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Position Paper

Italian association for the study of the liver position statement on SARS-CoV2 vaccination

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ABSTRACT

The vaccination campaign against Sars-CoV-2 commenced in Italy at the end of December 2020. The first ones to receive the immunization against the virus were the health workers and the residents of nursing homes, following which the vaccine would be available for the entire population, beginning with the most vulnerable individuals. SARS-CoV2 vaccines have been demonstrated to be safe for the general population, although no data for patients with liver diseases or those having undergone liver transplantation are available so far.

The present position statement AISF is an attempt to suggest, based on the published data on the impact of Sars-Cov-2 infection in patients with chronic liver disease, a possible priority for vaccination for this category of patients.

1. Introduction

Coronavirus disease-2019 (COVID-19) pandemic has severely impacted the health, social interaction, and daily activity aspects of human life. Effective vaccines against COVID-19 have been awaited eagerly since the beginning of the pandemic.

According to the World Health Organization, over 169 vaccines are currently under development, among which 26 have already entered the human clinical phase of trials. Several of the vaccine candidates have demonstrated good outcomes in terms of safety and immunogenicity in Phase 1/2 and Phase 2 studies [1]. Until January 2020, three vaccine candidates for COVID-19 had completed Phase 3 trials with the reports published, while 19 vaccine candidates were under Phase 3 trials. In the development of these vaccines, various approaches to stimulate the immune system for enhancing the humoral response have been used, including the traditional approaches, such as the vaccines containing an inactivated virus, protein subunits of the virus, and recombinant virus. In addition, innovative approaches, such as non-replicating viral vector vaccines, RNA-based vaccines, and DNA-based vaccines, have also been employed.

It is recommended that the allocation of the COVID-19 vaccine should maximize the vaccination benefits of both the individual recipients and the population as a whole. Such benefits include the reduction in SARS-CoV-2 infections as well as in the COVID-19–associated morbidity and mortality, which would, in turn, reduce the burden of the highly-strained healthcare sector. Identification of the groups to be prioritized for vaccination should also be aimed to maximize both individual and public health benefits and should be based on scientific evidence revealing those at the highest risk of developing SARS-CoV-2 infection or severe COVID-19-related diseases or death [2]. In this context, the present position

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statement aims to provide the Italian hepatology community with the most recent evidence and recommendations for SARS-CoV-2 vaccination in regard to patients with chronic liver disease.

2. Available vaccines

2.1. RNA based vaccines

In an RNA-based vaccine, although no antigen is delivered directly, the genetic information of the virus in the form of RNA is used as the trigger to generate the immune response. To date, two mRNA-based vaccines have received approval for emergency use from the FDA and the EMA, namely BNT162b2 mRNA (BioNTech and Pfizer) and mRNA-1273 (Moderna and National Institute of Allergy and Infectious Diseases-NIAID) [3,4].

The RNA sequence is generated *in silico*, a technology that permits rapid changes in the sequences if required, for example, in the case of the emergence of a novel spike protein variant of the virus.

The main concerns regarding this type of vaccine involve logistic considerations as these vaccines require frozen storage, due to which large-scale production and long-term storage stability issues could arise.

The BNT162b2 mRNA vaccine (BioNTech and Pfizer) has been proven safe and effective in preventing COVID-19 infection in a placebo-controlled, observer-blinded, pivotal efficacy Phase 3 trial. The vaccine was administered via intramuscular injection in two doses separated by an interval of 21 days (Day 0 and Day 21). The measured protection at least seven days after the second dose was 95% (95% credible interval of 90.3–97.6; the number of cases in the active arm was 8, while the number of cases in the placebo arm was 162). The vaccine also appeared to provide effective protection against disease severity (treatment group: 1 event; placebo group: 9 events). The protection was maintained in all the predefined subgroups of age, sex, ethnicity, obesity, clinical risk factors (Charlson Comorbidity Index $>$ 0 or obesity), country of enrolment.

