Article

JOURNAL OF UNIVERSITY OF BABYLON
For Pure and Applied Sciences (JUBPAS)

Vol.30; No.4.| 2022

Hepatic Injury in COVID-19 Patients

Hadeel Tariq Al-Shalash[1], Layan Yaseen Khaleel[2],Shaymaa Abdullah Ahmed [3]

[1]Al-Noor University College / Medical Laboratory Technology D. Iraq, hadeel.tariq@alnoor.edu.iq
[2]-University Of Mosul | College Of Veterinary, Microbiology Branch layanyaseen@uomosul.edu.iq
[3] Al-Noor University College / Anesthesia Technology D. Iraq, Shaymaa.abdullah@alnoor.edu.iq

***Corresponding author email: hadeel.tariq@alnoor.edu.iq**

Received:	14/10/2022	Accepted:	27/12/2022	Published:	31/12/2022

Abstract

The practical studies have already proved that the laboratory liver tests are highly useful in the evaluation and treatment of patients with hepatic dysfunction. It has been found that some of the enzymes and the end products of the metabolic pathway such as serum bilirubin, alanine amino transferase, aspartate amino transferase, ratio of aminotransferases, alkaline phosphatase, gamma glutamyl transferase, 5' nucleotidase, ceruloplasmin that are very sensitive for the abnormality occurred may be considered as an outstanding biochemical marker of liver dysfunction. It is noticed that the novel coronavirus Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) infection mostly leads to respiratory distress syndrome, at the same time liver injury is also documented. As a matter of fact, the mechanism of liver injury is limited and poorly understood. Therefore, the hepatic injury might be due to a consequence of systemic inflammatory response, viral infection of hepatocytes, or it comes as a result of intensive care treatment or drug toxicity. The host angiotensin-converting enzyme 2 (ACE2) receptors, which are widely distributed in type 2 alveolar cells, are the proposed route of viral entrance. It is interesting to note that ACE2 receptors are found in the liver's cholangiocytes, vascular endothelium, and gastrointestinal tract.

Histological pictures compatible with vascular alterations are observed, characterized by the increase in number of portal vein branches associated with lumen massive dilatation, partial or complete luminal thrombosis of portal and sinusoidal vessels, fibrosis of portal tract, focally markedly enlarged and fibrotic.

Keywords: Liver injury, ACE2, Chronic liver disease, liver morphology in COVID 19 disease, SARS-Cov-2 infection and liver biopsy

مجلة جامعة بابل للعلوم الصرفة والتطبيقية | ISSN: 2312-8135 | Print ISSN: 1992-0652 | www.journalofbabylon.com | jub@itnet.uobabylon.edu.iq | info@journalofbabylon.com

Article

JOURNAL OF UNIVERSITY OF BABYLON
For Pure and Applied Sciences (JUBPAS)

Vol.30; No.4.| 2022

إصابة الكبد لدى مرضى كوفيد -19

هديل طارق سعدون [1] ليان ياسين خليل [2] شيماء عبدالله احمد [3]

[1] كلية النور الجامعة \قسم تقنيات المختبرات الطبية\ العراق – نينوى hadeel.tariq@alnoor.edu.iq
[2] جامعة الموصل \كلية الطب البيطري \ قسم الاحياء المجهرية \العراق– نينوى layanyaseen@uomosul.edu.iq
[3] كلية النور الجامعة \قسم تقنيات التخدير \ العراق– نينوى Shaymaa.abdullah@alnoor.edu.iq

*Corresponding author email: hadeel.tariq@alnoor.edu.iq

Received:	14/10/2022	Accepted:	27/12/2022	Published:	31/12/2022

الخلاصة

لقد أثبتت الدراسات العملية بالفعل أن الفحوصات المخبرية للكبد مفيدة للغاية في تقييم وعلاج مرضى القصور الكبدي. لقد وجد أن بعض الإنزيمات والمنتجات النهائية للمسار الأيضي مثل مصل البيليروبين ، ألانين أمينو ترانسفيراز ، أسبارتات أمينو ترانسفيراز ، نسبة الأمينو ترانسفيراز ، الفوسفاتيز القلوي ، جاما جلوتاميل ترانسفيراز ، 5 'نيوكليوتيداز ، سيرولوبلازمين التي تعتبر حساسة للغاية لحدوث الشذوذ و يمكن اعتبارها علامة كيميائية حيوية بارزة لخلل في وظائف الكبد. كما لوحظ بشكل واضح أن فيروس كورونا المستجد المتلازمة التنفسية الحادة الوخيمة Corona Virus-2 (SARS-CoV-2)) قد أدى في الغالب إلى متلازمة الضائقة التنفسية ، ولكن في نفس الوقت تم توثيق إصابة الكبد أيضًا. في واقع الأمر ، فإن آلية إصابة الكبد محدودة وغير مفهومة بشكل جيد ، لذلك قد تكون الإصابة الكبدية نتيجة استجابة التهابية جهازية ، أو عدوى فيروسية لخلايا الكبد ، أو ناتجة عن علاج العناية المركزة أو الأدوية. تسمم . مستقبلات الإنزيم المحول للأنجيوتنسين 2 (ACE2) ، والتي يتم توزيعها على نطاق واسع في الخلايا السنخية من النوع 2 ، هي المسار المقترح لمدخل الفيروس. من المثير للاهتمام أن نلاحظ أن مستقبلات الإنزيم المحول للأنجيوتنسين 2 توجد في خلايا الكبد الصفراوية وبطانة الأوعية الدموية والجهاز الهضمي. كما لوحظت صور نسيجية متوافقة مع التغيرات الوعائية ، والتي تتميز بزيادة عدد فروع الوريد البابي المرتبطة بالتوسع الهائل في التجويف، والتخثر اللمعي الجزئي أو الكامل للأوعية البابية والجيوب الأنفية ، وتليف السبيل البابي ، والتضخم بشكل ملحوظ والتليف.

