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Review Article

Hepatobiliary complications in patients with covid-19: an integrative review

Complicações hepatobiliares em pacientes com covid-19: uma revisão integrativa

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ABSTRACT: *Introduction:* During the clinical course of COVID-19, liver injury has been observed to occur in a significant proportion of patients, especially in those with severe or critical illness. *Objective:* To synthesize the available information covering the mechanisms of COVID-19-induced hepatobiliary injury. *Methods:* This is an integrative literature review in PubMed and VHL databases using the descriptors: "Hepatobiliary Diseases", "COVID-19", "Gastrointestinal", "Pathophysiology" and "Liver". To refine the search the Boolean operators "AND" and "OR" were used, and articles relevant to the topic were selected. Initially, 193 articles were selected, from the last 10 years, in Portuguese and/or English. After analysis, 18 articles corresponded to the proposed objective. *Results:* Liver dysfunction was observed in 14 to 53% of COVID-19 patients, especially in those with severe disease. This is due to the postulated mechanism of viral entry through angiotensin-converting enzyme 2 receptors that are abundantly present not only in alveolar type 2 cells, but also in the gastrointestinal tract, vascular endothelium, and liver cholangiocytes. Liver involvement in COVID-19 is related to direct SARS-CoV-2 injury to the liver, systemic inflammatory reaction, liver injury from hypoxia, ischemia and reperfusion, aggravation of liver injury due to association of preexisting liver diseases with COVID-19, and drug-induced liver injury. *Conclusion:* Liver function disorders, especially hypoalbuminemia, elevated GGT and aminotransferase, are frequent in patients with COVID-19 disease. Even patients with severe disease, are more likely to present these liver function disorders.

KEY WORDS: Hepatobiliary Diseases; COVID-19; Gastrointestinal; Pathophysiology; Liver.

RESUMO: *Introdução:* Durante o curso clínico do COVID-19, observou-se que a lesão hepática ocorre em uma proporção significativa de pacientes, principalmente naqueles com doença grave ou crítica. *Objetivos:* Sintetizar as informações disponíveis que abrangem os mecanismos das lesões hepatobiliares induzidas pelo COVID-19. *Métodos:* Trata-se de uma revisão integrativa da literatura na base de dados PubMed e BVS usando os descritores: "Doenças Hepatobiliares", "COVID-19", "Gastrointestinal", "Fisiopatologia" e "Fígado". Para aprimoramento da busca foram utilizados os operadores booleanos "AND" e "OR", e selecionados artigos de relevância para o tema. Inicialmente, foram selecionados 193 artigos, dos últimos 10 anos, em português e/ou inglês. Após análise, 18 artigos corresponderam ao objetivo proposto. *Resultados:* A disfunção hepática foi observada em 14 a 53% dos pacientes com COVID-19, principalmente naqueles com doença grave. Isso acontece em razão do mecanismo postulado de entrada viral através dos receptores da enzima conversora de angiotensina 2 que estão abundantemente presentes não apenas nas células alveolares tipo 2, mas também no trato gastrointestinal, endotélio vascular e colangiócitos do fígado. O envolvimento hepático no COVID-19 está relacionado com lesão direta por SARS-CoV-2 ao fígado, reação inflamatória sistêmica, lesão hepática por hipóxia, isquemia e reperfusão, agravamento das lesões hepáticas devido a associação das doenças hepáticas preexistentes com a COVID-19 e lesão hepática induzida por drogas. *Conclusões:* Alterações da função hepática, sobretudo na hipoalbuminemia, elevação de GGT e aminotransferase, são frequentes em pacientes com doença por COVID-19. Inclusive, os pacientes com doença grave, têm maior probabilidade de apresentar esses distúrbios da função hepática.

PALAVRAS-CHAVE: Doenças Hepatobiliares; COVID-19; Gastrointestinal; Fisiopatologia; Fígado.

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INTRODUCTION

Infection by SARS-CoV-2, the severe acute respiratory syndrome that would later become known as COVID-19, was first identified in December 2019, in the city of Wuhan, in China. In late January 2020, COVID-19 infection worldwide was classified by the WHO as a pandemic. Although COVID-19 is principally a respiratory disease, it may also have extrapulmonary manifestations, including hepatobiliary complications. Most of these manifestations occur during the acute phase, especially in patients with the severe form of the disease. Others occur later in the progression of the disease, sometimes even subsequent to recovery, and these fall within the spectrum of disorders associated with what is increasingly being recognized as "long-COVID," in reference to prolonged symptoms of the disease. COVID-19 may also occur in patients with pre-existing gastrointestinal or liver disease, raising questions concerning the use of immunological therapies in these patients, the risk of contracting severe COVID-19, and possible negative outcomes. The mechanism underlying COVID-19-induced liver injury is probably multifactorial and associated with immunological dysregulation and the cytokine storm, hypoxic/ischemic injury, and drug-induced hepatotoxicity, in addition to the exacerbation of liver injuries by a combination of COVID-19 infection and pre-existing liver conditions.

The aim of the present study was thus to examine the available knowledge on hepatobiliary complications in COVID-19 patients with a view to providing a synthesis of available findings on the mechanisms underlying hepatobiliary lesions and shedding light on the identification and management of these manifestations.

METHODOLOGY

The present study is an integrative review of the literature. This method of investigation makes it possible to search for, critically evaluate and provide a synthesis of evidence found on a chosen topic, bringing together information that sheds light on currently available knowledge and enables identification of gaps that need to be filled by future research. The study involved the following steps: 1) identification of the topic and development of the research question; 2) establishing criteria for the inclusion and exclusion of studies; 3) determining which items of information will be extracted from the selected studies; 4) critical analysis of studies included based on levels of evidence; 5) discussion of results; and 6) presentation of integrative review[1].

The guiding question was formulated using the PICO (Patient, Intervention, Comparison, and Outcomes) strategy. The following research question was thus developed: which hepatobiliary complications may develop in patients with COVID-19?

