World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

PHYSIOLOGICAL ALTERATIONS IN THE LIVER FUNCTION OF COVID19 INFECTED PATIENTS REVIEW ARTICLE

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Article history:

Received: February 1st 2022
Accepted: March 1st 2022
Published: April 14th 2022

Abstract:

The coronavirus disease 2019 (COVID-19) is a viral respiratory illness which was first detected in Wuhan, Hubei Province, China. A few case studies demonstrated that 14–53% of the cases of COVID-19 reported abnormal levels of liver enzymes during disease progression. Patients with severe COVID-19 seem to have higher rates of hepatic dysfunction. Hepatic injury is common in severe COVID-19 patients, which may be caused by direct injury to the bile duct cells by a virus or indirectly by a cytokine storm. The liver function should be evaluated in all symptomatic COVID-19 patients. In patients with pre-existing liver diseases, special attention should be paid to monitoring and treatment. Immunocompromised persons with severe liver illness, hepatocellular carcinoma, as well as liver transplant patients should have more intense surveillance and personalized therapy methods. Despite the fact that there has been little investigation on patients infected by covid-19 with pre-existing liver illness, the present extensive study casts light on liver disease care during Covid-19.

Keywords:

1. INTRODUCTION

Coronavirus is a single-stranded RNA virus with an enclosed positive envelope. Humans and animals alike are susceptible to it. Human respiratory illnesses have been linked to it [1]. COVID-19, a pandemic caused by the novel SARS-CoV-2 coronavirus, is spreading rapidly. [2]. The SARS-COV-2 virus creates COVID-19, which causes fever, cough, and dyspnea, as well as moderate symptoms such changes in smell and taste, gastrointestinal issues, headaches, and skin indications [3,4,5]. SARS-CoV-2 infects cells via binding to the angiotensin converting enzyme 2 (ACE2) receptor [6]. At present time, there are no specific/targeted medications or vaccines available for SARS-CoV-2. The number of SARS-CoV-2 positive patients is rapidly growing in several parts of the world. As of April 18th, 2020, there were 2,251,633 positive cases and 154,329 deaths worldwide. covid-19 patients with liver damage have a higher mortality and severity. Non-survivors and severe COVID-19 patients have significantly higher serum AST levels than survivors and non-severe COVID-19 patients. Clinicians will be able to better manage the livers of covid-19 patients as a result of the findings of this investigation [7]. The amount of instances in republic of China raises, irregular liver function exam findings were seen in certain covid-19 patients, making the liver the organ that is most commonly injured outside of the respiratory system[8-10]. The clinical characteristics and outcomes of Chinese individuals with covid-19, on the contrary, may change as time goes on, and the pathological- clinical relationship signs as well as the mechanism of coronavirus liver damage remains considerably unknown. Hepatocyte degradation, punctate necrosis, fragment necrosis, bridging, or extensive necrosis with neutrophil infiltration were some of the histological abnormalities seen in COVID-19 patients' livers [11][12].

Within the hepatic lobules of deceased COVID-19 patients, lymphocyte infiltration and mild hepatic sinus dilation were found [11]. The mucosal epithelium was exfoliated, and the gallbladder was substantially filled [12]. The tiny bile duct had a thrombus [13]. SARSCoV-2 does not appear to induce liver harm directly. Liver injury can also be caused by drug-induced liver injury, a history of chronic liver disease, or a COVID-19-related increased inflammatory response [14].

2-Changes in liver function tests among COVID-19 patients

According to the diagnostic criteria , all hospitalized cases of covid-19 were established as SARS-CoV-2 infection by

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Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

