

World Journal of *Hepatology*

World J Hepatol 2021 October 27; 13(10): 1203-1458



EDITORIAL

- 1203** Transition of an acronym from nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease
Alam S, Fahim SM

OPINION REVIEW

- 1208** Non-invasive real-time assessment of hepatic macrovesicular steatosis in liver donors: Hypothesis, design and proof-of-concept study
Rajamani AS, Rammohan A, Sai VR, Rela M

REVIEW

- 1215** Impact of COVID-19 pandemic on liver, liver diseases, and liver transplantation programs in intensive care units
Omar AS, Kaddoura R, Orabi B, Hanoura S
- 1234** In the era of rapid mRNA-based vaccines: Why is there no effective hepatitis C virus vaccine yet?
Echeverría N, Comas V, Aldunate F, Perbolianachis P, Moreno P, Cristina J
- 1269** Pediatric non-cirrhotic portal hypertension: Endoscopic outcome and perspectives from developing nations
Sarma MS, Seetharaman J

MINIREVIEWS

- 1289** Acute-on-chronic liver failure in children
Islek A, Tumgor G
- 1299** Coronavirus disease 2019 in liver transplant patients: Clinical and therapeutic aspects
Loinaz-Seguro C, Marcacuzco-Quinto A, Fernández-Ruiz M
- 1316** Pediatric vascular tumors of the liver: Review from the pathologist's point of view
Cordier F, Hoorens A, Van Dorpe J, Creyten D
- 1328** Autoimmune hepatitis in genetic syndromes: A literature review
Capra AP, Chiara E, Briuglia S
- 1341** Assessing the prognosis of cirrhotic patients in the intensive care unit: What we know and what we need to know better
da Silveira F, Soares PHR, Marchesan LQ, da Fonseca RSA, Nedel WL
- 1351** Liver transplantation for pediatric inherited metabolic liver diseases
Vimalesvaran S, Dhawan A

- 1367 Liver and COVID-19: From care of patients with liver diseases to liver injury

Gaspar R, Castelo Branco C, Macedo G

ORIGINAL ARTICLE

Basic Study

- 1378 Direct modulation of hepatocyte hepcidin signaling by iron

Yu LN, Wang SJ, Chen C, Rausch V, Elshaarawy O, Mueller S

- 1394 Serum zonulin levels in patients with liver cirrhosis: Prognostic implications

Voulgaris TA, Karagiannakis D, Hadziyannis E, Manolakopoulos S, Karamanolis GP, Papatheodoridis G, Vlachogiannakos J

Retrospective Cohort Study

- 1405 Impact of biliary complications on quality of life in live-donor liver transplant recipients

Guirguis RN, Nashaat EH, Yassin AE, Ibrahim WA, Saleh SA, Bahaa M, El-Meteini M, Fathy M, Dabbous HM, Montasser IF, Salah M, Mohamed GA

Retrospective Study

- 1417 Machine learning models for predicting non-alcoholic fatty liver disease in the general United States population: NHANES database

Atsawarungrangkit A, Laoveeravat P, Promrat K

- 1428 Acute liver failure with hemolytic anemia in children with Wilson's disease: Genotype-phenotype correlations?

Pop TL, Grama A, Stefanescu AC, Willheim C, Ferenci P

Observational Study

- 1439 Clinical outcomes of patients with two small hepatocellular carcinomas

Pham AD, Vaz K, Ardalan ZS, Sinclair M, Apostolov R, Gardner S, Majeed A, Mishra G, Kam NM, Patwala K, Kutaiba N, Arachchi N, Bell S, Dev AT, Lubel JS, Nicoll AJ, Sood S, Kemp W, Roberts SK, Fink M, Testro AG, Angus PW, Gow PJ

CASE REPORT

- 1450 Focal nodular hyperplasia associated with a giant hepatocellular adenoma: A case report and review of literature

Gaspar-Figueiredo S, Kefleyesus A, Sempoux C, Uldry E, Halkic N

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Julio Coelho, MD, PhD, Professor, Department of Surgery, Federal University of Parana, Curitiba 80240-110, Parana, Brazil. coelhojcu@yahoo.com.br

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJH* as 0.61. The *WJH*'s CiteScore for 2020 is 5.6 and Scopus CiteScore rank 2020: Hepatology is 24/62.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xu Guo; Production Department Director: Xiang Li; Editorial Office Director: Xiang Li.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pylsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

October 27, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Liver and COVID-19: From care of patients with liver diseases to liver injury

Rui Gaspar, Catarina Castelo Branco, Guilherme Macedo

ORCID number: Rui Gaspar 0000-0003-0332-3844; Catarina Castelo Branco 0000-0002-8592-387X; Guilherme Macedo 0000-0002-9387-9872.

Author contributions: Gaspar R and Branco CC were responsible for acquisition and interpretation of data and drafting of the manuscript; and Macedo G was responsible for critical revision of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Gastroenterology

Rui Gaspar, Guilherme Macedo, Department of Gastroenterology and Hepatology, Centro Hospitalar de São João, Porto 4200, Portugal

Catarina Castelo Branco, Department of Internal Medicine, Centro Hospitalar e Universitário do Porto, Porto 4100, Portugal

Corresponding author: Rui Gaspar, MD, Doctor, Department of Gastroenterology and Hepatology, Centro Hospitalar de São João, Alameda Prof Hernani Monteiro, Porto 4200, Portugal. ruiropesgaspar@gmail.com

Abstract

The global pandemic of coronavirus disease 2019 (COVID-19) changed dramatically all priorities on medical society and created several challenges for clinicians caring for patients with liver diseases. We performed a comprehensive review about how COVID-19 can affect the liver, the influence of liver diseases on the risk of developing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 severity and also some strategies to overcome all the challenges clinicians have to face in the management of patients with liver diseases in a period of time when all the focus turned on COVID-19. We analyze the relationship between COVID-19 and non-alcoholic fatty liver disease, alcoholic liver disease, viral hepatitis, autoimmune liver disease, cirrhosis, hepatocellular carcinoma and liver transplantation, as well as the approach to SARS-CoV-2 vaccination.

