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Short Communication

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Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases

Paul J. Thuluvath[1,2,*], Polly Robarts[1], Mahak Chauhan[1]

[1]Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore MD, USA; [2]Department of Medicine, University of Maryland School of Medicine, Baltimore MD, USA

Background & Aims: Liver transplant (LT) recipients or other immunocompromised patients were not included in the registration trials studying the efficacy of vaccines against SARS-CoV-2. Although the clinical efficacy of COVID-19 vaccines in immunocompromised patients is unknown, many societies have recommended vaccination of this highly vulnerable patient population.

Methods: In this prospective study, we determined antibody responses to spike protein, 4 weeks after the 2nd dose of mRNA vaccines or after the single dose of Johnson & Johnson vaccine, in LT recipients and those with chronic liver disease (CLD) with and without cirrhosis.

Results: Of the 233 patients enrolled so far, 62 were LT recipients, 79 had cirrhosis (10 decompensated) and 92 had CLD without cirrhosis. Antibody titers were defined as undetectable (<0.40 U/ml), suboptimal (0.40–250 U/ml) and adequate (>250 U/ml). Of the 62 patients who had LT, antibody levels were undetectable in 11 patients and suboptimal (median titer 17.6, range 0.47–212 U/ml) in 27 patients. Among 79 patients with cirrhosis, 3 had undetectable antibody levels and 15 had suboptimal (median titer 41.3, range 0.49–221 U/L) antibody responses. Of the 92 patients without cirrhosis, 4 had undetectable antibody levels and 19 had suboptimal (median titer 95.5, range 4.9–234 U/L) antibody responses. Liver transplantation, use of 2 or more immunosuppression medications and vaccination with a single dose of the Johnson & Johnson vaccine were associated with poor immune response on multivariable analysis. No patient had any serious adverse events.

Conclusions: Poor antibody responses after SARS-CoV-2 vaccination were seen in 61% of LT recipients and 24% of those with CLD.

Lay summary: The clinical efficacy of COVID-19 vaccines in immunocompromised patients is unknown. We performed a prospective study to evaluate immune responses to COVID-19 vaccines (Moderna, Pfizer or Johnson & Johnson) in 62 liver transplant recipients, 79 patients with cirrhosis and 92 with chronic liver diseases without cirrhosis. We found that 17.8% of liver transplant recipients, 3.8% of those with cirrhosis and 4.3% of those with chronic liver diseases without cirrhosis had undetectable antibody levels. In total, 61.3% of liver transplant recipients and 24% of those with chronic liver diseases (with or without cirrhosis) had poor antibody responses (undetectable or suboptimal). Liver transplantation, use of immunosuppressive medications and vaccination with a single dose of Johnson & Johnson vaccine were associated with poor antibody responses when adjusted for other factors.

Introduction

Patients with chronic liver disease and cirrhosis have worse outcomes from COVID-19 compared to those without liver disease.[1–3] Therefore, liver societies have recommended vaccination against SARS-CoV-2 for all patients with chronic liver diseases. Although the data on the outcomes of liver transplant recipients with COVID-19 are inconsistent, there is a definite trend towards higher mortality risks in transplant recipients.[4,5] Liver transplant recipients or other immunocompromised patients were not included in the registration trials of mRNA vaccine studies for SARS-CoV-2. Although the clinical efficacy of COVID-19 vaccine in immunocompromised patients is unknown, many societies have recommended vaccination of this highly vulnerable patient population.[6–9] It has been suggested, based on circumstantial evidence, that it is prudent to vaccinate immunocompromised patients since the benefits outweigh the risks.[10,11] However, a recent study reported that only 17% of organ transplant recipients developed detectable antibodies to the SARS-CoV-2 spike protein after the first dose of mRNA vaccines.[12] Lower immune response was anticipated since humoral immunity is critical for antibody response after vaccination, but the response seen after the first dose was disappointingly low.

We hypothesized that liver transplant recipients and those with advanced liver disease will have suboptimal response to SARS-CoV-2 vaccines. To test this hypothesis, in this ongoing prospective study, we assessed antibody responses 4 weeks after the 2nd dose of mRNA vaccines or after the single dose of Johnson & Johnson vaccine in liver transplant recipients and in those with chronic liver diseases with or without cirrhosis.

