

NON-COMMISSIONED REVIEW

SARS-CoV-2 infection in patients with a normal or abnormal liver

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus causing coronavirus disease 19 (COVID-19), with an estimated 22 million people infected worldwide so far although involving primarily the respiratory tract, has a remarkable tropism for the liver and the biliary tract. Patients with SARS-CoV-2 infection and no antecedent liver disease may display evidence of cytolytic liver damage, proportional to the severity of COVID-19 but rarely of clinical significance. The mechanism of hepatocellular injury is unclear and possibly multifactorial. The clinical impact of SARS-CoV-2 infection in patients with underlying chronic liver disease, a cohort whose global size is difficult to estimate, has been assessed appropriately only recently and data are still evolving. Patients with cirrhosis are at higher risk of developing severe COVID-19 and worse liver-related outcomes as compared to those with non-cirrhotic liver disease. OLT patients have an intermediate risk. Specific interventions in order to reduce the risk of transmission of infection among this high-risk population have been outlined by international societies, together with recommendations for modified treatment and follow-up regimens during the COVID-19 pandemic. When a vaccine against SARS-CoV-2 becomes available, patients with fibrotic liver disease and those with OLT should be considered as prime targets for prophylaxis of COVID-19, as all other highly susceptible subjects.

KEYWORDS

chronic liver disease, cirrhosis, COVID-19, prioritization, SARS-CoV-2, vaccine

1 | INTRODUCTION

Since the first evidence of its transmissibility and infectivity, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and

coronavirus disease 2019 (COVID-19)¹ have been an international health concern, so much that the World Health Organization (WHO) declared public health emergency and pandemic status on March 2020. As of 20 August 2020, around 22,500,000 cases worldwide

Abbreviations: AASLD, The American Association for the Study of Liver Diseases; ACE2, angiotensin-converting enzyme 2; ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APASL, The Asian Pacific Association for the Study of the Liver; APCOLIS Study, APASL COVID-19 Liver Injury Spectrum Study; AST, aspartate aminotransferase; BMI, body mass index; CLD, chronic liver disease; CLIF-C, chronic liver failure consortium; CLIF-OF, chronic liver failure-organ failure; COVID-19, coronavirus disease 2019; CSSE, Center for Systems Science and Engineering; DAAs, direct-acting antivirals; EASL, European Association for the Study of the Liver; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICU, intensive care unit; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OR, odd ratio; RBD, receptor-binding domain; TBIL, total bilirubin; TIPS, transjugular intrahepatic portosystemic shunt; TUNEL, terminal deoxynucleotidyl transferase biotin-dUTP nick end labelling; ULN, upper limit of normal; WHO, World Health Organization; YNHHS, Yale-New Haven Health System.

have been reported according to the Center for Systems Science and Engineering (CSSE) at John Hopkins University, mostly in United States, Brazil and Russia, causing totally around 800,000 deaths.² In order to track seroprevalence estimates, it has also been developed a custom-built dashboard, which systematically monitors and synthesizes findings from hundreds of global SARS-CoV-2 serological studies.³ A growing number of patients with COVID-19 continue to succumb worldwide, mostly due to respiratory complications but also showing impairment of other organ systems, including the liver.

During the early phase of the pandemic, most case series reporting liver damage did not make a clear distinction between subjects infected by SARS-CoV-2 and a previously normal liver and those in whom the infection occurred in the setting of a pre-existing liver disease. Even less information was available on the stage of liver disease (ie non-fibrotic vs fibrotic: compensated vs decompensated), which may be of major importance since patients with cirrhosis are often fragile and may be immunocompromised. In fact, infections of all types are the major determinant of acute-on-chronic liver failure (ACLF), a leading cause of mortality in cirrhosis.⁴ When facing patients with COVID-19 who have liver disease, clinicians may have problems both in terms of choosing the putative treatment for COVID-19 and of managing the higher risk of hepatic decompensation.

