Special Communication

Use of COVID-19 vaccines in patients with liver disease and post-liver transplantation: Position statement of the Saudi Association for the Study of Liver diseases and Transplantation

Saleh A. Alqahtani[1,2], Mazin Barry[3], Ziad Memish[4,5,6], Almoutaz Hashim[7], Mona A. Alfares[8], Saad A. Alghamdi[1], Waleed K. Al-Hamoudi[9], Bandar Al-Judaibi[10,11], Waleed Alhazzani[12,13], Jaffar A. Al-Tawfiq[14,15,16], Faisal Abaalkhail[5,17]

[1]Liver Transplant Center, King Faisal Specialist Hospital and Research Center, [3]Department of Internal Medicine, Division of Infectious Diseases, College of Medicine, King Saud University, [4]Research and Innovation Center, King Saud Medical City, Ministry of Health, [5]College of Medicine, Alfaisal University, Riyadh, [9]Department of Medicine, College of Medicine, Gastroenterology and Hepatology Unit, King Saud University, [17] Department of Medicine, Gastroenterology Section, King Faisal Specialist Hospital and Research Center, Riyadh, [7]Department of Gastroenterology and Transplant Hepatology, College of Medicine, University of Jeddah, [8]Department of Infectious Disease, King Abdulaziz University Hospital, Jeddah, [14]Infectious Disease Unit, Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia, [2]Division of Gastroenterology and Hepatology, Johns Hopkins University, Baltimore, [16]Infectious Disease Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, [6]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, [11]Division of Transplantation, University of Rochester, Rochester, NY, [15]Infectious Disease Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA, [10]Department of Medicine, Division of Gastroenterology, and Multi-Organ Transplant Program, Western University and London Health Sciences Centre, London, Ontario, [12]Division of Critical Care, Department of Medicine and [13]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada

Abstract

Patients with chronic liver disease (CLD) and liver transplant recipients are at increased risk of morbidity and mortality from coronavirus disease 2019 (COVID-19). Although several studies demonstrated the safety and efficacy of COVID-19 vaccines in the general population, data in CLD patients and liver transplant recipients are lacking. Two COVID-19 vaccines were approved by the Saudi Food and Drug Authority and rolled out to several million recipients in Saudi Arabia. These vaccines are mRNA-based vaccine BNT162b2 from Pfizer/BioNTech and adenovirus-based AZD1222 from Oxford/AstraZeneca from three manufacturing sites (EU Nodes, Serum Institute of India, and South Korea Bio). The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) has reviewed the available evidence and issued interim recommendations for COVID-19 vaccination in CLD and liver transplant recipients. Since there is no evidence contradicting the safety and immunogenicity of the currently approved COVID-19 vaccines in patients with CLD and hepatobiliary cancer and liver transplant recipients, the SASLT recommends vaccination in those patient populations. CLD and hepatobiliary cancer patients and liver transplant recipients should be prioritized

Address for correspondence: Dr. Saleh A. Alqahtani, Liver Transplant Center, King Faisal Specialist Hospital and Research Center, Riyadh 12713, Saudi Arabia.
E-mail: salalqahtani@kfshrc.edu.sa

Submitted: 25-Apr-2021 **Accepted:** 01-May-2021 **Published:** 28-May-2021

Access this article online	
Quick Response Code:	**Website:** www.saudijgastro.com
	DOI: 10.4103/sjg.sjg_223_21

How to cite this article: Alqahtani SA, Barry M, Memish Z, Hashim A, Alfares MA, Alghamdi SA, *et al*. Use of COVID-19 vaccines in patients with liver disease and post-liver transplantation: Position statement of the Saudi association for the study of liver diseases and transplantation. Saudi J Gastroenterol 2021;27;201-7.

depending on the risk factors for severe COVID-19. In transplant recipients, the optimal timing of vaccination remains unknown; however, immunization is recommended after the initial immunosuppression phase. Patients with CLD and liver transplant candidates or recipients should be closely monitored after COVID-19 vaccination. These patient populations should be included in future clinical trials to provide further evidence on the efficacy and safety of COVID-19 vaccines.