Patients and methods

In this prospective study, all adult patients (>18 years) with established chronic liver disease or those who received liver transplantation were eligible for the study. The exclusion criteria were untreated or uncontrolled HIV infection, previous exposure to COVID-19 or those who did not complete a standardized

Keywords: mRNA vaccine; SARS-CoV-2; liver transplant; cirrhosis; immunocompromised.

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* Corresponding author. Address: Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore MD, USA.

E-mail address: thuluvath@gmail.com (P.J. Thuluvath).

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vaccination protocol (4 weeks between Moderna doses and 3 weeks between Pfizer doses) as per the manufacturer of the vaccine.

We collected clinical characteristics (age, sex, race, BMI), etiology of liver disease, comorbidities (diabetes, hypertension, chronic obstructive pulmonary disease, heart failure, inflammatory bowel disease, chronic kidney disease, malignancy, smoking history and ongoing alcoholism) and concomitant medications of all patients who were eligible for an mRNA or Johnson & Johnson vaccine by age, comorbidities or employment criteria. Presence or absence of cirrhosis was confirmed in all cases using clinical or biochemical evidence (splenomegaly, ascites, hepatic encephalopathy), Fibroscan, liver imaging, endoscopy or liver biopsy. If a patient had previous SARS-CoV-2 tests (reverse-transcription PCR, antigen or antibody tests), those were recorded, but they were excluded from the study if the tests were positive.

Dates of vaccination and the types of vaccine were confirmed in all patients. All potential side effects after the 1st and 2nd dose were collected. The following adverse events were reported: local injection site reaction including pain, swelling, redness, axillary swelling and tenderness on vaccination arm, and systemic reactions including fatigue, headache, muscle pain, chills, joint pain, fever, and nausea/vomiting.

Data were entered into an excel database in a de-identified mode by giving them a coded number. All data were saved in a password-protected format and filed in the GI Research share drive and only the study staff had access to the file to download for any study procedures or audit. The data will continue to be stored indefinitely in a confidential manner in a secured hospital shared drive according to the 21 CFR part 11 guidelines.

Our plan is to continue to follow our patients for 1-year to understand the differential attrition of antibody levels with time and also to assess the rate of laboratory confirmed COVID-19 infection in vaccinated patients.

Antibody testing

Patients were tested for SARS-CoV-2 protein by Roche semi-quantitative assay (Elecsys® Anti-SARS-CoV-2 semi-quantitative) via LabCorp.[13] The test has reported 99.98% negative and 96.6% positive agreement to detect antibodies to SAR-CoV-2 spike protein 15 days (as per the laboratory website) after the diagnosis of COVID-19 by a PCR test.[13] The accuracy of this test has also been confirmed in comparative studies.[14] The LabCorp uses ≥250 U/ml as evidence of immune response and <0.4 U/ml as undetectable.

Statistical analysis

Patients were stratified into 3 groups based on antibody levels (U/ml): ≤0.4 (undetectable), 0.4–249 (suboptimal), and ≥250 (optimal). Chi-square test was used to calculate the differences among these 3 groups. To identify independent variables that were associated with poor antibody response, the undetectable and suboptimal group were combined into one group. Variables that were significant (p <0.05) in the simple logistic regression model were included in the multiple logistic regression model.

The study was approved by the institutional review board (IRB, MMC# 2021-02). Informed consent was obtained verbally and the IRB reviewed and approved the verbal consent process that was recorded in the electronic medical records.

Results

A total of 233 patients were eligible for analysis at the time of reporting. Among these 233 patients, 110 received Moderna, 104 Pfizer and 19 received Johnson & Johnson vaccine. Of the 233 patients, 62 were liver transplant recipients, 79 had cirrhosis and 92 had chronic liver diseases without cirrhosis. Of the 79 patients with cirrhosis, 10 had decompensated cirrhosis. Patient characteristics, concomitant medications and antibody levels are shown in (Table 1 and Fig. 1). As can be seen in Table 1, most patients had multiple comorbidities.

