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Ursodeoxycholic acid is associated with a reduction in SARS-CoV-2 infection and reduced severity of COVID-19 in patients with cirrhosis

Binu V. John[1,2], Dustin Bastaich[3], Gwilym Webb[12], Teresa Brevini[4], Andrew Moon[5], Raphaella D. Ferreira[1], Allison M. Chin[6], David E. Kaplan[7,8], Tamar H. Taddei[9,10], Marina Serper[7], Nadim Mahmud[7], Yangyang Deng[3], Hann-Hsiang Chao[11], Fotios Sampaziotis[4,12] & Bassam Dahman[3]

From the [1]Division of Gastroenterology and Hepatology, Miami VA Medical System, Miami, Florida, USA; [2]Division of Digestive Health and Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida, USA; [3]Department of Health Behavior and Policy, Virginia Commonwealth University, Richmond, Virginia, USA; [4]Wellcome—MRC Cambridge Stem Cell Institute, Cambridge, UK; [5]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina, USA; [6]Herbert Wertheim Florida International University, Miami, Florida, USA; [7]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [8]Section of Gastroenterology and Hepatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA; [9]Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut, USA; [10]Section of Gastroenterology, VA Connecticut Healthcare System, West Haven, Connecticut, USA; [11]Department of Radiation Oncology, Central Virginia Health System, Richmond, Virginia, USA; and [12]Cambridge Liver Unit, Cambridge University Hospital, NHS Foundation Trust, Cambridge, UK

Abstract. John BV, Bastaich D, Webb G, Brevini T, Moon A, Ferreira RD, et al. Ursodeoxycholic acid is associated with a reduction in SARS-CoV-2 infection and reduced severity of COVID-19 in patients with cirrhosis. *J Intern Med.* 2023;**293**:636–647.

Background and aims. Studies have demonstrated that reducing farnesoid X receptor activity with ursodeoxycholic acid (UDCA) downregulates angiotensin-converting enzyme in human lung, intestinal and cholangiocytes organoids in vitro, in human lungs and livers perfused ex situ, reducing internalization of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the host cell. This offers a potential novel target against coronavirus disease 2019 (COVID-19). The objective of our study was to compare the association between UDCA exposure and SARS-CoV-2 infection, as well as varying severities of COVID-19, in a large national cohort of participants with cirrhosis.

Methods. In this retrospective cohort study among participants with cirrhosis in the Veterans Outcomes and Costs Associated with Liver cohort, we compared participants with exposure to UDCA, with a propensity score (PS) matched group of participants without UDCA exposure, matched for clinical characteristics, and vaccination status. The outcomes included SARS-CoV-2 infection, symptomatic, at least moderate, severe, or critical COVID-19, and COVID-19-related death.

Results. We compared 1607 participants with cirrhosis who were on UDCA, with 1607 PS-matched controls. On multivariable logistic regression, UDCA exposure was associated with reduced odds of developing SARS-CoV-2 infection (adjusted odds ratio [aOR] 0.54, 95% confidence interval [CI] 0.41–0.71, $p < 0.0001$). Among patients who developed COVID-19, UDCA use was associated with reduced disease severity, including symptomatic COVID-19 (aOR 0.54, 95% CI 0.39–0.73, $p < 0.0001$), at least moderate COVID-19 (aOR 0.51, 95% CI 0.32–0.81, $p = 0.005$), and severe or critical COVID-19 (aOR 0.48, 95% CI 0.25–0.94, $p = 0.03$).

Conclusions. In participants with cirrhosis, UDCA exposure was associated with both a decrease in SARS-CoV-2 infection, and reduction in symptomatic, at least moderate, and severe/critical COVID-19.

Keywords: COVID-19, farnesoid X receptor, primary biliary cholangitis, SARS-CoV-2, UDCA

Introduction

With an improved understanding of the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a pipeline of drugs has been evaluated and approved for use in the United States [1]. Coronavirus disease 2019 (COVID-19) is associated with a 2.38 times higher adjusted hazard of death at 30 days in patients with cirrhosis [2]. Even as COVID-19 has evolved into a more endemic condition, many patients, including those both vaccinated and unvaccinated, continue to get infected [3–6]. Vaccinations have been less effective in immunocompromised patients and have shown lower effectiveness for the Omicron BA.1 and BA.2 variants, compared to the alpha and beta variants earlier in the pandemic [5–8]. Therefore, medications that can prevent illness and ameliorate severe illness in patients with cirrhosis are an important need. However, several approved medications have significant side effects, including hepatotoxicity, which is of particular concern for patients with cirrhosis. For example, remdesivir causes elevations in transaminases and is more likely to be withheld in patients with chronic liver disease [9]. Although nirmatrelvir/ritonavir is associated with a low likelihood of hepatotoxicity in the general population, it is contraindicated in patients with decompensated cirrhosis [10, 11]. When it comes to preventative strategies, monoclonal antibodies, such as tixagevimab and cilgavimab (Evusheld) and bebtelovimab, were able to demonstrate effectiveness in the prevention and treatment of SARS-CoV-2 by targeting the angiotensin-converting enzyme 2 (ACE2)-spike interaction. However, these were not easy to administer due to intravenous use, high costs, and the need to administer them in a medical facility. Moreover, although these were effective in preventing SARS-CoV-2 infection and severe COVID-19 with earlier variants, they are no longer recommended with the increase in community prevalence of newer variants such as BA.Q.1 [12, 13]. Newer therapeutics that can prevent and/or treat SARS-CoV-2, complement vaccinations and existing antivirals, and are safe, effective, easy to administer, and affordable, for patients with chronic liver disease, are still warranted.

A recent study has shown that the farnesoid X receptor (FXR) is a direct regulator of ACE2 transcription in multiple COVID-19-affected tissues, including the gastrointestinal and respiratory systems [14]. FXR activation has been shown to upregulate ACE2 gene expression and receptor activity and worsen SARS-CoV-2 infection in an ex situ normothermic lung perfusion model. FXR inhibition, with the over-the-counter compound *z*-guggulsterone and ursodeoxycholic acid (UDCA) has been shown to downregulate ACE2 in human lung, cholangiocyte, and intestinal organoids, and in the corresponding tissues in mice and hamsters [14]. UDCA was further shown to reduce ACE2 expression in the nasal epithelium in humans [14]. Finally, a retrospective analysis using data among a limited number of liver transplant recipients from the Veterans Outcomes and Costs Associated with Liver (VOCAL) cohort, and patients with chronic liver disease from the COVID-Hep and SECURE-liver data, revealed an association between UDCA exposure and improved clinical outcomes following SARS-CoV-2 infection [14]. The above findings suggest that UDCA may have a potential role in preventing SARS-CoV-2 infection and reducing the severity of COVID-19 in patients who get infected. However, the patient cohorts studied had limited sample size and were underpowered to study if participants receiving UDCA were at reduced risk of developing SARS-CoV-2 infection to explore the potential role of chemoprevention. Because UDCA is frequently used to treat a number of liver diseases, including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), undifferentiated cholestatic illnesses, and gallstone disease, a population of participants with liver disease, including those and without UDCA exposure, would be ideal to test this association [15, 16].