Key Words: COVID-19; Liver diseases; Vaccination; SARS-CoV-2

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Coronavirus disease 2019 (COVID-19) has become a major health problem worldwide in the last few months, affecting the health system dramatically. Apart from the respiratory system, associated liver injury is one of the main concerns in severe acute respiratory syndrome coronavirus 2 infection and several mechanisms could explain liver abnormalities. In this mini-review, and different from other papers, we not only analyze liver injury by COVID-19, the effect of COVID-19 in liver diseases, its pathophysiology and strategies to keep an adequate care of liver patients, but also

and hepatology

Country/Territory of origin:

Portugal

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: May 28, 2021

Peer-review started: May 28, 2021

First decision: June 27, 2021

Revised: July 11, 2021

Accepted: August 31, 2021

Article in press: August 31, 2021

Published online: October 27, 2021

P-Reviewer: Khan MKA

S-Editor: Yan JP

L-Editor: A

P-Editor: Guo X



highlight the potential higher risk of severe disease or risk of infection in patients with different etiologies of liver disease. We also analyze the recent recommendations and prioritization regarding vaccination in patients with liver disease.

Citation: Gaspar R, Castelo Branco C, Macedo G. Liver and COVID-19: From care of patients with liver diseases to liver injury. *World J Hepatol* 2021; 13(10): 1367-1377

URL: <https://www.wjgnet.com/1948-5182/full/v13/i10/1367.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v13.i10.1367>

INTRODUCTION

Coronaviruses are single-stranded RNA viruses that mainly cause upper respiratory tract infections in humans. Two coronaviruses were previously described, severe acute respiratory syndrome coronavirus (SARS-CoV), causing an epidemic in 2003, and middle eastern respiratory syndrome coronavirus (MERS-CoV), causing an epidemic in 2012[1].

The new SARS-CoV-2 is responsible for one of the most important and devastating pandemic in the human history - the first case of severe pneumonia caused by SARS-CoV-2 was described on 3rd January 2020 in Wuhan, China, the first epicenter of the disease[2]. Since then, SARS-CoV-2 have widespread across the world, causing a global pandemic - in the beginning of May 2021, World Health Organization reported more than 150000000 infected patients and more than 3000000 deaths[3].

Coronavirus disease 2019 (COVID-19) has a variety of clinical presentations, with the majority of patients remaining asymptomatic or with mild symptoms, such as cough, anosmia, fatigue, diarrhea, headache or fever. However, 10%-15% will present acute hypoxemia or respiratory distress syndrome that might progress to multi-organ failure and death[4-7].

The respiratory tract is the main target of SARS-CoV-2 but several reports revealed a systemic involvement of the disease, including liver and the gastrointestinal tract[8].

In this review, we will highlight the relationship between COVID-19 and the liver.

LIVER INJURY IN COVID-19

It is well established that the respiratory tract is involved in the majority cases of SARS-CoV-2 infections but several studies reported COVID-19 associated liver injury, defined as liver damage during disease progression or treatment[9].

Elevated serum liver biochemistries in patients with COVID-19 was first described by Chen *et al*[10] in Wuhan where 43.9% of patients had elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Overall, the incidence of liver injury ranged from 14.8% to 78% and the most common changes are mild elevations of AST and/or ALT (mainly within 3 times the upper limit of normal)[11-13]. The wide range of incidence could be explained by the different cut-off values of upper limit of normal and geographical variability in prevalence and type of underlying chronic liver disease[7,14].

It was also described a possible relationship between liver injury and severity of the disease: Abnormalities in liver function were significantly higher in critically ill patients and associated with poorer outcome. One large Chinese study showed that 18% of non-severe COVID-19 patients had elevated ALT *vs* 56% in the group of severe COVID-19[1,15,16].

Liver biopsies in COVID-19 patients did not show any typical pattern of hepatic lesions and liver injury is probably associated with multiple mechanisms (Table 1)[1,7,9,17-26]: (1) Direct cytotoxicity by active replication of SARS-CoV-2 in hepatic cells due to abundance of its receptor in cholangiocytes - however, the major COVID-19 induced liver function abnormalities are in aminotransferases that might be explained by others factors such as mitochondrial dysfunction, SARS-CoV-2 induced hepatic steatosis, transaminase release due to breakdown of skeletal and cardiac muscle and venous and arterial thromboses; (2) Hyper-inflammatory reaction to COVID-19: Substantial elevations in serum ALT are usually associated with high levels of C reactive protein, D-dimer, ferritin and interleucine-6 and result from the development of the cytokine

Table 1 Mechanisms of coronavirus disease 2019 liver injury

Mechanisms	Pathophysiology
Direct cytotoxicity	Active replication of SARS-CoV-2 in hepatic cells
Hyper-inflammatory reaction	Cytokine storm and activation of immune system
Systemic hypoxia	COVID-19 cardiomyopathy
Drug-induced liver injury	Liver toxicity to medication used to treat COVID-19

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

storm and activation of the innate and adaptive immune system; (3) Systemic hypoxia and hepatic congestion related to cardiomyopathy (hypoxia hepatitis is frequent in the severe cases); and (4) Drug-induced liver injury: Mainly with lopinavir-ritonavir, tocilizumab and remdesivir.

COVID-19 AND LIVER DISEASES

The presence of previous liver disease could influence the prognosis of COVID-19 and SARS-CoV-2 could also pose some difficult challenges in care of liver diseases' patients (Table 2).

Non-alcoholic fatty liver disease and metabolic associated fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is one of the most common etiologies of liver disease in the world and the most emerging cause in developed countries, being expected to become the leading cause of liver transplantation worldwide[27,28]. Recently, a new concept has merged, metabolic associated fatty liver disease (MAFLD), diagnosed in the presence of hepatic steatosis and any of the following metabolic conditions: Diabetes mellitus, obesity/overweight or evidence of metabolic dysregulation in lean patients[29].