Of the 62 liver transplant recipients, antibody levels were detectable at very low levels (median 17.6, range 0.47–212 U/ml) in 27 patients and were undetectable (<0.4 U/ml) in 11 (17.8%) patients (Table 1). Only 24 (39.0%) had antibody levels above 250 U/ml. Of the 11 patients with undetectable antibody levels, 1 patient was on 3 drugs including prednisone, mycophenolate and tacrolimus, 8 patients were on tacrolimus + mycophenolate (n = 5) or prednisone (n = 3), 1 patient was on tacrolimus monotherapy and 1 patient was on sirolimus monotherapy.

Among 79 patients with cirrhosis, 15 had suboptimal antibody response and 3 had undetectable antibody levels. All 3 patients with undetectable antibody were on immunosuppression for autoimmune hepatitis (2 on prednisone + mycophenolate and 1 on prednisone +azathioprine). Of those with suboptimal antibody responses (median antibody levels 41.3, range 0.49–221 U/L), 1 patient with HIV was on immunosuppression (azathioprine), 2 were on azathioprine (1 with prednisone) and another with hepatocellular carcinoma was on lenvatinib. Three of 10 patients with decompensated cirrhosis did not respond to the vaccine.

Of the 92 patients without cirrhosis, 19 had suboptimal antibody (median antibody levels 95.5, range 4.9-234 U/ml) responses and 4 had undetectable antibody levels. Of those with undetectable antibody levels, 3 patients had autoimmune hepatitis (2 of them on mycophenolate and prednisone) and 1 had non-alcoholic steatohepatitis. Of the 19 patients with suboptimal antibody response, 5 were on azathioprine with prednisone, 3 were on azathioprine and 1 was on prednisone.

Sixteen of 19 (84.2%) patients who received Johnson & Johnson vaccine, 26 of 110 (23.6%) who received Moderna vaccine and 37 of 104 (35.6%) who received Pfizer vaccine had poor response (p <0.001, Table 2, Fig. 1B).

Table 2 shows the characteristics of patients stratified by 3 groups based on their antibody (U/ml) levels: ≤0.4 (undetectable), 0.4–249 (suboptimal), ≥250 (optimal). To identify variables associated with poor antibody responses, undetectable and suboptimal response were combined together (n = 79). On simple logistic regression analysis, few variables were associated with poor antibody response (Table S1) and these were etiology of liver disease, cirrhosis, liver transplant, 2-3 immunosuppression medications, the type of vaccine and renal insufficiency. Comorbidities were not associated with antibody responses. On multiple logistic regression analysis, liver transplantation, use of 2-3 immunosuppressive medications and vaccination with a single dose of Johnson & Johnson vaccine were associated with suboptimal response (Table 3, Fig. 1C). Although there was a trend, treatment with a single immunosuppressive medication was not significant on multiple logistic regression analysis.

None of the patients who received the vaccine had any serious adverse events. The common side effects (≥5%) after the

Table 1. Patient characteristics, comorbidities, medications and antibody response to COVID-19 vaccination stratified by liver transplantation, cirrhosis and chronic liver diseases without cirrhosis.

