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Hepatic System Complications in Patients After Covid-19

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ABSTRACT

Background: *COVID-19 a pandemic encountered currently has affected the world so adversely that it poses a great risk for human mankind. The vaccine has been developed and been used widely to provide immunizations. Almost 90% of immunization is provided by these vaccines. But unfortunately, the nation is now facing a second wave which happens to be a mutant species of the SARS CoV- 2. The seriousness regarding COVID infection has gone too low. This is because the layman is not much aware of the complications which occur with and after COVID infection. Thus, discussion on post-COVID complications is significant.*

Methods: *PUBMED and Sciencedirect database were searched and the studies investigating the relationship between COVID-19 infection and post covid hepatic complications were included in the review.*

Conclusion: *Society is more concerned about the days only when they're infected with this viral disease; they are not aware of the post-COVID complications in the latter days. Sufficient data are being published regarding the same day by day, where the hepatic system is usually neglected or not considered. COVID-19 is also associated with liver damage, and the risk of liver injury is greater in patients with serious or critical COVID-19 disease than in those with moderate disease. Direct virus infection, immune injury, drug-induced liver injury, and other mechanisms can trigger liver injury in COVID-19 patients. Hepatic Complications include Steatosis, Acute hepatitis, Portal inflammation, lobular cholestasis, ductular cholestasis, fibrinoid necrosis, Sinusoidal microthrombi, Granulomas, Thrombotic bodies, etc.*

Keywords: *Hepatic Complications; Post-COVID; Corona; Complications; COVID; Liver; Hepatic system.*

INTRODUCTION

The coronavirus almost affects all the organs in our body from the brain to the skin due to which the risk of facing a lot of post covid complications rises [1]. The pathophysiology of coronavirus involves the target receptor ACE2 [2].

Upon entering the healthy human body via the infected air droplets released from a sick patient, the coronavirus penetrates the cell after fusion with the ACE2 receptor. The coronavirus consists of spike glycoproteins on its cell surface, which helps in the penetration. There are two subunits S1 and S2. The S1 subunit gets cleaved by the TMPRSS2 and the S2 subunit fuses with the fusion protein on the ACE2 receptor.[3]This helps the genetic material of the virus to be transferred into the cell membrane of the human host. The genetic material of the virus is recognized as its own by the human cell. The process is proceeded by the formation of new viral RNA and its package to form new viruses. It then gets released out to the cell and infects other cells and organs, thus resulting in the proven signs and symptoms and leading to a variety of complications.

Neurologic Complications

The coronavirus affects the brain by two hypothesized mechanisms:

1) Via the olfactory nerve: the olfactory nerve is the only cranial nerve that is exposed to the environment, which makes it the perfect route through which the virus gains entry to the brain. Upon entering the brain, the virus interacts with the ACE2 receptor and causes inflammation.
2) Via blood-brain barrier: the endothelial cells consist of ACE2 receptor and hence after interacting with the receptor, the virus gets transported into the brain, crossing the BBB [4].

After entering the brain, the virus goes on to infect the brain cells causing brain encephalitis, stroke, hallucinations, delirium, Seizures, brain fog, anosmia, ageusia, and in rare cases Guillain barre syndrome and bell’s palsy.

Guillain barre syndrome is an autoimmune disorder involving the peripheral nervous system which is characterized by flaccid paralysis of limbs and often preceded by an infection [5]. The pathophysiology involves the entering of the SARSCOVI-2 virus which goes on to infect the other cells causing the stimulation of the immune system. This leads to the production of antiganglioside antibody which acts on the ganglioside of the muscles causing the demyelination of the motor neurons results in lymph dysfunction, eventually paralysis.

Ball’s palsy has been reported in some patients after taking the vaccine shots and rarely as a post covid complication.Bell's palsy is a temporary paralysis of the facial nerve, which results in the drooping of one side of the face and othersymptoms like the drooping eyelid, asymmetrical smile. This can be cured by taking the appropriate medications and acupuncture [6].

Respiratory Complications

Respiratory complicationsinclude acute respiratory distress syndrome and post covid fibrosis.The SARS- CoV2 affects the lungs by interacting with the ACE2 receptor and causing inflammation of the lungs. This leads to the decreased production of oxygen, because of which the infected person has to breathe frequently to cope with the lack of oxygen, which results in symptoms like breathlessness. Increased inflammation leads to scarring of the lungs which causes fibrosis and accumulation of fluid in the air sacs of the lungs leading to ARDS [7].

