Annals of Hepatology 19 (2020) 353–358

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Concise review

The liver in times of COVID-19: What hepatologists should know

Ezequiel Ridruejo[a,b,c,1], Alejandro Soza[c,d,*,1]

[a] Hepatology Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC", Ciudad Autónoma de Buenos Aires Argentina, Argentina
[b] Hepatology and Liver Transplant Unit, Hospital Universitario Austral Pilar, Provincia de Buenos Aires, Argentina
[c] Latin American Liver Research, Educational and Awareness Network (LALREAN) Pilar, Provincia de Buenos Aires Argentina, Argentina
[d] Department of Gastroenterology, School of Medicine, Pontificia Universidad Católica de Chile, Chile

ARTICLE INFO

Article history:
Received 28 April 2020
Accepted 4 May 2020
Available online 18 May 2020

Keywords:
SARS-CoV-2
Coronavirus
Liver disease
Transplantation
Cirrhosis

ABSTRACT

The ongoing pandemic of coronavirus disease 2019 (COVID-19) pandemic poses a serious threat to healthcare systems globally. Information regarding how the infection affects the liver and relevance of pre-existing liver disease as a risk factor for acquiring the infection or having a severe disease are still scarce. Also, considerations in liver transplant patients, those having hepatocellular carcinoma or under immunosuppressive therapy are being matter of analysis as information is being generated. Different treatments for COVID-19 are currently under study, some of which may be associated to hepatotoxicity. In the present review we discuss current data on the COVID-19 and liver, aiming to provide hepatologists with updated information to face this pandemic.

1. Overview

The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide [1]. On March 11, 2020, the World Health Organization (WHO) declared the SARS-CoV-2 outbreak a pandemic due to the constantly increasing number of cases outside China [2]. As of April 20, nearly 2.5 million confirmed cases and more than 155,000 deaths in 213 countries and territories worldwide had been reported in the COVID-19 pandemic, according to WHO. However, despite these increases that are widely reported, many people are being discharged from hospitals and making a full recovery.

As the number of cases grows around the globe, both through increased detection and viral spread, it is essential to develop strategies to protect persons who are most vulnerable to have severe illness from SARS-CoV-2 infection. The Centers for Disease Control and Prevention (CDC) has issued specific guidance for persons at greater risk for serious morbidity and mortality from COVID-19, including patients with chronic liver diseases among many others [3].

In this article, we review current data on how COVID-19 may affect the liver in patients with and without previous liver disease and how a pre-existing liver disease may affect COVID-19 outcomes. We aim to provide clinical hepatologists with updated information to face this pandemic in daily practice.

2. General considerations

The first and most evident consequence of COVID-19 pandemic is its impact on routine care of patients with chronic liver diseases. Traditional clinical care of patients with chronic diseases in ambulatory settings changed since the appearance of this pandemic. To avoid transmission, almost all face-to-face routine controls are suspended and follow-up by telemedicine or by phone is recommended[4,5]. Telemedicine may not be available in many countries, but any means of virtual consultation must be used to avoid clinical visits.

In patients with chronic liver disease all recommendations from local authorities for the general population should be applied. Since patients with cirrhosis may be at higher risk of poor outcome, counseling about warning symptoms should be provided. Immediate contact is recommended upon the appearance of signs or symp-

* Corresponding author.
E-mail address: asoza@med.puc.cl (A. Soza).
[1] These authors equally contributed to this work.

https://doi.org/10.1016/j.aohep.2020.05.001

toms compatible with COVID-19 and/or decompensated cirrhosis for urgent referral and management [5].

3. Evaluating patients with COVID-19 and abnormal liver tests

Liver dysfunction may be common in patients admitted for COVID-19. Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were reported in 16–53% of patients [6]. Patients with severe COVID-19 seem to have higher rates of liver dysfunction. In a large study from China, AST/ALT were elevated in 18.2/19.8% of patients with mild and in 39.4/28.1% with severe disease [7]. Another smaller study from China found similar results: AST was elevated in 62% of patients in the intensive care unit (ICU) compared with 25% in those who did not require care in the ICU [8]. In patients with subclinical disease, AST and ALT were elevated in 8.7 and 8.9% of patients, respectively [9]. In a study from New York, including 5700 patients, 58.4% developed AST values >40 U/L and 39% ALT >60 U/L [10]. In this same cohort, 56 patients (2.1%) developed acute hepatic injury defined as an elevation in AST or ALT of >15 times the upper limit of normal. Of these 56 patients, 3 were 18–65 years old (3/1373, 0.2%) and discharged alive, and 53 died: 25 were 18–65 years old (25/134, 18.7%) and 28 were >65 years old (28/469, 6.7%) [10]. Therefore, the frequency of liver dysfunction increases the more severe is the COVID-19.