nucleic acid testing of respiratory tract samples. The majority of covid-19 patients exhibited lymphocytopenia, leukopenia, and high C-reactive protein levels when they were admitted. The blood oxygen saturation of severe patients was typically 93 percent, with using apartial pressure of 300 for arterial oxygen and a percentage of inspired oxygen for inspired oxygen. In most critical instances, extreme hypoxemia besides abrupt respiratory failure developed. Furthermore, look for indications of infected shock as well as manifold organ dysfunction or failure, for instance; liver failure, renal damage, in addition to heart damage, were still present in the severe and critical patients (Fig. 1). Chen et al.[15] was the first to report abnormal liver enzymes in covid-19 patients. The levels of Alanine aminotransferase (ALT); aspartate aminotransferase (AST); as well as lactic dehydrogenase were all elevated in 43 (43.4%) of the 99 people with coronavirus from Wuhan. Only one case had exponentially high aminotransferase levels such as ALT of 7590 U/L and AST of 1445 U/L . However, no case of intrahepatic cholestasis or liver failure has been described. With extensive information on liver function testing. Coronavirus-19 has been confirmed in the United State for the first time in China [16] . On the fourth day of his sickness, the patient was brought to the hospital, and by the ninth day, his ALT and AST serum levels had climbed from 68 to 203 U/L and 37 to 89 U/L, respectively. According to another study, only one of 12 severe covid-19 patients from the city of Shenzhen had exhibited untypical liver enzymes (ALT 107 U/L and AST 62 U/L) [17]. The tight link between aberrant liver biochemistries and covid-19 severity has recently been revealed by increasing data. A total of 1099 Covid-19 patients from China's mainland, 39.4 percent having AST >40 U/L and 28.1% having ALT >40 U/L, with the majority of these cases being acute and critic [18]. Another multicenter retrospective investigation study 32 patients discovered that the average blood levels of ALT, AST, and bilirubin were significantly higher in more acute or critical occasions than the control cases. 17 serum levels of ALT and AST were significantly higher in acute to critical ones than what were registered in mild to moderate examples in 265 covid-19 patients from Shanghai [19

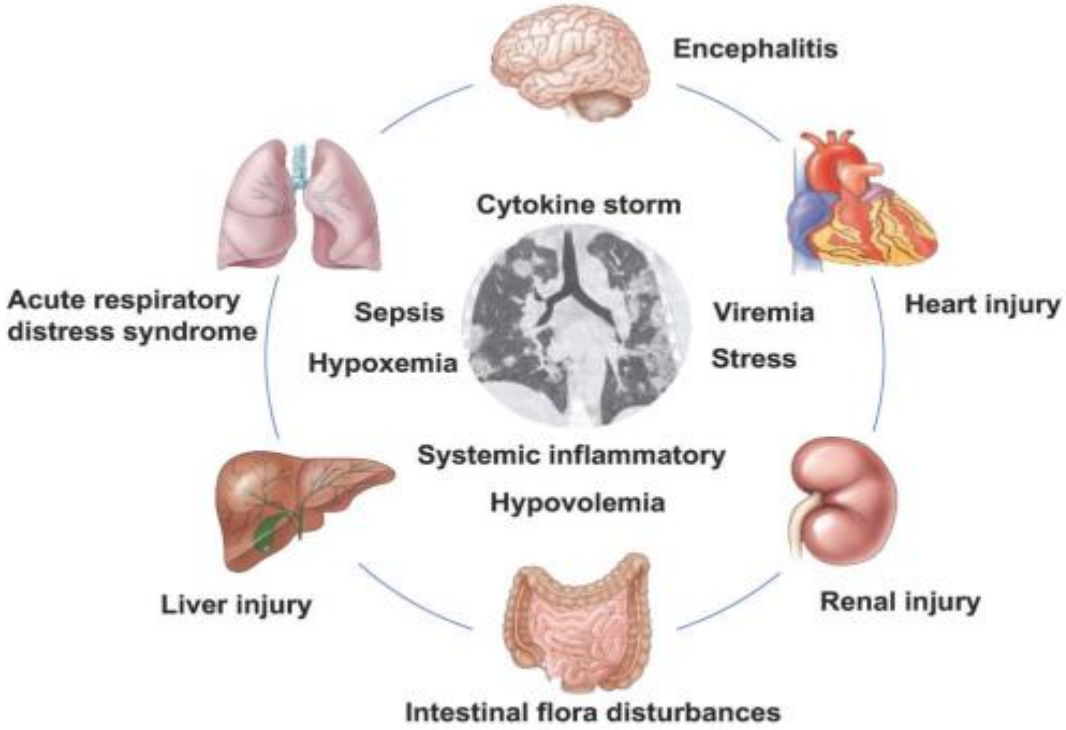

Fig. 1. Complications and disease mechanisms in patients with 2019 coronavirus infection.