الكلمات المفتاحية : إصابة الكبد، الإنزيم المحول للأنجيوتنسين 2، أمراض الكبد المزمنة ، مورفولوجيا الكبد في مرض كوفيد 19، عدوى سارس-كوف -2 وخزعة الكبد.

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

1-INTRODUCTION

Now, there have been confirmed instances of COVID-19 reported in every single country in the world, and the total number of cases has crossed one million to this point [1]. Following this, Novel Coronavirus Infected Pneumonia (NCIP) spread quickly over the world, the World Health Organization (WHO) declared NCIP an international public health emergency on January 30, 2020. People who are infected with the SARS-CoV-2 virus have a slightly increased risk of becoming critically ill and perhaps developing acute respiratory distress syndrome (ARDS), a condition that, in some instances, may result in death. However, this risk is quite low. It is generally agreed that SARS-CoV-2 infections will first manifest themselves in the respiratory system [2]. Initial clinical studies from China, the U.S., and Italy highlighted fever, cough, exhaustion, and shortness of breath. Later research revealed extra pulmonary signs of the disease. Initial clinical investigations highlighted fever, cough, exhaustion, and shortness of breath, but later study did not. Despite fever, cough, tiredness, and shortness of breath, a virus is thought to be the cause of the illness [3].

The mortality rate in China due to the Corona virus has ranged ranging from 5.8 percent in Wuhan to 0.7 percent throughout the remainder of the nation, with a percentage of those deaths happening in patients who were either elderly or had related diseases (obesity, hypertension, diabetes, cardiovascular disease, chronic lung disease and cancer) [4]. The progression of the disease and infection with the Corona virus can be broken down into three stages: stage I (early infection), stage II (pulmonary phase), and stage III. Stage I refers to the early infection stage, while stage II refers to the pulmonary phase. In this context, "Stage I" refers to the initial infection, and "Stage II" to the pulmonary phase of the disease (hyper inflammation phase) Secondary lung involvement (fever, cough) is the most common and serious clinical manifestation; however, infection with this SARS-CoV-2 virus can induce systemic and multi-organ disease, including gastrointestinal symptoms such nausea, vomiting, or diarrhea. This is despite the fact that secondary lung involvement is the most common and serious clinical manifestation [5].

Contrary to popular belief, subsequent lung involvement is not the most common or significant clinical symptom. This is not the case, despite the widespread belief that this is the case. After the lungs, the liver is frequently the second organ to suffer damage as a result of the sickness [6]. An increasing number of patients are developing gastrointestinal involvement, which can be recognized by symptoms such as nausea, vomiting, diarrhea, abdominal discomfort, and gastrointestinal bleeding. This condition affects an increasing proportion of people. In some of the cases, abnormalities in the laboratory, such as damage to the hepatic and pancreatic tissues, have been detected [7].

2-Postulated Mechanisms of Liver Injury

The severe acute respiratory syndrome (SARS) is an acute viral disease that is caused by the coronavirus that is associated with SARS (SARS-CoV) [5]. In November of 2002, it was found for the first time in Guangdong Province, China, as well as Hong Kong. However, it did not take long for it to spread to a total of 29 countries and regions all over the world [12]. Patients who are infected with SARS-CoV frequently suffer from a persistent fever, headache, and aches and pains in the muscles, in addition to a decreased white blood cell count and varied degrees of damage to the liver. The white blood cell count of the patients is also quite low [16].

A person's unique medical history and other factors influence the underlying causes of liver disease. There are a number of factors that might induce liver damage, including an underlying liver problem, medications used for COVID-19 treatment, direct exposure to the virus or a convoluted course of the disease. Each of these components might have an impact. Even after accounting for these factors, the mortality risk of COVID-19-positive patients with hepato-pancreatic injury is 3.4 times higher than that of COVID-19-positive patients without hepato-pancreatic injury (OR 3.39, 95 percent CI 3.15-3.65). Patients who test positive for COVID-19 but do not have hepato-pancreatic disease are impacted. however not at all the case (Virus-inhibiting medications, antibiotics, and steroids) of coronaviruses—SARS-CoV, MERS-CoV, and the recently identified SARS-CoV-2, which generates COVID-19—have been linked to liver damage . All three of these coronaviruses were revealed to be present in patients with severe acute respiratory syndrome. [8]. In COVID-19-positive patient populations, Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values that are indicators of liver injury were found to be increased in 4–39% and 4–58% of patients, respectively. [10]. The levels of alkaline phosphatase, also known as AlkP, were found to be abnormal in anywhere between 2 and 5 percent of the cohorts. Hypoalbuminemia was seen in individuals who tested positive for COVID-19 in 55 percent of the cases, and researchers discovered that some patients had low blood albumin levels as well as high serum bilirubin levels [11].

One to eighteen percent of the patients exhibited symptoms of hyperbilirubinemia. It would indicate that COVID-19-positive infections are associated with a much higher incidence of hepatic injury. Multiple studies came to the conclusion that between 1 and 11 percent of COVID-19 patients who were already suffering from hepatic impairment had chronic liver problems. Vaibhav Rastogi [13] compared to Li W. *et al* [16] who found an association between elevated levels of ALT, AST, AlkP, and total bilirubin and increased mortality in their retrospective cohort of 5771 COVID-19-positive people, It has been observed higher mortality and disease severity in COVID-19-positive patients who had suffered from hepato-pancreatic injury. COVID-19-positive patients with hepato-pancreatic damage had this finding. According to the findings of Vaibhav Rastogi [13], those who tested positive for COVID-19 and had an elevated level of AST also had a significantly more severe form of the disease as well

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

as liver damage in COVID-19. Hepatic damage caused by COVID-19 can be the consequence of a number of different pathophysiologic routes, including damage caused directly by the virus, damage caused by the immune system as a result of excessive inflammatory responses, and damage caused by drugs. COVID-19 has the potential to trigger each of these pathways. Because the virus has a direct cytopathic effect on the liver, SARS-CoV2 has the potential to induce damage to the liver. The liver tissue of the COVID-19 patient revealed signs of necrosis, microvesicular steatosis, and cellular infiltration when it was biopsied after the patient had passed away. The SARS-CoV2 virus gains access to cells by first establishing a connection with the membrane-bound ACE2 receptor, angiotensin-converting enzyme 2. This positions the cells in relation to the 17 markers in a way that increases their likelihood of dying .