The main exclusion criteria for the study population were based on reduced immunocompetence, including known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV), active autoimmune disease or a history of autoimmune disease, an immunocompromised condition due to known or suspected immunodeficiency, or active treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids. The other exclusion criteria were pregnancy or breastfeeding, a history of severe adverse reaction to a vaccine, and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention.

Most of the adverse events observed were transient reactogenicity events, with the incidence of the serious adverse events similar in both vaccine and placebo groups (0.6% and 0.5%, respectively).

The mRNA-1273 vaccine (Moderna and National Institute of Allergy and Infectious Diseases-NIAID) has also been proven safe and effective in preventing COVID-19 infection in a randomized, placebo-controlled, observer-blinded Phase 3 trial. The patients received two intramuscular injections separated at an interval of 28 days, and the results revealed symptomatic COVID-19 infection in 11 participants in the treatment group compared to 185 participants in the placebo group. Vaccine efficacy was 94.1% (95% credible interval of 89.3– 96.8%). All the 30 severe cases of COVID-19 infection occurred in the placebo group. The subgroup analysis did not reveal any differences in the outcomes for different age, sex, ethnicity, or risk factors for severe COVID-19 infection (defined as at least one of the following: chronic lung disease, cardiac disease, severe obesity, diabetes, liver disease, and HIV infection).

The main exclusion criteria were an immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (except for antiretroviral controlled HIV, which was permitted), and recent use of systemic immunosuppressants or immune-modifying drugs (in the previous six months). The other exclusion criteria were pregnancy or breastfeeding, known or suspected allergy or a history of anaphylaxis, urticaria, and any other significant adverse reaction to a vaccine or its components.

The profile of the adverse events for the mRNA-1273 vaccine was quite similar to that of the BNT162b2 mRNA vaccine. The vaccine arm presented a relatively higher frequency of adverse events, particularly a local reaction manifesting as pain at the site of vaccine injection. Severe adverse events were rare and similar in both groups (1.3% placebo; 1.5% treatment).

2.2. Replication-incompetent vectors

The non-replicating vector vaccines are based on another virus, usually an Adenovirus, that is engineered to express the spike protein of the concerned virus, while parts of the original genome necessary for replication are deleted. The vector delivered intramuscularly infects the host cells and expresses the viral spike protein on its surface. This technology was also used in an Ebola vaccine and has been demonstrated to enable the production of large quantities of vectors [5]. Moreover, direct manipulation of SARS-CoV-2 is not required.

The ChAdOx1 nCoV-19 vaccine (AZD1222), also known as Covishield (AstraZeneca and the University of Oxford), is based on chimpanzee adenovirus. This vaccine has been proven safe and effective in preventing COVID-19 infection in an interim analysis that includes data from four ongoing blinded, randomized, controlled trials. Meningococcal group A, C, W, and Y conjugate vaccine or normal saline was administered to patients in the control group [6]. The overall vaccine efficacy was 70.4% (30 COVID-19 infection cases in the vaccine arm vs. 101 in the control group). All the ten cases of COVID-19 infection requiring hospitalization belonged to the control group. Further trials are required to understand the level of efficacy of this vaccine and to optimize the dosage and the timing of administering the second dose of this vaccine. After vaccination with the COVID-19 Vaccine by AstraZeneca, in participants who were seronegative at baseline, seroconversion (measured as $a \geq$ 4-fold increase in S-binding antibodies compared to the baseline) was observed in $\geq$ 98% of the participants 28 days after the first dose and in $>$ 99% of the participants 28 days after the second dose.

Serious adverse events were similar between both groups (84 in the SARS-CoV-2 vaccine group vs. 91 in the control group). Two adverse events were considered to be possibly related to the experimental vaccine: transverse myelitis presented two weeks after the second dose and high-grade fever (40°) two days after the first dose that resolved rapidly.