Several studies investigated the possible relationship between NAFLD/MAFLD and the outcome of COVID-19. Ji *et al*[30] reported liver abnormalities in 50% at admission of COVID-19 and NAFLD patients and in 75% during hospitalization and NAFLD was an independent risk factor for COVID-19 progression[27]. Another study, a meta-analysis by Pan *et al*[31], showed that NAFLD increased the risk of disease progression among patients with COVID-19.

NAFLD patients may also suffer from comorbidities known to be important risk factors for severity of COVID-19 and that could negatively influence prognosis, such as hypertension, obesity or diabetes[27]. However, Zhou *et al*[32] established a synergic effect of NAFLD for severe COVID-19 in patients less than 60 years-old and independent of other comorbidities, showing that NAFLD alone could be an important prognostic factor. This might be explained by metabolically active fat, which is associated with[17,33]: (1) Chronic inflammatory changes and higher cytokine levels, making NAFLD patients more vulnerable to cytokine storm in COVID-19; and (2) Imbalance in host inflammatory and tolerance response to SARS-CoV-2. On the other hand, it was also demonstrated that COVID-19 patients exhibited higher levels of monocyte chemoattractant protein-1 that is associated with steatohepatitis exacerbation, increasing the risk of NAFLD progression[34].

Therefore, it is of paramount importance to carefully follow NAFLD and COVID-19 patients due to the higher risk of poorer outcomes in both diseases.

Alcoholic liver disease: Alcoholic liver disease is one of the main causes of liver disease and its patients were considered one of the most affected groups during the pandemic as they present[35-37]: (1) Higher risk of developing SARS-CoV-2 infection due to reduced immunity to bacterial and viral infection (due to heavy alcohol consumption) and also willingness to adopt prevention measures; (2) Worse COVID-19 outcomes with a study reporting to be the only liver disease with a significant odds ratio for death; and (3) Higher alcohol consumption during the time of social isolation, increasing the risk of decompensation.

Strategies to overcome all these difficulties should be implemented and include social and psychological support (locally or *via* telemedicine), educational sessions to deal with the risk of COVID-19 as well as regular appointments with hepatologists.

Table 2 Influence of liver diseases in risk of infection or outcome of coronavirus disease 2019

Higher risk of infection or severe outcome of COVID-19	Apparently non-higher risk of infection or severe outcome of COVID-19
Non-alcoholic fatty liver disease	Hemochromatosis
Alcoholic liver disease	Wilson's disease
Alpha-1 antitrypsin deficiency	Autoimmune liver disease
Cirrhosis	Hepatitis B infection
Hepatocellular carcinoma	

COVID-19: Coronavirus disease 2019.

A debatable question is the use of corticosteroids in alcoholic hepatitis: There are some recommendations suggesting to avoid steroids in this situation as it may delay viral clearance but benefits must be weighed against risks and there are some reports showing that prednisolone might be an effective and safe treatment in patients with SARS-CoV-2 infection and alcoholic hepatitis[38,39].

Other metabolic liver diseases: There is no data on the risk of infection and severity of COVID-19 in patients with hemochromatosis and Wilson's disease. It is always important to search for iron overload in patients with SARS-CoV-2 and abnormal liver tests as elevated ferritin levels could be associated to viral infection and mask an underlying hemochromatosis[40].

Alpha-1 antitrypsin might inhibit infection by SARS-CoV-2, has anticoagulation effects and protect against inflammation[41]. Therefore, patients with alpha-1 antitrypsin deficiency seems to have increased risk of infection and COVID-19 severity, mainly Pi*ZZ and/or low alpha-1 antitrypsin levels.

Autoimmune liver diseases: Autoimmune liver diseases are a group of diseases that include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

The management of autoimmune liver diseases was one of the main concerns of hepatologists during COVID-19 pandemic due to the use of immunosuppressive therapy. Previous reports with other coronaviruses (SARS-CoV or MERS-CoV) did not show worse outcomes in patients who were undergoing transplantation, chemotherapy or other immunosuppressive treatments and there was also some evidence that immunosuppressive therapy might have a protective effect against severe COVID-19[42,43]. Therefore, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) were against stopping immunosuppressive therapy as it may lead to disease flares that will need high doses of steroids, which will increase the susceptibility for SARS-CoV-2 infection. More recently, a multicenter study evaluated the outcomes of COVID-19 in patients with AIH and showed that the overall outcome of SARS-CoV-2 disease was favorable in patients without cirrhosis and that ongoing immunosuppression was not associated with increased risk of severe COVID-19[44]. Efe *et al*[44] also described that the risk of AIH relapse may be related with hyperstimulation of the immune system by COVID-19[45]. There is scarce information about COVID-19 and PBC or PSC - an Italian study found an incidence of SARS-CoV-2 infection of 5.6% in AIH patients but only 1.5% in PBC patients - the higher incidence in AIH might be related with the use of immunosuppressive therapy (not used in PBC)[46]. Another important finding, also described in other autoimmune and inflammatory conditions, is the development of new-onset PBC after COVID-19, where SARS-CoV-2 triggered the development of PBC in a genetically predisposed individual[45,47,48].

Viral hepatitis: COVID-19 did not seem to influence the course of hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. A meta-analysis by Mantovani *et al*[49] reported an incidence in COVID-19 patients of only less than 0.1% HCV infection and 0.1% of HBV infection. In fact, the major effect of COVID-19 is the impact in HCV elimination efforts. A Spanish study showed that the interruption of HCV screening, linkage to care and harm reduction programs, would substantially decrease HCV diagnosis and treatment, consequently, increase the number of HCV liver-related deaths, hepatocellular carcinoma (HCC) and decompensated cirrhosis[50]. Thus, it is of paramount importance to keep HCV elimination a major health priority through

innovative programs as telehealth or home-delivery HCV drugs[50].

Akin to HBV infection, one of the largest cohorts of patients with COVID-19 and past or current HBV infection did not show an association with acute liver injury. Patients that fulfill the criteria for HBV treatment or under corticosteroid therapy should receive antiviral treatment but it may not be necessary in all patients with COVID-19 and current or past HBV infection[51]. A study by Liu *et al*[52] also reported that HBV infection did not predispose COVID-19 patients to more severe outcomes. There is also a report of COVID-19 accompanied by HBV infection causing a fulminant hepatitis[53].