Cholangiocytes have ACE2 receptors that are remarkably similar to those found on type 2 alveolar cells. This is due to the fact that ACE2 receptors are expressed on cholangiocytes to a substantially greater extent than they are on hepatocytes. As a direct consequence of this, COVID-19 carries the same risk of causing damage to the liver as it does to the lungs [15]. As a direct consequence of this, the liver is one of the organs that COVID19 can impact. The coronavirus family seems to target the liver, regardless of whether the patient is healthy or has a pre-existing hepatic disease. Hepatitis patients with modest to moderate increases of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin levels are seen in the early stages of SARS. These patients also have high alanine and aspartate aminotransferase values (AST). In autopsies of SARS patients, angiotensin-converting enzyme 2 (ACE2), the receptor for cell entrance, is found in parenchymal cells and the vascular endothelium of other organs, including the liver, according to Li W. [16], who showed that SARS-CoV utilises this receptor.

Banales *et al* discovered that the liver's endothelial cells overexpress ACE2. As a result of this, the SARS-CoV may be able to infect the liver. Virus-induced damage to the bile duct cells rather than to the liver cells may be to blame for the liver injury found in COVID-19 patients because bile duct cell ACE2 receptor expression is higher than that of liver cell. This is due to the ACE2 receptor being expressed on bile duct cells. [17]

A number of meta-analyses have also found that COVID-19 patients with severe disease have a greater rate of liver injury and elevated ALT levels than patients having a less serious illness [26]. Angiotensin-converting enzyme allows the SARS-CoV-2 virus to enter cells (ACE2). Hepatocytes and the epithelial cells that line the bile ducts are both rich in ACE2. As a result, hepatocytes and the epithelial cells lining bile ducts could develop into viral target cells.[18]

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

3- Liver function test (LFT) abnormalities

The prevalence might be between 14 and 53 percent. There have been reports of between 4 and 7 extremely unusual incidences of acute liver injury in COVID-19 people. A number of aminotransferases, including The serum levels of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase, and bilirubin were found to be elevated. Forty abnormalities in liver function tests could be the result of immune-cytopathic damage brought on by the cytotoxic and inflammatory response brought on by the SARS-direct CoV. It is not feasible to determine if the liver damage was brought on by the SARS-CoV-2 virus, one of its complications [33]. or the adverse reactions brought on by the treatment drugs. The SARS-CoV-2 has the ability to influence the progression because of its direct toxicity to the liver, reactivation of a chronic hepatitis virus, and liver damage caused by drugs that target the SARS-CoV [34]. Tocilizumab, remdesivir, chloroquine, hydroxychloroquine, and statins, all of which are used to treat COVID-19, can affect the liver. Additionally, antibiotics and antifungal medicines used to treat bacterial and fungal pneumonia also have this potential. Around ten percent of patients in a randomized controlled study of remdesivir in China experienced high serum bilirubin, which was not substantially greater than the placebo group. The trial was conducted in China (9 percent). Remdesivir was found to elevate AST in 5% of patients, which did not differ considerably from the control group (12 percent) [8]. Another randomized controlled trial in this investigation indicated that the increase in AST and ALT was not substantially different with remdesivir than it was in the placebo group. This result was in line with the outcomes of the earlier trial. The results of this study mirrored those of a previous one in every way. [35]

People who are diagnosed with severe cases of COVID-19 were more likely to have abnormal LFTs than people who are diagnosed with mild cases of COVID-19. The severity of COVID-19 can be determined by whether or not the patient has hypoalbuminemia while they were hospitalized. The majority of instances of hepatic dysfunction are temporary and do not require any kind of specialized therapy. There are not a lot of data available on the histology of the liver in COVID-19 patients, and the majority of its traits aren't particularly unique. [36]

4- Histopathological Study of Liver in COVID-19 Patients

Xu *et al* [20] revealed the first postmortem findings of a patient who died of severe COVID-19 , the histological analysis of his liver revealed mild steatosis and little inflammation in the hepatic lobule and portal system. It is yet unclear if these changes are the effect of the viral infection or the medications used to treat it.. A peripheral blood examination revealed that the patient had a disease associated with inflammation, with significantly fewer even so, their peripheral blood contained hyperactive CD4 and CD8 cells. Hepatocellular dysfunction could result from

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

cytotoxicity granules in CD8 cells, CCR6+ Th17 CD4 T cells, and other factors were also shown to rise [25]. According to Tian S et al., [21] a postmortem investigation of liver tissue from four COVID-19 patients demonstrated mild sinusoidal dilatation and localized macrovesicular steatosis. In the portal regions, there was a small degree of lymphocytic infiltration, although this was not a significant finding. It was possible to extract RNA from the liver of one of the patients using RT-PCR, which is a type of reverse transcription-PCR. Despite the fact that the bile duct epithelium includes more ACE2 receptors, there is no evidence that the bile duct has been damaged [29]. Even though only a small percentage of patients had a liver biopsy during the SARS-CoV outbreak in 2002, between 23 and 60 percent of patients showed signs of hepatic impairment. This was the case despite the fact that only a minority of patients received one. This demonstrated moderate to severe lobular lymphocytic inflammation, in addition to the ballooning and death of hepatocytes. The high mitotic statistics, which are indicative of a condition that is rapidly expanding, were the aspect that stood out the most (positive Ki-67). In chronic hepatitis C infection, the Ki proliferative index of hepatocytes ranges between 0.45 and 1 percent. This indicates that hepatocytes are in a highly replicative phase because of this range. According to immunohistochemical studies, Hepatocytes' Ki proliferation index was considerably elevated during SARS-CoV infection than the Ki proliferative index of hepatocytes during chronic hepatitis C infection and liver regeneration [32].