3-COVID-19 liver damage caused by a coronavirus

Abnormal liver biochemistry has likewise been described in individuals with Sars and Mers [20-21], hinting that the corona virus infection can lead to liver damage. However, it's uncertain if the coronavirus is directly responsible for the liver damage. Sars-Cov-2 is closely linked to Sars-Cov, they

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Volume-9, April 2022
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both have the receptor itself, the primary target organ for infection caused by corona virus is the lung, which is produces angiotensin converting enzyme 2 (ACE2). However, it's uncertain if the coronavirus is directly responsible for the liver damage. SARS-CoV-2 is closely in relation with SARS-CoV, and they have alike receptor, angiotensin altering enzyme 2 (ACE2); with the lung being the primary object organ of corona virus infection. ACE2 is expressed in the liver, according to previous RNAseq data from the database of the human protein atlas [22]. However, ACE2 look is present in only a small percentage of cholangio-cytes, excepting Kupffer cells, hepato-cytes, or endothelial cells [23]. Data from two distinct cohorts of single cell sequencing recently suggested that ACE2 expression in human liver tissues is cholangiocyte-specific. According to single cell sequencing (succession) and immunohistochemistry; ACE2 was exclusively manifested in bile duct epithelial cells up to normal liver tissues, also only a small bit in hepatocytes. In a mouse model of acute liver injury regarding partial hepatectomy; ACE2 appearance in the liver was down-regulated on the first day, however the normal level was two folded on the third day and recovered to normal on the day seven when the liver rehabilitated and hepatocyte proliferation ceased. The findings suggested that compensatory proliferation of hepatocytes generated from bile duct epithelial cells mediated the elevation of ACE2 expression in the liver following acute liver damage[24-25]. In Covid -2 and SARS patient may or may not affect cholangiocytes via ACE2 destruction to liver cell in COVID-19 individuals with hepatocytes damage evidenced mostly as an increase in serum aminotransferases but not alkaline phosphatase. COVID-19 liver damage could thus have a different pathophysiology and cause.

4-COVID-induced liver damage pathophysiology

Hepatic damage during COVID-19 infections is thought to be caused by a number of processes (Fig. 2)

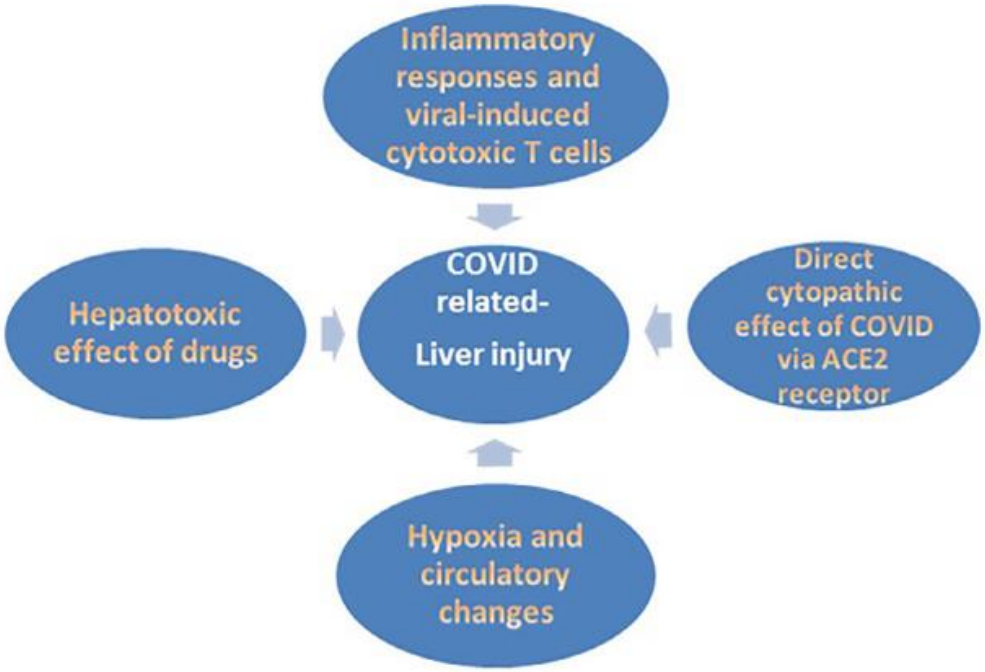

Fig. 2. Mechanisms of liver injury in COVID-19 infection.