Cirrhosis: Cirrhosis is one of the major causes of morbidity and mortality in the entire world and the second leading cause of digestive disease mortality[54].

Patients with cirrhosis have multiple mechanisms of immune dysfunction and are more susceptible to infection, not only to severe bacterial infection but also to viral and fungal-related disease[7,22,55]. However, data about risk of COVID-19 in this population is controversial, with Richardson *et al*[56] not suggesting a higher prevalence of cirrhotic patients in COVID-19 population while Kushner *et al*[57] reporting higher risk of infection, severity of the disease and hepatic decompensation. In cirrhotic patients, there is also a relationship between severity of liver disease and SARS-CoV-2 morbidity and mortality, with Child-Pugh C patients presenting higher frequency of Intensive Care Unit admission, renal replacement therapy and mortality [58].

Bajaj *et al*[59] showed that cirrhotic patients hospitalized with COVID-19 had similar mortality rates of patients admitted with cirrhosis alone but higher than patients with COVID-19 alone. An Italian study also demonstrated that cirrhotic patients that develop COVID-19 present a worse prognosis due to respiratory complications but also worsening of liver function leading to end-stage liver disease. They also found that the 30-d mortality in non-cirrhotic patients was significantly lower[60].

A very interesting finding in a multicenter cohort is that COVID-19 is associated with hepatic decompensation and, in this study, 24.3% had no respiratory symptoms at the time of diagnosis[4]. As so, testing to SARS-CoV-2 infection is advisable in patients with hepatic decompensation and early admission should be considered due to high rates of mortality.

SARS-CoV-2 infection can also cause acute-on-chronic liver failure characterized by hepatic decompensation events, extrahepatic organ failure and high rates of mortality.

EASL and World Gastroenterology Organization recommend that care should be maintained as this fragile population have a very high risk of decompensation. Prophylaxis of spontaneous bacterial peritonitis and encephalopathy, therapeutic paracentesis and variceal banding in high risk patients should be always performed in a COVID-19 free environment and following all the protective measures, as this will reduce the risk of further decompensation and hospitalization[37,61].

Cancer and hepatocellular carcinoma: Patients with COVID-19 and cancer are at increased risk of infection and worse outcomes[62]. A nationwide Chinese study that included 1590 patients (18% with history of cancer) reported higher risk of adverse events in patients with active or past history of cancer. This might be explained as cancer patients are more susceptible to infection (due to their systemic immunosuppressive state associated with malignancy but also with its treatment) and have increased risk of COVID-19 related serious events[63,64].

HCC is the sixth most commonly diagnosed and the fourth leading cause of cancer-related death in the world, being one of the major health challenges in liver clinic[65, 66]. There is scarce information on the impact of COVID-19 in patients with HCC - in a small study, Zhang *et al*[67] reported poorer outcomes in patients with HCC but also with other malignancies when compared to the general population.

The major impact of COVID-19 on HCC is related to the delay on the proper management of HCC. A French multicenter study reported a significant decrease in the rate of HCC patients referred for first diagnosis or treatment[68]. Several interpretations could be made but may be related to the increase delay of referral by other professionals, patients' fear to search for healthcare services, delay in the Hepatology appointments and limited assessment to diagnostic and therapeutic tools. They also found a higher rate of treatment delay longer than one month when compared 2019 to 2020[68].

Currently, AASLD and EASL recommend to continue HCC surveillance and treatment with an acceptable delay of a maximum of two months to reduce the number of patients presenting with HCC not amenable to curative treatment[43,69]. Whenever possible, telemedicine could replace clinic visits and multidisciplinary team

meetings, and all diagnostic and therapeutic procedures should be performed according to the COVID-19 prophylactic measures to avoid nosocomial spread on infection[60].

The real effect of COVID-19 on HCC management is still undetermined and only the middle-term follow-up will clarify the pandemic impact on HCC morbidity and mortality.

Liver transplantation: The risk and severity of COVID-19 in liver transplant patients is still unclear[70]. A multinational cohort reported a similar risk to the general population of contracting infection with SARS-CoV-2[71]. The proportion of liver transplant recipients hospitalized with COVID-19 was 82% and 19% died and advanced age, presence of non-liver cancer and elevated baseline creatinine were associated with higher mortality rates, while the type of immunosuppression and time since transplantation were not associated[71]. However, the European Liver and Intestine Transplantation Association established a registry and suggested that longer time of transplantation might have higher rates of mortality[72].

Liver transplantation programmes were heavily affected by COVID-19 pandemic by several reasons: Limited access to intensive care unit (ICU) due to the number of COVID-19 patients needing ventilation support, reduced number of organs because all major guidelines recommended against using organs from donors with SARS-CoV-2 infection and also limited access of patients to liver transplant centers[58].

It is crucial to maintain liver transplant programs to reduce liver diseases mortality, facing all the new challenges through innovative tools, in which telemedicine might play a key role.

The postoperative period is also a challenge and should follow a SARS-CoV-2 free pathway, with proper free-SARS-CoV-2 ICU to ensure high transplant success rates and preventing nosocomial infection[5]. In the perioperative period, patients' follow-up should be preferably through telemedicine and, in case of symptoms, the threshold for testing for SARS-CoV-2 infection should be low[5]. In case of COVID-19, patients should always present to the hospital for medical evaluation[5].

Regarding immunosuppression after liver transplants, all liver associations recommend to maintain medication as there is no data suggesting a higher risk of COVID-19 severity, while stopping will increase the risk of graft rejection[43,61,73]. However, in case of COVID-19, immunosuppression should be reduced, particularly antimetabolite dosages[43].

Vaccination: The development of SARS-CoV-2 vaccine is one of the major advances to mitigate all the health and economic issues. This development started in January 2020 and progressed very rapidly, being now available more than 5 vaccines. The process of vaccination is moving forward worldwide in order to achieve herd immunity as soon as possible.

