

Patients with pre- existing chronic liver disease, may be more susceptible to liver damage from COVID- 19. Biological drugs like tocilizumab and baricitinib might also cause HBV reactivation and thus lead to liver function deterioration. On the other hand, it is still unknown whether COVID- 19 infection exacerbates cholestasis in those with underlying cholestatic liver disease.

Drug-related liver injury.

Initial clinical guidelines recommended antiviral agents for COVID- 19, with some of them, including lopinavir/ritonavir, remdesivir, chloroquine, tocilizumab, umifenovir, Chinese traditional medicine, being potentially hepatotoxic in some patients (and a few have subsequently already been proven to be ineffective).

SEQUENCES OF PATHOPHYSIOLOGICALMECHANISMS PREDISPOSING TO METABOLIC ILLNESS AND LIVER STEATOSIS

Rationale to explain multi- organ and liver damage during COVID19 infection.

a) Initial role of wrong lifestyles (hypercaloric,nunbalanced, fructose- and refined carbohydrate- enriched diet, sedentary behaviour), on a genetic/racial, ethnical and environmental background. Changes in intestinal microbiota can also govern additional metabolic changes due to biotransformation of foods, local inflammatory changes, increased intestinal permeability to bacterial products lipopolysaccharides [38].
b) Expansion of visceral fat may occur in different phenotypes, independently of simple body weight (encompassing the term 'adiposity' or 'overfat'). The three subtypes at risk include normal weight but metabolically

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obese subjects (characterized by high visceral adiposity, about % overfat, normal lean mass, propensity to develop metabolic abnormalities), overweight individuals and obese sarcopaenic subjects (high visceral adiposity, decreased lean mass, likely several metabolic abnormalities). The subtype «normal weight obese» has increased (>30%) fat mass (not necessarily visceral adiposity), a normal lean mass, without metabolic abnormalities. Overfat conditions (in red) are predisposing to chronic metabolic inflammation, compromised immunity, increased risk of chronic disease and infections (including viral infections). Underweight, underfat individuals also share the same risk for chronic inflammation, compromised immunity, increased risk of chronic disease and infections [39].

c) The metabolically active vicious circle originates from the excess visceral fat with production of inflammatory molecules. In lean individuals or metabolically healthy subjects, anti- inflammatory cytokines (transforming growth factor beta (TGF- β), interleukin 10 (IL- 10), IL- 4, IL- 13, nitric oxide (NO)) activate M2 macrophage- and inhibit neutrophil- mediated inflammation. T lymphocytes, neutrophils, B1 and B2 cells, NK cells and innate lymphoid cells also populate the fat tissue. Hypertrophic or apoptotic adipocytes (in grey) in obese individuals can secrete pro- inflammatory molecules (leptin, resistin, IL- 6 and tumour necrosis factor- α) that activate a pro- inflammatory M1 macrophage. The pro- inflammatory metabolic status is a factor promoting insulin resistance, as well as defective immune response (poor T cell and macrophage function)

d) Further progression of the chronic pro- inflammatory status and insulin resistance paves the way to several metabolic risk factors contributing to the metabolic syndrome.

e) Chronic illness can follow with established risk factors.

f) Non- alcoholic fatty liver disease (NAFLD) and the spectrum of liver abnormalities are the consequence of the accumulated metabolic abnormalities. Excess lipolysis during insulin resistance will increase the influx of free fatty acids (FFA), synthesis of triglycerides, enrichment of FFA pool with lipotoxic products (lysophosphatidylcholine (LPC); diacylglycerol (DAG); ceramides). Products mediate endoplasmic reticulum (ER) stress, oxidant stress and activation of the inflammasome (multiprotein cytoplasmic complex that responds to damage- associated molecular patterns (DAMPs), as part of the innate immunity response).body mass index[40]

4. CORONA VIRUS IMPACTS ON GASTROINTESTINAL SYSTEM

The novel SARS-CoV-2 virus, belonging to the beta coronavirus genus, is an enveloped, positively charged, single-stranded RNA virus. It is highly homologous to SARS-CoV, the pathogen of SARS, and enters host cells via the angiotensin converting enzyme 2 (ACE2) receptor. ACE2 is highly expressed in gastrointestinal (GI) cells, such as esophageal epithelial cells and the absorptive enterocytes from ileum and colon .COVID-19 patients present not only with respiratory maladies, but also digestive symptoms, such as diarrhea, vomiting, nausea and abdominal pain . SARS-CoV-2 infections in the GI tract could cause bleeding and inflammation, which have an impact on the intestinal immune system and further influence the whole body immune system, thus worsening the disease process of COVID-19 in the lungs and other organs. Additionally, the viral balance in the GI tract is disordered during SARS-CoV-2 infection, which could further impact the homeostasis of microbiota[41].