The stoppage of the cell cycle that was most likely brought on by the SARS-CoV infection was the cause of the mitotic index. There is a strong possibility that COVID-19 and the other COVID strains 28 have the same pathogenesis.

A considerable increase in mitotic cells, as well as eosinophilic aggregates and balloon-like hepatocytes, was found on histological examination of liver biopsies taken from SARS patients. According to Chang *et al* [12] SARS-CoV may enhance the rate of apoptosis in liver cells, which may result in damage to the liver.

Other studies have demonstrated that the SARS-CoV directly attacks liver tissue and causes damage to the liver by utilizing a protein that is particular to SARS. Through a pathway that is dependent on caspases, this protein has the ability to induce apoptosis in cell lines derived from a variety of tissues, including the lung, kidney, and liver.[33]

It is important to keep in mind that the antibiotics (macrolides, quinolones), antivirals (ribavirin), steroids, and other medications used to treat individuals with SARS may induce damage to the liver, which may be permanent in certain cases. A number of antiviral drugs, such as Remdesivir, lopinavir, ritonavir, and corticosteroids, are potential of producing drug-induced liver damage [14]. This is because severe COVID-19 instances are associated with high levels of liver enzymes and pro-inflammatory markers. This was demonstrated by study of the researchers at the source [16] which found that differences in laboratory markers were more likely caused by the pharmaceutical therapy than they were by COVID-19 itself and this was verified by the findings of this study . The cytokine storm syndrome, which is brought on by COVID-

19, is another mechanism that has a high probability of being involved in the hepatopancreatic injury [8].

The fact that Xu *et al* [20] found significant microvascular steatosis in addition to mild lobular and portal activity lends credence to the theory that the injury was brought on by either an infection with SARS-CoV-2 or by drug-induced liver injury. A postmortem biopsy performed on The liver tissue of the COVID-19 patient showed microvesicular steatosis, necrosis, and cellular infiltration. Many theories and hypotheses have been proposed by researchers in this field to try to explain this occurrence.

According to the findings of Tai-Nin Chau and colleagues, the presence of acidophilic chemicals and ballooning of hepatocytes in liver specimens imply that apoptosis caused by caspase activation due to SARS-coronavirus is largely mediated through liver damage [18]. This conclusion was reached after the researchers found that liver specimens contained acidophilic chemicals. Within the liver, microvesicular fatty change, focal hemorrhages, and hepatocyte necrosis were documented by Poutanen *et al* [19], along with dispersed acidophilic particles. However, no viral inclusions were observed. The process of micro vesicular fatty change is the name given to the transformation of fatty acids that takes place in microvesicles.

About 14-53% of COVID 19 disease hospitalized patients are affected by this condition. The AST/ALT readings are usually one to two times higher than the other readings. In more severe cases, ULN GGT levels were found to be higher above the typical range. In both the mild and the severe cases, alkaline phosphatase levels were found to be normal. 75.2 percent of patients had nonspecific liver biopsy abnormalities, which included microvesicular steatosis, isolated necrosis, and mixed lobular and portal activity. Liver cell malfunction was the primary cause of the majority of the abnormalities found in the liver test [22]. A greater possibility that the condition will become more severe, as well as a prolonged period of viral shedding. In the examination of liver biopsy , there were a number of nonspecific observations made, some of which include microvesicular steatosis, mixed lobular and portal round-cell inflamatory activity, and localized hepatocyte necrosis. The results of the liver biopsy point to immune-mediated liver destruction by T cells rather than direct cytopathic damage by virus-specific effector cells, as found in other viral respiratory diseases [21]. This is indicated by the fact that the liver was destroyed. Hepatocytes that had undergone a significant amount of apoptosis in the liver were found to have larger mitochondria, dilated endoplasmic reticulums, and decreased glycogen granule reserves, as stated in a recent study [26]. In a histological study of the liver of corona patients, the following was found:

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

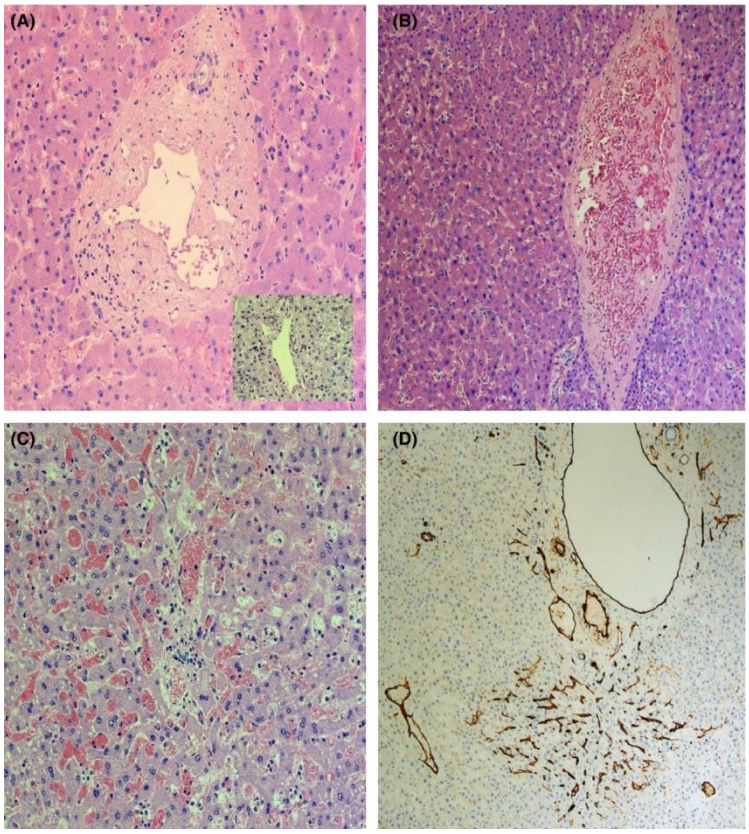

FIGURE 1 A: Regular liver architecture with scattered portal and lobular lymphocytes, moderate portal fibrosis; widened portal vein with fibrotic walls; bile duct without significant histological alteration. Compare normal portal tract in cadaveric liver (H&E, 100X); B: diffuse alterations of intrahepatic vascular structures characterized by severe dilatation and complete luminal thrombosis (H&E, 100X); C: portal vein and periportal sinusoids occlusive thrombosis (H&E, 100X); D: CD34 expression in abnormal portal vein branches endothelium and diffuse network of sinusoids in all parts of the lobule (100X) . [30]

There was only mild to moderate portal fibrosis; the biliary intrahepatic tree did not show any significant histological or structural alteration; and the lobular architecture was well preserved in all of the samples (Figure 1A). [30]

Intrahepatic vessels (portal branches and sinusoids) showed a wide range of structural abnormalities, as well as partial or whole luminal thrombosis (Figure 1B,C). CD 34 was found on aberrant sinusoids in all lobular zones of the liver (Figure 1A) (Figure 1D). No significant changes were seen in the central veins' lumen size or wall structure during the experiment [31].

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

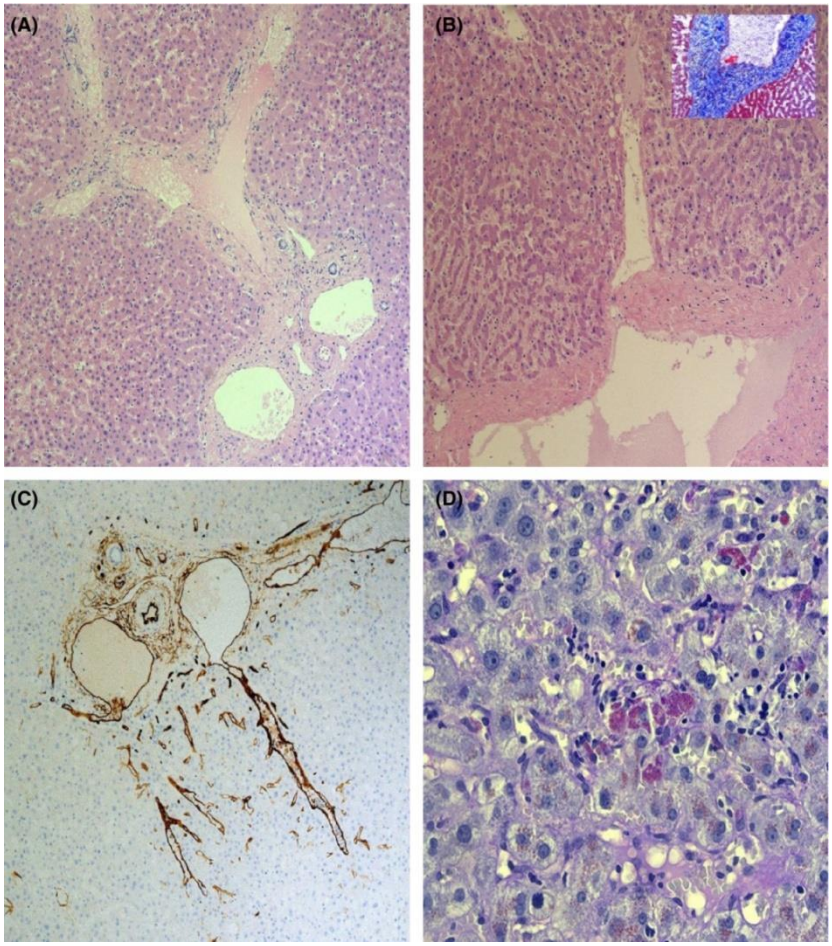

FIGURE 2 A: Roughly enlarged portal field with proliferations of portal veins and luminal severe dilatation (H&E, 100X); B: severe portal vein wall fibrosclerosis (H&E, 100X), highlighted by trichrome stain (inset) (100X); C: portal veins showing lumen focally herniated in periportal liver parenchyma and completely coated by hepatocytes (CD34, 100X); D: activated Kupffer cells with large cytoplasm containing necrotic debris (PAS diastase, 100X)(A)(B)(C)(D) . [30]

Portal veins were found to have increased in most areas, which was associated with substantial luminal dilatation (Figure 2A) as well as wall fibrosis in the majority of portal fields (Figure 2B). Additionally, the liver cellular plates fully encircled the lumen of many portal veins, which were found in the periportal liver parenchyma and focally herniated (Figure 2C) [30]. Findings have shown that the cytoplasm of Kupffer cells includes substantial levels of necrotic material (Figure 2D).