Despite some concerns about vaccines' adverse events, the safety profile is excellent and, based on current knowledge, there is no contra-indication for vaccination of liver disease patients, as the potential benefits are higher than the risks[74]. However, there is a report of auto-immune hepatitis developing post-COVID-19 vaccination[75].

Vaccination should also be prioritized in[74]: (1) Cirrhotic patients or with liver decompensation; (2) Hepatobiliary malignancies patients; (3) Chronic liver disease patients and risk factors for severe COVID-19; (4) Liver transplant recipients (prior to liver transplant whenever possible or 3-6 mo after transplantation); and (5) Healthcare professionals caring for these patients.

CONCLUSION

Liver abnormalities in COVID-19 patients are common and may result from direct cytotoxicity, hyper-inflammatory status or DILI. In addition, a direct relationship between grade of liver injury and severity of the disease was also established.

The existence of previous liver disease could influence the prognosis, with patients with NAFLD, cirrhosis and HCC presenting higher risk of severe COVID-19 and death (Table 2). In this population, vaccination should be considered a priority. On the other hand, the focus on SARS-CoV-2 infection lead to reduced access to care for patients with liver disease that must be reestablished to improve the outcome of these diseases.

In conclusion, the consequences of COVID-19 on liver ranges from its direct liver injury to the profound negative effect on liver disease patients' care which might increase liver disease burden and negatively influence prognosis.

REFERENCES

- 1 **Jothimani D**, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. *J Hepatol* 2020; **73**: 1231-1240 [PMID: 32553666 DOI: 10.1016/j.jhep.2020.06.006]
- 2 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]
- 3 **World Organization Health**. Weekly operational update on COVID-19 - 3 May 2021. [cited 20 May 2021]. Available from: <https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---3-may-2021>
- 4 **Moon AM**, Webb GJ, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, Genescà J, Gill US, James TW, Jones PD, Marshall A, Mells G, Perumalswami PV, Qi X, Su F, Ufere NN, Barnes E, Barritt AS, Marjot T. 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**: 705-708 [PMID: 32446714 DOI: 10.1016/j.jhep.2020.05.013]
- 5 **Mohammed A**, Paranj N, Chen PH, Niu B. COVID-19 in Chronic Liver Disease and Liver Transplantation: A Clinical Review. *J Clin Gastroenterol* 2021; **55**: 187-194 [PMID: 33394628 DOI: 10.1097/MCG.0000000000001481]
- 6 **Berlin DA**, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020; **383**: 2451-2460 [PMID: 32412710 DOI: 10.1056/NEJMcp2009575]
- 7 **Marjot T**, Webb GJ, Barritt AS 4th, Moon AM, Stamataki Z, Wong VW, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 348-364 [PMID: 33692570 DOI: 10.1038/s41575-021-00426-4]
- 8 **Nardo AD**, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int* 2021; **41**: 20-32 [PMID: 33190346 DOI: 10.1111/liv.14730]
- 9 **Sun J**, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. *Liver Int* 2020; **40**: 1278-1281 [PMID: 32251539 DOI: 10.1111/liv.14470]
- 10 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]
- 11 **Zhang C**, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]
- 12 **Musa S**. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? *Arab J Gastroenterol* 2020; **21**: 3-8 [PMID: 32253172 DOI: 10.1016/j.ajg.2020.03.002]
- 13 **Li J**, Fan JG. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. *J Clin Transl Hepatol* 2020; **8**: 13-17 [PMID: 32274341 DOI: 10.14218/JCTH.2020.00019]
- 14 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]
- 15 **Liu C**, Jiang ZC, Shao CX, Zhang HG, Yue HM, Chen ZH, Ma BY, Liu WY, Huang HH, Yang J, Wang Y, Liu HY, Xu D, Wang JT, Yang JY, Pan HQ, Zou SQ, Li FJ, Lei JQ, Li X, He Q, Gu Y, Qi XL. [Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study]. *Zhonghua Gan Zang Bing Za Zhi* 2020; **28**: 107-111 [PMID: 32077660 DOI: 10.3760/cma.j.issn.1007-3418.2020.02.003]
- 16 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
- 17 **Metawea MI**, Yousif WI, Moheb I. COVID 19 and liver: An A-Z literature review. *Dig Liver Dis* 2021; **53**: 146-152 [PMID: 32988758 DOI: 10.1016/j.dld.2020.09.010]
- 18 **Amin M**. COVID-19 and the liver: overview. *Eur J Gastroenterol Hepatol* 2021; **33**: 309-311 [PMID: 32558697 DOI: 10.1097/MEG.0000000000001808]
- 19 **Li Y**, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *J Med Virol* 2020; **92**: 1491-1494 [PMID: 32369204 DOI: 10.1002/jmv.25973]
- 20 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]
- 21 **Da BL**, Kushner T, El Halabi M, Paka P, Khalid M, Uberoi A, Lee BT, Perumalswami PV, Rutledge SM, Schiano TD, Friedman S, Saberi B. Liver Injury in Hospitalized Patients with COVID-19 Correlates with Hyper Inflammatory Response and Elevated IL-6. *Hepatol Commun* 2020 [PMID: 33230491 DOI: 10.1002/hep4.1631]
- 22 **Sonzogni A**, Previtali G, Seghezzi M, Grazia Alessio M, Gianatti A, Licini L, Morotti D, Zerbi P,