Keywords: Cirrhosis, COVID-19, liver disease, SARS-CoV-2, vaccine

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic continues to impact populations worldwide, though recent vaccine development and roll-out is expected to significantly decrease disease transmission and severity.[1] In Saudi Arabia, 404,054 confirmed COVID-19 cases, and 6,810 deaths have been reported as of April 13, 2021.[2] Patients with chronic liver disease (CLD), such as cirrhosis, autoimmune hepatitis, hepatobiliary malignancies, and liver transplant recipients are at increased risks of infections, morbidity, and mortality compared to the healthy population.[3,4] In addition, CLD patients are at increased risk of both acquiring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and developing severe disease, comprising between 2 and 11% of all severe cases.[5] COVID-19 mortality ranges between 19-51% in patients with cirrhosis and is directly proportional to the advanced Child-Turcotte-Pugh class.[6]

In a multi-center retrospective study in Saudi Arabia, including almost 1,500 COVID-19 patients, only 1.1% had cancer or immunodeficiency.[7] Another study of nearly 100 COVID-19 patients from a single center in Riyadh, Saudi Arabia, during the first month of the pandemic, reported no patients with CLD and COVID-19 but showed higher mortality in those with elevated aspartate transaminase (AST).[8] Of the 605 COVID-19 patients hospitalized in Riyadh during the peak months of the pandemic, 2.5% had CLD due to chronic hepatitis B virus (HBV) infection, 13% had thrombocytopenia, 25% had elevated alanine transaminase (ALT), and 54% had elevated AST.[9] In addition, elevated AST was associated with higher odds of severe infection, intensive care admission, and death. While our understanding of the relationship between COVID-19 and liver disease has expanded over the past year, such as hepatic manifestations in patients with COVID-19,[10,11] many important questions remain unanswered.

The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) is committed to the care of patients with liver disease. In 2020, the SASLT published two position statements on liver transplantation and the principles of care for patients with liver disease during the COVID-19 era.[12,13] Over 80 COVID-19 vaccine candidates have reached clinical development globally since the beginning of the pandemic. Currently, the Saudi Food and Drug Authority (SFDA) authorizes two COVID-19 vaccines: the mRNA-based vaccine BNT162b2 from Pfizer/BioNTech (approved in December 2020, placing Saudi Arabia as the fourth country in the world to roll it out)[14] and AZD1222 from Oxford/AstraZeneca from three manufacturing sites EU Nodes, Serum Institute of India, and South Korea Bio, based on a non-replicating adenovirus l vector (approved in February 2021).[15] As of May 12, 2021, over 10,584,301 vaccine doses have been administered in Saudi Arabia.[2] With the roll-out of COVID-19 vaccines, there is an urgent need to issue national guidelines for health care providers detailing the benefits and safety of these vaccines in patients with liver disease and those undergoing liver transplantation. Recently, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases released two position statements on COVID-19 vaccination in patients with liver disease and liver transplant recipients.[16,17] This article summarizes the current knowledge on the use of COVID-19 vaccines in patients with liver disease and proposes evidence-based recommendations relevant to this population in Saudi Arabia.

NON-COVID-19 VACCINATION IN PATIENTS WITH CLD AND HEPATOBILIARY CANCER

Patients with CLD, including autoimmune hepatitis and cirrhosis, demonstrate impaired immune responses to vaccination.[16] While data on hepatobiliary cancer patients are scarce, cirrhosis is often present at the time of diagnosis suggesting that vaccine responses could be similarly impaired.[16] Other factors contributing to the impaired immune response to vaccines in CLD and hepatobiliary cancer patients include disease severity, degree of decompensation, advanced age, comorbidities, and administration of immunosuppressant drugs and chemotherapy.[18,19]

Due to the increased risk of infection and its associated complications in CLD patients, we recommend vaccination against influenza, *Streptococcus pneumoniae*, hepatitis A virus, and HBV despite an impaired immune response to vaccines.[17]

NON-COVID-19 VACCINATION IN SOLID-ORGAN TRANSPLANT RECIPIENTS

Solid-organ transplant recipients, including those undergoing liver transplantation, demonstrate decreased vaccine immunogenicity due to the administration of anti-rejection immunosuppressive agents.[16] Due to the increased risk of infection in immunosuppressed transplant patients, vaccination is crucial, even if efficacy is not optimal. Importantly, a meta-analysis of 90 studies reporting on standard (non-COVID-19) vaccination in transplant recipients showed a similar risk of transplant rejection compared with non-vaccinated controls.[20] Additionally, preventing systemic or graft infection via vaccination may decrease the risk of graft failure.[21]

Vaccination immunogenicity in solid-organ transplant recipients depends on the timing of immunization after transplantation, the dosing and type of immunosuppressive agents, and the degree of immunosuppression.[22] For maximum vaccine efficacy, inactivated and live vaccines should be administered prior to transplantation or early in the course of CLD.[23] When this is not possible, post-transplant vaccination can be performed, taking into consideration the time when the immunosuppression is lowered to minimize the decrease in immune responses. Recent guidelines suggest that inactivated vaccines can be safely administered after transplantation, starting at 3 months post-transplant, with the exception of the influenza vaccine, which can be administered as early as 1-month post-procedure.[24] Live-attenuated vaccines can also be administered to selected post-transplant patients after a careful risk-benefit assessment, avoiding the peak of immune suppression.[16,24] In the early post-transplant period, close contacts of transplant patients, including household members and health care workers, should consider receiving all routine live vaccines if not vaccinated earlier.[24]