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

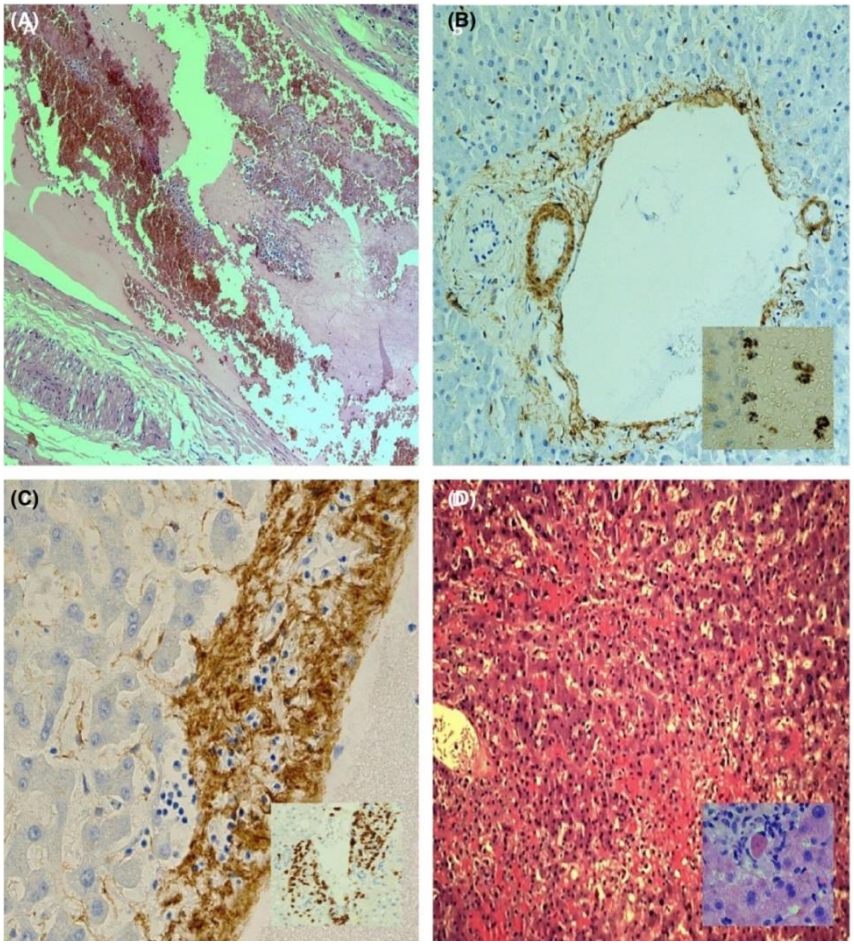

FIGURE 3 A: Example of genuine thrombosis: portal branch with clearly enlarged lumen obliterated by red cells mixed and stratified with lymphocytes and granulocytes (H&E, 100X); B: smooth muscle layer of portal vein lamina media extremely irregular fragmented (SMA, 100X); SAR-CoV-2 virions are demonstrated within vessel lumen and on endothelial cells (ISH) (inset); C: medium layer of a portal vein, partially lost and infiltrated by inflammatory cells lymphocytes, also attaching endothelial layer (SMA, 400X); CD3-positive lymphocytes attack endothelium and medium vessel layer (inset); D: severe confluent haemorrhagic necrosis in a patient with elevation of ALT > 10 N (H&E, 100X); inset showing liver necrosis by apoptosis (H&E, 400X)(A)(B)(C)(D) . [30]

The thrombotic process was thought to exclusively affect arteries with a significantly enlarged lumen and red cells mixed with lymphocytes and granulocytes as occupants. This measure was taken to prevent having to deal with the issue of post-mortem clothing. A diagnosis of thrombosis was only made after the two pathologists working together were able to come to a unanimous decision (Figure 3A). Large, tiny, or a blend of large and small droplets were all forms of steatosis detected in more than half of the samples. Only a small percentage of the samples had steatosis. Hepatic steatosis was identified in all 18 obese and 14 overweight patients with a BMI greater than or equal to 30 during the duration of the research. [30]

All of the morphological data support the concept that the arteries were damaged because of a decrease in blood flow. Because of this, lesions developed that resembled the histological appearance of hepatopulmonary syndrome and obliterative portal venopathy. This was the effect of the degradation.

About 6-9% of abnormality in the liver's blood circulation was also indicated by the development of an extensive network of sinusoids decorated with CD34 [9]. Intrahepatic blood circulation may be altered as a result of an increase in liver blood flow, which is occasionally accompanied by chest pain, and/or thrombotic events in the portal and sinusoidal veins. The liver's blood circulation can be affected by both of these causes. Blood circulation in the liver is affected by both of these variables. The majority of patients had high levels of D-dimer in their blood, which has been previously characterized as a risk factor for COVID 19 disease 11] and supports this notion. Histopathological findings from individuals who died of COVID-19 infection show a substantial number of medium and small-caliber branches of the lung vessels infected with thrombosis [29].

It may have noticed that three patients had excessively high transaminases because of severe arterial portal and sinusoidal thrombosis. Apoptosis and necrosis of the liver cells would have occurred as a result of this. Figure 3 has previously been linked to cases of obliterative portal venopathy. They range in severity from six to nine out of ten. A real-world example of thrombosis can be depicted as follows. In a portal vein's medium layer, SAR-CoV-2 virions can be observed on endothelial cells as well as in the vessel lumen (H&E, 100X); B: the smooth muscle layer is incredibly uneven and fragmented (SMA, 100X); C: an immune system attack on the endothelium layer is also a possibility. In the lungs, this form of attack has only lately been discovered [12].Data from histology in liver and other solid organs support the concept that defective coagulation, reduced blood circulation, or endothelial damage could be the major trigger mechanisms for COVID-19 damage [24]. According to the results of histology, this idea is supported. The finding that COVID-19 can cause harm not just to the liver, but also to a variety of other solid organs, which lends credence to this notion. In light of recent findings from a British research team that focused on the primary rule of the clotting system in COVID-19 liver injury, this technique is a good fit [28].

Despite the lack of proof, it is believed that viral infection triggers a cascade of pathogenic processes that proceed even if the virus is not present in the body. The results of the ISH approach for the identification of SARS-CoV-2 virus in the liver are noteworthy [27].