- Carsana L, Rossi R, Lauri E, Pellegrinelli A, Nebuloni M. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. *Liver Int* 2020; **40**: 2110-2116 [PMID: 32654359 DOI: 10.1111/liv.14601]
- 23 **Gordon DE**, Jang GM, Bouhaddou M, Xu J, Obernier K, O'Meara MJ, Guo JZ, Swaney DL, Tummino TA, Hüttenhain R, Kaake RM, Richards AL, Tutuncuoglu B, Foussard H, Batra J, Haas K, Modak M, Kim M, Haas P, Polacco BJ, Braberg H, Fabius JM, Eckhardt M, Soucheray M, Bennett MJ, Cakir M, McGregor MJ, Li Q, Naing ZCC, Zhou Y, Peng S, Kirby IT, Melnyk JE, Chorba JS, Lou K, Dai SA, Shen W, Shi Y, Zhang Z, Barrio-Hernandez I, Memon D, Hernandez-Armenta C, Mathy CJP, Perica T, Pilla KB, Ganesan SJ, Saltzberg DJ, Ramachandran R, Liu X, Rosenthal SB, Calviello L, Venkataramanan S, Lin Y, Wankowicz SA, Bohn M, Trenker R, Young JM, Cavero D, Hiatt J, Roth T, Rathore U, Subramanian A, Noack J, Hubert M, Roesch F, Vallet T, Meyer B, White KM, Miorin L, Agard D, Emerman M, Ruggero D, Garcia-Sastre A, Jura N, von Zastrow M, Taunton J, Schwartz O, Vignuzzi M, d'Enfert C, Mukherjee S, Jacobson M, Malik HS, Fujimori DG, Ideker T, Craik CS, Floor S, Fraser JS, Gross J, Sali A, Kortemme T, Beltrao P, Shokat K, Shoichet BK, Krogan NJ. A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. *bioRxiv* 2020 [PMID: 32511329 DOI: 10.1101/2020.03.22.002386]
- 24 **Cao B**, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020; **382**: 1787-1799 [PMID: 32187464 DOI: 10.1056/NEJMoa2001282]
- 25 **Muhović D**, Bojović J, Bulatović A, Vukčević B, Ratković M, Lazović R, Smolović B. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. *Liver Int* 2020; **40**: 1901-1905 [PMID: 32478465 DOI: 10.1111/liv.14516]
- 26 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383**: 1813-1826 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]
- 27 **Portincasa P**, Krawczyk M, Smyk W, Lammert F, Di Ciaula A. COVID-19 and non-alcoholic fatty liver disease: Two intersecting pandemics. *Eur J Clin Invest* 2020; **50**: e13338 [PMID: 32589264 DOI: 10.1111/eci.13338]
- 28 **Younossi ZM**, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: Implications for Liver Transplantation. *Transplantation* 2019; **103**: 22-27 [PMID: 30335697 DOI: 10.1097/TP.0000000000002484]
- 29 **Eslam M**, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbaek H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratzliff V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020; **73**: 202-209 [PMID: 32278004 DOI: 10.1016/j.jhep.2020.03.039]
- 30 **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]
- 31 **Pan L**, Huang P, Xie X, Xu J, Guo D, Jiang Y. Metabolic associated fatty liver disease increases the severity of COVID-19: A meta-analysis. *Dig Liver Dis* 2021; **53**: 153-157 [PMID: 33011088 DOI: 10.1016/j.dld.2020.09.007]
- 32 **Zhou YJ**, Zheng KI, Wang XB, Yan HD, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis. *J Hepatol* 2020; **73**: 719-721 [PMID: 32348790 DOI: 10.1016/j.jhep.2020.04.027]
- 33 **Lefere S**, Tacke F. Macrophages in obesity and non-alcoholic fatty liver disease: Crosstalk with metabolism. *JHEP Rep* 2019; **1**: 30-43 [PMID: 32149275 DOI: 10.1016/j.jhepr.2019.02.004]
- 34 **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**: 1367-1369 [PMID: 32266419 DOI: 10.1007/s00204-020-02734-1]
- 35 **Chick J**. Alcohol and COVID-19. *Alcohol Alcohol* 2020; **55**: 341-342 [PMID: 32400878 DOI: 10.1093/alcalc/agaa039]
- 36 **Rutledge SM**, Schiano TD, Florman S, Im GY. COVID-19 Aftershocks on Alcohol-associated Liver Disease: An Early Cross-Sectional Report from the U.S. Epicenter (Manuscript HEP4-20-0491). *Hepatol Commun* 2021 [PMID: 33821225 DOI: 10.1002/hep4.1706]
- 37 **Hamid S**, Alvares da Silva MR, Burak KW, Chen T, Drenth JPH, Esmat G, Gaspar R, LaBrecque D, Lee A, Macedo G, McMahon B, Ning Q, Reau N, Sonderup M, van Leeuwen DJ, Armstrong D, Yurdaydin C. WGO Guidance for the Care of Patients With COVID-19 and Liver Disease. *J Clin*