	All patients (n = 233, %)	Liver transplant (n = 62, %)	Cirrhosis (n = 79, %)[†]	Chronic liver disease w/o cirrhosis (n = 92, %)
Age, mean ± SD	63.0 ± 11.9	65.7 ± 8.7	63.8 ± 11.1	60.4 ± 13.9
Sex, female	115 (49)	21 (34)	39 (49)	55 (60)
BMI, mean ± SD	29.9 ± 6.2	29.1 ± 5.7	30.5 ± 6.9	30.1 ± 5.8
Race				
African American	42 (18)	10 (16)	15 (19)	17 (18)
Caucasian	180 (77)	48 (77)	61 (77)	71 (77)
Others[*]	11 (5)	4 (6)	3 (4)	4 (4)
Vaccine				
Moderna	110 (47)	33 (53)	41 (52)	36 (39)
Pfizer	104 (45)	24 (39)	31 (39)	49 (53)
Johnson & Johnson	19 (8)	5 (8)	7 (9)	7 (8)
Days between final dose and antibody test, mean ± SD	40.4 ± 21.1	38.9 ± 19.6	40.9 ± 23.9	40.8 ± 19.6
Antibody titer				
Undetectable	18 (7.8%)	11 (17.8%)	3 (3.8%)	4 (4.3)
<250 U/ml, median (range) (include undetectable)	61 (26.2)	27 (43.5), 17.6 (0.47-212)	15 (19), 41.3 (0.49-221)	19 (20.7), 95.5 (4.9-234)
>250 U/ml	154 (66)	24 (38.7)	61 (77.2)	69 (75)
Etiology of liver disease[#]				
AIH/PBC/PSC	61 (26)	8 (13)	17 (22)	36 (39)
Alcoholic liver disease	32 (14)	13 (21)	17 (22)	2 (2)
HBV/HCV	63 (27)	26 (42)	17 (22)	20 (22)
NAFLD	84 (36)	15 (24)	33 (42)	36 (39)
Other liver disease[**]	32 (14)	16 (26)	8 (10)	8 (9)
Immunosuppressant medication[#]				
Azathioprine	27 (12)	2 (3)	8 (10)	17 (18)
Prednisone	27 (12)	8 (13)	8 (10)	11 (12)
Tacrolimus	41 (18)	41 (66)	0 (0)	0 (0)
Other medications[***]	40 (17)	29 (47)	5 (6)	6 (7)
Comorbidities[#]				
Coronary artery disease	33 (14)	12 (19)	9 (11)	12 (13)
Chronic obstructive pulmonary disease	22 (9)	8 (13)	11 (14)	3 (3)
Renal impairment	65 (28)	40 (65)	17 (22)	8 (9)
Variable	92 (39)	29 (47)	39 (49)	24 (26)
Hyperlipidemia	133 (57)	35 (56)	43 (54)	55 (60)
Hypertension	159 (68)	50 (81)	55 (70)	54 (59)
Human immunodeficiency virus	2 (1)	0 (0)	2 (3)	0 (0)

AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
[*]Others: Hispanic and Asians.
[**]Other liver disease: hepatocellular carcinoma, hemochromatosis.
[***]Other medications: cyclosporine, mycophenolic acid, sirolimus and tyrosine kinase inhibitor.
[#]Numbers may not add up since some had more than 1 risk factor.
[†]Of 79 patients with cirrhosis: 69 had compensated cirrhosis and 10 had decompensated cirrhosis.

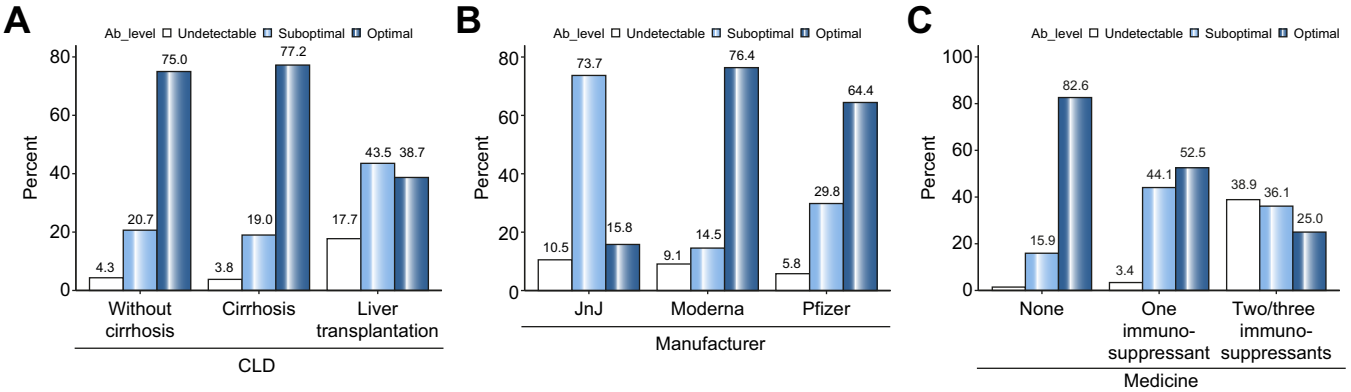

Fig. 1. Antibody response rates after SARS-CoV-2 vaccination. In patients stratified by (A) liver transplantation or chronic liver diseases with and without cirrhosis, (B) the type of vaccine (Johnson & Johnson, Moderna and Pfizer), and (C) the number of immunosuppressive medications (0, 1, 2-3). CLD, chronic liver disease.