Liver damage in patients with coronavirus infections might be directly caused by the viral infection of liver cells since pathological studies in patients with SARS confirmed the presence of the virus in liver tissue. Angiotensin-converting enzyme 2 (ACE2), the entry cell receptor for SARS-CoV2, is expressed in both liver cells and bile duct cells [11]. Since its expression is much higher in bile duct cells, COVID-19 liver injury appears to be more related to its damage than to liver cells injury [11]. But this remains to be confirmed in COVID-19 patients [6]. ALT/AST elevation may also be explained by drug hepatotoxicity, cytokine storm and/or pneumonia-associated hypoxia [6,11].

In most studies, liver dysfunction appears to be mild, transient, not clinically significant and to have no impact on COVID-19 outcomes [12]. Despite these results, patients with abnormal liver test of hepatocellular type or mixed type at admission had higher risk of progressing to severe disease during hospitalization in a recent study [13].

4. Cirrhosis and pre-existing liver diseases

The prevalence of pre-existing liver diseases in patients with COVID-19 ranges from 2 to 11% [6]. In the New York study only 0.4% of patients had pre-existing cirrhosis [10]. Even if its impact on COVID-19 disease is yet unknown, cirrhosis has been associated with increased mortality in patients with acute respiratory distress syndrome (ARDS) [14]. Given that cirrhotics have poor immune function and worse outcomes when critically ill, more intensive surveillance or individually tailored therapeutic approaches are needed for severe patients with COVID-19 with pre-existing liver diseases [6,14].

In a study from China including 202 patients, obesity and the presence of non-alcoholic fatty liver disease (NAFLD) were independently associated with an increased risk of COVID-19 disease progression and a higher likelihood of abnormal liver function from admission to discharge [15]. Other report from China including 214 patients showed that the presence of metabolic associated fatty liver diseases (MAFLD) and obesity were associated with increased risk of severe COVID-19 disease even after adjusting for age, sex, smoking, diabetes, hypertension, and dyslipidemia [16].

Besides the care of the critically ill, the care of compensated cirrhotics remains a challenge in this COVID-19 pandemic [5,17]. As previously mentioned, telemedicine/phone contact must be used, wherever possible. Visits to specialized centers and routine laboratory testing can be postponed and can be performed locally/off-site whenever needed.

There is some controversy regarding screening procedures for varices and hepatocellular carcinoma (HCC). Even if delayed screening is safe for most patients, it may increase the relative risk of complications like variceal hemorrhage at the population level or diagnosis of HCC at a later stage [5,17]. Decision should be made according to available resources at each center and individual risk assessment. Urgent endoscopic procedures, such as variceal bleeding, bacterial cholangitis or other life-threatening conditions should not be delayed and carried out according recommendations [18].

In case of decompensated disease, care should be maintained according to guidelines but considering minimal exposure to medical staff, by using telemedicine/visits by phone wherever possible/required to avoid admission [5]. It is recommended to testing for SARS-CoV-2 in patients with acute decompensation.

5. Patients with hepatocellular carcinoma

There is no information about HCC and COVID-19. Nevertheless, patients with cancer may have a higher risk of COVID-19 and poorer outcomes from COVID-19 than individuals without cancer. It is recommended to pay more intensive attention in case of rapid deterioration in patients with cancer [19].

In patients with HCC, care and treatment should be maintained according to guidelines, including continuing systemic therapies, but considering minimal exposure to medical staff, by using telemedicine/visits by phone whenever possible/required [5]. The International Liver Cancer Association (ILCA) has released a guideline with recommendations for treatment of HCC during COVID-19 pandemic that can be consulted for further information [20].