- Gastroenterol* 2021; **55**: 1-11 [PMID: [33230011](#) DOI: [10.1097/MCG.0000000000001459](#)]
- 38 **Sanders JM**, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020; **323**: 1824-1836 [PMID: [32282022](#) DOI: [10.1001/jama.2020.6019](#)]
 - 39 **Zelman S**, Holzwanger E, Malik R, Dickstein A, Aron MD. Alcoholic Hepatitis and COVID-19: The Question of Steroids. *ACG Case Rep J* 2020; **7**: e00504 [DOI: [10.14309/crj.0000000000000504](#)]
 - 40 **Aamar**, A. O., Jose; Aloreidi, Khalil; Bandaru, Praneeth; Reddy, Madhavi; Etienne, Denzil, Hemochromatosis in a Patient With Coronavirus Disease 2019. *Amer J Gastroenterol* 2020; **115**: S1326-S1326
 - 41 **Yang C**, Keshavjee S, Liu M. Alpha-1 Antitrypsin for COVID-19 Treatment: Dual Role in Antiviral Infection and Anti-Inflammation. *Front Pharmacol* 2020; **11**: 615398 [PMID: [33362565](#) DOI: [10.3389/fphar.2020.615398](#)]
 - 42 **Di Giorgio A**, Nicastro E, Speziani C, De Giorgio M, Pasulo L, Magro B, Fagioli S, D' Antiga L. Health status of patients with autoimmune liver disease during SARS-CoV-2 outbreak in northern Italy. *J Hepatol* 2020; **73**: 702-705 [PMID: [32413378](#) DOI: [10.1016/j.jhep.2020.05.008](#)]
 - 43 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: [32298473](#) DOI: [10.1002/hep.31281](#)]
 - 44 **Efe C**, Dhanasekaran R, Lammert C, Ebik B, Higuera-de la Tijera F, Aloman C, Rıza Calışkan A, Peralta M, Gerussi A, Massoumi H, Catana AM, Torgutalp M, Purnak T, Rigamonti C, Gomez Aldana AJ, Khakoo N, Kacmaz H, Nazal L, Frager S, Demir N, Irak K, Ellik ZM, Balaban Y, Atay K, Eren F, Cristoferi L, Batbay E, Urzua A, Snijders R, Kıyıcı M, Akyıldız M, Ekin N, Carr RM, Harputluoğlu M, Hatemi I, Mendizabal M, Silva M, Idilman R, Silveira M, Drenth JPH, Assis DN, Björnsson E, Boyer JL, Invernizzi P, Levy C, Schiano TD, Ridruejo E, Wahlin S. Outcome of COVID-19 in Patients With Autoimmune Hepatitis: An International Multicenter Study. *Hepatology* 2021; **73**: 2099-2109 [PMID: [33713486](#) DOI: [10.1002/hep.31797](#)]
 - 45 **Rodriguez Y**, Novelli L, Rojas M, De Santis M, Acosta-Ampudia Y, Monsalve DM, Ramírez-Santana C, Costanzo A, Ridgway WM, Ansari AA, Gershwin ME, Selmi C, Anaya JM. Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. *J Autoimmun* 2020; **114**: 102506 [PMID: [32563547](#) DOI: [10.1016/j.jaut.2020.102506](#)]
 - 46 **Rigamonti C**, Cittone MG, De Benedittis C, Rizzi E, Casciaro GF, Bellan M, Sainaghi PP, Pirisi M. Rates of Symptomatic SARS-CoV-2 Infection in Patients With Autoimmune Liver Diseases in Northern Italy: A Telemedicine Study. *Clin Gastroenterol Hepatol* 2020; **18**: 2369-2371.e1 [PMID: [32480009](#) DOI: [10.1016/j.cgh.2020.05.047](#)]
 - 47 **Marabotto E**, Ziola S, Shejani AD, Giannini EG. COVID-19 and liver disease: Not all evil comes to harm. *Liver Int* 2021; **41**: 237-238 [PMID: [33159405](#) DOI: [10.1111/liv.14721](#)]
 - 48 **Bartoli A**, Gitto S, Sighinolfi P, Cursaro C, Andreone P. Primary biliary cholangitis associated with SARS-CoV-2 infection. *J Hepatol* 2021; **74**: 1245-1246 [PMID: [33610679](#) DOI: [10.1016/j.jhep.2021.02.006](#)]
 - 49 **Mantovani A**, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Int* 2020; **40**: 1316-1320 [PMID: [32329563](#) DOI: [10.1111/liv.14465](#)]
 - 50 **Buti M**, Domínguez-Hernández R, Casado MA. Impact of the COVID-19 pandemic on HCV elimination in Spain. *J Hepatol* 2021; **74**: 1246-1248 [PMID: [33358780](#) DOI: [10.1016/j.jhep.2020.12.018](#)]
 - 51 **Yip TC**, Wong VW, Lui GC, Chow VC, Tse YK, Hui VW, Liang LY, Chan HL, Hui DS, Wong GL. Current and Past Infections of HBV Do Not Increase Mortality in Patients With COVID-19. *Hepatology* 2021; **74**: 1750-1765 [PMID: [33961298](#) DOI: [10.1002/hep.31890](#)]
 - 52 **Liu R**, Zhao L, Cheng X, Han H, Li C, Li D, Liu A, Gao G, Zhou F, Liu F, Jiang Y, Zhu C, Xia Y. Clinical characteristics of COVID-19 patients with hepatitis B virus infection - a retrospective study. *Liver Int* 2021; **41**: 720-730 [PMID: [33351265](#) DOI: [10.1111/liv.14774](#)]
 - 53 **Yigit Y**, Haddad M, Elmoheen A, Shogaa MR, Tawel R, Mohamed YK, Salem W, Fawzy Eltawagny M. Can COVID-19 Cause Flare-Ups of Acute Hepatitis B? *Case Rep Infect Dis* 2021; **2021**: 8818678 [PMID: [33564481](#) DOI: [10.1155/2021/8818678](#)]
 - 54 **Johnson KB**, Campbell EJ, Chi H, Zheng H, King LY, Wu Y, Delemos A, Hurairah A, Corey K, Richter JM, Chung RT. Advanced disease, diuretic use, and marital status predict hospital admissions in an ambulatory cirrhosis cohort. *Dig Dis Sci* 2014; **59**: 174-182 [PMID: [23990035](#) DOI: [10.1007/s10620-013-2832-5](#)]
 - 55 **Qian Q**, Fan L, Liu W, Li J, Yue J, Wang M, Ke X, Yin Y, Chen Q, Jiang C. Direct Evidence of Active SARS-CoV-2 Replication in the Intestine. *Clin Infect Dis* 2021; **73**: 361-366 [PMID: [32638022](#) DOI: [10.1093/cid/ciaa925](#)]
 - 56 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefe J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: [32320003](#) DOI: [10.1001/jama.2020.6775](#)]