Table 2. Patient characteristics, comorbidities, and medications stratified by undetectable, suboptimal and optimal response to COVID-19 vaccination.

Variable	Undetectable (n = 18)	Suboptimal (n = 61)	Optimal (n = 154)	*p* value
Age, mean (SD)	64.8 (9.73)	63.9 (12.24)	62.4 (12.05)	0.58
Sex, female	9 (50%)	32 (52%)	74 (48%)	0.84
Race				
Caucasian	13 (72%)	47 (77%)	120 (78%)	0.66
African American	5 (28%)	10 (16%)	27 (18%)	
Others	0 (0%)	4 (7%)	7 (5%)	
BMI, mean (SD)	30.6 (6.3)	28.7 (6.1)	30.3 (6.1)	0.19
Smoking				
No	7 (39%)	28 (46%)	88 (57%)	0.14
Yes	1 (6%)	11 (18%)	17 (11%)	
Former	10 (56%)	22 (36%)	49 (32%)	
Etiology[#]				
AIH/PBC/PSC	8 (44%)	21 (34%)	32 (21%)	0.07
Alcoholic	2 (11%)	10 (16%)	20 (13%)	
HBV/HCV	3 (17%)	18 (30%)	37 (24%)	
NAFLD	5 (28%)	11 (18%)	57 (37%)	
Others	0 (0%)	1 (2%)	8 (5%)	
Cirrhosis	3 (17%)	15 (25%)	61 (40%)	0.03
Compensated cirrhosis	2 (11%)	13 (21%)	54 (35%)	0.03
Decompensated cirrhosis	1 (6%)	2 (3%)	7 (5%)	0.88
Liver transplant	11 (61%)	27 (44%)	24 (16%)	<0.0001
Comorbidities				
0	2 (11%)	13 (21%)	44 (29%)	0.08
1	8 (44%)	19 (31%)	44 (29%)	
2	2 (11%)	15 (25%)	36 (23%)	
3	5 (28%)	7 (11%)	22 (14%)	
4	0 (0%)	6 (10%)	8 (5%)	
5	1 (6%)	1 (2%)	0 (0%)	
Renal impairment	10 (56%)	23 (38%)	32 (21%)	0.001
Immunosuppression (n)				
0	2 (11%)	22 (36%)	114 (74%)	<0.0001
1	2 (11%)	26 (43%)	31 (20%)	
2-3	14 (78%)	13 (21%)	9 (6%)	
Vaccine manufacturer				
Moderna	10 (56%)	16 (26%)	84 (55%)	<0.0001
Pfizer	6 (33%)	31 (51%)	67 (44%)	
Johnson & Johnson	2 (11%)	14 (23%)	3 (2%)	

AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
[#]When there was more than 1 etiology, classified by predominant cause for statistical analysis.

1st dose were local pain at the injection site (53%) and fatigue (16%). After the 2nd dose, the side effects were local pain at the injection site (49%), fatigue (23%), fever (8%), chills (6%), headache (7%) and myalgia (6%) (Table S2), As reported previously in healthy individuals, the side effects were more common after the 2nd dose of mRNA vaccines.

Discussion

In this study, 61% of liver transplant recipients and 24% of patients with chronic liver diseases had poor antibody responses. After adjusting for other variables, treatment with 2 or more immunosuppressive medications or having a liver transplant were associated with poor antibody responses. Although only 19 patients had a single dose vaccine from Johnson & Johnson, it was associated with a poor antibody response. The poor antibody responses to SARS-CoV-2 vaccines in 61% of transplant recipients and 24% of patients with chronic liver disease are a major concern.