Cardiopulmonary Complications

The coronavirus is known to cause a lot of cardiological complications ranging from heart attack to myocardial infarction. The mechanism by which the SARS- CoV 2 causes these complications is due to its interaction with the ACE 2 receptors present in the heart cells. The virus causes inflammation in the heart muscle, decreasing its capacity to pump the blood efficiently, disruption in the heart signaling, interfering with the conduction of abnormal heart rhythms, leading to arrhythmia or worsening of the pre-existing condition. When the lungs get inflamed due to the infection, which decreases the amount of oxygen for respiration [8].

This leads to an increased burden for the lungs which pumps more rapidly to cope up with the decreased oxygen. This results in the inflammation of the heart cells. Also, upon interacting with the endothelial cells, there occurs the formation of blood clots which goes on to clog the blood vessels leading to myocardial infarction [9].

Renal Complications

The coronavirus infection leads to acute kidney injury. This is due to the interaction of the virus with the ACE 2 receptors in the tubular epithelial cells, podocytes, and endothelial cells which get inflamed and lead to acute tubular necrosis (ATN), collapsing focal segmental glomerulonephritis (FSGS), and endotheliitis of the glomerular capillaries respectively. All these eventually lead to acute kidney injury [10].

Hepatobiliary Complications

Although it's known that the covid usually affects the lungs, it can also lead to various complications which also involve liver inflammation. The virus affects the liver since there are ACE 2 receptors present in the liver. The liver inflammation is signified by the elevation in the liver enzymes such as ALT and AST [11].

Musculoskeletal Complications

Musculoskeletal symptoms should be combined with laboratory findings, such as inflammatory and infection-related parameters (Interleukin-6, Procalcitonin, and C - reactive protein).Although not much has been studied about the musculoskeletal complications, the signs are only anecdotally due to indirect causes, mostly arising from the inflammatory and/or immune reaction, but other pathways, such as direct virus disruption to the endothelium or peripheral nerves, may be speculated [12]. But it has been hypothesized that pulmonary inflammation can lead to systemic inflammation and release of chemokines and cytokines like CXCL 10, IFN gamma, IFN 1 beta, IL 6, IL 8, IL 17, TNF alpha …etc. This can lead to skeletal muscle and bone and muscle complications like myalgias, atrophy, weakness, fatigue, bone mineral loss, osteonecrosis, and chondrolysis. It has also been reported that rhabdomyolysis may occur as a result of acute kidney injury [13].

Dermatologic Complications

The mostreported complication is the incidence of covid toes post-infection. It is a chilblain-like skin infection that not only occurs in the toes but also in other extremities like the finger. Covid toes begin with a red coloration on the fingers and toes which then gradually turns purple.it can also form blisters, itch, or pain. Some people develop painful raised bumps or areas of rough skin. Sometimes there can be puss under the skin [14].

Gastrointestinal

One of the host receptors for SARS-CoV-2 cell entry is ACE2. In the small intestine and colon, ACE2 mRNA and protein are abundant, especially in enterocytes [15]. This can contribute to a variety of issues, including the symptoms of SARS-CoV 2 infection include anorexia, nausea, and diarrhea.

MATERIALS AND METHODS

PUBMED and Sciencedirect database and bibliographies of retrieved articles were searched and the studies which were investigating the relationship between COVID-19 infection and post covid hepatic complications were selected and included in the review. Potential sources of heterogeneity between studies were explored and publication bias was evaluated.

DISCUSSION

SARS-CoV-2 (coronavirus disease 19, or COVID-19) is a novel coronavirus that mainly causes pulmonary injury, but has also been linked to hepatic injury, as evidenced by serum markers and histologic evaluation [16]. Drug-induced liver injury (DILI), extreme SARS COVreplications in the liver, and inter-organ cross-talk in acute inflammation are all possible causes of abnormal liver function in patients with COVID-19 [17]. SARS-CoV initiates protein S by using the angiotensin-converting enzyme 2 (ACE2) and the serine protease TMPRSS2 [18]. ACE2 and TMPRSS2 are expressed in the epithelia of the small intestine, upper esophagus, liver, colon, and bile duct cells [19]. SARS-CoV is believed to use angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor. ACE2 is highly expressed on liver endothelial cells, suggesting that the liver may be a possible SARS-CoV target.