- 57 **Kushner T**, Cafardi J. Chronic Liver Disease and COVID-19: Alcohol Use Disorder/Alcohol-Associated Liver Disease, Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, Autoimmune Liver Disease, and Compensated Cirrhosis. *Clin Liver Dis (Hoboken)* 2020; **15**: 195-199 [PMID: [32537135](#) DOI: [10.1002/clid.974](#)]
- 58 **Marjot T**, Moon AM, Cook JA, Abd-El Salam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: [33035628](#) DOI: [10.1016/j.jhep.2020.09.024](#)]
- 59 **Bajaj JS**, Garcia-Tsao G, Biggins SW, Kamath PS, Wong F, McGeorge S, Shaw J, Pearson M, Chew M, Fagan A, de la Rosa Rodriguez R, Worthington J, Olofson A, Weir V, Trisolini C, Dwyer S, Reddy KR. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. *Gut* 2021; **70**: 531-536 [PMID: [32660964](#) DOI: [10.1136/gutjnl-2020-322118](#)]
- 60 **Iavarone M**, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, Perricone G, Massironi S, Spinetti A, Buscarini E, Viganò M, Carriero C, Fagioli S, Aghemo A, Belli LS, Lucà M, Pedaci M, Rimondi A, Rumi MG, Invernizzi P, Bonfanti P, Lampertico P. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020; **73**: 1063-1071 [PMID: [32526252](#) DOI: [10.1016/j.jhep.2020.06.001](#)]
- 61 **Boettler T**, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2**: 100113 [PMID: [32289115](#) DOI: [10.1016/j.jhepr.2020.100113](#)]
- 62 **Tsamakis K**, Gavriatopoulou M, Schizas D, Stravodimou A, Mougkou A, Tsiptsios D, Sioulas V, Spartalis E, Sioulas AD, Tsamakis C, Charalampakis N, Mueller C, Arya D, Zarogoulidis P, Spandidos DA, Dimopoulos MA, Papageorgiou C, Rizos E. Oncology during the COVID-19 pandemic: challenges, dilemmas and the psychosocial impact on cancer patients. *Oncol Lett* 2020; **20**: 441-447 [PMID: [32565968](#) DOI: [10.3892/ol.2020.11599](#)]
- 63 **Liang W**, Guan W, Chen R, Wang W, Li J, Xu K, Li C, Ai Q, Lu W, Liang H, Li S, He J. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21**: 335-337 [PMID: [32066541](#) DOI: [10.1016/S1470-2045\(20\)30096-6](#)]
- 64 **Gosain R**, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff MS. COVID-19 and Cancer: a Comprehensive Review. *Curr Oncol Rep* 2020; **22**: 53 [PMID: [32385672](#) DOI: [10.1007/s11912-020-00934-7](#)]
- 65 **Pascual S**, Miralles C, Bernabé JM, Irurzun J, Planells M. Surveillance and diagnosis of hepatocellular carcinoma: A systematic review. *World J Clin Cases* 2019; **7**: 2269-2286 [PMID: [31531321](#) DOI: [10.12998/wjcc.v7.i16.2269](#)]
- 66 **Harris PS**, Hansen RM, Gray ME, Massoud OI, McGuire BM, Shoreibah MG. Hepatocellular carcinoma surveillance: An evidence-based approach. *World J Gastroenterol* 2019; **25**: 1550-1559 [PMID: [30983815](#) DOI: [10.3748/wjg.v25.i13.1550](#)]
- 67 **Zhang L**, Zhu F, Xie L, Wang C, Wang J, Chen R, Jia P, Guan HQ, Peng L, Chen Y, Peng P, Zhang P, Chu Q, Shen Q, Wang Y, Xu SY, Zhao JP, Zhou M. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020; **31**: 894-901 [PMID: [32224151](#) DOI: [10.1016/j.annonc.2020.03.296](#)]
- 68 **Amadeo G**, Brustia R, Allaire M, Lequoy M, Hollande C, Regnault H, Blaise L, Ganne-Carrié N, Séror O, Larrey E, Lim C, Scatton O, El Mouhadi S, Ozenne V, Paye F, Balladur P, Dohan A, Massault PP, Pol S, Dioguardi Burgio M, Vilgrain V, Sepulveda A, Cauchy F, Luciani A, Sommacale D, Leroy V, Roudot-Thoraval F, Bouattour M, Nault JC; Paris Liver Cancer Group. Impact of COVID-19 on the management of hepatocellular carcinoma in a high-prevalence area. *JHEP Rep* 2021; **3**: 100199 [PMID: [33163949](#) DOI: [10.1016/j.jhepr.2020.100199](#)]
- 69 **Boettler T**, Marjot T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Jalan R, Moreau R, Cornberg M, Berg T. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. *JHEP Rep* 2020; **2**: 100169 [PMID: [32835190](#) DOI: [10.1016/j.jhepr.2020.100169](#)]
- 70 **D'Antiga L**. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl* 2020; **26**: 832-834 [PMID: [32196933](#) DOI: [10.1002/lt.25756](#)]
- 71 **Webb GJ**, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, Catana MA, Cargill T, Dhanasekaran R, García-Juárez I, Hagström H, Kennedy JM, Marshall A, Masson S, Mercer CJ, Perumalswami PV, Ruiz I, Thaker S, Ufere NN, Barnes E, Barritt AS 4th, Moon AM. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol* 2020; **5**: 1008-1016 [PMID: [32866433](#) DOI: [10.1016/S2468-1253\(20\)30271-5](#)]
- 72 **Belli LS**, Duvoux C, Karam V, Adam R, Cuervas-Mons V, Pasulo L, Loinaz C, Invernizzi F, Patrono D, Bhoori S, Ciccarelli O, Morelli MC, Castells L, Lopez-Lopez V, Conti S, Fondevila C, Polak W. COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry. *Lancet Gastroenterol Hepatol* 2020; **5**: 724-725 [PMID: [32505228](#) DOI: [10.1016/S2468-1253\(20\)30183-7](#)]
- 73 **APASL Covid-19 Task Force**. Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hepatol Int* 2020; **14**: 415-428 [PMID: [32447721](#) DOI: [10.1007/s12066-020-00934-7](#)]

[10.1007/s12072-020-10054-w](https://doi.org/10.1007/s12072-020-10054-w)

- 74 **Cornberg M**, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. *J Hepatol* 2021; **74**: 944-951 [PMID: [33563499](https://pubmed.ncbi.nlm.nih.gov/33563499/) DOI: [10.1016/j.jhep.2021.01.032](https://doi.org/10.1016/j.jhep.2021.01.032)]
- 75 **Bril F**, Al Diffalha S, Dean M, Fettig DM. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty? *J Hepatol* 2021; **75**: 222-224 [PMID: [33862041](https://pubmed.ncbi.nlm.nih.gov/33862041/) DOI: [10.1016/j.jhep.2021.04.003](https://doi.org/10.1016/j.jhep.2021.04.003)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