Bibliographical research was carried out in the PubMed and BVS databases. All the articles identified by the search of the BVS database were also indexed in Medline. Only articles written between 2020 and 2022 were selected. The following search strategy was employed:

In the PubMed database:

("digestive system diseases"[MeSH Terms] OR ("digestive"[All Fields] AND "system"[All Fields] AND "diseases"[All Fields]) OR "digestive system diseases"[All Fields] OR ("hepatobiliary"[All Fields] AND "diseases"[All Fields]) OR "hepatobiliary diseases"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("pathophysiologies"[All Fields] OR "physiopathology"[MeSH Subheading] OR "physiopathology"[All Fields] OR "pathophysiology"[All Fields]) AND ("liver"[MeSH Terms] OR "liver"[All Fields] OR "livers"[All Fields] OR "liver s"[All Fields])

In the BVS database:

Hepatobiliary Diseases AND COVID-19 AND Gastrointestinal AND Pathophysiology AND Liver

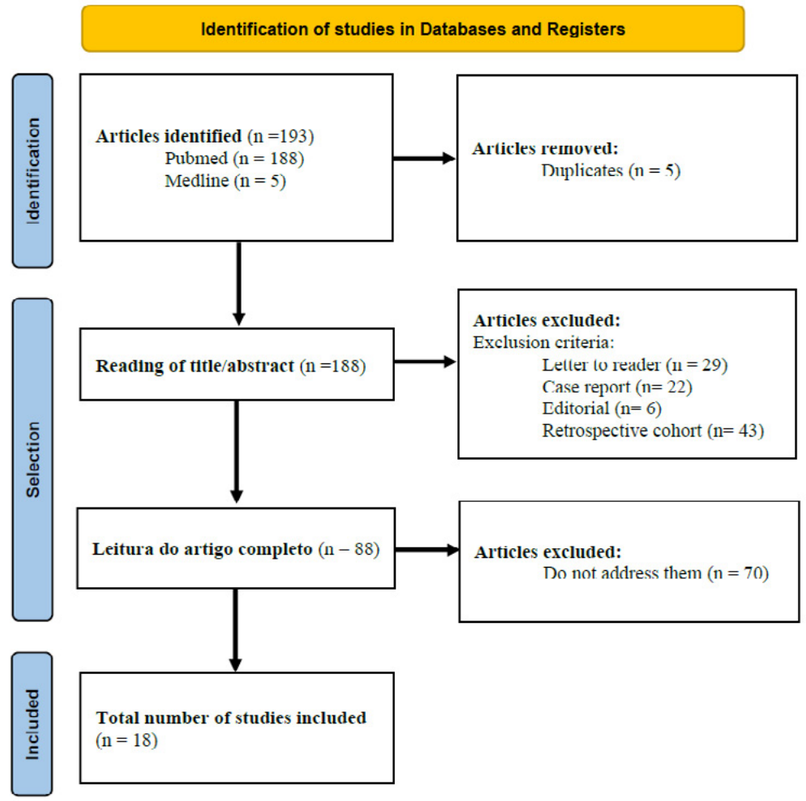
The difference between the two search strategies was due to the peculiarities of each database. For the PubMed database, the descriptors "Hepatobiliary Diseases", "COVID-19", "Pathophysiology" and "Live" were used in all fields and generated 188 articles. In the BVS database, the same descriptors were used but only searched for in the title, abstract and subject sections, generating five articles.

The RAYYAN – Intelligent Systematic Review – tool was used for systematic selection of articles, in accordance with the search strategy outlined in the PRISMA Statement 2020 (Figure 1).

Inclusion and exclusion criteria were used to screen the articles. Duplicate articles were removed, along with those that did not address the main focus of the research on hepatobiliary complications in patients with COVID-19. The main aim of the search was to find scientific articles that describe clinical hepatobiliary manifestations of COVID-19, the mechanisms underlying hepatobiliary tract injury, pathological manifestations, biliary injury and cholestasis, the relation between COVID-19 and pre-existing liver diseases, liver injury secondary to COVID-19 treatment, and other possible causes of increased liver function tests in critically ill patients.

Relevant articles were analyzed and classified according to level of evidence, as determined by analysis of the methodology adopted, to determine the quality of the scientific evidence presented. For the purposes of the present study, the articles were categorized from Level 1, for systematic review- and meta-analysis-type studies to Level 3 for literature review-type studies. The results are presented in Table 1.

Figure 1 - Selection of articles with flowchart of systematic review (PRISMA).



RESULTS

The articles selected were mostly literature review type studies, systematic reviews, and meta-analyses of retrospective studies, as can be seen in Table 1, which shows the articles selected and descriptions thereof.

Table 1 - Summary of studies included in integrative review.

Author	Periodical/ Year	Objective	Study Type	Results	Level of Evidence
Bertolini et al.[11]	Hepatology 2020	To analyze liver function tests (LFTs) and possible associations with COVID-19 infection.	Literature Review	Slightly abnormal plasma levels on LFTs, especially for aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are frequently observed in COVID-19 patients on admission to hospital and are associated with severe disease and an increase in inflammatory markers.	III

continue

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Author	Periodical/ Year	Objective	Study Type	Results	Level of Evidence
Oyelade et al.[38]	Trop Med Infect Dis 2020	To discuss mechanisms and results of liver injury associated with COVID-19 and its impact on chronic liver disease (CLD);	Literature review	Hepatic injury due to SARS-CoV-2 is probably multifactorial, involving direct viral cytopathic liver injury, immune-mediated liver injury, COVID-19 complications, including hypoxia/ischemia, micro/macrovascular thromboses, and drug-induced liver injury. The main risk factors for adverse results in individuals with CLD and COVID-19 are advanced age, advanced stage of liver disease, and comorbidities. Cirrhosis patients with COVID-19 are at increased risk of decompensation.	III
Jothimani et al.[49]	J Hepatol 2020	To analyze liver injury mechanisms associated with COVID-19 and pre-existing diseases.	Literature review	Rates are higher in the elderly and those with underlying comorbidities, such as diabetes, hypertension and heart disease. Recent reports have shown that around 2% to 11% of COVID-19 patients present underlying chronic liver disease. Levels of AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin were significantly in non-survivors than in survivors.	III
Metawea et al.[15]	Dig Liver Dis 2021	To discuss the physiopathology of COVID-19-induced liver injury and the prognostic effect of laboratory liver markers on the outcome of the disease.	Literature review	The most commonly found enzymatic alterations concerned ALT, AST, GGT and hypoalbuminemia.	III
Zhong et al.[27]	Signal Transduction and Targeted Therapy/2020	To provide a synthesis of information on digestive system injury in COVID-19 and information to assist management of gastrointestinal and liver issues in COVID-19.	Literature review	Liver injury associated with COVID-19 is a multifactorial process, and may involve drug-induced liver injury, systemic inflammatory reaction, liver injury induced by hypoxia, ischemia, and reperfusion. It is also possible that the liver is directly damaged by the SARS-CoV-2 virus.	III
Kumar et al.[3]	Nature Public Health Emerg Collection/2020	To study the occurrence of liver injury in COVID-19, to identify any differences in liver dysfunction with varying severity of the disease and to analyze cases where pre-existing liver diseases are present.	Systematic review and meta-analysis	The most commonly found abnormalities were hypoalbuminemia, and elevated GGT, ALT, or AST. The relative risk of these abnormalities was higher in patients with severe COVID-19 compared to non-severe cases of the disease.	I
Alqahtani et al.[44]	United Eur Gastroenterol J 2020	To provide an overview of current evidence on hepatobiliary complications in COVID-19, and of the series of cases available, and to critically elucidate the mechanisms proposed and furnish recommendations for physicians.	Literature review	Liver function abnormalities – principally heightened AST. Direct viral hepatotoxicity, systemic viral infection and potential sepsis or exacerbation of an underlying liver disease should be considered. SARS-CoV-2 may selectively affect the liver, in particular cholangiocytes through ACE2. Cautious use of antiviral agents in patients with decompensated liver disease and the interaction of different kinds of medication should be considered.	III
Ahmad et al.[22]	World J Gastroenterol 2021	To compare liver injuries associated with COVID-19 with an increase in LFTs in the context of pre-existing liver diseases and COVID-19.	Literature review	The alterations most commonly seen were elevated ALT, and AST in cases of patients with severe COVID-19. In patients with both pre-existing liver diseases and SARS-CoV-2 infection, the abnormalities predominantly concerned liver enzymes.	III