In march 2021 following reports of blood clots in people vaccinated with ChAdOx1 nCoV-19 vaccine, the EMA's safety committee conducted a preliminary review of safety data. The Committee confirmed that: the benefits of the vaccine in combating the still widespread threat of COVID-19 continue to outweigh the risk of side effects and that the vaccine is not associated with an increase in the overall risk of thromboembolic events. However, the vaccine may be associated with very rare cases of thromboembolic events in patients with thrombocytopenia.

2.3. Safety of the SARS-CoV2 vaccines in patients with liver diseases

In the case of the three vaccines stated above, detailed data regarding liver safety remains unpublished, although abnormal liver biochemistry was reported in just one of the 12.012 participants who received the ChAdOx-1-nCoV vaccine. In the Pfizer vaccination study, only 217 individuals (0.6%) among the 37,706 partic-

Table 1
Pharmacological and safety characteristics of Covid-19 vaccines.

	Pfizer-BioNTech	Moderna	Astra-Zeneca
Technology	mRNA	mRNA	Adenovirus
EMA approval	21 December 2020	6 January 2021	31 January 2021
Minimum age	16 yrs	18 yrs	18 yrs
Schedule	2 doses (30 μg) (0–21 days)	2 doses (100 μg) (0–28 days)	Needs definition
Length of response	Unknown	Unknown	Unknown
In vitro development of Neutralizing ABs	Yes	Yes	Yes
Efficacy	Yes	Yes	Yes
1. Prevention of symptomatic disease following 2° dose	94.1% (95% CI, 89.3 - 96.8%)	94.6% (95% CI, 89.9–97.3)	70•4% (95% CI, 54.8–80.6)
2. Prevention of transmission	Not Reported	Not Reported	Not Reported
Patients with liver disease enrolled in RCTs	$N = 217$	$N = 196$	Excluded
Patients who received OLT or on immunosuppressive therapies	Excluded	Excluded	Excluded

Legend: EMA, European Medicine Agency; AB, antibody; RCT, randomized controlled trial; OLT, orthotopic liver transplantation.

ipants had liver disease, among which only three (< 0•1%) had a moderate to severe level of liver disease. The Moderna trial also had a similarly low proportion of liver disease patients (196 [0•6%] among the 30,351 participants). The ChAdOx1-nCoV-19 vaccine trial explicitly excluded the patients with pre-existing liver disease [7]. Notably, in all of the above-stated studies, the criteria defining liver disease and its severity were unclear. In addition, all the trials listed systemic immunosuppression as an exclusion criterion, thereby preventing the inference on the immunosuppressed liver transplant recipients or the patients with autoimmune liver disease.

The studies on other vaccines did not report any association of the vaccination with significant side effects or safety signals in patients with cirrhosis [8–10].

In patients who have undergone organ transplantation, although theoretically there is a risk of vaccination-induced graft rejection, a causal link between vaccination and rejection has never been demonstrated. Seasonal influenza vaccine, which is the most evaluated vaccine to date, presented either no induction (0.6%) of anti-HLA antibodies at all [11] or a rare event (2.9%) of induction of Donor Specific Antibodies (DSA) or anti-HLA antibodies following the vaccination in a cohort of 169 solid-organ transplant recipients, with no evidence suggesting higher rejection rates following the influenza vaccination. In kidney transplant recipients, vaccination against influenza with the adjuvanted A(H1N1) 2009 the pandemic vaccine was associated with an increase in the anti-HLA antibodies, with no increase in the acute rejection rate. Certain case series have suggested an association between adjuvanted influenza vaccination and acute rejection, although these observations have not been confirmed in larger studies [12].

The most debatable post-transplant immunization decision is regarding whether live vaccines could ever be safely administered in a post-transplant setting. According to the current recommendations, live vaccines should not be administered post-transplant due to the following concerns: (1) administration of live vaccines to an immunocompromised patient could result in a life-threatening infection with the pathogenic viral strain, and (2) immunosuppression could prevent the generation of a protective immune response even after vaccination [13,14]. However, since none of the currently approved vaccines against Covid-19 are live vaccines, there are no obvious reasons to suspect their safety in immunosuppressed patients.