SARS patients' liver biopsies revealed a substantial increase in mitotic cells, as well as eosinophilic bodies and balloon-like hepatocytes, implying that SARS-CoV may cause liver injury by inducing apoptosis. Other research has found that SARS-CoV's unique protein 7a can trigger apoptosis in cell lines from various organs (including the lung, kidney, and liver) through a caspase-dependent pathway, confirming the possibility that SARS-CoV directly targets liver tissue and causes injury [20].

The fundamental concern has been whether the virus infects the liver directly, or whether the liver damage is entirely due to the "cytokine storm" that certain patients experience, or whether a mixture of these factors is present [16].

Angiotensin converting enzyme receptor 2 is thought to be the virus's primary mode of entry into the cell (ACE2). It is abundant on cholangiocytes but uncommon on hepatocytes; however, it may be upregulated on hepatocytes during periods of physiologic stress. Others had varying degrees of steatosis, congestion, and ischemia, but no other severe gross pathology.

Macro vesicular steatosis, mild acute hepatitis, and minimal-to-mild portal inflammation were the most common histological findings along with some less common observations that were also discovered and recorded [17].

Steatosis

Wasa common condition. In 75% of the patients, macrovesicular steatosis was discovered. There was no sign of true microvesicular steatosis in the fat droplets, which were mainly macrovesicular. Liver function dysfunction may become a predictor of exacerbation and degradation in COVID19 patients. SIRS, cytokine storms, ischemia/reperfusion damage, medications, and underlying liver disease can all cause liver injury, and SARSCoV2 can also target liver cells directly through ACE2. It's important to keep an eye out for the risk of liver damage when diagnosing and treating COVID19 [21].

Acute Hepatitis

Mild acute hepatitis, also known as lobular necroinflammation, was found in half of the cases. The percentage increases to 60% when cases of no inflammation but focal apoptotic hepatocytes are included. These foci included apoptotic cells, lymphocytes, and special histiocytes. Plasma cells were a rare occurrence. In COVID19 patients, immune deficiency such as lymphopenia and elevated cytokine levels (including cytokine storms) is common and may be related to disease severity and mortality. The impact of glucocorticoids on disease prognosis in COVID19 patients with autoimmune hepatitis is unknown, further research is required. However COVID19 patients with systemic immunodeficiency and cirrhosis or liver cancer may be more susceptible to SARSCoV2 [16-21].

Portal Inflammation

As a consequence of the inflammation, the number of portal mononuclear cells increased just barely (lymphocytes and few portal macrophages) There was a shortfall of eosinophils and neutrophils. A few plasma cells were found here and there, but none were significant enough to rule out autoimmune hepatitis or drug-induced liver injury with autoimmune characteristics [22-23].

Biliary Findings

Biliary findings are suggestive of lobular cholestasis, which was generally mild and focal, whereas others had ductular cholestasis, which was suggestive of sepsis. Interlobular bile ducts were present in a normal distribution (no ductopenia), and the ducts appeared normal (tubular structures made up of cholangiocytes) [24].

Vascular Pathology

Phlebosclerosis, which is identical to veno-occlusive disease (VOD) was present. There was pathological muscle hypertrophy and venous phlebosclerosis in the portal arterioles. Fibrinoid necrosis and Microthrombi sinusoidal presence were observed in portal arterioles [25-27].

Granulomas

Granulomatous inflammation was present and there were portal and lobular granulomas with a “fibrin ring” morphology.Multiple necrotizing granulomas developed grossly, with visible abscesses, and had Schistosoma egg-like structures. Non-necrotizing granulomas in two portal tracts resembled primary biliary cholangitis (PBC) [28].

Thrombotic bodies

The pale ovoid sinusoidal inclusions seemed like apoptotic hepatocytes when seen under low magnification. Close observation showed that these inclusions were present in the sinusoidal spaces, and these structures were called "thrombotic bodies" when stained with CD61, which was positive, suggesting that these aggregates were rich in platelets [29-30].

The Mechanism by which COVID-19 causes Liver Injury

The fundamental causes of COVID-19-induced liver damage are currently unknown. In reality, liver injury can be multifactorial and unique to each individual. To begin with, a hyper-inflammatory response to COVID-19 may play a role in liver injury. The percentage of neutrophils and CRP were positively correlated with the severity of liver function injury, while lymphocyte percentages were negatively correlated. Reduced ratios of neutrophils, lymphocytes, and monocytes are independent risk factors for the incidence of liver injury; reduced ratios of neutrophils, lymphocytes, and monocytes are independent risk factors for the occurrence of liver injury. Hepatic inflammation, which involves the activation of the innate immune system and a cytokine storm, is a well-known cause of liver injury [31].