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Author	Periodical/ Year	Objective	Study Type	Results	Level of Evidence
Garrido et al.[4]	Alimentary Pharmacol Therap 2020	To provide an overview of the results of liver function tests in cases of SARS-CoV-2 infection and the impact of COVID-19 in patients with underlying CLD.	Literature review	Available evidence suggests that liver injury may be the result of the direct pathogenic effect of the virus, systemic inflammation, or the toxicity of drugs commonly used in such patients. Although it would seem that patients with CLD do not run a higher risk of infection, those with cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease or hepatic autoimmune diseases may be at greater risk of developing severe COVID-19.	III
Napodano et al.[5]	Scandinavian Journal of Immunology/ 2020	To provide an overview of liver injury, liver transplant, and the possible consequences of COVID-19 in patients with pre-existing liver diseases.	Literature review	Abnormalities in the distribution of biochemical markers of inflammation, cardiac markers, markers of muscle injuries, renal and liver function, and coagulation parameters were noted in COVID-19 patients, such as would lead to the classification of COVID-19 as a systemic pathology. Uncontrolled cytokine release and immuno-inflammatory responses are crucial for the progression of the disease, altering various physiopathological circuits related to the onset and severity of the disease.	III
Youssef et al.[6]	Wiley Public Health Emergency Collection/ 2020	To evaluate liver dysfunction among patients infected with SARS-CoV-2 to investigate the potential relation between acute liver injury and COVID-19.	Systematic review and meta-analysis	Found patients with severe COVID-19 to present significantly elevated levels of ALT, AST and bilirubin and prolonged prothrombin time. Lower levels of albumin were also associated with severe COVID-19. Liver dysfunction was associated with a severe COVID-19 outcome.	I
Moreira et al.[20]	Clinics and Research in Hepatology and Gastroenterology/ 2021	To analyze the physiopathology and possible molecular mechanisms involved in COVID-19-induced liver injury.	Integrative review	The hepatobiliary lesion mechanisms include direct lesion, humoral and cellular inflammatory response, hypoxemia caused by reduced effective circulating volume, reinfection through the portal system, and the use of drugs to treat the disease. The literature also notes that expression of angiotensin-converting enzyme 2 receptors and transmembrane protease 2 serine receptors is substantial in cholangiocytes and also present in hepatocytes, increasing the risk of viral cell entry.	III
Cichoż et al.[30]	World Journal of Gastroenterology/ 2021	To examine the relation between COVID-19 and the liver and potential liver injury mechanisms.	Literature review	Deterioration of liver function leads to a worse prognosis, increases the risk of severe SARS-CoV-2 infection and prolongs hospitalization. Abnormal liver function test results may be predictors of the severity of COVID-19. COVID-19 patients affected by liver dysfunction are principally men, the elderly and patients with high BMI. Hepatic injury observed during hospitalization may be caused simultaneously by the use of potentially hepatotoxic drugs, in particular antivirals such as lopinavir and ritonavir. Patients who also have chronic liver diseases are prone to develop more severe COVID-19.	III
Kovalic et al.[7]	Hepatology/2021	To characterize liver injury and other clinical characteristics of severe cases of COVID-19.	Systematic review and meta-analysis	Comorbidities, including coronary artery disease, cerebrovascular disease, and chronic obstructive pulmonary disease are more prevalent in hospitalized patients with severe/critical COVID-19 disease. These patients are also more likely to present abnormal liver chemistry.	I

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Author	Periodical/ Year	Objective	Study Type	Results	Level of Evidence
McConnell et al.[28]	Hepatology Communications/ 2022	To discuss the effects of SARS-CoV-2 and the inflammatory environment created in endothelial cells and platelets in general and in the liver in particular.	Literature review	Liver injury is characterized primarily by elevated AST and ALT. Severe SARS-CoV-2 infection is associated with acute or chronic liver failure in cirrhotic patients.	III
Arif et al.[8]	Hong Kong Academy of Medicine/2021	To provide information on the incidence, patterns, risk factors, and histopathological findings in relation to the severity of liver injury associated with COVID-19.	Systematic Review	Higher levels of AST than of ALT. Risk factors for liver injury: male sex, lymphopenia, gastrointestinal involvement, advanced age, increased neutrophil count, and use of hepatotoxic drugs. Histopathological findings indicate that COVID-19 has direct cytopathic effects and causes liver function test derangements secondary to inflammation, hypoxia, and vascular insult.	I
Velarde et al.[9]	Rev Gastroenterol Mex/2020	To review the literature available on the subject and demonstrate the effect of COVID-19 on the liver.	Literature review	Most of the series of cases reported alterations in ALT and AST, increased levels of total bilirubin and low serum albumin. Liver disease is associated with more severe cases of COVID-19. On the other hand, it is known that cirrhosis of the liver is a state of immune dysfunction that involves immunodeficiency and systemic inflammation. It is, therefore, a reasonable assumption that such patients would be more susceptible to SARS-CoV-2 infection.	III
Anirvan et al.[29]	Eur J Gastroenterol Hepatol 2021	To understand the implications of increased levels of cytokines as a cause of liver injury in COVID-19.	Literature review	Physiopathological process mediated by inflammation, altered coagulation and activation of RAAS, culminating in microvascular insult, hepatocyte injury and continued inflammation.	III

Key: LFT – liver function tests; AST - aspartate aminotransferase; ALT - alanine aminotransferase; CLD – chronic liver disease; ALP – alkaline phosphatase; GGT - gamma-glutamyl transferase; ACE2 – angiotensin-converting enzyme 2

Analysis of the articles showed that COVID-19 patients normally presented higher levels on liver function tests, primarily with respect to aspartate aminotransferase (AST) and alanine aminotransferase (ALT), with increases of 20-22.5% and 14.6-20.1%, respectively. Levels of bilirubin, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are also higher in 6% to 21% of patients[2]. Elevated levels of ALT and AST are more common in cases of severe COVID-19 than in mild COVID-19[3,4,5,6,7,8,9]. One study reported 78% of fatal cases of COVID-19 to have presented clinical evidence of liver injury related to alterations in these enzymes[10]. One retrospective observational study reported that altered liver tests at admission to hospital and during hospitalization may also be associated with less satisfactory clinical results[11]. Transaminase levels have been reported that are generally one- to threefold the upper limit normal (ULN) and, on rare occasions, five times the ULN. In general, predictors of transaminase peaks higher than five times normal include age, male sex, body mass index (BMI), diabetes mellitus, medication, and inflammatory markers[11].