We shall review from a clinical perspective some practice points relevant for the hepatologist caring for COVID-19 patients: (1) Is the liver merely a bystander to severe COVID-19? (2) Are patients with liver disease at risk for a severe outcome of COVID-19? (3) How should we alter the management of liver patients during the pandemic?

2 | DOES SARS-CoV-2 INFECTION CAUSE DAMAGE TO A HEALTHY LIVER?

SARS-CoV-2 infects cells through the angiotensin-converting enzyme 2 (ACE2) host cell receptor, which is mainly present on the alveolar cells (type 2).⁵ Crystallization of the SARS-CoV-2 RBD (receptor-binding domain)-ACE2 complex was achieved as soon as possible to understand the structural basis of ACE2 recognition by SARS-CoV-2. The spike (S) protein of coronaviruses facilitates viral entry into target cells and it may also be a target for future therapies. Shang et al illustrated the crystal structure of the RBD of the engineered spike protein of SARS-CoV-2 in complex with ACE2.⁶ Interestingly, ACE2 expression is abundant in lung, heart, ileum, kidney, bladder, gastrointestinal tract and liver.⁷ ACE2 receptors at the enterocyte level (glandular cells of gastric, duodenal and distal enterocytes) may explain gastrointestinal involvement, resulting usually in malabsorption, unbalanced intestinal secretion and activated enteric nervous system.⁸ Regarding liver involvement, the level of ACE2 expression in cholangiocytes is high (59.7%) and similar to type 2 alveolar cells, and higher than hepatocytes (2.9%).⁹ Even if there is this difference between liver and biliary tract, it does not mean that liver is unaffected by the virus. Recently, Wang et al examined liver

Bullet points:

- Patients with SARS-CoV-2 infection and no previous liver disease may develop mild-to-moderate liver injury, proportional to the severity of COVID-19.
- Patient with cirrhosis, and to a lesser degree those with OLT, when infected with SARS-CoV-2 have a high risk of death.
- The prevalence of chronic liver disease among patients with COVID-19 is undefined at a global level.
- Patients with chronic liver disease should be prioritized for immunization once a SARS-CoV-2 vaccine becomes available.

material from infected patients by electron microscopy, immunohistochemistry, TUNEL assay and pathological studies, concluding that liver involvement is a crucial cause of hepatic impairment in COVID-19 patients. Indeed, SARS-CoV-2 causes conspicuous hepatic cytopathy, with massive apoptosis and presence of binuclear hepatocytes as predominant histological features.¹⁰

During SARS-CoV-2 infection, patients may have gastrointestinal manifestations, as reported from China.¹¹ In a meta-analysis of 60 studies comprising around 4000 patients, the pooled prevalence of all gastrointestinal symptoms was 17.6%. Among patients with non-severe COVID-19, 11.8% complained of gastrointestinal symptoms, while 17.1% of severe COVID-19 patients had gastrointestinal manifestations.¹² As mentioned above, liver involvement is documented as well, with hepatic dysfunction in severe cases. Severe acute liver injury has been reported with higher mortality.¹³ In fact, liver damage mainly arose with a pattern of elevated serum liver biochemistries in hospitalized patients with COVID-19 (primarily elevated AST and ALT, and slightly elevated bilirubin), ranging from 14% to 53%. Interestingly, it occurs more commonly in more severe COVID-19 cases than in mild cases.¹⁴ Recently, a retrospective cohort study of 1827 patients within the Yale-New Haven Health System (YNHHS) confirmed a higher probability of severe infection in patients with increased age, male gender, higher BMI and abnormal liver tests. Moreover, liver injury was predominantly hepatocellular rather than cholestatic, and these patients had liver abnormalities both at admission (AST 66.9%, ALT 41.6%, ALP 13.5%, TBIL 4.3%) and peak hospitalization (AST 83.4%, ALT 61.6%, ALP 22.7%, TBIL 16.1%). In this report, a multivariate analysis revealed the association between admission and peak hospitalization liver tests and clinical outcomes (ICU admission, mechanical ventilation, and death). According to these data, patients with abnormal AST at admission have a higher risk of mechanical ventilation (OR 3.09, $P < 0.001$), as are those with abnormal AST, ALT and ALP at peak hospitalization (OR 5.87, 2.70 and 3.76, respectively). A subset of patients experienced liver transaminases $> 5 \times$ ULN during hospitalization (AST 16.6%, ALT 20.6%). Among them medications used in COVID-19 treatment (lopinavir/ritonavir, hydroxychloroquine, remdesivir and