Therefore, the objective of our study was to investigate the association between UDCA use and the development of SARS-CoV-2 infection, and the severity of COVID-19, in a large national cohort of participants with cirrhosis.

Methods

Study design

We studied the VOCAL disease cohort participants. The cohort includes Veterans with cirrhosis obtained from the Veterans Health Administration Corporate Data Warehouse (CDW) using ICD9-CM or ICD10-CM primary or secondary codes for cirrhosis recorded at two outpatient or one inpatient encounter(s) [17, 18]. Participants were those who had their first documented diagnosis of cirrhosis between January 2008 and December 2018, with follow-up until 11 February 2022. We merged the

data of participants in the VOCAL cohort with the VA COVID-19 shared resource, which documents Veterans who have been tested for, diagnosed with, or vaccinated against COVID-19. Assemblies of the VOCAL cohort, and details of COVID-19 diagnosis and vaccine administration, have been previously described [19–21].

Institutional review boards at participating VA medical centers approved the study and waived the requirement for informed consent.

Exposure and variables

We examined participants who were exposed to UDCA at or after the time of the start of the study, which was the first documented case of COVID-19 in the VA system (3/1/2020). Participants were followed throughout the study period until the date of data abstraction (2/11/2022). Participants whose UDCA exposure was considered active and continuous, based on documentation of individual dispensed supply that extended through the study period, were only included if they were on UDCA for at least 3 months during the study period.

Outcome

The primary outcome was SARS-CoV-2 infection, based on a documented positive SARS-CoV-2 PCR during the study period. Secondary outcomes included symptomatic COVID-19, at least moderate COVID-19, severe or critical COVID-19, and COVID-19-related death. Severity of COVID-19 was defined based on the National Institute of Health (NIH) COVID-19 severity scale, adjudicated based on an individual chart review of participants with a positive SARS-CoV-2 PCR [1].

Propensity score matching

Propensity scores (PSs) of being treated with UDCA were derived using a parametric method. A multivariable logistic regression predicting UDCA treatment status was estimated with all of the measured covariates included as predictors. Those covariates were the subject's vaccination status (with BNT162b2, mRNA-1273, or a viral vector vaccine) [5, 6], age group [22], sex [23], race/ethnicity [24], alcohol as etiology of liver disease [25, 26], body mass index [27], diabetes mellitus [28], smoking status (either current or former) [29], AUDIT-C score [25, 26], cirrhosis comorbidity index (of no co-morbidities vs. any) [30, 31], hypertension [30], chronic obstructive pulmonary disease [30, 31], electronic Child Turcotte Pugh [32], location [33], and baseline lab results (alanine aminotransferase, platelet count, creatinine, total bilirubin, international normalized ratio, and MELD-Na). Vaccination status was adjusted for receipt of full vaccination, and booster dose. Full vaccination was defined as participants who received at least two doses of an mRNA vaccine or a single dose of the Janssen Ad.26.CoV2.S viral vector vaccine, in accordance with CDC terminology [34]. Patients were considered fully vaccinated 14 days after the second dose of an mRNA or after the single dose of the Janssen viral vector vaccine.

Model diagnostics and *c*-statistics were used to select the PS model. A 1:1 matching using the closest neighbor method with a less that 0.25 caliper was used. The balances of those measured covariates between the UDCA and non-UDCA treatment-matched groups were evaluated using the standardized percent bias. The covariates were considered well balance if the standardized percent bias was within 10%. The Love plot was used to demonstrate the balance statistics.

Statistical analysis

Descriptive statistics were compared between UDCA exposed and unexposed groups before and after PS-matching, and *p*-values were calculated using Wilcoxon tests comparing the median of continuous variables or chi-squared tests for binary and categorical variables.

The associations of exposure to UDCA and SARS-CoV-2 infection, symptomatic, at least moderate, severe, or critical COVID-19, and COVID-19-related death were examined through multivariable conditional logistic regression models. These conditional models account for the within-matched pair differences and were adjusted for covariates that were not well matched in the PS matching, including sex, etiology of liver disease, diabetes mellitus, and cirrhosis comorbidity index. The two groups could not be matched on sex and etiology of liver disease because participants on UDCA were more likely to be female and more likely to have PBC. There were very few participants in the overall and PS-matched cohorts with PBC that were not on UDCA. The predicted probabilities of each outcome for the UDCA and for the non-UDCA groups were estimated from the corresponding conditional logistic regression at the mean values and distribution of the sample.

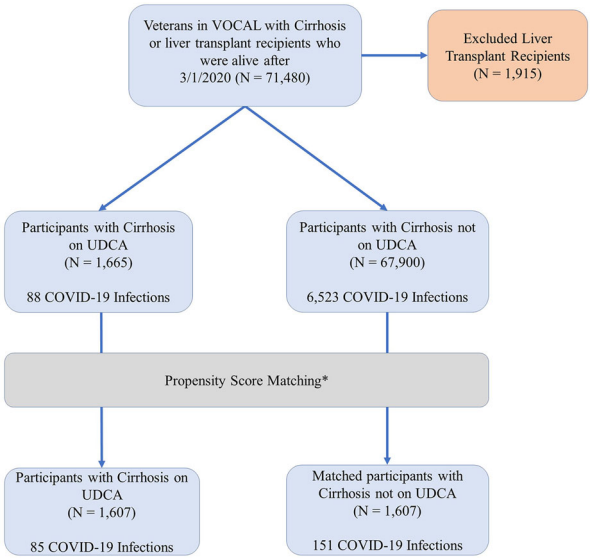

Fig. 1 *Study flowchart.*

We also performed a separate analysis examining the association of the dose of UDCA (in mg/kg body weight) in the multivariable conditional logistic regression model. Additionally, we investigated potential interaction between full vaccination status and UDCA response.

Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SAS statistical software (version 9.4; SAS Institute, Inc).