CLINICAL TRIALS OF COVID-19 VACCINES IN LIVER DISEASE PATIENTS

Clinical trials of the Pfizer/BioNTech, Oxford/AstraZeneca, and Moderna COVID-19 vaccines reported excellent safety profiles and marked efficacy (62–95%) in preventing symptomatic COVID-19.[25-27] Consequently, these three COVID-19 vaccines have gained rapid regulatory approval in many countries. Despite large clinical trials including over 100,000 participants, data regarding the overall safety and efficacy of COVID-19 vaccines in solid-organ transplant recipients and CLD patients, including those with hepatobiliary cancer, are lacking, and the data on tolerability, reactogenicity, and immunogenicity profiles are limited.[16,28,29]

The eligibility criteria for Pfizer/BioNTech and Moderna COVID-19 vaccine phase 3 trials included patients with stable chronic medical conditions, such as compensated CLD, human immunodeficiency virus, HBV, and hepatitis C virus (HCV).[28] The classification of liver disease and its severity in these trials were unclear. In the Pfizer/BioNTech vaccination study, only 217 (0.6%) of the 37,706 participants had liver disease, and only 3 (<0.1%) had moderate-to-severe liver disease.[28] The Moderna trial included a similar proportion of patients with liver disease (196 [0.6%] of 30,351), while the AstraZeneca/Oxford vaccine trial did not report the inclusion of patients with CLD.[28] Abnormal liver tests were reported in only 1 of the 12,021 participants receiving the AstraZeneca/Oxford vaccine in clinical trials.[28] The clinical studies of these vaccines excluded patients on systemic immunosuppression, and thus the results cannot be extrapolated to liver transplant recipients and those with autoimmune liver disease.[28]

KNOWLEDGE GAPS REGARDING COVID-19 VACCINATION IN LIVER DISEASE PATIENTS

Vaccine safety and efficacy data for patients with liver disease are limited, and many unanswered questions remain. Such questions include the exact association of the AstraZeneca/Oxford vaccine with rare thromboembolic complications. In two case series of 11 and 5 patients with thrombotic thrombocytopenia after Vaxzevria vaccine, almost all patients had a platelet count less than 75,000 per mm^3 and a peak international normalized ratio (INR) of 1.66, 11 patients were previously healthy, none had liver disease, and 9 patients had a fatal outcome.[30,31] It is hypothesized that antibodies to platelet factor 4, similar to autoimmune heparin-induced thrombocytopenia, play a role. On April 7, 2021, the European Medicines Agency indicated that thromboembolic episodes in association with this vaccine are rare,[32] and several health authorities have taken the decision of not recommending the vaccine for younger populations because of the higher risk-benefit ratio.

The occurrence of thromboembolic events is particularly challenging in cirrhosis patients with thrombocytopenia

and elevated INR, who are in a hypercoagulable state,[33] as well as in patients after liver transplantation who are at an increased risk of hepatic artery thrombosis.[34] However, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) stated that such adverse event is likely to be 1 case per 250,000 vaccinated people (0.0004%), and 1 death in a million,[35] as compared to COVID-19 with a rate of 8% for pulmonary embolism and up to 23% for deep venous thrombosis, in addition to strokes in 1.6% and overall thrombocytopenia in 30%,[36] with benefits clearly outweighing the risks in all populations. On April 16, 2021, the Global Advisory Committee on Vaccine Safety (GACVS) issued a statement acknowledging the very rare and new adverse event named thrombosis with thrombocytopenia syndrome (TTS), involving unusual and severe blood clotting events associated with thrombocytopenia after vaccination with both AstraZeneca COVID-19 vaccines (Vaxzevria and Covishield). Contrasting data from the UK suggests that the risk is approximately four cases per million adults (1 case per 250,000) who receive the vaccine, while the rate is estimated to be approximately 1 per 100,000 in the European Union. GACVS supports further research to understand age-related risk while available data suggest an increased risk in younger adults; future studies need to validate this observation. On the issue of sex-related risk, although more cases have been reported in females, it is important to underscore that more women received the vaccine and that some TTS cases have also been reported in men. GACVS recommends conducting safety surveillance on all COVID-19 vaccines and providing data to local authorities.[37]