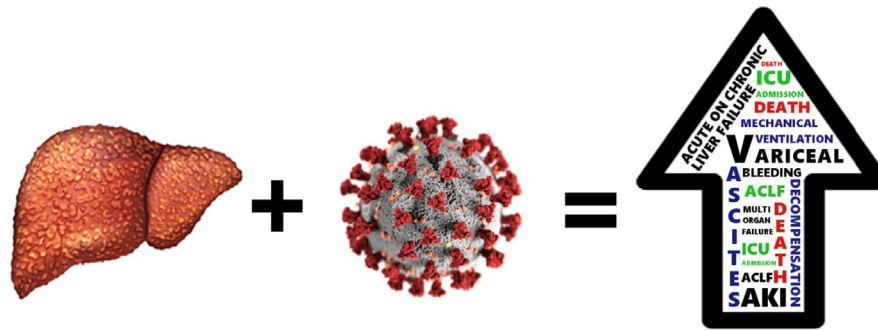


FIGURE 1 The consequences of SARS-CoV-2 infection on a chronic damaged liver: a worsening in clinical outcomes

tocilizumab) were associated with peak hospitalization aminotransferase elevations $> 5 \times \text{ULN}$.¹⁵

Overall, data support a modest cytopathic acute liver damage by SARS-CoV-2 through a direct cytopathic effect, due to infection of hepatocytes mediated by the highly expressed ACE2 receptors. Liver injury may also be caused by an uncontrolled immune response due to inflammatory activity, or as a consequence from therapies, manifesting as drug-induced liver injury (DILI).¹⁶ Other evidence based on autopsies in patients who succumbed to COVID-19 supports the theory that macrovascular and microvascular thrombosis may play a predominant role in the pathophysiological pathway, determining hypoxic-ischaemic hepatic necrosis.¹⁷ Another interesting hypothesis is that high levels of positive final expiratory pressure might cause hepatic congestion and hence abnormal liver blood tests, but data suggest that many hospitalized patients with COVID-19, even without mechanical ventilation, have similar biochemical abnormalities, dismissing this aetiology.¹⁸ In any case, hepatocellular damage occurring in COVID-19 patients with an otherwise healthy liver rarely, if ever, causes acute liver failure.

3 | SARS-CoV-2 AND LIVER INJURY AMONG PATIENTS WITH CHRONIC LIVER DISEASE

COVID-19 studies initially focused on respiratory tract involvement, ignoring the effects of SARS-CoV-2 on organs such as liver or gut which were considered as secondarily impaired. At the beginning, a rapid short-time increase in publication data was motivated by the lack of knowledge against this sudden viral outbreak. For this reason, data quality was inevitably affected by the pressure to publish. Therefore, effects of COVID-19 on underlying well-defined chronic liver disease have been properly analysed only recently. Nevertheless, even current data miss well-defined characteristics of patients regarding hepatic status and function (ie aetiology, chronic liver disease or cirrhosis, Child-Pugh/MELD or other scores. There is a lack of data about the interaction between chronic liver disease and COVID-19, because pre-existing liver conditions or the exact cause of them have not been extensively studied in most of the studies. Even data regarding hepatotropic viruses are lacking, despite the

fact that the outbreak started in regions in which the prevalence of these viruses is high. Recently, Lens et al in a Spanish multicentre study aimed to evaluate the incidence of SARS-CoV-2 in patients under 'active' antiviral therapy with tenofovir and DAAs, 341 and 1764, respectively. Only 1 patient on DAA therapy and 8 patients under tenofovir antiviral therapy had a confirmed PCR diagnosis of SARS-CoV-2. Interestingly, seven among them needed hospitalization but none of them died.¹⁹