6. Liver transplant candidates

The main arguments for reducing liver transplantation during the COVID-19 pandemic are: 1) The unacceptable high morbidity and mortality (20.5%) of patients undergoing elective surgery in the incubation period of COVID-19 [21]; 2) The need to reserve ICU beds and related resources for COVID-19 patients; 3) The potential risk of starting potent immunosuppressive therapy in a time of high risk of SARS-CoV-2 infection. Accordingly, it is recommended that donors and recipients are routinely tested for SARS-CoV-2 before transplantation [5]. The potential risk of nosocomial COVID-19 should be part of the consent for procedures including liver transplantation.

The COVID-19 pandemic has completely changed the way we take care of patients with cirrhosis. Reserving health resources for the sickest in an attempt to reduce hospital utilization may result in an impact in the care of patients with cirrhosis unfolding in three waves: (1) A period of resource utilization only for emergencies among patients with liver disease; (2) A “return to normal” period with increase in decompensations and overload of deferred morbidity care; (3) A protracted period of suboptimal outcomes due to missed diagnoses, disease progression, increased waiting list mortality and loss to follow-up [17]. Liver transplantation activity has decreased in most centers, many completely halting living-donor liver transplantation (LDLT). Instead of a complete shutdown of liver transplant programs, a more individualized decision should be made based on the currently

available local resources and the particular phase of the pandemic.

7. Post-livertransplant and patients on immunosuppression

Patients on immunosuppressive drugs – either to avoid rejection in transplanted patients or for treatment of autoimmune liver disease – are considered at higher risk of severe illness [3]. Immunosuppression may increase risk for infection or reactivation of viral agents [22] and specifically for respiratory infections such as influenza, immunocompromised patients have an increased risk for more severe disease [23]. A report from Italy shows that mortality after liver transplantation is concentrated in patients older than 65 years and transplanted more than 10 years ago [24]. Nevertheless, it is interesting to note that small series have reported good clinical outcomes of patients infected with SARS-CoV-2 while in on immunosuppression, presumably because the cytokine release syndrome with increased serum levels of IL-6, IL-8 and TNF-α is blunted in these population [25,26]. It has been reported persistent viral shedding in posttransplant patients with COVID-19 [27].

Currently there is no rationale for reducing or adjusting immunosuppressive medications in stable patients in anticipation of COVID-19. Immunizations should be encouraged, with focus on influenza and Streptococcus pneumoniae. A different setting is the patient already infected with SARS-CoV-2, in whom it should be considered reducing corticosteroid dose to a dose sufficient to avoid adrenal insufficiency. Azathioprine or mycophenolate dose may be reduced if there is lymphopenia or pulmonary deterioration [28]. Minimizing in-person visits and prioritizing telemedicine is recommended.

8. Potential treatments for COVID-19 and liver implications of such therapies

At the time of writing this article, 442 interventional trials for COVID-19 are listed in ClinicalTrials.gov (162 in phase 3 and 4), but no accepted specific drug therapy has been approved. When possible and available, patients should receive these experimental therapies in the context of a clinical study. Nonetheless, many drugs are being used either off label or in compassionate use programs, therefore an understanding of potential liver-related side-effects of these medications is required.

SARS-CoV-2 is an enveloped single-stranded RNA positive-sense virus with a genome comprising 29,903 nucleotides [29]. This RNA encodes for structural and 16 non-structural proteins. Among the structural proteins, S (spike), M (membrane), E (envelope) and N (nucleocapsid) [30] are critical for virion attachment and assembly and potentially susceptible for drug/antibody inhibition. Among the 16 non-structural proteins (nsp), two proteases (3-chymotrypsin-like protease and papain-like protease), and the RNA-dependent RNA polymerase (RdRp) are some targets for drug therapy [31]. The structure of the RdRp was recently resolved [32], a step toward design of new specific antivirals.

Targeting the host immune response to the viral infection is a different approach, aiming at controlling the systemic hyperinflammation ("cytokine storm") [33] found in patients who progress to severe stages of the disease.