THE MECHANISM OF GASTROINTESTINAL SYMPTOMS INDUCED BY COVID-19

1. Direct Infection of Gastrointestinal Cells.
2. Gastrointestinal Damage Caused by Lung Infection.
3. Gastrointestinal Symptoms Caused by Drug Side Effects.

Direct Infection of Gastrointestinal Cells.

Virus entry into cells is an important part of crossspecies transmission. All coronaviruses encode a surface glycoprotein and spike protein, which binds to host cell receptors and mediates virus entry.SARS-CoV-2 mainly enters cells through the ACE2 receptor.Therefore, the expression and distribution of ACE2 in humans is a potential infection pathway for SARS-CoV-2.ACE2 is widely found in human small intestinal epithelial cells. ACE2 is more strongly expressed in type II epithelial cells . Other studies provided additional evidence that coronavirus may infect the

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 708-719 www.ijprajournal.com ISSN: 2456-4494

gastrointestinal tract, since high expression of ACE2 has been detected in intestinal epithelial cells, esophagus, and lungs.ACE2 is a key enzyme in the renin-angiotensin system (RAS) and plays an important role in regulating intestinal inflammation and diarrhea .Loss of ACE2 leads to the ANG II accumulation [42]. Although ACE2 knockdown results in elevated levels of ANG II in the mouse colon, ACE2 does not perform its function primarily through the RAS system in the intestine but rather directly regulates the homeostasis of intestinal amino acids, expression of antimicrobial peptides, and ecology of the gut microbiome. Accordingly, more than 90% of patients with pellagra will eventually develop colitis. Herefore, we speculate that binding of SARS-CoV-2 with ACE2 in the gastrointestinal tract reduces the level available receptors, affects the absorption of tryptophan, and ultimately destroys the steady state of the intestinal flora, which is one of the causes of gastrointestinal symptoms such as diarrhea.

1. **Gut-lung axis:** severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds with angiotensin-converting enzyme 2 (ACE2) to enter the lung, resulting in the accumulation of angiotensin II (ANG II) and the decrease of angiotensin (1-7) (Ang1–7). ANG II combined withAT1R promotes cytokine release and increases CCR9+CD4+T cells. CCL25 promotes the recruitment of C-C chemokine receptor type 9 (CCR9) +CD4+T cells into the small intestine. The changed flora then promotes the polarization of Th17 cells, and finally IL-17A causes the recruitment of neutrophils. Cytokines and bacteria also enter the lung through the bloodstream, further affecting the lung inflammation.
2. **Gut-liver axis:** SARS-CoV-2 binds with ACE2 to enter the intestine, inhibits the absorption of the B0AT1/ACE2 transport pathway, and then affects the activation of mammalian target of rapamycin (mTOR) to reduce the expression of antimicrobial peptides. The intestinal flora is transferred to the liver through the portal vein, where it binds to toll-like receptors, causing hepatitis. The liver also can transport metabolites to the intestine through the biliary tract.

Gastrointestinal Damage Caused by Lung Infection

Changes in the composition and function of the gastrointestinal flora affect the respiratory tract through the common mucosal immune system. Disorders of the respiratory tract flora also impact the digestive tract through immune regulation.This effect is called the gut-lung axis‖.Effector CD4+ T cells entering the intestinal mucosa are key for mucosal immunity and chronic enteritis. C-C chemokine receptor type 9 (CCR9) is a necessary chemokine receptor for CD4+ T cells to enter the small intestine. Jian Wang found that lung-derived CCR9+CD4+ T cells were increased after viral infection. The small intestinal epithelium can express CCL25 ,which promotes the recruitment of CCR9+CD4+T cells into the small intestineleading to intestinal immune damage and destroying the homeostasis of the intestinal flora[43].