Given the global burden of chronic liver disease, it should be evaluated how different underlying liver conditions influence liver injury and the severity of SARS-CoV-2 infection. However, the literature has progressively focused on cirrhosis. As far as pre-existing chronic liver impairment is concerned, it should be remembered that it is a condition which determines immunosuppression. This status may contribute to the significantly increased risk of mortality among those patients (Figure 1), as demonstrated by a large cohort study that included a population of 17,425,445 adults investigating death-associated factors in hospital among people with confirmed COVID-19 (HR, 95% CI 2.34, 1.94-2.83 for liver disease).²⁰ Similar results were obtained by Docherty et al; they conducted a prospective observational cohort study and found worst outcomes in terms of survival in SARS-CoV-2-affected patients who were older, male sex and with chronic comorbidities including moderate/severe liver disease.²¹ Moon et al not only confirmed these findings, but also added that, in their population of SARS-CoV-2-infected patients, those with cirrhosis experienced hepatic decompensation, even in the absence of respiratory symptoms.²² Few studies specified in detail what kind of chronic liver disease their population was affected from, whether the patients were cirrhotic already, aetiology and viral status. This makes somehow difficult the estimate of the global prevalence of chronic liver disease among COVID-19 populations and the course of the disease in this specific setting. Table 1 shows a summary of available data. A meta-analysis of 11 observational studies for a total of 20,134 adult individuals assessed a relatively low overall prevalence of chronic liver disease at baseline, being 3% (95% CI 2%-4%).²³ Some data on prevalence of liver disease can be extrapolated from a case series of 5,700 patients providing characteristics and early outcomes of patients hospitalized in New York City; 0.4% of the patients were known to be cirrhotic, 0.2% had a viral chronic liver disease, but no information was given about

TABLE 1 Studies including COVID-19 patients with chronic liver disease

Study	Cirrhotic patients, n (%)	Patients with non-cirrhotic chronic liver disease, n (%)	Aetiology
Moon et al ²²	103	49	-
Richardson et al ²⁴	19	11	HBV, HCV
Qi et al ²⁵	21	-	HBV, HCV, alcohol, autoimmune, schistosomiasis, others
Iavarone et al ²⁶	50	-	HCV, HBV, alcohol, others
Singh et al ²⁷	50	200	-
SECURE Cirrhosis Registry ³²	425	372	Alcohol, NASH, HCV, HBV, autoimmune

TABLE 2 Outcomes among patients with cirrhosis

Study	Study design	Number of patients included	Mean age (years)	Mean follow-up (months)	Mortality rate, %	Any event of liver decompensation, %
Moon et al ²²	Retrospective	152	61	1	30.9	25.7
Qi et al ²⁵	Retrospective multicentre	21	68	-	23.8	52.3
Iavarone et al ²⁶	Retrospective multicentre	50	67	1	34	48
SECURE Cirrhosis Registry ³²	Multicentre	957	59	3	32	46

non-alcoholic steatohepatitis nor non-alcoholic fatty liver disease. However, data about obesity, diabetes and metabolic disease were collected. It cannot be excluded that a great number of patients with early, ongoing liver involvement were underestimated, thus resulting in underrating of prevalence and outcomes.²⁴

Among studies conducted on cirrhotic patients, Qi et al²⁵ investigated the clinical course and risk factors for mortality in these affected patients. In fact, they provide a report on the demographic characteristics, comorbidities, laboratory and radiographic findings, and clinical outcomes in twenty-one SARS-CoV-2-infected patients with pre-existing cirrhosis. They finally concluded that the cause of death in most cases was due to respiratory failure rather than progression of liver disease such as development of acute-on-chronic liver failure. However, a multicentre retrospective study with a cohort of fifty cirrhotic patients gave interesting conclusions. The study aimed to evaluate the impact of COVID-19 on the clinical outcome of liver disease. It found a significant association between SARS-CoV-2 infection and liver decompensation; this being measured as higher scores both in Child-Pugh and MELD parameters. Consequently, COVID-19 was associated with elevated mortality, with a thirty-day rate of 34%, and that was independently predicted by CLIF-OF, CLIF-C, MELD and severity of lung failure.²⁶ Notably, Singh et al²⁷ obtained similar results among a much wider population of patients with chronic liver disease. They compared outcomes between those with and without pre-existing liver dysfunction; as expected, the former group experienced higher risk of hospitalizations and mortality, which were confirmed even after propensity score matching. They hypothesized that poorer outcomes in cirrhotic patients may be attributed to many factors, such as an interplay of local liver injury and systemic disturbances, the expression of ACE2 receptors in