The duration of vaccine-induced immune responses post-transplantation and the optimal timing of prime and booster vaccinations remain unknown. Additionally, future research should focus on vaccination efficacy with specific immunosuppression regimens, differential efficacies of single doses, and additional booster doses. Acute cellular rejection (ACR) following vaccination and the best choice of vaccine should also be explored for transplant patients.[17,28]

RECOMMENDATIONS FOR COVID-19 VACCINATION IN CLD PATIENTS

In agreement with international recommendations,[16,17] the SASLT proposes that patients with CLD should be prioritized for COVID-19 vaccination. While vaccine safety and efficacy data are missing for CLD and hepatobiliary cancer patients, given the high risk of morbidity and mortality in those populations, the potential benefits of the vaccine are likely to outweigh probable small risks.[16,38] If the vaccine supply is limited, patients with higher Model for End-Stage Liver Disease (MELD) should be prioritized, but all CLD patients should be vaccinated as soon as feasible.[17] Similar to other vaccines, the COVID-19 vaccine should be recommended to household members and health care workers caring for CLD patients to reduce exposure to SARS-CoV-2.[16] Maintaining non-pharmacologic interventions (NPIs) such as mask-wearing, hand washing, and physical distancing remains crucial both for the patients and their close contacts.

Here, we summarize the interim guidance for COVID-19 vaccination in CLD patients [Table 1]:

- For patients with CLD being treated with antivirals (anti-HBV or anti-HCV drugs) or being treated for primary biliary cholangitis or autoimmune hepatitis; the SASLT recommends continuing therapy and administering the COVID-19 vaccine.
- For patients with hepatocellular carcinoma who are receiving the COVID-19 vaccine, the SASLT recommends continuing locoregional or systemic therapy without interruption.
- For CLD patients with recent infections or fever, the SASLT recommends ruling out active infection prior to receiving a COVID-19 vaccine (consultation with an infectious diseases expert may be necessary).
- Currently used COVID-19 vaccines are anticipated to have favorable efficacy and safety profiles in immunosuppressed patients and should be administered utilizing the standard dose and schedule.
- For patients being considered for liver transplantation, we suggest administering the COVID-19 vaccine before transplantation, whenever possible, to ensure satisfactory immune responses.
- For all CLD patients, including those who are vaccinated for COVID-19, the SASLT recommends adhering to NPIs (i.e. universal masking, physical distancing, and hand hygiene).

RECOMMENDATIONS FOR COVID-19 VACCINATION IN LIVER TRANSPLANT RECIPIENTS

Based on the currently available evidence of vaccination for non-COVID-19 pathogens in organ transplant patients, liver transplant candidates should receive the COVID-19 vaccine before transplantation, whenever possible. Those anticipated to undergo imminent liver transplantation should, therefore, be prioritized in the vaccination campaign.

If COVID-19 vaccination is not possible before transplantation, then vaccination 12 weeks after

Table 1: Key recommendations on COVID-19 vaccination

Patients with chronic liver disease	Liver transplant recipients
• Recommended for all patients; if the vaccine supply is limited, patients with higher Model for End-Stage Liver Disease should be prioritized	• Recommended for all liver transplant recipients
• Antiviral therapies in patients with CLD, locoregional, or systemic therapy in patients with hepatocellular carcinoma, and treatment for primary biliary cholangitis or autoimmune hepatitis need NOT be interrupted while receiving COVID-19 vaccination	• In patients with a severe COVID-19 risk, the COVID-19 vaccine can be given 6 weeks after transplant (mRNA vaccine preferable); otherwise, 3 or more months post-transplant is suggested
• For patients with recent infections or fever, ruling out active infection prior to receiving a COVID-19 vaccine is recommended	• Reducing immunosuppression may cause acute cellular rejection (ACR), and hence, NOT recommended
• Whenever possible, candidates for liver transplant should receive a COVID-19 vaccine BEFORE transplantation	• Patients need to be evaluated for ACR or viral hepatitis if they have a persistent elevation of liver test parameters post COVID-19 vaccination
• Household members and health care workers are advised to take a COVID-19 vaccine, along with maintaining non-pharmacological interventions (NPIs), such as universal masking, hand hygiene, and physical distancing	• Deceased donor liver transplantation should NOT be delayed in recipients of COVID-19 vaccines
	• COVID-19 vaccination of close contacts (household members and health care professionals) is recommended along with strict adherence to preventive measures

transplantation is recommended, avoiding the peak period of high-intensity immunosuppression, which may attenuate the vaccine response.[16] In these cases, vaccination of close contacts (health care professionals and household members) is highly advisable, together with strict adherence to NPIs. In selected post-liver transplant recipients with risk factors for severe COVID-19, vaccination could be considered as early as 6 weeks post-transplantation on a case-by-case basis, and in consultation with the infectious disease experts.