Gastrointestinal Symptoms Caused by Drug Side Effects

Antibiotic-associated diarrhea is the most common adverse reaction to antibacterial drugs, especially macrolides, cephalosporins, and β-lactam antibiotics. A retrospective analysis from Guangzhou, China, of the treatment process for 260 SARS-CoV patients found that macrolides, fluoroquinolones, or cephalosporin antibiotics were used and that the proportion of patients with diarrhea was 24.2%.Some serious intractable diarrhea may be related to the use of oseltamivir and arbidol, the incidence of diarrhea in patients using these drugs is ~55.2%.Other antiviral drugs that can cause diarrhea include chloroquine phosphate, lopinavir, and remdesivir, as well as Chinese patent medicines such as lianhuaqingwen capsules Additionally, exposure to broad-spectrum antibiotics is the main risk factor for primary Clostridioides difficile infection (CDI), the leading cause of nosocomial diarrhea [44]

Gastrointestinal symptoms in COVID-19 patients

a) Concurrent gastrointestinal symptoms, notably diarrhea, anorexia, vomiting and nausea.
b) Onset of GI signs prior to respiratory symptoms.
c) Only GI clinical signs with absence of respiratory symptoms.

In COVID-19 patients with gastrointestinal symptoms, diarrhea was one of the most common characteristics along with other symptoms such as vomiting, nausea, loss of appetite and abdominal pain[45]

II. CONCLUSION:

COVID-19 mainly in severe cases in addition to lung involves different organs such as heart, liver, and kidney, as well as hematological and nervous system, and induce multi-organ failure. COVID- 19 may directly invade the host

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cells of different organs through the ACE2 receptor due to the presence of this receptor in these organs. On the other hand, activation of the complement system, cytokine storm, dysregulated immune responses, coagulation dysfunction, and infiltration of inflammatory cells in COVID- 19 infection can induce the multi-organ failure in these patients. Overall, understanding the clinical, laboratory and radiological features of COVID-19 in critically ill patients with multi-organ dysfunction should be clarified for clinicians. Consequently, increasing the knowledge on the pathophysiology of COVID- 19 induced multi- organ failure may ultimately result in better ways to treat COVID-19 patients and decrease the associated morbidity and mortality.

S.No	ORGAN AFFECTED BY CORONAVIRUS	EFFECTS	REFERENCES
1	Lungs	Cough Breath shortness Chest pain,dyspnea (Acute respiratory distress syndrome) Pneumonia	1. MelindaMichelen,NJ,CS.In patients of covid 19, What are the symptoms and clinical features of mild and moderate cases?2020,April 1,2020. 2. WHO , COVID-19 Clinical management, World Health Organization ,2021 . 3. James Kingsland , Hilary Guite, COVID-19: Could a clot-busting drug help save the livesof Patients on ventilators?,medicalnewstoday ,Published online on April 9 2020.
2	Cardiovascular system	Myocardial injury Chronic dilated cardiomyopathy Hypertension	1. Wood,Lauren UConn health doctor. Covid-19 directly targets the cardiovascular system, UConn , June 16,2020.34. 2. Yu C.M, Wong R.S, Wu E.B, Cardiovascular complications of severe acute respirator syndrome‖,Postgrad Med J, 2006 Feb;82(964):140-144. 3. Earney PM, Whelton M, Reynolds K, Global burden of hypertension: analysis of worldwide data, Lancet ,2005 Jan 15-21;365(9455):217-223.
3	Liver	Acute liver injury Cholestasis	1. Mantovani A,Beatrice G, D A, Coronavirus disease 2019and prevalence of chronic liver disease: meta analysis, liver Int, 04 April 2020.38. 2. Huang C, Wang Y, Li X, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China‖ , Lancet ,2020 Feb 15;395(10223):497-506.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 708-719 www.ijprajournal.com ISSN: 2456-4494

4	Gastrointestinal system	Diarrhoea Nausea/vomiting Loss of appetite Abdominal pain Anorexia	1. Xiao A, Tang M, Zheng X, Evidence for gastrointestinal infection of SARS-COV2, Gastroenterology,2020 May;158(6):1831-1833.

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