liver and bile duct cells, medications and hypoxia. Table 2 shows the outcomes of COVID-19 patients with chronic liver disease. However, outcomes seem not to be excessively modified by current therapies, both in non-liver-injured and in liver-injured patients, probably because current medical management is largely supportive with no targeted therapy available. Several drugs including lopinavir-ritonavir, remdesivir, hydroxychloroquine and azithromycin have been tested in clinical trials,²⁸ but none of them have been proven to be a definite therapy yet. Convalescent plasma was routinely used for the treatment of critically ill COVID-19-infected patients when available,²⁹ even if it was shown to have no significant advantage in preventing mortality.³⁰

The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study) showed that pre-existing liver disease is associated with a hepatic injury severe enough to cause liver failure in cirrhosis. These data were taken from 13 Asian countries and 62 investigators, with 228 CLD patients included 43 (18.9%) with cirrhosis (including 18 decompensated cirrhosis) and 185 (81.1%) without cirrhosis. More cirrhotic than non-cirrhotic patients had acute liver injury at admission (32.6% vs 20%, $P < .001$) and also developed new-onset liver injury in hospital (39.5% vs 7%, $P < .001$).³¹

A large-scale collaborative registry project has been created to collect data on patients with liver disease at any stage or liver transplants who develop laboratory-confirmed COVID-19, both for patients who are hospitalized or managed in the community. The aim is to allow for analysis of baseline characteristics associated with specific outcomes in COVID-19 among those with liver disease. In the latest update, the total cohort include 957 patients, 88% of them being hospitalized and 63% of them being men. The median age was 59 years. Among these patients, 372 have chronic liver disease but

not cirrhosis, whether 425 have it. The major aetiology was alcohol (31%), followed by NASH (22%), HCV and HBV infection, and autoimmune hepatitis. 46% of patients experienced an event of decompensation, new ascites or worsening of pre-existing being the most common; others developed encephalopathy (26%) or had variceal haemorrhage (4%). Finally, 160 affected patients were liver-transplanted. The rate of hospitalization, intensive care admission and invasive ventilation was similar among non-cirrhotic, transplanted and cirrhotic patients, but there was a trend of increased risk of death in these categories, being 7%, 19% and 32%,³² respectively.

4 | MANAGEMENT OF PATIENTS WITH CHRONIC LIVER DISEASE IN THE COVID-19 ERA

It is important for medical staff to get acquainted with how to manage chronic liver disease patients infected by SARS-CoV-2 in order to establish prompt interventions to reduce poor outcomes. After the initial outbreak, guidelines and recommendations worldwide have been developed as soon as possible and they have mostly drawn up similar recommendations. AASLD gave some recommendations, which suggest not to stop ongoing antiviral treatment for HBV and HCV, but to consider delaying initiation of HCV therapy; to limit procedures by performing only the urgent or therapeutic ones (liver biopsy, paracentesis, positioning of TIPS, endoscopy for variceal bleeding).³³ A specific field of interest regards autoimmune liver disease. In this setting, Di Giorgio et al³⁴ investigated the health status of patients with autoimmune liver disease during SARS-CoV-2 outbreak in northern Italy, suggesting that, in these patients, tapering or withdrawing immunosuppressive treatment is not required. The same advice is given from Lleo et al³⁵ adding that a flare of AIH secondary to unnecessary drug reduction or withdrawal would require a higher dose of steroids and thus potentially increased risk of infection.