Table 1 presents a summary of the characteristics of the currently available vaccines against Covid-19.

3. Remarks

The vaccines against SARS-CoV2 approved by the European Medical Agency have been demonstrated to be safe in the general population. However, no data regarding the effect of these vaccines on the patients with liver diseases or those having undergone liver transplantation are reported so far, which indicates an urgent requirement for real-world registries and studies on these patient populations.

3.1. Effectiveness of the SARS-CoV2 vaccines in patients with liver diseases

Since the ongoing randomized controlled trials for vaccines against COVID-19 lack data on patients with liver diseases, for now, the efficacy of these vaccines in this population has to be inferred from the previously reported data for other vaccines. According to previous studies, although the response to vaccines is not attenuated in patients with mild-to-moderate liver disease of any etiology, the rates of seroconversion after hepatitis B virus vaccination and the durability of humoral immunity after pneumococcal and influenza vaccination were observed to be markedly reduced in the patients with cirrhosis [8–10]. Therefore, the patients with cirrhosis might also exhibit attenuated immune responses to COVID-19 vaccination.

Clinical guidelines recommend both pre-transplant and post-transplant vaccination against a variety of pathogens. Since the liver transplant candidates may have to wait for long durations to undergo the transplantation, it is recommended that the vaccinations and the boosts be administered while on the waiting list. Furthermore, certain patients awaiting transplantation have demonstrated suboptimal responses to vaccination, while the antibody responses were further attenuated when the vaccines were administered post- transplantation [15].

Therefore, it is highly recommended to vaccinate patients prior to transplantation, especially at early stages (a less decompensated disease with a lower score of the model for end-stage liver disease) to avoid any influence of the end-organ disease on the immunogenicity of the vaccine. The rates of immunity against vaccine-preventable viruses in the adult patients undergoing liver transplantation have not been studied extensively [16] and the optimal time for post-transplantation vaccine administration remains unknown. Most centers commence the vaccinations approximately 3–6 months after the transplantation as by then the baseline immunosuppression levels have been reached.

4. Remarks

Although there are limited data on the effectiveness of vaccines against SARS-COV2 in patients with chronic liver disease, the data available for other vaccines in this population suggest that immune response is expected to be attenuated in cirrhotic and immunosuppressed patients even when no attenuation is observed in the noncirrhotic patients.

Since the immunological response to the novel vaccines against SARS-CoV-2 and its duration in patients with liver disease and the

liver transplant candidates and recipients remain unknown so far, it is of paramount importance to continue to observe the rules on social distancing, wearing a mask, and following disinfection precautions.

4.1. Whether to prioritize the patients with liver disease for Covid-19 vaccination

The decision-making regarding the prioritization of a particular population for vaccine administration is complex and requires considering numerous variables related to both the individual and the community. The possibility of prioritizing the patients with the liver disease requires considering the direct benefits to this population, the risk of transmission of infection from this population to the healthy population, and the risk of harm that could be caused to the other, nonprioritized groups due to delayed vaccinations. A precise perspective on the last two points is not possible owing to the lack of data available on the transmission figures from the patients with liver disease and because the number of vaccine doses available and the daily capacity to deliver the vaccines are probably the most important variables for designing a nationwide vaccination program.

On the other hand, data on the impact of Covid-19 infection on patients with liver disease are available in relatively greater numbers.

4.2. Covid-19 infection in patients with chronic liver diseases, cirrhosis, or hepatocellular carcinoma (HCC)

It is reported that liver diseases of viral etiology are not associated *per se* with the severity or outcome of COVID-19 disease, and this finding has been consistent across Asia, Europe, and the US [17,18]. Moreover, according to recent data from the European Reference Network for Rare Liver Diseases, autoimmune liver diseases and the related-immunosuppressive therapy do not represent a specific risk factor for COVID-19 disease, and the risk, as in other etiologies, is determined by the stage of cirrhosis [19].