The findings of liver autopsies carried out in COVID-19 patients may confirm and help to evaluate liver injury that may first have been indicated by increased levels of transaminases and alkaline phosphatase. These patients may exhibit large increases in transaminases, drastic liver failure, or cholestatic characteristics with jaundice and pruritus. In one study of COVID-19 patients who exhibited significant increases in LFTs, the biopsies showed similar characteristics, including: mild portal mononuclear infiltrate; preserved bile ducts; mild steatosis or micro-vesicular cytoplasmic vacuolization; mild lymphocytic lobular hepatitis with occasional acidophilic bodies, pigmented macrophages and Kupffer cells clusters; and occasional mitotic figures[12]. More dramatic cases of marked lobular hepatitis suggest that SARS-CoV-2 may be a cause of hepatitis. In one case report, a 35-year-old female COVID-19 patient presented drastic liver failure. Liver biopsy showed panlobular hepatitis with numerous histiocytes, zone 3 necrosis, mild steatosis and hemophagocytosis. No auxiliary technique was available to confirm SARS-CoV-2 in the liver, but the clinical profile of this patient suggested a diagnosis of SARS-CoV-2-induced hepatitis[13].

In general, it was reported that 2% to 11% of COVID-19 patients had chronic underlying liver disease and 14% to 53% of COVID-19 patients developed liver dysfunction, especially those with severe COVID-19. Liver dysfunction was significantly higher in severely sick patients and was associated with a negative outcome[14].

The studies found that COVID-19 patients often presented a history of use of anti-thermal medication, such paracetamol, overdoses of which are a well-established cause of liver injury[15].

DISCUSSION

Overview of clinical hepatobiliary manifestations of COVID-19

Alterations in liver enzymes in COVID-19 patients tend to be observed on admission to hospital or during hospitalization. Liver function tests (LFT) include measurement of hepatocyte injury that can be observed by way of enzymatic alterations in aspartate transferase (AST) and alanine transferase (ALT). Damage to the bile duct or cholestasis may be indicated by levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). Markers of hepatic clearance/biliary secretion capacity can be seen from levels of bilirubin and the capacity for synthesis can be measured using the prothrombin and albumin time. These enzymes are not necessarily specific to the hepatobiliary tract, and it is therefore necessary to carry out another test to detect hepatobiliary lesions. It should be noted that, owing to the role the liver plays in the production of albumin, acute phase reagents, and coagulation factors, the high proportion of cases with liver injury suggests that liver dysfunction is correlated with multisystemic dysfunction.

In critically ill COVID-19 patients, altered LFTs may be related to cytokine storm syndrome (CSS), triggered by SARS-CoV-2 infection and may contribute to the state of shock and coagulopathy, which affect liver perfusion and result in cell death. More severe cases are associated with lower levels of albumin, high levels of circulating B and T lymphocytes, higher levels of Spikes (S) proteins in the cytoplasm of hepatocytes, and dysfunction in organelles such as mitochondria and the endoplasmic reticulum. These phenomena can be explained by cell dysfunction caused directly by the virus and/or systemic inflammation, the hepatotoxic potential of medications used to treat COVID-19, or other as yet unmapped protein membranes or co-stimulants that affect the relation between ACE2 and the S proteins[3,4].

A number of complications associated with SARS-CoV-2 infection have been described. There include cases of COVID-19 patients who developed acute liver failure and presented respiratory symptoms of acute respiratory distress (ARDS) with multiple organ failure[16]. The cause of acute liver failure in COVID-19 patients is difficult to ascertain, since there is the possibility of injury caused by drugs or multiple organ failure when SDRA or sepsis is present. There are also reports of COVID-19 patients developing primary liver diseases, such as autoimmune hepatitis (AIH) and primary biliary cirrhosis[17]. There are also cases of patients who, subsequent to recovering from the initial clinical manifestations of COVID-19, developed cholangiopathy, which is a form of secondary sclerosing cholangitis found in severely ill patients and characterized by prolonged and marked cholestasis[18].

The mechanism underlying hepatobiliary tract injury

It is worth pointing out that the mechanisms underlying hepatobiliary tract injury are not fully understood, although it is known that multiple factors are involved. Aspects of COVID-19 that may be associated with hepatobiliary lesions include the direct consequences of viral replication, systemic and immune-mediated inflammatory effects, vascular alterations that may result in ischemia, damage caused by medication, and exacerbation of a pre-existing condition.

- **Direct viral infection**

Direct SARS-CoV-2 virus infection occurs by way of connection to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface, followed by activation of the S protein by transmembrane protease serine 2 (TMPRSS2). Entry of the virus into the cell is pre-activated by a convertase pro-protein of the target cell called furin, reducing its dependence on the proteases of the target cell for cell entry. Furin is found in the lungs, liver, and small intestine, and enables efficient entry into the cells, bypassing immunological vigilance and promoting transmission. Relative expression of these proteins determines the capacity of the virus to infect a certain kind of cell[19,20].

After the virus enters the host cell, the lesion is caused by the potential direct virus-mediated cell damage with dysregulation of the renin-angiotensin-aldosterone system (RAAS). This is a consequence of negative regulation of ACE2 related to entry of the virus, leading to reduced cleavage of angiotensin I and II. Damage to the endothelial cells and thrombo-inflammation lead to micro- and macrovascular thromboses[21].

Autopsies were used to analyze human tissue and organoid cultures and this confirmed the presence of the ACE2 and TMPRSS2 receptor in hepatic parenchyma cells and cholangiocytes, in addition to the viral protein being found in liver stem-cells, hepatocytes and cholangiocytes[22]. Distribution of ACE2 in the liver is peculiar: it is highly expressed in the endothelial layer of small blood vessels, but not in the sinusoidal endothelium. One study found the cell surface ACE2 receptor to be more expressed in cholangiocytes (59.7%) than in hepatocytes (2.6%). The level of expression of ACE2 in cholangiocytes was similar to that of type 2 alveolar cells in the lungs, indicating that the liver may be a potential target of SARS-CoV-2[18,4,10,11]. Increased ACE2 expression was also found in hepatocytes in cases involving liver injury[19].

Immuno-histochemistry (IHC) for SARS-CoV-2 emphasized portal macrophages in the cases studied[23]. In biopsies carried out in patients with COVID-19-associated liver injury, in situ hybridization (ISH) and electron microscopy demonstrated the presence of viral antigens, indicating that the liver may be infected directly[24]. SARS-CoV-2 causes intracellular cytotoxic action in the hepatocytes, with destruction of cell membranes and diffuse edema in structures such as the rough endoplasmic reticulum and mitochondria. This reduces the production of proteins and affects biosynthesis of ATP in the hepatocytes, as well as diminishing mitochondrial activity and oxidative stress in the endoplasmic reticulum. The virus also seems to be capable of inducing mitochondrial β-oxidation defects, causing direct interference in hepatic lipogenesis. This contributes to steatohepatitis secondary to the virus, worsens the metabolic

condition of the liver, and exacerbates comorbidities such as non-alcoholic fatty liver disease (NAFLD)[3].