A database of periodically updated drug-drug interaction between experimental COVID-19 therapies and common drugs can be reviewed at the drug interactions site of the Liverpool University (covid19-druginteractions.org). Information regarding drug-induced liver injury can be obtained in the NIH maintained site LiverTox [34].

8.1. Remdesivir

Remdesivir (GS-5734), interestingly for hepatologists, is a nucleotide analog pro-drug synthesized in the quest for finding anti-hepatitis C (HCV) treatments [35,36]. It has structural similarity to tenovofir. This compound was later found to have activity against Ebola virus in animal models [37], but failed in clinical trials [38]. Remdesivir has been used in more than 500 patients for Ebola virus disease (EVD). Liver toxicity was not reported, but this is difficult to rule out, given the frequent occurrence of abnormal liver enzymes at baseline as a feature of EBD. Robust *in silico*, *in vitro* and animal models data support the anti-viral activity of remdesivir against SARS-CoV-2 and related viruses [39–42]. A recent report of compassionate use of remdesivir for COVID-19 showed promising effectivity (68% clinical improvement and 18% mortality in severe patients) [43]. This report was not controlled and excluded patients with ALT or AST > 5 times the upper limit of normal. In the 53 analyzed patients, 23% patients had increased liver enzymes, leading to remdesivir discontinuation in 2 patients. No report of bilirubin elevation was mentioned. Remdesivir is an intravenous drug and currently 5- and 10-day treatment duration are being explored. No hepatic or renal adjustments are recommended, but in trials it has been used mainly with creatinine clearance >30 mL/min. The cyano group in the remdesivir molecule provides specificity of action, avoiding inhibition of host mitochondrial DNA polymerase, thus reducing the potential for lactic acidosis or mitochondrial toxicity. There are at least 6 ongoing clinical trials of remdesivir for COVID-19 with several thousands of patients enrolled, all excluding patients with ALT or AST >5 times the upper limit of normal. Based on current experience of other nucleoside/nucleotide analogs in patients with cirrhosis it may be anticipated a better safety profile compared to other drug classes. It has been suggested to control liver enzymes daily if remdesivir is used [44]. No relevant drug-drug interactions are predicted for this compound. Remdesivir is likely to be the first approved anti-viral treatment for SARS-CoV-2, so – if approved – it will require collecting real world experience in registries especially when used in a more diverse population, specifically in patients with liver disease or abnormal baseline liver enzymes and patients receiving other medications to reveal any important drug interaction.

8.2. Other nucleoside/nucleotide analogs

Several nucleoside/nucleotide analogs have been proposed as therapies for COVID-19. Favipravir is an approved guanine analog approved in Japan for treating infuenza. It has been explored in a small clinical trial with inconclusive results [45]. Galidesivir is an iv nucleoside analog currently in a phase 1 trial for COVID-19 in Brazil. It has been proposed that anti-HCV drugs such as sofosbuvir and ribavirin could be re-purposed for treating SARS-CoV-2 [46,47]. The hepatic safety of these compounds is largely known to hepatologists, but unfortunately to date no conclusive data is available about effectivity against COVID-19.

8.3. Protease inhibitors

Lopinavir/ritonavir is an approved protease inhibitor used for HIV infection. A randomized controlled trial showed that in hospitalized patients with FiO_2 < 94%, lopinavir/ritonavir showed no clinical benefit [48]. Hepatotoxicity was reported in 2–10%. Lopinavir/ritonavir has numerous drug-drug interactions, especially with immunosuppressive drugs such as mTOR and calcineurin inhibitors. Most centers have discontinued its use.

8.4. Chloroquine/hydroxychloroquine

Chloroquine and its derivative hydroxychloroquine are old antimalarial and immunomodulatory drugs that have shown *in vitro* activity against SARS-CoV-2 in tissue culture, with an EC50 in the micromolar range [42,49]. The proposed mechanism of action of chloroquine is not clear. Inhibition of glycosylation of host receptors and prevention of endosome acidification may play a role in entry inhibition, but immunomodulatory mechanisms have also been proposed [50]. Hydroxychloroquine with or without azithromycin was assessed in a study of 36 patients [51]. Due to the uncontrolled nature of the study and the small sample size, no conclusive evidence of clinical efficacy could be established. Chloroquine and hydroxychloroquine have been linked to arrhythmias due to QTc prolongation. In a pre-print article a high-dose chloroquine was linked to increased mortality and led to prematurely halting the study [52]. These drugs are not usually associated to liver toxicity [53], but there are significant drug-drug interactions, particularly with anti-rejection immunosuppressants.