Hypoxia and heart failure have been linked to hypoxic hepatitis in covid-19 patients who are critically ill [26]. On elevating right atrial pressure and impeding venous return, intense levels of positive end-expiratory pressure (PEEP) can lead to hepatic congestion also. However, abnormal liver laboratory tests are common in steady patients who are in no need to mechanical ventilation, therefore these mechanisms cannot account for all occurrences of liver disease. Besides, the aminotransferase increase pattern in this group of individuals differs from that of hypoxic hepatitis [27] SARS-CoV-2 has direct cytopathic effects by interacting with ACE2 receptors, which are found on a variety of tissues comprising the heart, lungs, kidney, liver as well as blood vessels [28]. According to single-cell RNA-seq data from healthy human hepatic tissues, cholangiocytes

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Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
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(59.7%) have much higher ACE2 expression than hepatocytes (2.6%) [29]. Despite the wide range of ACE2 expression, cholestatic injury isn't a common symptom of COVID-19 disease, and ALP and bilirubin levels were raised in a small number of patients only [30-31]. In certain studies, GGT, a potential diagnostic marker for cholangiocyte case, was shown to be up to 72 percent higher in highly infected COVID-19 individuals [32-33]. Wang, et al. [34], Characteristic coronavirus particles having spikes in the cytoplasm of hepatocytes were detected using ultrastructural analysis of postpartum liver tissue samples from two patients deceased from covid-19. Symptoms of virus-induced hepatocyte damage include mitochondrial enlargement, cell membrane dysfunction as well as endoplasmic reticulum dilatation. Furthermore, the ability of the virus to multiply in hepatocytes was demonstrated in this investigation. This is the first research to link the cytopathic liver cell affection caused by SARSCoV-2 leads to liver dysfunction. There are discrepancies in the expression of ACE2 in SARS-CoV-affected organs [35]. The presence of ACE2 receptors in the liver does not explain SARS-ability CoV-2's to infect the liver .It's possible that viral invasion will increase ACE2 expression in hepatocytes. Extra-ACE2 receptors or co-receptors [34] are another possibility.

ACE2 hepatic expression was much higher in female tissue, which could explain why females with COVID-19 have a better prognosis than males [36-37]. Also necessary for viral particle proteolytic activation and dissemination is TMPRSS2, a SARS-CoV2-interacting host receptor demonstrated, revealed in hepatocytes besides cholangiocytes [38]. More research is required to determine why COVID-19-induced liver function abnormalities are usually shown as an increase in serum aminotransferases in preference alkaline phosphatase and bilirubin levels. More research is needed to determine why COVID-19 leads to abnormal liver function (functions) are (is) mostly exhibited as an increase in serum aminotransferases instead of bilirubin and alkaline phosphatase. Furthermore, inflammatory response to Covid-19 could exacerbate hepatocytes damage. Testing in Lab discloses an rise in plasma cytokines as well as other inflammatory reactants for example as interleukin(IL) -1, IL-6, and tumor necrosis factor in some patients, resulting to cytokine storm. Hepatic immune-mediated injury is caused by viral-induced cytotoxic (CD8) T cells, as well as the activation of a imperfectly regulated innate immunological reply. [39]. The gastrointestinal vascular barrier and changes in the gut flora are another potential cause. Because severe COVID-19 infections are prothrombotic, More research is needed to confirm that the liver alters cytokines and clotting factors are mad public, which is a causal factor in COVID-19 disease pathogenesis [40].

-COVID-19 infection causes abnormal liver 5functioning

During the course of the SARS-CoV-2 infection, in approximately half of cases , abnormal liver blood tests were discovered. In a thorough systematic review relating to eleven studies investigating the liver laboratory parameters concerning 2541 patients infected with SARS CoV-2, increased AST and/or ALT (25%), increased LDH (20%), raised bilirubin (3%), and normal ALP were detected in almost all instances [41], because of the pattern of overexpression of ACE2 on cholangio-cytes, this could indicate limited virus-related liver damage. Both AST and ALT levels were commonly raised in the largest reported trial to date, which included 5700 participate (58.4 percent and 39.0 percent of patients, correspondingly) [42], GGT levels were found to be above 3 ULN in 41% of patients according to the research [32], while GGT was found to be raised in severe cases yet not linked with increased ALP in another investigation [43]. Furthermore, COVID-19 infection was not always linked to significant changes in the lest of liver function [44]. A few suitcases of acute liver failure in patients infected with the virus have been recorded [45]. Because it is not always caused by the liver, other causes (reasons) of transaminitis must addressed, such as myositis, ischemia, and cytokine

