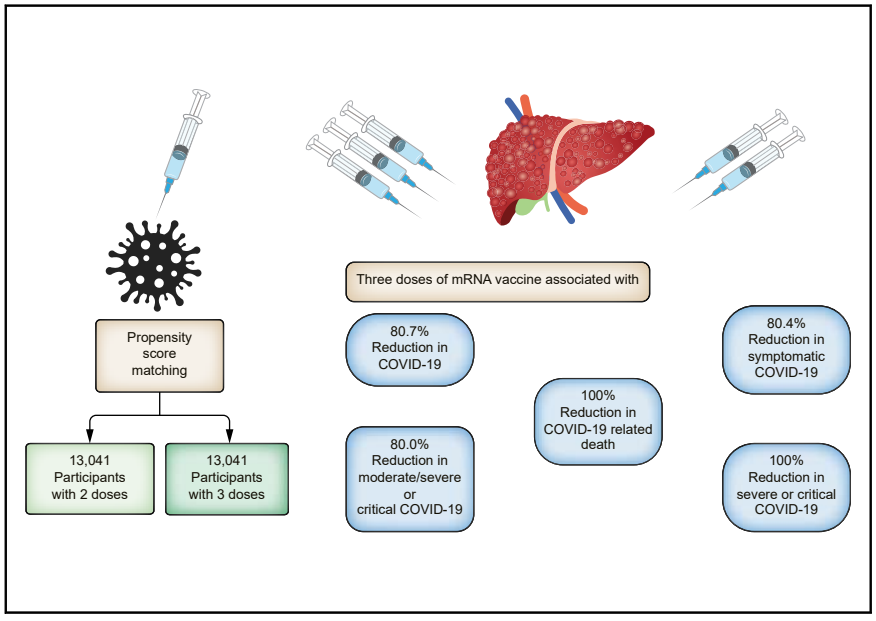
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

Third dose of COVID-19 mRNA vaccine appears to overcome vaccine hyporesponsiveness in patients with cirrhosis

Graphical abstract



Highlights

- Study comparing 3 *vs.* 2 doses of an mRNA vaccine among patients with cirrhosis during the Delta and Omicron surge.
- 3 doses associated with 81% reduction in COVID-19, 100% reduction in severe/critical COVID-19.
- Protection greater in patients with compensated than decompensated cirrhosis.
- 3 doses of the Pfizer BNT162b2 superior to 3 doses of Moderna mRNA-1273 vaccine.

Authors

Binu V. John, Raphaella D. Ferreira, Akash Doshi, …, Yangyang Deng, Dustin Bastaich, Bassam Dahman

Correspondence

Binu.John@miami.edu (B.V. John).

Lay summary

Cirrhosis is associated with decreased responsiveness to several vaccines, including those against COVID-19. In this study of 26,082 participants with cirrhosis during the delta and omicron surge, receipt of the third dose of the vaccine was associated with an 80% reduction in COVID-19, a 100% reduction in severe/critical COVID-19, and a 100% reduction in COVID-19-related death. These findings support the importance of a third dose of mRNA vaccine among patients with cirrhosis.

https://doi.org/10.1016/j.jhep.2022.07.036
Published by Elsevier B.V. on behalf of European Association for the Study of the Liver. J. Hepatol. 2022, 77, 1349–1358

Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

Third dose of COVID-19 mRNA vaccine appears to overcome vaccine hyporesponsiveness in patients with cirrhosis

Binu V. John[1,2,*], Raphaella D. Ferreira[1], Akash Doshi[3], David E. Kaplan[4,5], Tamar H. Taddei[6,7], Seth A. Spector[8,9], Elizabeth Paulus[8,9], Yangyang Deng[10], Dustin Bastaich[10], Bassam Dahman[10]

[1]Division of Gastroenterology and Hepatology, Miami VA Medical System, Miami, FL, USA; [2]Division of Digestive Health and Liver Disease, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA; [3]University of Miami Miller School of Medicine, Miami, FL, USA; [4]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Gastroenterology and Hepatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA; [6]Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, USA; [7]VA Connecticut Healthcare System, West Haven, CT, USA; [8]Department of Surgery, University of Miami Miller School of Medicine, Miami, FL, USA; [9]Department of Surgery, Miami VA Medical System, Miami, FL, USA; [10]Department of Health Behavior and Policy, Virginia Commonwealth University, Richmond, VA, USA

Background & Aims: Cirrhosis is associated with immune dysregulation and hyporesponsiveness to several vaccines including those against COVID-19. Our aim was to compare outcomes between patients with cirrhosis who received 3 doses of either the Pfizer BNT162b2 mRNA or Moderna mRNA-1273 vaccines to a propensity-matched control group of patients at similar risk of infection who received 2 doses.

Methods: This was a retrospective cohort study of patients with cirrhosis who received 2 or 3 doses of a COVID-19 mRNA vaccine at the Veterans Health Administration. Participants who received 3 doses of the vaccine (n = 13,041) were propensity score matched with 13,041 controls who received 2 doses, and studied between July 18, 2021 and February 11, 2022, when B.1.617.2 (delta) and B.1.1.529 (omicron) were the predominant variants. Outcomes were aggregated as all cases with COVID-19, symptomatic COVD-19, with at least moderate COVID-19, or severe or critical COVID-19.