There is evidence suggesting that individuals with non-alcoholic fatty liver disease (NAFLD) have a higher risk of progression to severe COVID-19 disease. However, whether this risk is driven by NAFLD *per se* or by the other metabolic comorbidities of NAFLD, such as obesity and diabetes, that have already been proven to be risk factors for COVID-19 severity, remains unclear [20]. Alcoholic liver disease (ALD) has been demonstrated to be a specific predictor of all-cause mortality in patients with COVID-19 disease [21]. A potential explanation for this is that a superimposed cytokine storm elicited by SARS-CoV-2 exacerbates the heightened inflammatory state of the patients with ALD, thereby producing worse outcomes [22]. Moreover, there has been significant concern regarding increased alcohol intake during the COVID-19 pandemic, which has rendered this association further relevant. The patients with cirrhosis have a high risk of contracting infections owing to a cirrhosis-associated immune dysfunction that affects both innate and adaptive immunity [23].

Bacterial, viral, as well as fungal infections, are associated with a risk of acute decompensation of cirrhosis and mortality, because of which they are considered the most important precipitating factors for acute or chronic liver failure [24,25]. The mechanisms underlying the infection-induced decompensation involve systemic inflammation induced by the interaction between pathogens and the host's immune system as well as by the "danger signals" released from the affected organs [26]. Remarkably, COVID-19 disease is associated with both severe systemic inflammation and multiorgan dysfunction (including liver injury) in the general population [27,28], while the worsening of liver function (increase in the MELD score) is observed frequently in the patients having both cirrhosis and COVID-19 disease [29]. Furthermore, acute decompensation of cirrhosis was observed in 20–46% of the patients with both cirrhosis and COVID-19 disease [30,31].

Studies from Asia, North America, and Europe have consistently demonstrated that patients with cirrhosis are at a higher risk of developing severe COVID-19 disease (≈ 5-fold higher risk) compared to those without cirrhosis [30–33]. In addition, the patients with both cirrhosis and COVID-19 disease exhibit significantly higher mortality compared to those with COVID-19 disease and without cirrhosis (≈ 3-fold higher risk) [29–35]. The factors associated with mortality in the patients with cirrhosis were age, Child-Pugh class B or C, MELD score, and comorbidities (assessed using the Charlson's comorbidity index) [29,30,32].

In comparison to the patients with other types of cancers, the patients with hepatocellular carcinoma (HCC) appeared to have a higher susceptibility to the COVID-19 infection because the hepatic injury caused by SARS-CoV-2 could decompensate the underlying cirrhosis [36]. In a recent study, HCC was identified as a determinant of mortality in a cohort of patients with both chronic liver disease and COVID-19 disease [21]. Moreover, the data on the humoral and cellular immune responses to vaccination in cancer patients are scarce and mostly address the concerns of influenza vaccination. Observational clinical studies have indicated lower mortality and morbidity rates associated with influenza in the cancer patients who received influenza vaccination, suggesting an efficient immune response upon vaccination [37].

4.3. Covid-19 disease in patients who have undergone liver transplantation

Recent data suggest no independent association between previous liver transplantation and death following SARS-CoV-2 infection [38]. Conversely, older age and medical comorbidities such as renal impairment and diabetes are associated with SARS-CoV-2-related mortality [38]. Therefore, downregulation of the immune system [39] and long-term liver transplant recipients having metabolic comorbidities should be focused on rather than early post-transplant period [40].

It is recommended to preferentially consider the traditional risk factors for adverse outcomes in COVID-19 infection when considering the risks and benefits of hospital attendance, immunosuppression, and social-distancing requirements in the case of liver transplant recipients during the ongoing COVID-19 pandemic [38].