Pericyte activation was found in all of the samples, which is a further noteworthy finding of relevance. Pericytes are well-known for their involvement in the recruitment of inflammatory cells, and an inflammatory process may cause myofibroblast-like cell transformation in pericytes, leading to rapid and profuse production of extracellular matrix proteins and, eventually, vessel wall fibrosis. People who tested positive for

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

COVID-19 had their wedge liver samples obtained postmortem (age: 71.2 years; range: 87-32 years) [25]. These patients died from severe respiratory failure after being hospitalized for periods ranging from one to twenty-one days (the median was seven days). The sampling procedure included partial autopsies of the lungs, heart, and liver in some patients and a complete autopsy excluding the brain in others. Both sampling methods were used. None of the individuals brought to the hospital had a history of liver disease, and while they were there, none of them displayed any clinical indications or symptoms of liver failure. Morbid obesity is defined as a body mass index (BMI) more than 30 and includes conditions like chronic heart failure and hypertension [31], and many of the individuals in our study had multiple serious illnesses at the same time.

Contrary to expectations, there were morphological changes in the intrahepatic blood vessel structure (portal branches and sinusoids) as well as varying degrees of partial and full luminal recent thrombosis that were evidently occurring despite the anticipated inflammation damage. Patients with congenital deficiencies in coagulation factors or diseases that affect blood flow to the liver, such as hepato-porotic cirrhosis, share many of these traits [27]. The luminal space was severely dilated in the great majority of portal fields, which was accompanied by an increase in the number of portal veins. The peri-portal liver parenchyma was also observed to have a localized herniation in a large number of the samples. In the cytoplasm of Kupffer cells, a substantial amount of necrotic material was detected, which also demonstrated that these cells are extraordinarily active. Patients who participated in this study were all overweight or obese, thus it should come as no surprise that steatosis was prevalent. Many of the samples tested positive for steatosis [23]. Hepatic vascular involvement was clearly demonstrated by the principal histological characteristics present in all of the cases. The abnormality of the portal intrahepatic system is also a characteristic of chronic hepatic vascular involvement. Thrombosis and luminal ectasia were the hallmarks of acute hepatic vascular involvement. Most samples included the endothelial marker CD 34, which showed up on sinusoidal blood vessels in the peri-portal region. This was uncovered as a result of the investigation. Sinusoidal arterialization is the medical term for what is considered an incredibly unusual finding: an increase in blood pressure. Each and every sample was subjected to the C4d immunohistochemistry test, but there were no positive results [31].

5- Conclusion

COVID-19 is caused by the new coronavirus, and data on epidemiology and communicable diseases is developing rapidly. As the outbreak progressed, many cases appeared that had non-respiratory symptoms and signs, represented by infection of the liver and digestive system. Because the presence of viral RNA in saliva and feces of infected patients has been documented and diagnosed, it is easy for gastroenterologists and hepatologists to identify these symptoms early and take the necessary diagnostic and therapeutic precautions for these patients.

info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

According to the information contained in international medical reports, hepatic symptoms associated with SARS-CoV-2 are common and more severe in people who suffer from chronic diseases such as blood pressure, diabetes, obesity and inflammatory liver disease. Therefore, it is necessary for these people to be aware of the hepatic effects of the disease, So that the cases likely to require hospitalization in a timely manner. On the other hand, COVID-19 infection in patients with pre-existing hepatopathy carries a higher risk and potential for liver dysfunction, and therefore healthcare professionals responsible for these patients are advised to alert about the development of potential complications. Patients with COVID-19 frequently have high liver enzyme levels, which causes liver damage. According to recent statistics, patients with severe COVID-19 instances experience complete toxicity more frequently than those with mild disease. Hepatotoxicity in COVID-19 patients may have a systemic inflammatory basis, drug-induced liver injury, or worsening of pre-existing chronic liver disease as the underlying mechanism. The liver also processes the current medications used to treat COVID-19.

Conflict of interests.

There are non-conflicts of interest.

References

1- S. A. Alqahtani1, and J. M. Schattenberg, "Liver injury in COVID-19: The current evidence". € 3 United European Gastroenterology Journal 2020, Vol. 8(5) 509–519, 2020

2- D.N. Alexander, M. Schneeweiss-Gleixner and B. May et al. "Pathophysiological mechanisms of liver injury in COVID-19". *Liver International*. 2021;41:20–32., DOI: 10.1111/liv.14730

3- Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, and F.S. Wang, "Pathological findings of COVID-19 associated with acute respiratory distress syndrome". *The Lancet respiratory medicine*, 8(4), 420-422, 2020.

4-. WHO. "Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-2019)". February 16-24, 2020

5- H.K. Siddiqi, and M.R. Mehra, "COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal". The Journal of Heart and Lung Transplantation, 39(5), 405-407. 2020.

6- A. Rismanbaf, and S. Zarei, "Liver and Kidney Injuries in COVID-19 and Their Effects on Drug Therapy"; a Letter to Editor. Arch Acad Emerg Med 2020;8: e17.

7- I. Garrido, R. Liberal, and G. Macedo, "COVID-19 and liver disease-what we know on 1st May 2020". Aliment Pharmacol Ther. 2020;52:267–75,

8- R. Vaibhav, B. Ranjit, S. Devina, T. Hale, F. Lexie, P. Dipendra and G.R. Latha, et al. "Prevalence of hepatopancreatic injury and clinical outcomes in patients with COVID-19 in USA". International Journal of Emergency Medicine, 2021. 14:68 https://doi.org/10.1186/s12245-021-00393-2

9- L. Xu, J. Liu, M. Lu, D. Yang, X. Zheng. "Liver injury during highly pathogenic human coronavirus infections". Liver Int. 2020; 40(5):998–1004. https://doi. org/10.1111/liv.14435

10-Y. Zhang, L. Zheng, L. Liu, M. Zhao, J. Xiao, Q. Zhao. "Liver impairment in COVID-19 patients": A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int. 2020 40:2095.

11- Y. Huang, Z. Gao, "Study of the relationship SARS and hepatitis virus B". Chin J Clini Hepatol. 2003;6:342-343..