In vitro studies have shown that human bile duct organoids are susceptible to SARS-CoV-2 and support viral replication. Cultured primary hepatocytes and cholangiocytes and organoids infected with the virus were found to overexpress pro-inflammatory cytokines and negatively regulate metabolic processes, raising the possibility that infection may alter the profile of pro-inflammatory or pro-fibrogenic cytokines. Biliary transport and biliary acid signaling may be damaged by negative regulation of biliary acid transporters and chloride channels[25].

- **Cytokine release**

COVID-19 is related to elevated levels of inflammatory markers and cytokines cause by virus-induced immune dysregulation and hyperinflammation. This condition is occasioned by inhibition of type I interferon (IFN) signaling, T-cell lymphodepletion, positively regulated pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α) which induce hyperactivation of the innate immune system with cytokine storm syndrome (CSS). From this point on, monocytes, macrophages and T-cells are attracted to the location, thereby further increasing inflammation. This results in immune-mediated hepatocellular damage caused by virus-induced cytotoxic T cells (CD8) and induction of a dysregulated innate immune response[26]. This may also result in an accumulation of immune cells in the gastrointestinal tract and in hepatocellular cholestasis through negative regulation of hepatobiliary uptake and of excretory systems. Some authors have suggested that immunosuppression is beneficial in so far as it reduces the release of cytokines, leading to better outcomes[19].

In some COVID-19 patients, the disease is not severe in the initial stages, but the condition of the patient suddenly deteriorates, and the patient rapidly enter a state of multiple organ failure. This may be associated with an inflammatory cytokine storm induced by an excessive immune response[22]. This also triggers acute respiratory distress syndrome (ARDS), resulting in damage to the liver and lungs[27,6,7,28,8,29].

Indications of liver function in severe cases of COVID-19 include increases in levels of inflammatory mediators such as C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimers, interleukin-6 (IL-6), and IL-2, suggesting a direct connection between the presence of CSS and the severity of the disease[30].

- **Hypoxic and thrombotic injury**

Hypoxic alterations induced by respiratory insufficiency, systemic coagulopathy, and right-sided heart failure are all mechanisms that may be associated with hepatobiliary injury resulting from severe COVID-19 complications. Viral infection of the endothelial cells causes endothelial dysfunction and release of factor VIII, von Willebrand's factor and fibrinogen, resulting in thrombosis. Pathological findings of vascular thrombosis in the gastrointestinal tract and in the liver sustain the hypothesis that hypercoagulability and thrombosis play a role in generating liver injury[8].

Predictors of liver dysfunction in cases of severe COVID-19 include greater activation of the coagulative and fibrinolytic routes, slightly depressed platelet counts, an increased neutrophil count and a higher proportion of neutrophils in relation to lymphocytes and ferritin. Although these are relatively non-specific inflammatory markers, they reflect the degree of severity of the disease, coinciding with a failure of innate immune regulation. The altered immunological balance activates coagulation and NETose and, subsequently, affects the systemic metabolism of iron secondary to macrophage activation[31].

CSS may also result in disseminated intravascular coagulation (DIC). DIC is found in critical patients and those who do not survive COVID-19, as evidenced by elevated levels of D dimer and prolonged prothrombin time, in addition to pulmonary embolism and thrombotic microangiopathy in multiple organs[27]. One study of 49 patients testing positive for COVID-19 revealed generalized vascular involvement in the intrahepatic portal system, taking the form of acute (thrombosis and luminal ectasia) or chronic (fibrous thickening of the vascular wall) alterations, with abnormal configuration of the intra-hepatic blood vessels. These findings suggest that coagulation dysfunction or endothelial damage may constitute the main triggering mechanism in pathogenesis of liver-related damage cause by COVID-19.

SARS-CoV-2 can infect endothelial cells and cause diffuse endothelitis. Subsequent microvascular dysfunction leads to hypercoagulability, tissue edema, and organ ischemia. Hepatic ischemia-reperfusion injury (HIRI) is a common physiopathological process. The main mechanism is closely related to reactive species of oxygen, neutrophils, Kupffer cells, and calcium overload. Hepatic ischemia-reperfusion may activate Kupffer cells, neutrophils and platelets, causing a series of destructive cellular reactions, leading to inflammation and cell damage. Meanwhile, the disruption of microcirculation caused by the damage to hepatic sinusoidal endothelial cells may further exacerbate the hepatic ischemia and oxygen deficiency. Over 40% of COVID-19 patients with various levels of hypoxemia require oxygen therapy. Liver injury generally occurs in patients with hypotensive shock or severe hypoxemia. The lymphatic vessels are involved in the pathological process of acute liver injury by way of elimination of the virus, absorption and transport of exudate produced by inflammation, inflammatory cytokines, cell death detritus, and the transport of immune cells, such as T cells[8,27].

Hypoxia-reperfusion injury contributes to liver failure in so far as it involves a dynamic process of cell damage, which includes a dual system composed of an ischemic phase and a reperfusion-induced inflammatory response. Interruption of adequate blood supply triggers a series of metabolic disorders in cells, subsequently leading to an increase in reactive species of oxygen and their peroxidation products. Transcription factors sensitive to oxidation are then activated, further stimulating the release of various pro-inflammatory factors such as IL-1, IL-6, and TNF-alpha, and promoting immune activation of TCD4+ and TCD8+ lymphocytes and macrophages that produce factors stimulating colonies in the liver subsequent to reperfusion[20].

Pathological manifestations in the hepatobiliary tract

Autopsy livers from COVID-19 patients were found to exhibit a variety of histological alterations, some of which may be the result of organ failure, intubation, shock, and aggressive intervention. Some of the alterations reported seem to be related to specific systemic effects of SARS-CoV-2 infection, such as thrombosis. Pre-existing liver diseases may make it difficult to interpret the findings, particularly in the case of inflammation or more pronounced fibrosis in the liver.

Macroscopically, the livers of patients who died of COVID-19 generally show varying degrees of steatosis, as evidenced by a pallid yellow appearance, congestion, nutmeg appearance, and ischemia. Microscopically, steatosis is also the most commonly reported hepatic finding in autopsies of COVID-19 patients[5]. Steatosis is found in 50-83% of autopsy livers and is generally classified as mild, but may also be moderate or severe, and may take the form of large or small droplets of fat. Lobular inflammation is generally mild, but may occasionally be moderate or severe, with dispersed foci of necroinflammation, covering lymphocytes and histiocytes, and occasionally acidophile bodies[32]. Some authors also report focal confluent necrosis or more extensive centrilobular ischemic necrosis, resulting from the antagonistic events related to severe COVID-19, and not only the viral infection itself[8,23,32]. Additional findings reported in a subset of cases include cholestasis, ductular cholestasis suggestive of sepsis, ductular reaction, activation of Kupffer cells , and evidence of regeneration of the liver with mitotic activity or thickening of hepatic plates in reticulin stains[23,33]. Other studies have described portal and lobular inflammation in the liver on autopsy in COVID-19 patients, with portal inflammation reported in over half of cases autopsied, including lymphocytes with infrequent plasma cells, eosinophils or neutrophils[7,32,33].