Results

Participants

We identified 71,480 participants in the VOCAL cohort who were alive at the start of the study period, and 1915 liver transplant recipients were excluded (Fig. 1). Of the 69,565 retained participants with cirrhosis, 1665 were on UDCA during the study period. The overall study participants were predominantly male ($n = 67,161$, 96.5%) and white ($n = 42,416$, 61.0%), with a median age of 62.9 years (interquartile range 10.6), consistent with a veteran population. The most common etiology of liver disease was alcohol (29.4%), followed by nonalcoholic fatty liver disease (NAFLD) (27.3%) and chronic hepatitis C ($n = 16,612$, 23.2%).

Liver diseases other than HCV, NAFLD, cholestatic liver disease, and alcohol were the etiology in 3.3% of the UDCA exposed, and 1.4% of the unexposed participants—these included autoimmune hepatitis, hepatitis B virus infection, hemochromatosis, and cryptogenic cirrhosis.

The majority of participants were vaccinated, with 53.4% ($n = 37,128$) receiving at least two doses of either the Pfizer BNT162b2 or Moderna mRNA-1273 vaccine, 3.1% ($n = 2142$) receiving a single dose of the Janssen Ad26.CoV2.S vaccine.

Participants who had UDCA exposure ($n = 1665$) were younger (62.1 vs. 62.9 years, $p < 0.0001$), less likely to be male (92.4% vs. 96.7%, $p < 0.0001$), smoker (26.5% vs. 31.2%, $p < 0.0001$), have a high AUDIT-C score (7.3% vs. 15.5%, $p < 0.0001$), have compensated cirrhosis (73.9% vs. 83.1%), and more likely to be white (64.3% vs. 60.9%, $p = 0.005$), located in the Northeast (18.4% vs. 15.6%), the Midwest (24.1% vs. 22.7%), be diabetic (56.7% vs. 49.8%, $p < 0.0001$), vaccinated with an mRNA vaccine (57.2% vs. 53.3%), and receive a booster dose (30.2% vs. 24.1%, $p < 0.0001$). Participants exposed to UDCA were more likely to have PBC (4.9% vs. 0.0%) and PSC (2.8% vs. 0.1%) (Table 1).

Of these, 1607 participants with cirrhosis and UDCA exposure were matched 1:1 with 1607 controls with cirrhosis and without UDCA exposure. The UDCA exposed and unexposed participants were well matched in all baseline and clinical characteristics with the exception of sex, liver disease etiology, diabetes, and cirrhosis comorbidity index (Table 1 and Fig. 2).

Indications for UDCA in study participants

A chart review of 777 participants was performed to identify indications for UDCA among study participants. The indications included PBC in 11.3% of participants, PSC in 5.2%, gall stones/sludge in 27.5% (most common among those who were non-candidates for cholecystectomy due to cirrhosis or other comorbidities), abnormal liver enzymes but not meeting diagnostic criteria for PBC or PSC in 25.1%, and other indications (granulomatous hepatitis, post-bariatric surgery, secondary biliary cirrhosis, suspected small duct PSC, and unclear reasons) in 30.9%.

UDCA exposure and COVID-19

The outcomes of SARS-CoV-2 infection were observed in 236 participants in the PS-matched cohort and were lower among participants with

Table 1. *Descriptive statistics for study patients.*

	Full sample			Matched sample		
Variables	UDCA ($N = 1665$)	No UDCA ($N = 67{,}900$)	*p Value*	UDCA ($N = 1607$)	No UDCA ($N = 1607$)	*p Value*
Age (years), median (IQR)	62.1 (11.9)	62.9 (10.5)	**<0.0001**	62.2 (11.9)	61.8 (11.2)	0.9152
Sex, *N* (%)			**<0.0001**			**0.0492**
Male	1538 (92.4%)	65,623 (96.7%)		1493 (92.9%)	1520 (94.6%)	
Female	127 (7.6%)	2277 (3.4%)		114 (7.1%)	87 (5.4%)	
White, *N* (%)	1070 (64.3%)	41,346 (60.9%)	**0.0053**	1030 (64.1%)	1027 (63.9%)	0.9122
Location, *N* (%)			**0.0047**			0.4242
Northeast	307 (18.4%)	10,590 (15.6%)		288 (17.9%)	274 (17.1%)	
Southeast	275 (16.5%)	12,152 (17.9%)		267 (16.6%)	277 (17.2%)	
Midwest	401 (24.1%)	15,439 (22.7%)		394 (24.5%)	410 (25.5%)	
South	352 (21.1%)	14,444 (21.3%)		336 (20.9%)	359 (22.3%)	
Northwest	110 (6.6%)	5318 (7.8%)		107 (6.7%)	83 (5.2%)	
Southwest	220 (13.2%)	9957 (14.7%)		215 (13.4%)	204 (12.7%)	
Etiology			**<0.0001**			**<0.0001**
EtOH	437 (26.3%)	20,006 (29.5%)		425 (26.5%)	427 (26.6%)	
EtOH + HCV	189 (11.4%)	12,527 (18.5%)		181 (11.3%)	264 (16.4%)	
HCV	249 (15.0%)	15,913 (23.4%)		242 (15.1%)	383 (23.8%)	
NAFLD	607 (36.5%)	18,370 (27.1%)		583 (36.3%)	510 (31.7%)	
PBC	81 (4.9%)	15 (0.0%)		78 (4.9%)	0 (0%)	
PSC	47 (2.8%)	88 (0.1%)		46 (2.9%)	2 (0.1%)	
Other	55 (3.3%)	981 (1.4%)		52 (3.2%)	21 (1.3%)	
BMI, median (IQR)	28.2 (8.6)	28.0 (8.2)	0.3104	28.1 (8.5)	28.5 (8.3)	0.7053
Diabetes, *N* (%)	944 (56.7%)	33,821 (49.8%)	**<0.0001**	901 (56.1%)	958 (59.6%)	**0.0417**
Smoker, *N* (%)	441 (26.5%)	21,200 (31.2%)	**<0.0001**	429 (26.7%)	441 (27.4%)	0.6338
AUDIT-C score, *N* (%)			**<0.0001**			0.0647
Low	1543 (92.7%)	57,379 (84.5%)		1487 (92.5%)	1458 (90.7%)	
High	122 (7.3%)	10,521 (15.5%)		120 (7.5%)	149 (9.3%)	
Cirrhosis Comorbidity, *N* (%)			**<0.0001**			**0.0036**
0	216 (13.0%)	7556 (11.1%)		207 (12.9%)	219 (13.6%)	
1 + 0	393 (23.6%)	19,508 (28.7%)		385 (24.0%)	450 (28.0%)	
1 + 1	262 (15.7%)	14,591 (21.5%)		257 (16.0%)	296 (18.4%)	
3 + 0	135 (8.1%)	3922 (5.8%)		126 (7.8%)	114 (7.1%)	
3 + 1	621 (37.3%)	21,103 (31.1%)		595 (37.0%)	499 (31.1%)	
5 + 0	6 (0.4%)	180 (0.3%)		6 (0.4%)	8 (0.5%)	
5 + 1	32 (1.9%)	1040 (1.5%)		31 (1.9%)	21 (1.3%)	
COPD	599 (36.0%)	25,303 (37.3%)	0.2824	581 (36.2%)	541 (33.7%)	0.1388
Hypertension	1536 (92.3%)	63,271 (93.2%)	0.1373	1489 (92.7%)	1473 (91.7%)	0.2938
eCTP Class, *N* (%)			**<0.0001**			0.7160
A	1231 (73.9%)	56,393 (83.1%)		1197 (74.5%)	1177 (73.2%)	
B	377 (22.6%)	10,343 (15.2%)		359 (22.3%)	378 (23.5%)	
C	57 (3.4%)	1164 (1.7%)		51 (3.2%)	52 (3.2%)	