Although we measured antibody to spike protein in this study, it has been shown to correlate very well with neutralizing antibodies.[15] Our findings are based on a relatively small sample size, but clinicians should be aware of these observations and provide appropriate guidance regarding continued social distancing to immunocompromised patients including those

Table 3. Multiple logistic regression analysis showing variables that were significantly associated with suboptimal/undetectable (combined) antibody response to vaccine.

	Odds ratio estimates			
Effect	**Point estimate**	**95% Wald confidence limits**		***p* value**
Liver transplantation (yes *vs.* no)	2.71	1.03	7.13	0.04
One immunosuppressant *vs.* none	3.12	1.12	8.68	0.66
2-3 immunosuppressants *vs.* none	14.38	5.09	40.66	<0.0001
Moderna vaccine *vs.* Johnson & Johnson	0.02	0.01	0.10	<0.0001
Pfizer vaccine *vs.* Johnson & Johnson	0.06	0.02	0.24	0.03

Etiology of liver disease, presence of cirrhosis and renal impairment were not significant in multiple logistic regression analysis.

with cirrhosis who receive vaccination for SARS-CoV-2 infection since those who are vaccinated may have a false sense of security and may ignore current social distancing protocols.

Patients with cirrhosis are considered immunocompromised, but only 23% had poor responses. On our multivariate analysis, cirrhosis was not associated with a poor antibody response which is reassuring. Since 214 of 233 patients received 2-dose mRNA vaccines, we cannot make any firm comments on the relative efficacy of single dose Johnson & Johnson vaccine compared to mRNA vaccines. However, it is important to note that only 3 of 19 (15.8%) patients who received Johnson & Johnson had a good a response, and these findings merit further research. Based on our preliminary data, we would discourage single dose vaccines in immunocompromised individuals. Although Moderna vaccine showed a better response than Pfizer vaccine (76.4% *vs*. 64.4%), it is premature to comment on it based on a non-randomized study. Our observations suggest that most immunocompromised patients, irrespective of the cause, may not mount adequate antibody responses in a consistent manner. The degree of immunosuppression may also be important since being on one immunosuppressive medication was not independently associated with a poor response. Since this study focused specifically on liver transplant recipients and those with chronic liver diseases, we cannot comment on other immunosuppressed patients. Most of our patients who did not respond well had multiple comorbidities, but these same patients would also be at a higher risk of death if they were to develop COVID-19. Comorbidities were not associated with poor antibody responses, but our observations will need further corroboration in larger studies.

We have previously reported inadequate immune responses in patients with cirrhosis who received hepatitis B vaccination.[16] It is currently not known whether booster doses of mRNA or Johnson & Johnson vaccines are likely to improve antibody responses. It is also currently not known whether there is a correlation between low antibody levels and susceptibility to SARS-CoV-2 infection or its severity. At the time of reporting, we have not seen any clinical evidence of vaccination failure in our small cohort. We did not measure antibody levels after the first dose of mRNA vaccines and do not have long term follow-up data on antibody titers. There are other limitations to our study. We excluded those who had a history of COVID-19, but did not screen our patients for antibodies to the nucleocapsid protein of SARS-CoV-2 to rule out previous asymptomatic exposure. Additionally, we did not perform T-cell function tests and we did not have healthy controls for comparison. More studies with larger sample sizes with longitudinal assessment are urgently needed. Despite some of these limitations, we believe our observations are very important and meaningful. There were no serious safety signals in our patients and hence we suggest continuing vaccination of our immunocompromised individuals, with the caveat that they should be informed of their probable suboptimal response to vaccination. Until we have more data, we should also recommend continued social distancing for immunocompromised patients who receive anti-SARS-CoV-2 vaccination and future studies should consider booster doses in those with undetectable and suboptimal antibody responses.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
PJT contributed to the conception and design, analysis, interpretation of the data, and the critical revision for important intellectual content. PR and MC collected the data and did the analysis. All authors approved the final version, and agree to be accountable for all aspects of the work.

Data availability statement
De-identified data available on request.

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Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.08.008.

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