12- H.L. Chang, K.T. Chen, S.K. Lai, et al. "Hematological and biochemical factors predicting SARS fatality in Taiwan". J Formos Med Assoc. 2006;105(6):439-450.

13- R. Vaibhav, B. Ranjit, S. Devina, T. Hale, F. Lexie, P. Dipendra and G. Latha, "Prevalence of hepatopancreatic injury and clinical outcomes in patients with COVID-19 in USA". International Journal of Emergency Medicine, 2021, 14:68 https://doi.org/10.1186/s12245-021-00393-2

14- S.A. Alqahtani, J.M. Schattenberg, "Liver injury in COVID-19: The current evidence". United European Gastroenterol J. 2020; 8(5):509–19. https://doi. org/10.1177/2050640620924157.

15- X. Chai, L. Hu, Y. Zhang, W. Han, Z. Lu, A. Ke, et al. "Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection". biorxiv. 2020

16- W. Li, M.J. Moore, N. Vasilieva, et al. "Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus". Nature. 2003;426(6965):450-454.

17- J.M. Banales, R.C. Huebert, T. Karlsen, M. Strazzabosco, N.F. LaRusso, G.J. Gores. "Cholangiocyte pathobiology". Nat Rev Gastroenterol Hepatol. 2019;16(5):269-281.

18- T.N. Chau, K.C. Lee, H. Yao, T.Y. Tsang, T. C. Chow, Y.C. Yeung,., ... & Lai, C. L. "SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases". *Hepatology*, 2004, *39*(2), 302-310.

19-S.M. Poutanen, D.E. Low, B. Henry, S. Finkelstein, D. Rose, K. Green, R. Tellier, et al. "Identification of severe acute respiratory syndrome in Canada". N Engl J Med 2003;348:1995–2005.

20-Z. Xu, L. Shi, Y. Wang, et al. "Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med", 2020. https://doi.org/10.1016/S2213-2600(20)30076-X

21- B. Siddesh, B. Rehana, G. Vikraman and L.B. Herbert, "Liver disease in the Era of Coronavirus Disease 19 (COVID-19) pandemic". DOI: 10.29328/journal.acgh.1001023

22- S. Tian, Y. Xiong, H. Liu, H. Niu, J. Guo, M. Liao, et al. "Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies". Mod Pathol 2020;33(6):1007–1014.

23- Clinical insights for hepatology and liver transplant providers during the covid-19 pandemic American Association for the Study of Liver Diseases. Available at, www.aasld.org. Released March 23, 2020.

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652

24- W. Liang, W. Guan, R. Chen, W. Wang, J. Li, K. Xu, et al. "Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China". Lancet Oncol 2020; 21(3):335–337.

25- T. Boettler, P.N. Newsome, M.U. Mondelli, M. Maticic, E. Cordero, M. Cornberg, et al. "Care of patients with liver disease during the COVID-19 pandemic": EASL-ESCMID position paper. JHEP Rep 2020;2(3):100113.

26- Y. Wang, S. Liu, H. Liu, et al. "SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19". J Hepatol 2020. Doi: 10.1016/j.jhep.2020.05.002

27- M.L. da Silva, R.F. Marson, M.I.G Solari, N.B. Nardi. "Are liver pericytes just precursors of myofibroblasts in hepatic diseases? Insights from the crosstalk between perivascular and inflammatory cells in liver injury and repair". Cells. 2020; 9(1):188. https://doi.org/10.3390/ cells9010188

28- X.H. Yao, T.Y. Li, Z.C. He, Y.F. Ping, H.W. Liu, S.C. Yu, H.M. Mou, L.H. Wang, H.R. Zhang, W.J. Fu, T. Luo, "A pathological report of three COVID-19 cases by minimally invasive autopsies". Zhonghua Bing Li Xue Za Zhi. 2020;49:E009. https://doi.org/10.3760/cma.j.cn112151-20200 312-00193. [Epub ahead of print]

29- N. Tang, D. Li, X. Wang, et al. "Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia". J Thromb Haemost. 2020;18:844-847

30- A. Sonzogni, G. Previtali, M. Seghezzi, M. Grazia Alessio, A. Gianatti, L. Licini,... and M. Nebuloni, "Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations". *Liver International*, *40*(9), 2020, 2110-2116.DOI: 10.1111/liv.14601

31- X.H. Yao, T.Y. Li, Z.C. He, Y.F. Ping, H.W. Liu, S.C. Yu,... and X.W. Bian, "A pathological report of three COVID-19 cases by minimal invasive autopsies". *Zhonghua bing li xue za zhi= Chinese journal of pathology*, 2020, *49*(5), 411-417. doi: 10.3760/cma.j.cn112151-20200312-00193.

32- J.Y. Cho, S.S. Kim, Y.S. Lee, J.H. Lee, J.H. Kim, and Korean Association for the Study of the Liver, "Management of liver diseases during the pandemic of coronavirus disease-19". *Clinical and Molecular Hepatology*, 2020, *26*(3), 243. https://doi.org/10.3350/cmh.2020.0111

33-The Korean Society for Transplantation (KST). Recommendation on COVID-19. KST web site,. Accessed 14 May 2020.

34-Korea Centers for Disease Control and Prevention (KCDC). Prevention and management of COVID-19 in healthcare facility. KCDC web site,. Accessed 1 May 2020.

35- Da Silva ML, Marson RF, Solari MIG, Nardi NB. Are liver pericytes just precursors of myofibroblasts in hepatic diseases? Insights from the crosstalk between perivascular and inflammatory cells in liver injury and repair. Cells. 2020;9(1):188. https://doi.org/10.3390/ cells9010188 .

36- M.N. Bangash, J. Patel, D. Parekh, "COVID-19 and the liver: little cause for concern". Lancet Gastroenterol Hepatol 2020;5:529-530.

مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية مجلة جامعة بابل للعلوم الصرفة والتطبيقية
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com ISSN: 2312-8135 | Print ISSN: 1992-0652