5. Recommendations

The patients with noncirrhotic chronic liver disease should receive vaccination against SARS-CoV2 according to the priority criteria established for the general population, i.e., based on age and comorbidities. In patients with autoimmune liver disease, the immunosuppressive treatment should not be withdrawn or weaned during the time of vaccination, even if a lower degree of protection is expected, similar to that in the other immunosuppressed populations.

The patients with noncirrhotic NAFLD might be at a higher risk of COVID-19 severity, possibly due to comorbidities such as obesity and diabetes. Nonetheless, additional studies are required to clarify whether NAFLD patients should be prioritized for vaccination against SARS-CoV2.

The patients with noncirrhotic ALD might be at a higher risk of COVID-19 severity. However, additional studies are required to clarify whether ALD patients should be prioritized for vaccination against SARS-CoV2.

The choice of the vaccine to be administered in the case of patients with noncirrhotic chronic liver disease should be based on

the general recommendations by the Italian Medical Agency (AIFA) considering the age and other comorbidities of the patients involved.

The patients with cirrhosis with/without hepatocellular carcinoma should be prioritized for vaccination against SARS-CoV2 as these patients present a high risk of a severe clinical course and COVID-19-associated mortality.

As there is a lack of precise data on the effect of vaccines on patients with liver disease or those who have undergone a liver transplant, the choice of the vaccine to be administered should be based on the general recommendations by the Italian Medical Agency (AIFA) and the local availability of the vaccines.

The patients awaiting liver transplantation should be prioritized due to a high risk of mortality in the pre-transplant phase.

The patients who have undergone liver transplantation and are currently on immunosuppressive therapy may require prioritization in the vaccine drive as they are, theoretically, at an increased risk of infection.

Vaccination of the partners, caregivers, and relatives residing with the patients with cirrhosis and those who have undergone transplantation should be encouraged due to the following concerns: (i) the response to other vaccinations is reported to be weaker in the patients with cirrhosis and those who have undergone transplantation, and (ii) reduced transmission from vaccinated patients is expected, even if not demonstrated as yet.

Declaration of Competing Interest

None.