8.5. Host mediated treatments

Tocilizumab is a humanized monoclonal antibody against the interleukin 6 (IL-6) receptor that is being used in patients in advanced stages of the disease to treat the cytokine release syndrome [54]. Small series and case reports suggest beneficial effects [55,56], but there are no results of randomized controlled trials. Liver enzyme elevation is common with tocilizumab, but only rarely linked to severe liver injury [57]. Tocilizumab increases the risk of hepatitis B virus (HBV) reactivation [58].

9. Teaching and research activities

Clinical activity is inseparable from teaching and research, and hepatology is no exception. Medical students and residents rotating in different departments are potential vectors of COVID-19. At the same time, they have an enormous opportunity to contribute to patient care and learn invaluable lessons from this pandemic [59]. In a bold move, Italy decided to rush 10,000 interns into service, as the medical services started to collapse [60]. Two main challenges arise in the current situation: (1) Ensuring adequate protection and safety of all health personnel, including medical students and residents. (2) Adapting medical education to flexible online methods to avoid important gaps in the medical curriculum. This requires flexibility and creativity.

A flood of publications regarding COVID-19 has emerged since January 2020. It has been criticized that in the pursuit of getting fast publication, the quality of the research and peer evaluation has suffered. Papers in preprint servers (not peer-reviewed) are being cited more than ever. Many investigators are turning their energy to study the effect of this infection in patients in their respective fields, organizing patient registries and writing recommendations for societies. It is advised that hepatologists maintain a high degree of skepticism while reading the medical literature. Engaging with journalists to accurately translate technical information and correcting erroneous information in social media is also advisable to fight misinformation and fake news.

Clinical research unrelated to COVID-19 has been greatly altered during this pandemic, due to quarantines and concerns regarding patient an research team safety. The FDA issued a guidance calling for ensuring safety of clinical trials participants and flexibility for amending clinical protocols, particularly for including alternatives to in-patient visits [61]. Basic research has been similarly affected. One potential positive side of the situation is that researchers in quarantine may have more time to focus on writing, which has resulted in an uptick in the number of new submissions for some journals [62] and also an increase in the request for reviewing papers.

10. Conclusion

Pre-existing liver disease appears to have little impact on COVID-19 outcomes. ALT/AST abnormalities are common, especially in patients with severe disease, but its impact is unknown. There are many explanations for these abnormalities. Further research should focus on the causes of liver injury in COVID-19 and the effect of existing liver-related comorbidities on treatment and outcomes of COVID-19. Its outcomes and different factors influencing it may vary between countries and between continents. Local information from each country is particularly important to understand this heterogenous disease.

There is no doubt that COVID-19 is having a major impact on clinical practice and patient care. Although all attention is focused today on COVID-19, the care of patients with chronic diseases should not be neglected, since this could have catastrophic outcomes.

Abbreviations

COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization
CDC	Centers for Disease Control and Prevention
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ICU	intensive care unit
ACE2	angiotensin-converting enzyme 2
ARDS	acute respiratory distress syndrome
NAFLD	non-alcoholic fatty liver disease
MAFLD	metabolic associated fatty liver diseases
HCC	hepatocellular carcinoma
ILCA	International Liver Cancer Association
IL	interleukin
TNF-α	tumor necrosis factor-alpha
nsp	non-structural proteins
RdRp	RNA-dependent RNA polymerase
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
EVD	Ebola virus disease
HBV	hepatitis B virus

Conflict of interest

AS declares being the receiver of an investigator initiated research grant from Gilead and having stock ownership in Gilead Sciences Inc.

Funding

This study was funded by grant FONDECYT N° 1191389 from CONICYT (Comité Nacional de Ciencia y Tecnología) to A.S.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33, http://dx.doi.org/10.1056/NEJMoa2001017.
[2] WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020 n.d. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020 [accessed 22.04.20].
[3] People Who Are at Higher Risk for Severe Illness CDC n.d. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html [accessed 22.04.20].