Liver transplant recipients appear to have a lower prevalence of anti-SARS-CoV-2 antibodies and suffer a more pronounced decline of antibody levels at 3 and 6 months after COVID-19 when compared with matched immunocompetent controls.[39] A recent study evaluated the immune response of the first dose of SARS-CoV-2 mRNA vaccine by measuring antibodies to the S1 or receptor-binding domains of the spike protein in 436 transplant recipients including 47 liver transplant recipients.[40] A lower percentage of patients receiving anti-metabolite maintenance immunosuppression therapy (37%) developed an anti-spike antibody response compared to those not receiving such immunosuppressive therapy (63%). Recipients of mRNA-1273 were more likely to develop an antibody response (69%) than those receiving BNT162b2 (31%), although both vaccines were safe and there were no major adverse events including ACR.[40] However, these observations are only preliminary and complete immunogenicity data including both humoral and cellular responses after two vaccine doses as well as comparative data across all available vaccines are lacking in transplant patients.[41]

Currently, routine evaluation of vaccine response is not recommended in the general population due to uncertainties surrounding the sensitivity of serologic tests and results interpretation and the lack of knowledge regarding the antibody levels needed to provide clinical protection against SARS-CoV-2. In solid transplant recipients, determining the appropriate clinical response with decreasing anti-spike antibody titers would present an additional challenge since, for example, questions about whether to give a booster dose and establishing the appropriate interval of repeating vaccine antibody response tests will remain unanswered.

Here, we summarize the interim guidance for COVID-19 vaccination in liver transplant recipients [Table 1]:

- For liver transplant recipients, the SASLT recommends COVID-19 vaccination. Remarks: The optimal timing to administer the COVID-19 vaccine in liver transplant recipients is not established. It is reasonable to administer vaccination ≥ 3 months after liver transplantation. This period coincides with lowering immunosuppressive drugs and stable graft function. However, in those at high risk of severe COVID-19, vaccines for COVID-19, preferably an mRNA vaccine, may be given as soon as 6 weeks after transplant.
- For liver transplant recipients, the SASLT recommends against reducing immunosuppression to elicit an immune response to COVID-19 vaccination. Such

reduction in immunosuppressive agents increases the risk of ACR.

- For patients with ACR after liver transplant, those being treated for ACR, or who are on high doses of corticosteroids, the SASLT suggests delaying COVID-19 vaccination until ACR resolves and baseline immunosuppression is re-established.
- For patients with persistent elevation of liver test parameters after COVID-19 vaccination, the SASLT recommends evaluating patients for ACR or viral hepatitis.
- Liver transplantation is a lifesaving procedure, and thus, deceased donor liver transplantation should NOT be delayed for those who receive COVID-19 vaccines.
- For patients who are due to receive the second COVID-19 vaccine dose immediately post-transplant, the SASLT suggests postponing the dose for up to 6 weeks in order to elicit an optimal immune response.
- For potential living liver donors and recipients (high priority groups), the SASLT suggests administering the second dose of COVID-19 vaccine at least 2 weeks before transplantation. If COVID-19 vaccination is not available during that time, we recommend against delaying transplantation surgery.
- For family members and caregivers of liver transplant recipients, the SASLT suggests administering COVID-19 vaccination whenever possible.
- For liver transplant recipients and their close contacts, the SASLT recommends strict adherence to preventive measures (i.e. mask wearing, physical distancing, and hand hygiene) to minimize infection exposure.
- Until further data regarding post-vaccination immune response assessment becomes available, the SASLT recommends against the routine measurement of COVID-19 antibodies in liver transplant recipients.

CONCLUSIONS

SARS-CoV-2 continues to spread, placing CLD patients and liver transplant recipients at elevated risk of morbidity and mortality. Several COVID-19 vaccines have demonstrated safety and efficacy in clinical trials in the general population and have received widespread approval globally. Two of those vaccines, BNT162b2 and AZD1222, have been authorized and administered to millions in Saudi Arabia. Since there is no evidence contradicting the safety and immunogenicity of the currently approved vaccines in patients with CLD and hepatobiliary cancer or in liver transplantation candidates, the SASLT recommends COVID-19 vaccination in those patients. CLD and hepatobiliary cancer patients and liver transplant candidates should be prioritized depending on the risk factors for severe COVID-19. In transplant recipients, the optimal timing of vaccination remains unknown; however, vaccination is recommended after 3 months from liver transplant surgery.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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