References

[1] Azzi Y, Bartash R, Scalea J, et al. COVID-19 and solid organ transplantation: a review article. Transplantation 2021;105:37–55.
[2] McClung N, Chamberland M, Kinlaw K, et al. The advisory committee on immunization practices' ethical principles for allocating initial supplies of COVID-19 vaccine-United States, 2020. Am J Transplant 2021;21:420–5.
[3] Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603–15.
[4] El Baden LR, Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2020;384:403–16.
[5] Matz KM, Marzi A, Feldmann H. Ebola vaccine trials: progress in vaccine safety and immunogenicity. Expert Rev Vaccines 2019;18:1229–42.
[6] Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99–111.
[7] Marjot T, Webb GJ, Barritt AS, et al. SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question. Lancet Gastroenterol Hepatol 2021;6:156–8.
[8] Aggeletopoulou I, Davoulou P, Konstantakis C, et al. Response to hepatitis B vaccination in patients with liver cirrhosis. Rev Med Virol 2017;27:e1942.
[9] McCashland TM, Preheim LC, Gentry MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. J Infect Dis 2000;181:757–60.
[10] Härmälä S, Parisinos CA, Shallcross L, et al. Effectiveness of influenza vaccines in adults with chronic liver disease: a systematic review and meta-analysis. BMJ Open 2019;9:031070.
[11] Baluch A, Humar A, Eurich D, et al. Randomized controlled trial of high–dose intradermal versus standard-dose intramuscular influenza vaccine in organ transplant recipients. Am J Transpl 2013;13:1026–33.
[12] Valour F, Conrad A, Ader F, et al. Vaccination in adult liver transplantation candidates and recipients. Clin Res Hepatol Gastroenterol 2020;44:126–34.
[13] Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309–18.
[14] Feldman AG, Hsu EK, Mack CL. The Importance of prioritizing pre and post-transplant immunizations in an era of vaccine refusal and epidemic outbreaks. Transplantation 2020;104:33–8.
[15] Fagiuoli S, Colli A, Bruno R, et al. Management of infections pre-and post-liver transplantation: report of an AISF consensus conference. J Hepatol 2014;60:1075–89.
[16] Gardiner A, Liu K, Bonnichsen M, et al. Immunity to vaccine-preventable viral infections in Australians being evaluated for liver transplantation. Transplantation 2019;103:2318–22.
[17] Liu R, Zhao L, Cheng X, et al. Clinical characteristics of COVID-19 patients with hepatitis B virus infection-a retrospective study. Liver Int 2021;41:720–30.
[18] Butt AA, Yan P, Chotani RA, et al. Mortality is not increased in SARS-CoV-2 infected persons with hepatitis C virus infection. Liver Int 2021; online ahead of print. doi:10.1111/liv.14804.
[19] Marjot T, Buescher G, Sebode M, et al. SARS-CoV-2 infection in patients with autoimmune hepatitis. J Hepatol 2021 Available at: https://doi.org/. doi:10.1016/j.jhep.2021.01.021.
[20] Stefan N, Birkenfeld AL, Schulze MB. Global pandemics interconnected-obesity, impaired metabolic health and COVID-19. Nat Rev Endocrinol 2021;17:135–49.
[21] Kim D, Adeniji N, Latt N, et al. Predictors of outcomes of COVID-19 in patients with chronic liver disease: US multi-center study. Clin Gastroenterol Hepatol 2020; online ahead of print. doi:10.1016/j.cgh.2020.09.027.
[22] Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med 2020;8:46–7.
[23] Piano S, Brocca A, Mareso S, et al. Infections complicating cirrhosis. Liver Int 2018;38:126–33.
[24] Trebicka J, Fernandez J, Papp M, et al. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. J Hepatol 2020; online ahead of print. doi:10.1016/j.jhep.2020.11.019.
[25] Fernández J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870–80.
[26] Arroyo V, Angeli P, Moreau R, et al. The systemic inflammation hypothesis: towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol 2021;74:670–85.
[27] Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. Immunity 2020;53:19–25.
[28] Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. Liver Int 2020;40:2394–406.
[29] Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020;73:1063–71.
[30] Marjot T, Moon A, Cook J, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. J Hepatol 2021;74:567–77.
[31] Sarin SK, Choudhury A, Lau GK, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). Hepatol Int 2020;14:690–700.
[32] Bajaj JS, Garcia-Tsao G, Biggins SW, et al. 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;70:531–6.
[33] Lee YR, Kang MK, Song JE, et al. Clinical outcomes of coronavirus disease 2019 in patients with pre-existing liver diseases: a multicenter study in South Korea. Clin Mol Hepatol 2020;26:562–76.
[34] Berenguer J, Ryan P, Rodríguez-Baño J, et al. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect 2020;26:1525–36.
[35] Hashemi N, Viveiros K, Redd WD, et al. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: a multicentre United States experience. Liver Int 2020;40:2515–21.
[36] Chan SL, Kudo M. Impacts of COVID-19 on liver cancers: during and after the pandemic. Liver Cancer 2020;9:491–502.
[37] Bitterman R, Eliakim-Raz N, Vinograd I, et al. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev 2018;2:CD008983.
[38] Webb GJ, Marjot T, Cook JA, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. Lancet Gastroenterol Hepatol 2020;5:1008–16.
[39] Gambato M, Germani G, Perini B, Gringeri E, Feltracco P, Plebani M, Burra P, Russo FP. A challenging liver transplantation for decompensated alcoholic liver disease after recovery from SARS-CoV-2 infection. Transpl Int 2021 Feb 8Epub ahead of print. PMID: 33556199). doi:10.1111/tri.13842.
[40] Bhoori S, Rossi RE, Citterio D, et al. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. Lancet Gastroenterol Hepatol 2020;5:532–3.