[4] Keesara S, Jonas A, Schulman K. Covid-19 and health care's digital revolution. N Engl J Med 2020., http://dx.doi.org/10.1056/NEJMp 8352005.

[5] Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Rep 2020;2:100113, http://dx.doi.org/10.1016/j.jhepr.2020.100113.

[6] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428–30, http://dx.doi.org/10.1016/S2468-1253(20)7-13005.

[7] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2002032.

[8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506, http://dx.doi.org/10.1016/S0140-6736(20)30183-5.

[9] Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan China: a descriptive study. Lancet Infect Dis 2020;20:425–34, http://dx.doi.org/10.1016/S1473-3099(20)30086-4.

[10] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020, http://dx.doi.org/10.1001/jama.2020.6775.

[11] Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020, http://dx.doi.org/10.1111/liv.14435.

[12] Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020, http://dx.doi.org/10.1016/S2468-1253(20)30084-4.

[13] Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. Characteristics of liver tests in COVID-19 patients. J Hepatol 2020, http://dx.doi.org/10.1016/j.jhep.2020.04.006.

[14] Gacouin A, Locufier M, Uhel F, Letheulle J, Bouju P, Fillatre P, et al. Liver cirrhosis is independently associated with 90-day mortality in ARDS patients. Shock 2016;45:16–21, http://dx.doi.org/10.1097/SHK.0000000000000487.

[15] Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis. J Hepatol 2020, http://dx.doi.org/10.1016/j.jhep.2020.03.044.

[16] Zheng KI, Gao F, Wang X-B, Sun Q-F, Pan K-H, Wang T-Y, et al. Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metabolism 2020;154244, http://dx.doi.org/10.1016/j.metabol.2020.154244.

[17] Tapper EB, Asrani SK. COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. J Hepatol 2020, http://dx.doi.org/10.1016/j.jhep.2020.04.005.

[18] AASLD. Gastroenterologyprofessional society guidance on endoscopic procedures during the COVID-19pandemic n.d. https://www.aasld.org/about-aasld/covid-19-resources [accessed 7.05.20].

[19] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335–7, http://dx.doi.org/10.1016/S1470-2045(20)6-63009.

[20] Management of HCC during COVID-19: ILCA Guidance – International Liver Cancer Association n.d. https://ilca-online.org/management-of-hcc-during-covid-19-ilca-guidance/ [accessed 23.04.20].

[21] Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine 2020;100331, http://dx.doi.org/10.1016/j.eclinm.2020.100331.

[22] Noreña I, Fernández-Ruiz M, Aguado JM. Viral infections in the biologic therapy era. Expert Rev Anti Infect Ther 2018;16:781–91, http://dx.doi.org/10.1080/14787210.2018.1521270.

[23] Memoli MJ, Athota R, Reed S, Czajkowski L, Bristol T, Proudfoot K, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. Clin Infect Dis 2014;58:214–24, http://dx.doi.org/10.1093/cid/cit725.

[24] Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. Lancet Gastroenterol Hepatol 2020, http://dx.doi.org/10.1016/S2468-1253(20)30116-3.

[-25] D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl 2020, http://dx.doi.org/10.1002/lt.25756.

[26] Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 2020;79:667–8, http://dx.doi.org/10.1136/annrheumdis-2020-217424.

[27] Qin J, Wang H, Qin X, Zhang P, Zhu L, Cai J, et al. Perioperative presentation of COVID-19 disease in a liver transplant recipient. Hepatology 2020:31257, http://dx.doi.org/10.1002/he.

[28] Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology 2020, http://dx.doi.org/10.1002/hep.31281.

[29] Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020;579:265–9, http://dx.doi.org/10.1038/s41586-020-2008-3.

[30] Fehr AR, Perlman S, Coronaviruses:. an overview of their replication and pathogenesis. Methods Mol Biol 2015;1282:1–23, http://dx.doi.org/10.1007/978-1-4939-2438-7_1.

[31] Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol 2020;92:418–23, http://dx.doi.org/10.1002/jmv.25681.

[32] Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, et al. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science 2020, http://dx.doi.org/10.1126/science.abb7498.