(*Continued*)

Table 1. *(Continued)*

Variables	Full sample UDCA ($N = 1665$)	Full sample No UDCA ($N = 67{,}900$)	*p Value*	Matched sample UDCA ($N = 1607$)	Matched sample No UDCA ($N = 1607$)	*p Value*
Baseline lab results, median (IQR)						
Alanine aminotransferase (IU/mL)	26.0 (22.0)	24.0 (20.0)	0.3681	26.0 (21.0)	25.0 (21.0)	0.8457
Alkaline phosphatase (IU/mL)	113.0 (91.0)	91.3 (53.5)	**<0.0001**	113.0 (89.0)	96.0 (62.0)	**<0.0001**
Platelet count ($\times 10^9$/L)	146.0 (104.8)	158.0 (103.0)	**<0.0001**	147.0 (104.5)	150.0 (105.0)	0.2976
Creatinine (mg/dL)	1.1 (0.6)	1.0 (0.6)	0.4042	1.1 (0.6)	1.1 (0.7)	0.0094
Total bilirubin (mg/dL)	0.9 (1.0)	0.8 (0.7)	**<0.0001**	0.9 (1.0)	0.8 (1.0)	0.3035
International normalized ratio	1.2 (0.3)	1.1 (0.3)	0.7383	1.2 (0.3)	1.2 (0.3)	0.9276
MELD-Na	10.0 (11.0)	9.0 (9.0)	**<0.0001**	10.0 (11.0)	11.0 (11.0)	0.1203
Vaccination, *N* (%)			**0.0030**			
BNT162b2/mRNA-1273 vaccine	952 (57.2%)	36,176 (53.3%)		915 (56.9%)	903 (56.2%)	0.4254
Viral vector vaccine	56 (3.4%)	2086 (3.1%)		55 (3.4%)	44 (2.7%)	
Unvaccinated	657 (39.5%)	29,638 (43.7%)		637 (39.6%)	660 (41.1%)	
Receipt of a booster dose	503 (30.2%)	16,377 (24.1%)	**<0.0001**	478 (29.7%)	476 (29.6%)	0.9384

Note: Etiology of "other" includes autoimmune hepatitis, HBV, cryptogenic, and hemochromatosis.
Bold values signifies $p < 0.05$.
Abbreviations: AUDIT-C: alcohol use disorders identification test-concise; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eCTP, electronic Child Pugh Turcotte; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; IQR, interquartile range; MELD-Na, model for end-stage liver disease adding serum sodium parameter; NA, not available; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

UDCA exposure compared to controls on both unadjusted (5.3% vs. 9.4%, $p < 0.0001$) and adjusted analysis (4.91% vs. 8.79%, $p < 0.0001$) (Fig. 3a,b).

On multivariable analysis, the factors associated with the development of SARS-CoV-2 infection included diabetes mellitus (adjusted odds ratio [aOR] 1.68, 95% confidence interval [CI] 1.26–2.25, $p = 0.0004$), etiology of liver disease other than HCV, alcohol, cholestatic liver disease, or NAFLD (aOR 2.27, 95% CI 1.06–4.86, $p = 0.04$), while receipt of full vaccination was protective (aOR 0.67, 95% CI 0.51–0.87, $p = 0.003$). After adjusting for potential confounders, UDCA exposure was associated with significantly reduced odds of developing SARS-CoV-2 infection (aOR 0.52, 95% CI 0.39–0.70, $p < 0.0001$) (Table 2).

Association of UDCA exposure and varying severities of COVID-19

A total of 179 participants in the PS-matched cohort developed symptomatic COVID-19. Receipt of full vaccination was associated with 33% reduction (aOR 0.67, 95% CI 0.51–0.94, $p = 0.02$), and a cirrhosis comorbidity score of 0 was associated with a 42% reduction in symptomatic COVID-19. Diabetes mellitus (aOR 1.54, 95% CI 1.11–2.14, $p = 0.01$) and etiology of liver disease other than HCV, alcohol, NAFLD, and cholestatic liver

Table 2. *Association of coronavirus disease 2019 (COVID-19) and ursodeoxycholic acid (UDCA) exposure in participants with cirrhosis using conditional logistic regression*