The Asian Pacific Association for the Study of the Liver (APASL) recommends constant checking of liver function tests in most instances and to screen for hepatitis B surface antigen, as it is do not underestimate drug-induced liver injury (especially when remdesivir is administered). They focus on considering chronic liver disease, a risk factor for COVID-19 progression, recommending to limit contact with healthcare workers and encouraging telemedicine. As far as HCC surveillance is concerned, they recommend to continue regular follow-up in high-risk subjects and using alpha-fetoprotein's trend, two-month delay is considered acceptable in case of ultrasound surveillance. Among already diagnosed, uninfected, HCC patients who are on treatment, HCC treatment should proceed as deemed appropriate, and if already on kinase inhibitors they recommend to continue therapy, whether immunotherapy might be rescheduled every 4-6 weeks. It was suggested that liver biopsy could be performed in not infected with SARS-CoV-2 patients, if histology is expected to have a major impact on management and therapy (suspected autoimmune flares or rejection). A non-invasive tool from Baveno VI

criteria may be used to identify patients with high risk of variceal bleeding, but urgent or emergency endoscopy procedures should be performed anyway, as are other urgent procedures (ie therapeutic paracentesis, transjugular intrahepatic portosystemic shunt, endoscopy for variceal bleeding, band ligation, urgent biliary procedures for cholangitis and sepsis). Orthotopic liver transplantation should be limited to emergency and urgent cases according to local resource limitations and status of the outbreak, and avoided use of deceased or live donors with evidence of COVID-19. Immunosuppression doses should not be reduced in long-term liver-transplanted patients in the absence of SARS-CoV-2 infection, but reduction may be considered in patients with moderate COVID-19 (lymphopenia, fever or worsening pneumonia). Patients with autoimmune liver disease and mild COVID-19 should continue their usual immunosuppression and other medications, while severe COVID-19 should be managed according to local protocols, but corticosteroids should not be discontinued.³⁶

Similar recommendations are given in the EASL-ESCMID position paper,³⁷ that distinguishes among patients with compensated chronic liver disease, decompensated chronic liver disease and its complications, and COVID-19 in chronic liver disease. For the first two groups, the authors conclude having the same approach as suggested by AASLD and APASL. When SARS-CoV-2 infects patients with cirrhosis, instead, they underlined that treatment for cirrhosis-associated complications such as portal hypertension, ascites, hepatic encephalopathy and spontaneous bacterial peritonitis should be continued. In patients with HCC, locoregional therapies should be postponed whenever possible and immune-checkpoint inhibitor therapy temporarily withdrawn, but the decision on whether to continue kinase inhibitors in non-severe COVID-19 should be taken on a case-by-case basis. In the delicate condition of patients with COVID-19 after liver transplantation, dose adjustment of calcineurin and/or mTOR inhibitors might be required depending on the antiviral therapy initiated.

5 | SPECIFIC INDICATIONS TO CONTROL VIRUS SPREADING AMONG PATIENTS WITH LIVER DISEASE

After the Chinese outbreak, Italy and Europe were significantly affected between March and May 2020. Italy and European States locked countries down for two months, and currently the Italian status seems to have overcome the first peak of the pandemic with a progressive reduction of both new cases and total positive patients, according to data from the Italian Department of Civil Protection.³⁸ Taking into account all evidence mentioned so far, the real question is how to deal with the post-pandemic phase. Tapper et al focused on the impact of COVID-19 in cirrhosis care over three waves. The first one concerned the acute phase of the pandemic, resulting in a strong prioritization of delivery of care. The second wave includes the backlog of deferred care and its consequences. The third one, instead, focuses on the concrete steps required to preserve quality

of care. This includes an intensification of the preventative care usually provided to patients with cirrhosis, even with proactive chronic disease management, telehealth programmes, and a full reorganization of care delivery.³⁹ Many interventions aim to reduce chances of infection in this high-risk population. All over the world social distancing, quarantine and lockdown have been the main strategy and the only effective way so far to mitigate further spread of the virus. Fauver et al demonstrated that domestic spread recently became the main source of new SARS-CoV-2 infections in the United States,⁴⁰ suggesting how lockdown and more restrictions may have been fundamental to control the outbreak. The next objective should be trying to cohabit with SARS-CoV-2, respecting meticulous rules about strict hygiene and sanitary organization, until a vaccine is developed. As far as sanitary organization is concerned, one cannot ignore the huge effort hepatologists have to face, trying to maintain standard care and to restore regular times of follow-up, avoiding at the same time nosocomial dissemination of the virus to their patients and promoting telemedicine in the outpatient setting.⁴¹