Direct Injury

Biopsies taken from the liver tissue of a COVID-19 patient who died showed moderate microvascular steatosis and mild portal and lobular activity [28]. In four further autopsies done after the death, The COVID-19 patient showcased moderate sinusoidal zone 3 symptoms.The symptoms include dilatation, patchy hepatic necrosis, and a slight rise in sinusoidal lymphocytes.The most common pathologic changes in the live [32]. SARS-CoV-2 reaches host cells by binding to angiotensin-converting enzyme 2 (ACE2) on the cell surface, according to research. The most powerful cell receptor is ACE2, which mediates SARS-CoV-2 entrance into target cells [33-34].

Furthermore, cholangiocyte damage biomarkers such as gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) have been detected in some patients [35].

The majority of COVID-19 patients have elevated overall bilirubin levels, which is associated with damage to biliary epithelial cells. This suggests that SARS-CoV-2 can bind directly to cholangiocytes that express ACE2 and cause cholangiocyte injury.

In addition todirect SARS COV insult, Immune damage, systemic inflammatory response syndrome (SIRS), cytokine storms, ischemia, and hypoxia reperfusion injury, and drug-induced injury are thought to be the primary pathways that cause secondary liver injury in COVID-19 patients [34-36].

Antibody-Dependent Enhancement (ADE)

Antibody-dependent enhancement of infection (ADE) can occur in SARS32 patients in addition to receptor-mediated viral infection.[37]The association of a virus-specific antibody with the Fc receptor (FcR) and/or complement receptor (CR) to increase the virus's ability to penetrate granulocytes, monocytes, and macrophages is referred to as ADE. The virus replicates continuously in the cells above, resulting in increased virus development and escalating infection [37].

Antibodies against the SARS-CoV spike protein have previously been shown to activate ADE, allowing SARS-CoV to infect immune cells that do not express ACE2 and causing immune damage [38]. A significant number of cells involved in the immune response can be found in the liver. It's unclear if ADE can help SARS-CoV-2 infect immune cells via a non-ACE2-dependent pathway and engage in SARS-CoV-2-induced liver injury.

Systemic Inflammatory Response Syndrome (SIRS) and Cytokine Storms

Inflammatory factors such as IL, TNF, and endotoxin are substantially higher in patients with the extreme acute respiratory syndrome (SARS) that have liver function dysfunction than in patients with normal liver function, according to research, implying that systemic inflammatory response syndrome (SIRS) and cytokine storms are a risk factor for liver impairment in SARS patients [39-40]. Pathological results have demonstrated that hepatocytes in patients with severe COVID-19 exhibit nonspecific inflammatory changes, including hepatocyte swelling and steatosis, the mild proliferation of hepatic sinus cells, hyperplasia of Kupffer cells, and infiltration of a small number of lymphocytes.The levels of IL-2-receptor (IL-2R) and IL-6 in the serum of COVID-19 patients have also been shown to be slightly elevated and to correlate with disease severity [41]. Furthermore, cytokines secreted by Th1 and Th2 cells in COVID-19 patients' serum, such as tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-18 (IL-18), interleukin-4 (IL-4), and interleukin-10 (IL-10), as well as peripheral blood pro-inflammatory CCR4 + CCR6 + Th17 cells, were substantially increased [4-43]. The liver plays an important role in the immune system and houses a vast number of immune-related cells. After becoming contaminated with SARS-CoV-2, a large number of immune cells can become overactive and secrete excessive cytokines, chemokines, and other proteins, such as TNF-IFN-IL-6IL-8, *etc*., resulting in acute respiratory distress syndrome and SIRS, as well as ischemia and hypoxia, which lead to death.

These findings indicate that SARS-CoV-2 infection-induced SIRS and cytokine storms may be one of the major mechanisms of liver injury.

Ischemia and Hypoxia Reperfusion Injury

COVID-19 patients have different levels of hypoxia, with more than 40% requiring oxygen therapy [40]. Ischemia, hypoxia, and even shock may occur as a result of complications such as aspiration distress syndrome, SIRS, and multiple organ dysfunction. Hepatocyte survival can be hampered by lipid aggregation, glycogen intake, and adenosine triphosphate deficiency during ischemia and hypoxia.

Furthermore, the hypoxia of respiratory distress syndrome triggers an oxidative stress response, which induces a persistent rise in reactive oxygen species levels. Reactive oxygen species and their peroxidation products can stimulate redox-sensitive transcription factors, triggering the release of a variety of pro-inflammatory factors and causing liver damage.