Variable	Any COVID-19	Symptomatic COVID-19	Moderate/severe/critical COVID-19	Severe/critical COVID-19	COVID-19-related death
	aOR (95% CI) *p Value*				
Number of events	236	179	79	39	18
UDCA	0.52 (0.39, 0.70)	0.50 (0.36, 0.69)	0.45 (0.27, 0.75)	0.46 (0.23, 0.93)	0.58 (0.22, 1.54)
	<0.0001	**<0.0001**	**0.0020**	**0.0293**	**0.2730**
Fully vaccinated	0.67 (0.51, 0.87)	0.67 (0.51, 0.93)	0.50 (0.32, 0.80)	0.43 (0.22, 0.84)	0.25 (0.08, 0.76)
	0.0033	**0.0164**	**0.0039**	**0.0141**	**0.0142**
Diabetes	1.68 (1.26, 2.25)	1.54 (1.11, 2.14)	1.60 (0.98, 2.60)	1.38 (0.70, 2.74)	1.73 (0.60, 4.96)
	0.0004	**0.0097**	0.0614	0.3548	0.3085
Circom (none vs. any)	0.63 (0.40, 1.01)	0.58 (0.34, 0.98)	0.40 (0.16, 1.01)	0.31 (0.07, 1.29)	Not estimable
	0.0533	0.0428	0.0522	0.1071	–
Male vs. female	0.81 (0.48, 1.37)	0.71 (0.41, 1.25)	0.98 (0.39, 2.49)	1.25 (0.30, 5.29)	Not estimable
	0.4274	0.2347	0.9732	0.7625	–
Etiology (ref = alcohol)					
Cholestatic liver disease	1.45 (0.68, 3.08)	1.85 (0.82, 4.16)	2.66 (0.93, 7.65)	0.96 (0.12, 7.90)	Not estimable
	0.3365	0.1383	0.0693	0.9678	–
Hepatitis C + alcohol	1.06 (0.69, 1.63)	0.92 (0.55, 1.55)	1.05 (0.52, 2.10)	0.87 (0.32, 2.34)	0.88 (0.16, 4.86)
	0.7875	0.7549	0.9022	0.7809	0.8853
Hepatitis C	1.11 (0.75, 1.64)	1.13 (0.72, 1.78)	0.68 (0.33, 1.42)	0.35 (0.10, 1.26)	0.35 (0.04, 3.18)
	0.6150	0.5840	0.3069	0.1082	0.3526
NAFLD	0.88 (0.61, 1.26)	1.03 (0.68, 1.55)	1.05 (0.59, 1.88)	1.21 (0.56, 2.61)	1.99 (0.61, 6.47)
	0.4771	0.9041	0.8701	0.6345	0.2523
Other	2.27 (1.06, 4.86)	2.85 (1.26, 6.44)	0.77 (0.10, 5.88)	1.56 (0.19, 12.56)	1.38 (0.14, 13.15)
	0.0358	**0.0119**	0.7993	0.6765	0.7813

Note: These adjusted odds ratios were estimated from separate logistic regression models for each of the individual outcomes. Not estimable due to small sample size.
Bold values signifies $p < 0.05$.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Circom: cirrhosis comorbidity index; eCTP, electronic Child Pugh Turcotte; NAFLD, nonalcoholic fatty liver disease.

disease (aOR 2.85, 95% CI 1.26–6.44, $p = 0.01$) were associated with an increased risk of symptomatic COVID-19. After adjusting for potential confounders, UDCA exposure was associated with significantly reduced odds of developing symptomatic COVID-19 (aHR 0.50, 95% CI 0.36–0.69, $p < 0.0001$) (Table 2).

A total of 79 participants developed at least moderate COVID-19. Being fully vaccinated (aOR 0.50, 95% CI 0.32–0.80, $p = 0.004$) was protective against at least moderate COVID-19. After adjusting for potential confounders, UDCA exposure was associated with significantly reduced odds of developing at least moderate COVID-19 (aHR 0.45, 95% CI 0.27–0.75, $p = 0.002$) (Table 2).

During the study period, 39 of the participants in the PS-matched group developed severe or critical COVID-19. Factors associated with severe or critical COVID-19 include being fully vaccinated, which was protective (aOR 0.43, 95% CI 0.22–0.84, $p = 0.01$). After adjusting for potential confounders, UDCA exposure was associated with a significantly reduced odds of developing severe or critical COVID-19 (aHR 0.46, 95% CI 0.23–0.93, $p = 0.01$) (Table 2).

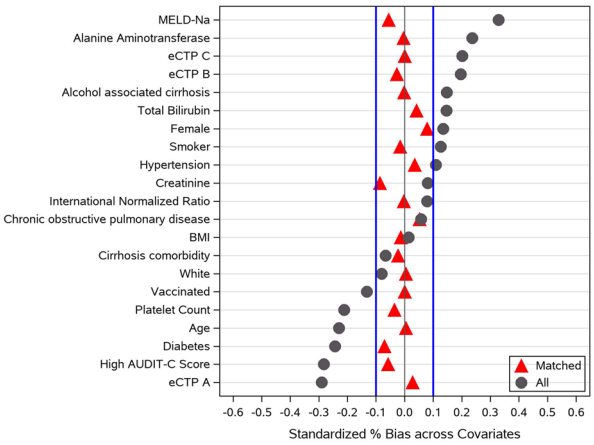

Fig. 2 *Standardized variable differences plot between participants on and not on ursodeoxycholic acid (UDCA), before and after propensity score matching.*

Eighteen participants developed COVID-19-related death, defined as death due to severe or critical COVID-19. Factors that were protective against COVID-19-related death included full vaccination status (aOR 0.25, 95% CI 0.08–0.76, $p = 0.01$). After adjusting for potential confounders, UDCA exposure was not associated with COVID-19-related death (aOR 0.58, 95% CI 0.22–1.54, $p = 0.27$) (Table 2).

A post hoc power analysis revealed that the power to detect statistically significant differences in COVID-19-related death between the two groups was only 31.0%.

We observed no significant interaction observed between UDCA exposure and full vaccination status for any of the outcomes, including SARS-CoV-2 infection ($p = 0.23$), symptomatic COVID-19 ($p = 0.17$) moderate/severe/critical COVID-19 ($p = 0.29$), severe/critical COVID-19 ($p = 0.77$), or COVID-19-related death ($p = 0.13$) (Table S1). This indicates that the associations between UDCA exposure and COVID-19-related outcomes were similar among participants who were fully vaccinated and those who were not.

Dose of UDCA and COVID-19 outcomes

We repeated the above multivariable conditional logistic regression by including the dose of UDCA (in mg of UDCA/kg body weight) in the models (Table 3). We observed that an incremental 5 mg/kg body weight dose of UDCA dose was

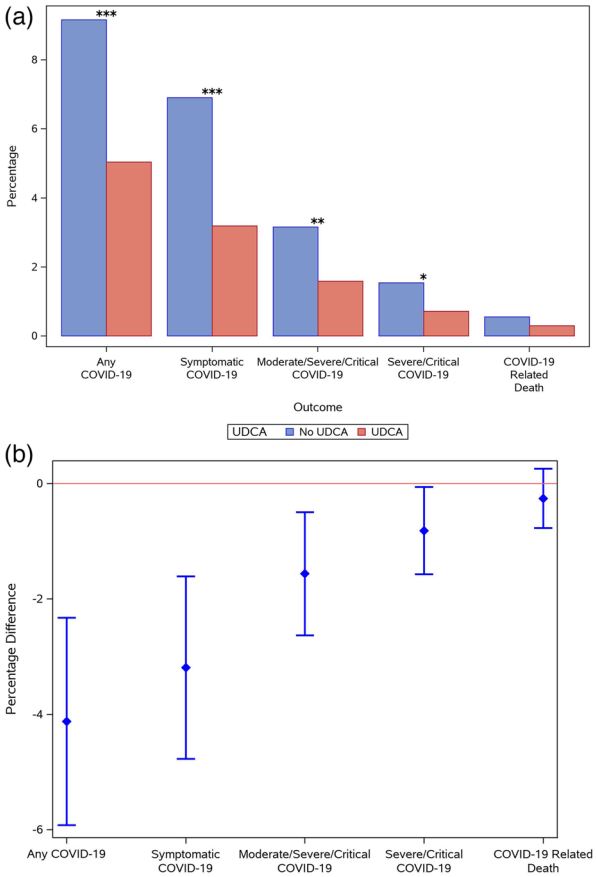

Fig. 3 *(a) Unadjusted distribution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) severities by ursodeoxycholic acid (UDCA) receipt in participants with cirrhosis; (b) adjusted differences (UDCA recipients–nonrecipients) of SARS-CoV-2 infection and COVID-19 severities among participants with cirrhosis.*