Autopsy livers have also exhibited vascular alterations such as those occurring in dilatated portal veins -some herniated to the adjacent parenchyma or with fibrotic walls - thrombosed veins, sinusoidal thrombi, and abnormal expression of CD34 - a glycoprotein that functions as a cell adhesion factor in affected areas of the lobules. Fragmentation of the layer of smooth muscle in portal veins and infiltration through inflammatory cells are also described[12]. In 70% of autopsies, samples of sinusoidal platelet aggregation were also found. In this series, microvascular thrombosis was found in roughly 32% of non-hospitalized patients who did not receive anticoagulant therapy, compared to 3% in hospitalized patients. Others found platelet thrombi and fibrin in the sinusoids of these livers and portal vein thrombi. Apart from sinusoidal dilatation, other vascular alterations, such as dilatation of the portal vein and congestion, have also been reported[12,23,28,33,34].

Biliary lesion and cholestasis in COVID-19

Cholestasis is another possible manifestation of COVID-19-related hepatic injury. This occurs as a result of expression of ACE2 in biliary epithelial cells, leading to direct viral infection. Reports of cholestasis subsequent to COVID-19 infection suggest, however, that the development of this condition is related to the endotheliopathy caused by the coagulation process associated with the virus. This was observed in branches of the hepatic artery in the portal tract that exhibit endothelial swelling and luminal narrowing, endophlebitis of the portal vein, which is inflammation of the inner side of a vein, endotheliatitis, which is characterized by adhesion of leukocytes to the vascular wall, and thrombotic material in branches of the portal vein[35].

It should be noted that cholangiopathy has been described as one of the long-term manifestations of COVID-19. It is a form of secondary sclerosing cholangitis in severely ill patients. Histological examination generally reveals these patients to have acute and/or chronic obstruction of the large ducts, without ductopenia. Some patients presented histological evidence of mild cholestatic injury, with mixed portal inflammatory infiltrate, a slight bile duct injury, canalicular cholestasis with cholestatic rosette and, occasionally, small biliary infarctions. Other patients presented clear characteristics of biliary obstruction, such as extensive periportal edema, neutrophilic portal inflammatory infiltrate, severe ductular reaction and deep cholestasis with biliary infarctions[36].

Pre-existing liver diseases

Chronic liver disease (CLD) and, in particular, cirrhosis, are associated with alterations in innate and adaptive immunity, leading to increased susceptibility to infections and abnormal systemic responses during infections. This is known as cirrhosis-associated immune dysfunction (CAID) and includes activation of macrophages, damage to the functioning of neutrophils and lymphocytes, Toll-like receptor dysfunction, a significant increase in intestinal permeability with alterations to the intestinal microbiome, and pro-thrombotic complications. It has also been shown that expression of the ACE2 receptor in hepatocytes exacerbates fibrotic or cirrhotic conditions[37]. Patients with pre-existing liver conditions are therefore more susceptible to SARS-CoV-2 infection and more likely to develop liver injury[5,21]. The stage of CLD and associated comorbidities negatively influence clinical outcomes in these patients, and there is a progressive increase in morbidity and mortality, which may indicate an increase in the Child-Pugh (CP) and the MELD (model for end-stage liver disease) scores. Hepatic decompensation due to COVID-19 may result in an increase in mortality of around 63.2%, compared to 26.2% for patients without decompensation[4,22,36,38,39].

The level of expression of ACE2 in adipose tissue is greater than in lung tissue. Obese patients have a high risk of developing non-alcoholic fatty liver disease (NAFLD), which, in turn, leads to a higher risk of developing severe COVID-19, a greater likelihood of abnormal liver function during hospitalization and a longer virus clearance time[40]. Patients with NAFLD may be subject to comorbidities such as diabetes and hypertension, which increase the risk of severe COVID-19 infection. Patients with NAFLD generally present elevated levels of cytokines, making them more susceptible to COVID-19-related CSS. It has also been shown that patients with COVID-19 infection exhibit increased serum levels of monocyte chemoattractant protein 1,

which is a chemokine known to exacerbate steatohepatitis. The virus may thus increase the likelihood of long-term progression from NAFLD to non-alcoholic steatohepatitis (NASH) [30,34,40,41].

Patients with chronic hepatitis B are more vulnerable to COVID-19, but other studies have revealed that chronic viral hepatitis does not appear to be proportionate to the severity of COVID-19[42]. In relation to treatment of viral hepatitis in patients co-infected with COVID-19, continuation of treatment for hepatitis B and hepatitis C is recommended, so long as it has already been initiated prior to COVID-19 infection. In the case of patients with autoimmune liver disease, immunosuppressant therapy makes these patients more at risk of severe infection, but the current guidelines of the European Association for the Study of the Liver (EASL) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend not reducing immunosuppressant therapy in patients with autoimmune liver disease[47].

Liver injury secondary to COVID-19 treatment

Alterations in liver function tests in COVID-19 patients have been reported on admission to hospital, suggesting that patients may develop these symptoms prior to commencing medication. However, some medication used to treat or manage the symptoms of SARS-CoV-2 patients, including paracetamol, antivirals, antibiotics, corticosteroids and immunomodulators, are potentially hepatotoxic and it may be difficult to determine whether liver symptoms are related to viral infection or to treatment. Treatment with a combination of lopinavir-ritonavir, oseltamivir, remdesivir and antimicrobials may, for example, cause diarrhea, nausea, and vomiting[43,44].

One retrospective study of the relation between the use of medication and LFTs in 148 COVID-19 patients found that 48% of the patients who presented no LFT abnormalities on admission to hospital developed such abnormalities around one week after admission. While 58% of those who developed LFT abnormalities after admission received lopinavir-ritonavir, only 31% of those with normal LFTs received these drugs[45]. Lopinavir/ritonavir, an antiretroviral protease inhibitor, may cause transitory generalized asymptomatic increases in serum levels of aminotransferases. The risk of hepatotoxicity associated with lopinavir in patients with advanced liver disease is low, despite increased minimal plasma levels of lopinavir[4].

One retrospective cohort study showed that patients with pre-existing chronic liver disease presented a high risk of drug-induced liver injury when receiving antiviral therapy. In vitro pharmacokinetic studies have indicated that some antiviral medication may inhibit the main hepatic transporters[46]. Hydroxychloroquine is frequently used to treat severe COVID-19 but has been associated with hepatotoxicity, the highest risk being in severely ill patients. LFTs generally show slightly elevated levels and return to normal when hydroxychloroquine treatment is discontinued. Liver biochemistry may, however, be significantly altered, and fulminant liver failure has also been reported[41]. Ketamine is commonly used as a sedative during intubation and may occasionally cause secondary sclerosing cholangitis. One published case, however, has reported that administration of ketamine resulted in a sharp increase in alkaline phosphatase and radiographic findings of intrahepatic biliary dilatation and beading, with biochemistry returning to normal when ketamine treatment was discontinued[47].