[33] Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant 2020, http://dx.doi.org/10.1016/j.healun.2020.03.012.

[34] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

[35] Cho A, Saunders OL, Butler T, Zhang L, Xu J, Vela JE, et al. Synthesis and antiviral activity of a series of 1′-substituted 4-aza-7,9-dideazaadenosine C-nucleosides. Bioorg Med Chem Lett 2012;22:2705–7, http://dx.doi.org/10.1016/j.bmcl.2012.02.105.

[36] Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of ebola and emerging viruses. J Med Chem 2017;60:1648–61, http://dx.doi.org/10.1021/acs.jmedchem.6b01594.

[37] Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016;531:381–5, http://dx.doi.org/10.1038/nature17180.

[38] Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of ebola virus disease therapeutics. N Engl J Med 2019;381:2293–303, http://dx.doi.org/10.1056/NEJMoa1910993.

[39] Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017:9, http://dx.doi.org/10.1126/scitranslmed.aal3653.

[40] de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA 2020;117:6771–6, http://dx.doi.org/10.1073/pnas.1922083117.

[41] Williamson B, Feldmann F, Schwarz B, Meade-White K, Porter D, Schulz J, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. BioRxiv 2020, http://dx.doi.org/10.1101/2020.04.15.043166.

[42] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269–71, http://dx.doi.org/10.1038/s41422-020-0282-0.

[43] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe covid-19. N Engl J Med 2020, http://dx.doi.org/10.1056/NEJMoa2007016.

[44] Massachusetts General Hospital. El hígado y el COVID-19 n.d. http://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/el-higado-y-covid-19.pdf [accessed 23.04.20].

[45] Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv 2020, http://dx.doi.org/10.1101/2020.03.17.20037432.

[46] Elfiky AA, Anti-HCV. nucleotide inhibitors, repurposing against COVID-19. Life Sci 2020;248:117477, http://dx.doi.org/10.1016/j.lfs.2020.117477.

[47] Elfiky AA. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci 2020:117592. doi:10.1016/j.lfs.2020.117592.

[48] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med 2020., http://dx.doi.org/10.1056/NEJMoa 2822001.

[49] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020, http://dx.doi.org/10.1093/cid/ciaa237.

[50] Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res Perspect 2017;5:e00293, http://dx.doi.org/10.1002/prp2.293.

[51] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949, http://dx.doi.org/10.1016/j.ijantimicag.2020.105949.

[52] Borba M, Val F, de A, Sampaio VS, Alexandre MA, Melo GC, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). medRxiv 2020, http://dx.doi.org/10.1101/2020.04.07.20056424.

[53] Hydroxychloroquine. LiverTox: Clinical and research information on drug-induced liver injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. doi:10.1007/s40278-019-58063-3.

[54] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4, http://dx.doi.org/10.1016/S0140-6736(20)30628-0.

[55] Michot J-M, Albiges L, Chaput N, Saada V, Pommeret F, Griscelli F, et al. Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report. Ann Oncol 2020, http://dx.doi.org/10.1016/j.annonc.2020.03.300.
[56] Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol 2020, http://dx.doi.org/10.1002/jmv.25801.
[57] Tocilizumab. LiverTox: Clinical and research information on drug-induced liver injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
[58] Chen L-F, Mo Y-Q, Jing J, Ma J-D, Zheng D-H, Dai L. Short-course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. Int J Rheum Dis 2017;20:859–69, http://dx.doi.org/10.1111/1756-185X.13010.
[59] Ahmed H, Allaf M, Elghazaly H. COVID-19 and medical education. Lancet Infect Dis 2020, http://dx.doi.org/10.1016/S1473-3099(20)30226-7.
[60] Italy rushes new doctors into service as coronavirus deaths rise above 2,500 – Reuters n.d. https://www.reuters.com/article/us-health-coronavirus-italy/italy-rushes-new-doctors-into-service-as-coronavirus-deaths-rise-above-2500-idUSKBN214245 [accessed 22.04.20].
[61] FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency FDA n.d. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency [accessed 22.04.20].
[62] Science in the time of coronavirus. Nat Methods 2020;17:355. doi:10.1038/s41592-020-0807-y.