associated with a reduction in SARS-CoV-2 infection (aOR 0.83, 95% CI 0.72–0.95, $p = 0.01$), symptomatic COVID-19 (aOR 0.82, 95% CI 0.70–0.95, $p = 0.01$), at least moderate COVID-19 (aOR 0.77, 95% CI 0.61–0.97, $p = 0.03$), but not severe/critical COVID-19 (aOR 0.81, 95% CI 0.59–1.12, $p = 0.20$), or COVID-19-related death (aOR 0.93, 95% CI 0.60–1.44, $p = 0.74$) (Table 3).

Discussion

Our data shows that in a large national cohort of participants with cirrhosis, UDCA exposure is associated with a reduction in the development of SARS-CoV-2 infection as well as symptomatic,

Table 3. *Association of coronavirus disease 2019 (COVID-19) and dose of ursodeoxycholic acid (UDCA) among propensity score matched participants with cirrhosis using conditional logistic regression*

Variable	Any COVID-19	Symptomatic COVID-19	Moderate/severe/critical COVID-19	Severe/critical COVID-19	COVID-19-related death
	aOR (95% CI) *p Value*				
Number of events	236	179	79	39	18
5 mg/kg of UDCA	0.83 (0.72, 0.95)	0.82 (0.70, 0.95)	0.77 (0.61, 0.97)	0.81 (0.59, 1.12)	0.93 (0.60, 1.44)
	0.0054	**0.0099**	**0.0274**	0.2048	0.7438
Fully vaccinated	0.66 (0.50, 0.87)	0.68 (0.50, 0.93)	0.50 (0.31, 0.79)	0.42 (0.22, 0.83)	0.25 (0.08, 0.75)
	0.0026	**0.0140**	**0.0032**	**0.0128**	**0.0139**
Diabetes	1.68 (1.26, 2.25)	1.54 (1.11, 2.14)	1.60 (0.98, 2.61)	1.40 (0.70, 2.76)	1.77 (0.62, 5.07)
	0.0004	**0.0093**	0.0604	0.3397	0.2899
Circom (none vs. any)	0.65 (0.41, 1.02)	0.59 (0.34, 1.00)	0.41 (0.16, 1.03)	0.31 (0.07, 1.33)	Not estimable
	0.0627	**0.0496**	0.0570	0.1147	–
Male vs. female	0.80 (0.47, 1.35)	0.70 (0.40, 1.23)	0.96 (0.38, 2.43)	1.23 (0.29, 5.21)	Not estimable
	0.3682	0.2153	0.9326	0.7776	–
Etiology (ref = alcohol)					
Cholestatic liver disease	1.34 (0.62, 2.86)	1.68 (0.74, 3.81)	2.49 (0.86, 7.23)	0.83 (0.10, 6.88)	Not estimable
	0.4549	0.2137	0.0928	0.8623	–
Hepatitis C + alcohol	1.07 (0.70, 1.65)	0.93 (0.56, 1.57)	1.05 (0.52, 2.12)	0.88 (0.33, 2.38)	0.90 (0.16, 4.98)
	0.7512	0.7928	0.8903	0.8018	0.9066
Hepatitis C	1.13 (0.77, 1.68)	1.17 (0.74, 1.83)	0.70 (0.33, 1.46)	0.36 (0.10, 1.30)	0.36 (0.04, 3.27)
	0.5306	0.5035	0.3364	0.1185	0.3657
NAFLD	0.86 (0.60, 1.24)	1.00 (0.67, 1.51)	1.02 (0.57, 1.83)	1.17 (0.54, 2.53)	1.93 (0.60, 6.26)
	0.4112	0.9865	0.9378	0.6880	0.2734
Other	2.13 (1.00, 4.57)	2.66 (1.18, 6.00)	0.72 (0.09, 5.48)	1.41 (0.18, 11.31)	1.16 (0.12, 11.08)
	0.0514	**0.0183**	0.7477	0.7467	0.8995

Note: These adjusted odds ratios were estimated from separate logistic regression models for each of the individual outcomes. Not estimable due to small sample size.
Bold values signifies $p < 0.05$.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Circom, cirrhosis comorbidity index; NAFLD, nonalcoholic fatty liver disease.

at least moderate, and severe/critical COVID-19. Although evaluation of a VOCAL cohort of liver transplant recipients and a combined US-European cohort from the SECURE-Hep and COVID-Hep registries showed decreased severity of COVID-19 in participants on UDCA, the association of UDCA with a decrease in SARS-CoV-2 infection is novel and were not observed in those cohorts, likely due to the small number of participants on UDCA [14]. Moreover, the larger sample size also provided adequate power to demonstrate a dose response with UDCA, where a 5 mg/kg increase in dose was associated with a reduction in SARS-CoV-2 infection, symptomatic COVID-19, and moderate/severe/critical COVID-19. The findings in this study raise the possibility that UDCA may potentially have a chemopreventive role in COVID-19. Because participants were on UDCA prior to the development of COVID-19, we are unable to demonstrate association between UDCA treatment for COVID-19 and outcomes.

Our data compliments a study, including animal models and human volunteers, which shed light on the biological plausibility of FXR inhibition using UDCA and improved COVID-19-related outcomes. In a small cohort of eight healthy volunteers without liver disease or SARS-CoV-2 infection, it was shown that a standard dose of UDCA at 15 mg/kg/day for 5 days reduces ACE2 levels in the nasal epithelium [14]. Additionally, the COVID-Hep and SECURE-Liver registries were examined for patients with cholestatic liver disease on UDCA and developed COVID-19. A total

of 31 participants on UDCA were identified, compared with 155 PS-matched controls. Receipt of UDCA was associated with reduced hospitalization, ICU admission, and death, after PS matching for sex, age, diabetes, stage of liver disease (Child Turcotte Pugh class), and NAFLD [14]. A second validation cohort examined liver transplant recipients from the VOCAL cohort, comparing 24 participants who received UDCA, with 72 candidates who did not. In this cohort, UDCA exposure was associated with a significant decrease in moderate/severe/critical COVID-19 [14]. However, no differences in rates of SARS-CoV-2 infection or symptomatic COVID-19 were observed. Compared to the two abovementioned studies with small numbers of participants, the current study examined 1607 UDCA exposed and 1607 control participants in a patient population of participants with cirrhosis. The data presented in this manuscript is able to demonstrate that UDCA is associated with a decrease in SARS-CoV-2 infection.