There have also been reports of patients who presented with acute hepatitis similar to autoimmune hepatitis after vaccination with RNAm. These patients were aged between 35 and 80 years and presented with symptoms specific to the liver between 4 and 35 days after the first dose or 7 days after the second dose. Liver biopsies in these patients showed classic autoimmune hepatitis (AIH) morphology, with prominent interface hepatitis, marked lobular inflammation, and, in some cases, centrilobular necrosis. One patient with primary sclerosing cholangitis was diagnosed with AIH after vaccination[48]. All patients responded to immunosuppressant therapy. It is possible that the RNAm SARS-CoV-2 vaccine disrupts self-tolerance and triggers autoimmune responses by way of cross-reactivity with host cells. However, it is also possible that these patients had subclinical AIH that was revealed by the vaccine or coincidentally presented subsequent to vaccination.

Other causes of elevated liver function in critically ill patients

In critical COVID-19 patients, liver injury may be caused by alterations in hemodynamics and oxygen supply. Hypoxic hepatitis may cause significant increases in aminotransferases in the context of respiratory insufficiency, heart failure, or shock. During acute heart failure, which may occur in critically ill COVID-19 patients, systemic arterial pressure drops suddenly, leading to reduced hepatic artery perfusion and hepatocellular hypoxia. Pathogenesis includes not only hepatic ischemia, but also hepatic vein congestion caused by heightened central venous pressure, which may predispose hepatocytes to even more serious hypoxic injury. It is not clear whether these hemodynamic alterations have the potential to generate alterations in liver function tests[49]. The use of high levels of positive end-expiratory pressure (PEEP) may cause hepatic congestion by increasing pressure in the right atrium and impeding venous return.

FINAL CONSIDERATIONS

Liver function abnormalities, especially hypoalbuminemia, and elevated levels of GGT and aminotransferase, are common in COVID-19 patients, and patients with the severe form of the disease are more likely to present with these. COVID-19-related liver injury is likely multifactorial, involving direct SARS-CoV-2-induced liver injury, systemic inflammatory reaction, liver injury cause by hypoxia, ischemia and reperfusion, exacerbation of liver injury associated with prior history of liver disease, or drug-induced liver injury.

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REFERENCES

1. Souza MT, Silva MD, Carvalho R. Revisão integrativa: o que é e como fazer. Einstein São Paulo. 2010;8:1020-6. https://doi.org/10.1590/S1679-45082010RW1134.
2. Kulkarni AV, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. Aliment Pharmacol Ther. 2020;52(4):584-99. Doi: 10.1111/apt.15916.
3. Kumar-M P, Mishra S, Jha DK, Shukla J, Choudhury A, Mohindra R, et al. Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. Hepatol Int. 2020;14(5):711-22. Doi: 10.1007/s12072-020-10071-9.
4. Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease—what we know on 1st May 2020. Aliment Pharmacol Ther. 2020;52(2):267-75. Doi: 10.1111/apt.15813.
5. Napodano C, Pocino K, Stefanile A, Marino M, Miele L, Gulli F, et al. COVID-19 and hepatic involvement: The liver as a main actor of the pandemic novel. Scand J Immunol. 2021;93(3):e12977. Doi: 10.1111/sji.12977.
6. Youssef M, H Hussein M, Attia AS, M Elshazli R, Omar M, Zora G, et al. COVID-19 and liver dysfunction: A systematic review and meta-analysis of retrospective studies. J Med Virol. 2020;92(10):1825-33. Doi: 10.1002/jmv.26055.
7. Kovalic AJ, Huang G, Thuluvath PJ, Satapathy SK. Elevated Liver Biochemistries in Hospitalized Chinese Patients With Severe COVID-19: Systematic Review and Meta-analysis. Hepatol Baltim Md. 2021;73(4):1521. Doi: 10.1002/hep.31472.
8. Arif T, Khalid S. Incidence, patterns, risk factors, and histopathological findings of liver injury in coronavirus disease 2019 (COVID-19): a scoping review. HKMJ. 2021. https://doi.org/10.12809/hkmj208732
9. Velarde-Ruiz Velasco JA, García-Jiménez ES, Remes-Troche JM. Manifestaciones hepáticas y repercusión en el paciente cirrótico de COVID-19. Rev Gastroenterol Mex. 2020;85(3):303-11. Doi: 10.1016/j.rgmx.2020.05.002
10. Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, et al. Clinical characteristics of 82 cases of death from COVID-19. PloS One. 2020;15(7):e0235458. Doi: 10.1371/journal.pone.0235458.
11. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. Hepatol Baltim Md. 2020;72(4):1169-76. Doi: 10.1002/hep.31487.
12. Sonzogni A, Previtali G, Seghezzi M, Grazia Alessio M, Gianatti A, Licini L, et al. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. Liver Int Off J Int Assoc Study Liver. 2020;40(9):2110-6. Doi: 10.1111/liv.14601.
13. Melquist S, Estepp K, Aleksandrovich Y, Lee A, Beiseker A, Hamedani FS, et al. COVID-19 presenting as fulminant hepatic failure: A case report. Medicine (Baltimore). 2020;99(43):e22818. Doi: 10.1097/MD.0000000000022818
14. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428-30. doi: 10.1016/S2468-1253(20)30057-1.
15. Metawea MI, Yousif WI, Moheb I. COVID 19 and liver: An A–Z literature review. Dig Liver Dis. 2021;53(2):146-52. Doi: 10.1016/j.dld.2020.09.010.
16. Weber S, Mayerle J, Irlbeck M, Gerbes AL. Severe liver failure during SARS-CoV-2 infection. Gut. 2020;69(7):1365-7. http://dx.doi.org/10.1136/gutjnl-2020-321350
17. Hong JK, Chopra S, Kahn JA, Kim B, Khemichian S. Autoimmune hepatitis triggered by COVID-19. Intern Med J. 2021;51(7):1182–3. Doi: 10.1111/imj.15420.
18. Edwards K, Allison M, Ghuman S. Secondary sclerosing cholangitis in critically ill patients: a rare disease precipitated by severe SARS-CoV-2 infection. BMJ Case Rep. 2020;13(11):e237984. Doi: 10.1136/bcr-2020-237984.
19. Shih AR, Misdraji J. COVID-19: gastrointestinal and hepatobiliary manifestations. Hum Pathol. 2022. Doi: 10.1016/j.humpath.2022.07.006
20. Moreira JL de S, Barbosa SMB, Gonçalves Júnior J. Pathophysiology and molecular mechanisms of liver injury in severe forms of COVID-19: An integrative review. Clin Res Hepatol Gastroenterol. 2021;45(6):101752. Doi: 10.1016/j.clinre.2021.101752
21. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(23):2950-73. Doi: 10.1016/j.jacc.2020.04.031.
22. Ahmad A, Ishtiaq SM, Khan JA, Aslam R, Ali S, Arshad MI. COVID-19 and comorbidities of hepatic diseases in a global perspective. World J Gastroenterol. 2021;27(13):1296–310. Doi: 10.3748/wjg.v27.i13.1296.
23. Zhao CL, Rapkiewicz A, Maghsoodi-Deerwester M, Gupta M, Cao W, Palaia T, et al. Pathological findings in the postmortem liver of patients with coronavirus disease 2019 (COVID-19). Hum Pathol. 2021;109:59-68. Doi: 10.1016/j.humpath.2020.11.015.
24. Fiel MI, El Jamal SM, Paniz-Mondolfi A, Gordon RE, Reidy J, Bandovic J, et al. Findings of Hepatic Severe Acute Respiratory Syndrome Coronavirus-2 Infection. Cell Mol Gastroenterol Hepatol. 2021;11(3):763–70. Doi: 10.1016/j.jcmgh.2020.09.015.
25. Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. J Hepatol. 2020;73(4):807-16. Doi: 10.1016/j.jhep.2020.05.002.
26. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson

JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet Lond Engl. 2020;395(10229):1033–4. Doi: https://doi.org/10.1016/S0140-6736(20)30628-0

27. Zhong P, Xu J, Yang D, Shen Y, Wang L, Feng Y, et al. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. Signal Transduct Target Ther. 2020;5:256. Doi: 10.1038/s41392-020-00373-7.

28. McConnell MJ, Kondo R, Kawaguchi N, Iwakiri Y. Covid-19 and Liver Injury: Role of Inflammatory Endotheliopathy, Platelet Dysfunction, and Thrombosis. Hepatol Commun. 2021;6(2):255–69. Doi: 10.1002/hep4.1843.

29. Anirvan P, Narain S, Hajizadeh N, Aloor FZ, Singh SP, Satapathy SK. Cytokine-induced liver injury in coronavirus disease-2019 (COVID-19): untangling the knots. Eur J Gastroenterol Hepatol. 2021;33(1S):e42. Doi: 10.1097/MEG.0000000000002034.

30. Cichoż-Lach H, Michalak A. Liver injury in the era of COVID-19. World J Gastroenterol. 2021;27(5):377-90. Doi: 10.3748/wjg.v27.i5.377.

31. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol. 2020;5(6):529-30. Doi: 10.1016/S2468-1253(20)30084-4.

32. Schmit G, Lelotte J, Vanhaebost J, Horsmans Y, Van Bockstal M, Baldin P. The Liver in COVID-19-Related Death: Protagonist or Innocent Bystander? Pathobiol J Immunopathol Mol Cell Biol. 2021;88(1):88-94. Doi: 10.1159/000512008

33. Lagana SM, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, et al. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. Mod Pathol Off J U S Can Acad Pathol Inc. 2020;33(11):2147-55. Doi: 10.1038/s41379-020-00649-x.

34. Kaltschmidt B, Fitzek ADE, Schaedler J, Förster C, Kaltschmidt C, Hansen T, et al. Hepatic Vasculopathy and Regenerative Responses of the Liver in Fatal Cases of COVID-19. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2021;19(8):1726-9.e3. Doi: 10.1016/j.cgh.2021.01.044

35. Roth NC, Kim A, Vitkovski T, Xia J, Ramirez G, Bernstein D, et al. Post-COVID-19 Cholangiopathy: A Novel Entity. Am J Gastroenterol. 2021;116(5):1077-82. Doi: 10.14309/ajg.0000000000001154.

36. Singh S, Khan A. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study. Gastroenterology. 2020;159(2):768-71.e3. Doi: 10.1053/j.gastro.2020.04.064

37. Huang M liang, Li X, Meng Y, Xiao B, Ma Q, Ying S song, et al. Upregulation of angiotensin-converting enzyme (ACE) 2 in hepatic fibrosis by ACE inhibitors. Clin Exp Pharmacol Physiol. 2010;37(1):e1-6. Doi: 10.1111/j.1440-1681.2009.05302.x.

38. Oyelade T, Alqahtani J, Canciani G. Prognosis of COVID-19 in Patients with Liver and Kidney Diseases: An Early Systematic Review and Meta-Analysis. Trop Med Infect Dis. 2020;5(2):80. Doi: 10.3390/tropicalmed5020080.

39. Moon AM, Webb GJ, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. J Hepatol. 2020;73(3):705-8. Doi: 10.1016/j.jhep.2020.05.013

40. Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. J Hepatol. 2020;73(2):451-3. doi: 10.1016/j.jhep.2020.03.044.

41. Boeckmans J, Rodrigues RM, Demuyser T, Piérard D, Vanhaecke T, Rogiers V. COVID-19 and drug-induced liver injury: a problem of plenty or a petty point? Arch Toxicol. 2020;94(4):1367-9. Doi: 10.1007/s00204-020-02734-1.

42. Chen X, Jiang Q, Ma Z, Ling J, Hu W, Cao Q, et al. Clinical Characteristics of Hospitalized Patients with SARS-CoV-2 and Hepatitis B Virus Co-infection. Virol Sin. 2020;35(6):842-5. Doi: 10.1007/s12250-020-00276-5.

43. Mohamed DZ, Ghoneim MES, Abu-Risha SES, Abdelsalam RA, Farag MA. Gastrointestinal and hepatic diseases during the COVID-19 pandemic: Manifestations, mechanism and management. World J Gastroenterol. 2021;27(28):4504-35. Doi: 10.3748/wjg.v27.i28.4504.

44. Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: The current evidence. United Eur Gastroenterol J. 2020;8(5):509-19. Doi: 10.1177/2050640620924157.

45. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2020;18(7):1561-6. Doi: 10.1016/j.cgh.2020.04.002.

46. Ambrus C, Bakos É, Sarkadi B, Özvegy-Laczka C, Telbisz Á. Interactions of anti-COVID-19 drug candidates with hepatic transporters may cause liver toxicity and affect pharmacokinetics. Sci Rep. 2021;11(1):17810. Doi: 10.1038/s41598-021-97160-3.

47. Falcão MB, Pamplona de Góes Cavalcanti L, Filgueiras Filho NM, Antunes de Brito CA. Case Report: Hepatotoxicity Associated with the Use of Hydroxychloroquine in a Patient with COVID-19. Am J Trop Med Hyg. 2020;102(6):1214-6. Doi: 10.4269/ajtmh.20-0276.

48. Garrido I, Lopes S, Simões MS, Liberal R, Lopes J, Carneiro F, et al. Autoimmune hepatitis after COVID-19 vaccine - more than a coincidence. J Autoimmun. 2021;125:102741. Doi: 10.1016/j.jaut.2021.102741.

49. Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. J Hepatol. 2020;73(5):1231-40. Doi: 10.1016/j.jhep.2020.06.006.

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