The pathophysiological changes described above will exacerbate hepatocyte ischemia and hypoxia, alter toxic metabolite excretion, and worsen liver function damage. As a result, in patients with serious and vital COVID-19 disorder, ischemia and hypoxia can be among the key mechanisms for liver damage.

Drug Hepatotoxicity

Drug-induced liver injury is the third most common cause of liver damage, after viral hepatitis and fatty liver disease (including alcoholic and non-alcoholic). Traditional Chinese patent medicines containing saikosaponins [44-45]. antitumor drugs, antituberculosis drugs, antimalarial drugs, and antibiotics are all important causes of liver injury [46-47].

The majority of COVID-19 patients have a fever, and all of them take antipyretic and analgesic medications, which include acetaminophen and are believed to cause liver harm if taken in excess.

There is currently no proven antiviral treatment, but many patients in the epidemic were given Lopinavir, Abidor, Ritonavir, and other antiviral medications. The CYP3A metabolic pathways can contain electrophilic material, oxygen-free radicals, etc., they can be covalently bound with macromolecular compounds inside the liver cells, induce system membrane lipid peroxidation, Disruption of cell internal and external Ca2 + homeostasis, affect the activity of essential organelles such as mitochondria and endoplasmic reticulum, and ultimately contribute to liver cell loss and death.

Recurrence or Aggravation of an Existing Liver Disease

Globally, chronic liver disease is a big health issue. About 300 million people in China suffer from untreated infectious hepatitis, alcohol-related liver disease, non-alcoholic fatty liver disease, and autoimmune hepatitis. Immune deficiency is typical in COVID-19 patients, including lymphopenia and elevated cytokine levels (including cytokine storms), and it can be a contributing factor for disease incidence and mortality.

Prevention and Treatment

When antiviral and complementary therapies are administered to suppress viral replication, decrease inflammation, and increase immunity in COVID-19 patients with minor liver biochemical anomalies, the primary disease should be managed aggressively, and liver-protective and enzyme-lowering medications should not be used as a preventative measure.
Clinicians should assess and judge the causes of acute liver injury and take corrective precautions when closely observing ALT, AST, complete bilirubin, direct bilirubin, albumin, and PTA in patients with acute liver injury (INR).

Acute liver disease should also be recognised, and liver-protecting and enzyme-lowering products, which have a reasonably well-understood structure and mode of action, should be considered.

Nonetheless, an excessive number of medication types (generally no more than 2) should not be given, and the dose should not be excessive. Respiratory and circulatory care should be improved in patients with serious and vital COVID-19 disease with liver damage, which should be believed to be exacerbated by cytokine storms and microcirculation ischemia and hypoxia.

Extracorporeal membrane oxygenation (ECMO) can be used if extracorporeal membrane oxygenation is needed to increase a patient's blood oxygen saturation. Patients with acute liver failure should be closely monitored and given symptomatic and compassionate care, as well as having their hypoproteinemia fixed.

Stopping or lowering the volume of the suspected medications should be addressed in cases of liver injury caused by drugs, in addition to traditional anti-inflammatory liver defense therapy, and the degree of liver damage should be determined, followed by a modification of the care plan. Treatment with anti-HBV or anti-HCV should not be stopped, but hormones in high doses should not be used.

Overall, the prevention and treatment of liver injury in SARS patients will serve as a model for COVID-19 liver injury patients. For example, in the early stages of the disease, aggressive avoidance and modulation of the inflammatory response are beneficial not only to mitigating nonspecific liver inflammation but also to avoid the occurrence of systemic inflammatory response syndrome to lower the risk of moderate illness being serious or critical.

CONCLUSION

COVID-19 is also associated with liver damage, and the risk of liver injury is greater in patients with serious or critical COVID-19 disease than in those with moderate disease. Direct virus infection, immune injury, drug-induced liver injury, and other mechanisms can trigger liver injury in COVID-19 patients. Recurrence or exacerbation of the underlying liver disease, among other things, systemic inflammatory reaction, ischemia and hypoxia, and recurrence or exacerbation of the underlying liver disease, to name a few. Since the liver is the body's primary processing organ, it is vital to have a healthy liver function that has a major impact on the body's anabolism and disease prognosis.
As a result, physicians should pay more attention to the occurrence of liver damage when diagnosing and treating COVID-19 patients, as well as examine the pathogenesis of liver injury in COVD-19 patients in-depth to establish a fair individualized clinical plan.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare

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