Limitations

This was a retrospective cohort study, and we acknowledge limitations with the study design, including residual confounding. Although we matched participants with and without UDCA exposures for known variables associated with COVID-19 severity, matching cannot fully account for differences between the two groups because almost all participants with PBC are on UDCA. Moreover, gallstone disease was the most common indication for UDCA in this cohort, likely because many participants with cirrhosis were likely noncandidates for cholecystectomy. Therefore, as expected, female sex and cholestatic liver disease were more common in the UDCA group, which persisted after PS matching. However, we adjusted for all variables that were not balanced in the PS-matching in the conditional multivariable logistic regression. Additionally, a retrospective multi-institutional cohort from Spain suggested that participants with PBC may have worse outcomes from COVID-19 [35]. This suggests that the association of UDCA with SARS-CoV-2 infection may be greater than what was demonstrated. Second, the study was underpowered to detect differences in COVID-19-related death. With the widespread use of vaccines, and the effectiveness of vaccination against severe outcomes in cirrhosis, COVID-19-related death has become less common. Despite the large sample size, the power to detect differences in COVID-19-related death in our sample was only 31% because of the low number of COVID-19-related death. Third, the majority of participants on UDCA were for gallstone disease, and for cholestatic liver disease that did not meet criteria for PBC or PSC. Although these are non-traditional indications for UDCA, this reflects its real-world use. We did adjust for abnormal liver enzymes in our PS matching to balance the two groups, but we are unaware of any data to suggest that gallstone disease could serve as a potential confounder. Most importantly, although our findings are hypothesis-generating and supplement data in experimental animal and human models, no recommendations on UDCA use in either the prevention or treatment of COVID-19 can be made in the absence of prospective randomized controlled trials.

Strengths

The strengths of this study include a large national cohort of participants with UDCA exposure, who were matched using PSs to similar participants without UDCA exposure, matched for characteristics associated with the risk of COVID-19, including vaccination status [30, 31]. The sample size likely offered adequate power to demonstrate the association of a decrease in SARS-CoV-2 infection with UDCA, which was not demonstrated in previous cohorts with fewer participants. Outcomes were determined by reviewing the medical records of each participant with SARS-CoV-2 infection using the NIH COVID-19 severity scale, which is superior to hospitalization or ICU admissions, that can occur due to non-COVID-19 reasons in this population. The data may provide useful metrics for sample size calculations to design future clinical trials.

Conclusion

Among patients with cirrhosis, exposure to UDCA is associated with a reduction in the development of SARS-CoV-2 infection. Among participants who developed COVID-19, the preexisting use of UDCA was associated with a reduction in symptomatic COVID-19, at least moderate COVID-19, and severe or critical COVID-19. Although these findings corroborate in vitro and ex vivo data in animal and human experimental models, prospective randomized controlled trials are needed to confirm these findings.

Author contributions

Data curation; formal analysis; investigation; methodology; validation; writing—review and editing: Dustin Bastaich. *Conceptualization; investigation; writing—review and editing*: Gwilym Webb. *Conceptualization; methodology; writing—review and editing*: Teresa Brevini, Marina Serper. *Conceptualization; investigation; methodology; writing—review and editing*: Andrew Moon. *Data curation; investigation; validation; writing—review and editing*: Raphaella D. Ferreira. *Data curation; investigation; writing—review and editing*: Allison M. Chin. *Investigation; methodology; writing—review and editing*: David E. Kaplan. *Investigation; methodology; writing—review and editing*: Tamar H. Taddei. *Investigation; methodology; writing—review and editing*: Nadim Mahmud. *Formal analysis; investigation; methodology; writing—review and editing*: Yangyang Deng. *Project administration; resources; writing—review and editing*: Hann-Hsiang Chao. *Conceptualization; investigation; validation; writing—review and editing*: Fotios Sampaziotis. *Data curation; formal analysis; methodology; software; supervision; writing—review and editing*: Bassam Dahman.

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Conflict of interest statement

None of the authors has personal or financial conflict of interests to declare concerning this publication.

Ethics statement

Approved by the Miami VA Institutional Review Board.

Disclaimer

The authors prepared this work in their personal capacity. The opinions expressed in this article are the author's own and do not reflect the view of the Department of Veterans Affairs or the United States government.

References

1 COVID-19 Treatment Guidelines Panel. *Coronavirus disease 2019 (COVID-19) treatment guidelines*. Bethesda, MD: National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 4/17/22
2 Ge J, Pletcher MJ, Lai JC, N3C Consortium. Outcomes of SARS-CoV-2 infection in patients with chronic liver disease and cirrhosis: a national COVID cohort collaborative study. *Gastroenterology*. 2021;**161**(5):1487–501.e5.
3 *Centers for disease control and prevention COVID-19 data tracker*. Atlanta, GA: Available at https://covid.cdc.gov/covid-data-tracker/ Accessed 11/10/22
4 John BV, Deng Y, Schwartz KB, Taddei TH, Kaplan D, Martin P et al. Post-vaccination COVID-19 infection is associated with reduced mortality in patients with cirrhosis. *Hepatology*. 2022;**76**(1):126–38.
5 John BV, Deng Y, Scheinberg A, Mahmud N, Taddei TH, Kaplan D et al. Association of BNT162b2 mRNA and mRNA-1273 vaccines with COVID-19 infection and hospitalization among patients with cirrhosis. *JAMA Intern Med*. 2021;**181**(10):1306–14.
6 John BV, Sidney Barritt A 4th, Moon A, Taddei TH, Kaplan DE, Dahman B et al. Effectiveness of COVID-19 viral vector Ad.26.COV2.S vaccine and comparison with mRNA vaccines in cirrhosis. *Clin Gastroenterol Hepatol*. 2022;**20**(10):2405–8.e3.
7 Ferreira RD, John BV. Viral vector vaccines are victorious against COVID-19 in patients with cirrhosis. *Dig Dis Sci*. 2023;**68**:349–51
8 John BV, Bastaich DR, Ferreira RD, Doshi A, Taddei TH, Kaplan DE, et al. COVID-19 vaccine effectiveness and community prevalence of alpha, delta and Omicron variants in patients with cirrhosis. *Gut*. 2022. doi: 10.1136/gutjnl-2022-327799. Epub ahead of print.
9 Zampino R, Mele F, Florio LL, Lorenzo B, Roberto A, Maria G, et al. Liver injury in remdesivir-treated COVID-19 patients. *Hepatol Int*. 2020;**14**(5):881–3. https://doi.org/10.1007/s12072-020-10077-3
10 Wong GL, Hui VW, Yip TC, Lui GC, Hui DS, Wong VW. Minimal risk of drug-induced liver injury with molnupiravir and ritonavir-boosted nirmatrelvir. *Gastroenterology*. 2022 17;**164**(1):151–3. S0016-5085(22)01062-9.
11 Fact sheet for healthcare providers: emergency use authorization for PAXLOVID™. https://www.fda.gov/media/155050/download. Acccessed 11/30/22
12 Wang Q, Guo Y, Iketani S, Nair MS, Li Z, Mohri H et al. Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4 and BA.5. *Nature*. 2022;**608**(7923):603–8
13 The COVID-19 Treatment Guidelines Panel's Statement on Omicron Subvariants. Pre-exposure prophylaxis, and therapeutic management of non-hospitalized patients with COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-omicron-subvariants/ Accessed 11/30/22
14 Brevini T, Maes M, Webb GJ, John BV, Gelson ETH, Forrest S, et al. FXR inhibition may protect from SARS-CoV-2 infection by reducing ACE2. *Nature*. 2023;**615**(7950):134–142