The current consensus is that SARS-CoV-2 infection will persist in the general population up to two years from now in the absence of active immunoprophylaxis. Hence, without a specific treatment, a vaccine is urgently required.⁴² Because of the lack of aetiological therapies, vaccines are still considered the most promising way to eradicate SARS-CoV-2.⁴³ A relevant question regards vaccine timing of development. In the recent past, vaccine industries urgently tried to respond to epidemics of H1N1 influenza, Ebola, Zika, and now SARS-CoV-2. A H1N1 influenza vaccine was developed relatively rapidly, while vaccines for SARS-CoV, Ebola and Zika did not follow similar performances. Moreover, the SARS-CoV and Zika epidemics ended before conclusion of vaccine development. Nowadays, multiple platforms are under development.⁴⁴ Safety, immunogen's high efficacy, stability, few doses for potency and easier large-scale production of engineered mRNA make mRNA vaccines more suitable for a rapid response to the COVID-19 pandemic and to prevent a second wave.^{45,46} Anyway, several technical issues still affect vaccine development.⁴⁷ In addition, although the safety of live attenuated or killed vaccines has been extensively studied, the potential of inducing infection still exists.⁴⁸ Currently, no clinically applicable vaccine against COVID-19 is available. At the moment, various SARS-CoV-2 vaccines are in development, and a constantly updated list is available from the WHO, showing 18 candidate vaccines in clinical trials and 129 candidate vaccines in preclinical evaluation.⁴⁹ Nevertheless, the mRNA-1273 vaccine is undergoing a phase I safety and immunogenicity trial,⁵⁰ and published positive results support advancement to later-stage clinical trials.⁵¹ A phase 2 trial of mRNA-1273 in 600 healthy adults, evaluating doses of 50 and 100 µg, is ongoing (ClinicalTrials.gov number, NCT04405076). When a vaccine becomes available, a vaccination schedule with prioritization of high-risk patients, including cirrhotic patients, should be organized, in order to reduce poor outcomes.

In conclusion, patients affected by cirrhosis should be considered as increased risk patients. Liver dysfunction that characterizes cirrhosis modifies the pathophysiology in many systems of the body;

the management of these dysfunctions has been diligently improved over the years, but no effective recommendations have been given about clinical and logistical management of these patients during a pandemic. The outcomes in patients with cirrhosis with SARS-CoV-2 infection are strongly influenced by the susceptibility of these patients. Nevertheless, nobody has thought before this pandemic about how to manage access to clinical facilities in case of rigid restrictions, like those applied during lockdown. Therefore, this lack of adequate emergency programmes created a gap in the follow-up of chronic and susceptible patients in every medical field, as in hepatology. The delay in screening programmes of cancers and pathology complications may produce an increase in long-term mortality⁵² because of many factors: loss in follow-up of low-compliance patients; saturation of clinical capacity to reschedule examinations in short-term; and difficulty to increase number of daily examinations due to COVID-regulations regarding distance and sanitization. Therefore, we strongly recommend stratifying patients when rescheduling screening examinations or monitoring suspicious complications in high-risk patients. Moreover, when the vaccine becomes available, we strongly suggest considering cirrhotic patients among those who need to be vaccinated first. National Health Organizations should generate protocols not only for the ongoing pandemic, but mainly for a second wave which may be even more severe than the first one, especially where the first wave is gone and SARS-CoV-2 is spreading at a slower rate. In that case, we recommend protecting cirrhotic patients considering them at high risk of death or complications, allowing them to access vaccination and care programmes as a priority.

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