release syndrome

Upper levels of bilirubin, ALT and AST, and were linked to a substantial rise in the intensity with COVID-19 infection in another big published meta-analysis that included twenty reviewing studies with 3428 COVID-19 infected individuals [47]. According to one major study, liver damage throughout COVID-19 infection is linked to a 9-fold increased danger of acute infection [32]. In SARS and MERS, tests concerning liver function was also identified as a significant risk factor for a poor result and death [48,49]. Many recent investigations have found that severe patients had higher serum ALT, AST, and GGT levels than non-severe or mild patients [50,51].Increased access levels of these indicators were connected with relation to patient mortality in a recent meta-analysis [52]. Other research has related higher levels of those variables to a worsening lung CT score [53], an increase in the number of patients requiring ICU care [54], as well as a lengthier stay in the hospital [55]. Elevated liver parameters were found to be present in 58.06 percent to 78 percent of COVID-19 mortality cases

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Volume-9, April 2022
ISSN: 2749-3644

[56-57].According to Lei et alstudy .'s [52], AST was the initial reference point identified to be raised upon hospital admission, and it was also related with the highest mortality. Guan et al.[51] In a recent study involving nearly 1100 Chinese patients, researchers discovered that high serum AST and ALT levels were seen in nearly (18%) and (29%) of patients having non-severe COVID-19 infection, respectively, in comparison with 56% and 28% of patients patient suffered from acute COVID-19 disease [51]. Previous research [52] suggests that immune-mediated systemic inflammation plays a crucial role in hepatocyte damage related with severe COVID-19 contagion. Gordon et al. recently proposed that mitochondrial proteins may interact directly with the virus, suggesting a possible mechanism for the increased aminotransferase -dominant profile of liver [57]. According to Wang et al.[54] aberrant liver enzyme are linked to disease severity, upper radiology scores and higher alveolar-arterial oxygen partial pressure difference, upper GGT, upper ferritin, inferior albumin and reduced CD4+ T cells and B lymphocytes [34]. Patients suffering from aberrant liver markers of the hepatocellular type or the mixed ones had a higher risk of advance to sever illness, according to Cai et al.[32] who recorded that in patients with abnormal liver markers of hepatocellular type or mixed one, upon admittance had greater chances of advance to acute disease stage [32]. In cirrhotic COVID-19 infected, the AST/ALT ratio, total bilirubin, and ALT/ALP ratio were found to helped predict survival [58]. The pooled incidence of elevated liver enzymes was 23.1 percent at early exhibition and 24.4 percent throughout the disease, according to a current meta-analysis of 15,407 COVID-19 patients [60]. Another new research project from Q Wang et al. [61] looked at non-permanent divergence in COVID-19 disease progression and found that 12.6 percent of patients suffering from both increased ALT and AST in moderate cases and (46.2%) in severe cases had both elevated ALT and AST. The vast majority of patients' ALT levels rose between days four and seventieth of their hospitalization, having an average of (7.3 and 10.7 days) in acute and slight cases, correspondingly. Decreased lymphocyte count, increased neutrophil count, and male gender are all common characteristics linked to heightened indications of liver disease [52]. On CT imaging, the severity of lung lesions could be a sign of liver damage. As a result, individuals with severe pulmonary lesions must have their liver function closely monitored in order to detect any hepatic injury early[53]. In moderate COVID-19 cases, liver damage is usually transitory and doesn't need to be treated [33]. According to the AASLD, all COVID-19 patients having uncommon liver functions must be tested for HCV and HBV, furthermore any unneeded imaging should be evaded [61]

CONCLUSIONS

This review discusses the consequences of COVID-19 infection on the liver, and the prognostic significance of liver laboratory testing. illness outcome markers to better understand the mechanisms of COVID-19 infection and drug-induced disease, more research is needed. There is currently inadequate proof for COVID-19 infected hepatocytes or virus-related liver damage as well as it is difficult to characterize the immune system's role in the virus's liver injury. The therapeutic rehearsal of handling COVID-19 patients with liver damage requires a mechanistic knowledge of the connection between SARS-CoV-2 infection and liver disease. In the future, further research should be focused on the mechanism of event hepatic injury in COVID-19, as well as the impact of undiagnosed liver disease , COVID-19 treatment and the result.

Author's contribution

Amera Kamal Mohammed: Conceptualization and design, as well as article drafting, statistics analysis as well as interpretation of data.
Thanaa Abdulmahdi: The gathering of information
Iqbal hussain abdulkareem: revising of the article.

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