15 Achufusi TGO, Safadi AO, Mahabadi N. Ursodeoxycholic acid. [Updated 2022 Jan 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545303/
16 John BV, Khakoo NS, Schwartz KB, Aitchenson G, Levy C, Dahman B et al. Ursodeoxycholic acid response is associated with reduced mortality in primary biliary cholangitis with compensated cirrhosis. *Am J Gastroenterol.* 2021;**116**(9):1913–23
17 John BV, Aitcheson G, Schwartz KB, Khakoo NS, Dahman B, Deng Y, et al. Male sex is associated with higher rates of liver-related mortality in primary biliary cholangitis and cirrhosis. *Hepatology.* 2021;**74**(2):879–1
18 John BV, Schwartz K, Scheinberg AR, Dahman B, Spector S, Deng Y, et al. Evaluation within 30 days of referral for liver transplantation is associated with reduced mortality: a multicenter analysis of patients referred within the VA health system. *Transplantation.* 2022;**106**(1):72–84.
19 John BV, Deng Y, Khakoo NS, Taddei TH, Kaplan DE, Dahman B. Coronavirus disease 2019 vaccination is associated with reduced severe acute respiratory syndrome coronavirus 2 infection and death in liver transplant recipients. *Gastroenterology.* 2021;**162**(2):645–7.e2. S0016-5085(21)03722-7
20 John BV, Ferreira RD, Doshi A, Kaplan DE, Taddei TH, Spector SA, et al. Third dose of COVID-19 mRNA vaccine appears to overcome vaccine hyporesponsiveness in patients with cirrhosis. *J Hepatol.* 2022;**77**(5):1349–58
21 John BV, Doshi A, Ferreira RD, Taddei TH, Kaplan DE, Spector SA, et al. Comparison of infection-induced and vaccine-induced immunity against COVID-19 in patients with cirrhosis. *Hepatology.* 2022;**77**(1):186–96
22 Elkrief A, Hennessy C, Kuderer NM, Samuel MR, Elizabeth W-B, Rachel PR, et al. COVID-19 and cancer consortium. Geriatric risk factors for serious COVID-19 outcomes among older adults with cancer: a cohort study from the COVID-19 and cancer consortium. *Lancet Healthy Longev.* 2022;**3**(3):e143–52
23 Bwire GM. Coronavirus: why men are more vulnerable to Covid-19 than women? *SN Compr Clin Med.* 2020;**2**:1–3
24 Rentsch CT, Kidwai-Khan F, Tate JP, Lesley SP, Joseph TK, Melissa S, et al. Patterns of COVID-19 testing and mortality by race and ethnicity among United States veterans: A nationwide cohort study. *PLoS Med.* 2020;**17**(9):e1003379.
25 Marjot T, Moon AM, Cook JA, Sherief A-E, Costica A, Matthew JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. *J Hepatol.* 2021;**74**(3):567–77.
26 Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of outcomes of COVID-19 in patients with chronic liver disease: US multi-center study. *Clin Gastroenterol Hepatol.* 2021;**19**(7):1469–79.e19
27 Kompaniyets L, Goodman AB, Belay B, David SF, Marissa SS, Samantha JL, et al. Body mass index and risk for COVID-19-related hospitalization, intensive care unit admission, invasive mechanical ventilation, and death – United States, March-December 2020. *MMWR Morb Mortal Wkly Rep.* 2021;**70**(10):355–61.
28 Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: deleterious impact on infected patients. *J Infect Public Health.* 2020;**13**(12):1833–9
29 Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. *Tob Induc Dis.* 2020;**18**:20. doi: 10.18332/tid/119324
30 Ejaz H, Alsrhani A, Zafar A, Humera J, Kashaf J, Abualgasim EA, et al. COVID-19 and comorbidities: deleterious impact on infected patients. *J Infect Public Health.* 2020;**13**(12):1833–9.
31 Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. *Gastroenterology.* 2014;**146**(1):147–e16.
32 Kaplan DE, Dai F, Aytaman A, Michelle B, Rena F, Kristel H, et al. VOCAL study group. Development and performance of an algorithm to estimate the Child-Turcotte-Pugh score from a National Electronic Healthcare Database. *Clin Gastroenterol Hepatol.* 2015;**13**(13):2333–41.
33 COVID data tracker-variant proportions. https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed 11/30/2022
34 Frequently asked questions about COVID-19 vaccination. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html. Accessed 1/24/23
35 Ampuero J, Lucena A, Hernández-Guerra M, Moreno-Moraleda I, Arenas J, Conde I. Primary biliary cholangitis and SARS-CoV-2 infection: incidence, susceptibility and outcomes. *Gut.* 2022;**71**:2138–40

Correspondence: Binu V. John, Division of Gastroenterology and Hepatology, Miami VA Medical System; University of Miami Miller School of Medicine, Miami, Florida, USA.
Email: Binu.John@miami.edu

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Association of COVID-19 and UDCA exposure by vaccination status in participants with Cirrhosis using conditional logistic regression ■