Results: Receipt of the third dose of a COVID-19 mRNA vaccine was associated with an 80.7% reduction in COVID-19 (95% CI 39.2-89.1, p <0.001), an 80.4% reduction in symptomatic COVID-19, an 80% reduction in moderate, severe or critical COVID-19, (95% CI 34.5-87.6%, p = 0.005), a 100% reduction in severe or critical COVID-19 (95% CI 99.2-100.0, p = 0.01), and a 100% reduction in COVID-19-related death (95% CI 99.8-100.0, p = 0.007). The magnitude of reduction in COVID-19 was greater with the third dose of BNT 162b2 than mRNA-1273 and among participants with compensated rather than decompensated cirrhosis.

Conclusions: Administration of a third dose of a COVID-19 mRNA vaccine was associated with a more significant reduction in COVID-19 in patients with cirrhosis than in the general population, suggesting that the third dose can overcome vaccine hyporesponsiveness in this population.

Lay summary: Cirrhosis is associated with decreased responsiveness to several vaccines, including those against COVID-19. In this study of 26,082 participants with cirrhosis during the delta and omicron surge, receipt of the third dose of the vaccine was associated with an 80% reduction in COVID-19, a 100% reduction in severe/critical COVID-19, and a 100% reduction in COVID-19-related death. These findings support the importance of a third dose of mRNA vaccine among patients with cirrhosis.

Introduction

Administration of 2 doses of an mRNA vaccine was associated with decreased immunogenicity, a delayed but modest reduction in COVID-19 infection, and an excellent reduction in COVID-19-related hospitalization or death in patients with cirrhosis early in the pandemic.[1,2] However, since the initial identification of the SARS CoV-2 virus, there have been changes in the prevalence of variants of concern, including the B.1.617.2 (delta) and B.1.1.529 (omicron) variants, resulting in decreased vaccine efficacy in the general population.[3,4] Two mRNA vaccines, the Pfizer BNT 162b2 and the Moderna mRNA-1273 vaccines were approved by the FDA in the United States. Both vaccines were initially approved under emergency use authorization as a 2-dose regimen. Subsequently, the FDA recommended that a third dose of an mRNA vaccine be administered to transplant recipients, patients with malignancies on chemotherapy, and those on immunosuppressive therapies; however, no specific recommendations were made for patients with cirrhosis. Though a third dose of an mRNA vaccine is now recommended for the general adult population in the United States, there is limited data about the additional benefit of a third dose of an mRNA vaccine, compared to 2 doses alone, for patients with cirrhosis.

Cirrhosis is associated with immune dysregulation and vaccine hyporesponsiveness.[5,6] The above, combined with the increased community prevalence of variants of concern, can reduce vaccine effectiveness among patients with cirrhosis. It is unknown whether administering a third dose will enhance the

Keywords: COVID-19 vaccines; booster dose; BNT162b2 mRNA; mRNA-1273; chronic liver disease; hepatic decompensation.
Received 25 March 2022; received in revised form 5 July 2022; accepted 6 July 2022 available online 28 September 2022

* Corresponding author. Address: University of Miami Miller School of Medicine, Chief of Gastroenterology and Hepatology, Miami VA Medical Center, Miami FL 33125, USA. Tel.: (305) 575 3160.
E-mail address: Binu.John@miami.edu (B.V. John).

https://doi.org/10.1016/j.jhep.2022.07.036

effectiveness of COVID-19 vaccination and help overcome the vaccine hyporesponsiveness associated with cirrhosis.

The aim of this study was to determine the association of receipt of a third dose of the BNT162b2 mRNA or 1273-mRNA vaccine with COVID-19, symptomatic COVID-19, and moderate, severe or critical COVID-19 amongst patients with cirrhosis, compared to a propensity-matched group of patients who received only 2 doses.

Patients and methods

Study design

This was a retrospective cohort study using the Veterans Outcomes and Costs Associated with Liver disease (VOCAL) cohort, with over 120,000 well-characterized Veterans with cirrhosis from the Veterans Health Administration corporate data warehouse, based on ICD9-CM or ICD10-CM primary or secondary codes for cirrhosis (ICD9-CM 571.5, ICD10-CM: K70.3x) recorded at 2 outpatient or 1 inpatient encounter(s) between January 2008 and December 2018, with follow-up to February 11th, 2022.[7] Details of COVID-19 vaccine administration, and SARS-CoV-2 infections and clinical course were identified from the Veterans Affairs (VA) COVID-19 shared data resource and individual chart review.[8,9] Institutional review boards at each participating VA medical center approved the study and waived the requirement for informed consent.

Inclusion and exclusion criteria

Eligibility criteria included patients with cirrhosis aged 18 years or older who were alive on the date of the first administration of a COVID-19 mRNA vaccine in the VA (12/18/20). We excluded liver transplant recipients, unvaccinated or partially vaccinated patients, and patients who received a COVID-19 vaccine other than mRNA. This resulted in the retention of participants who received either 2 or 3 doses of the BNT162b2 mRNA or the mRNA-1273 vaccines between December 18, 2020, and February 11th, 2022. Since the earliest date of administration of the third dose of an mRNA vaccine in this cohort was July 18, 2021, and the earliest start of patient follow- up for outcomes was 8/1/2021, the period under study and the outcomes reported in this manuscript had no overlap with studies from the VOCAL cohort published early in the pandemic.[1,8]

Variables

The participants who received 3 doses of an mRNA vaccine were matched to participants who received only 2 doses of an mRNA vaccine on *a priori* selected baseline factors associated with severe COVID-19 infection. These variables included age group (5 categories),[10] sex,[11] race/ethnicity,[12] comorbidities as measured by the cirrhosis comorbidity score (circom),[13,14] hypertension,[13] chronic kidney disease,[13] chronic obstructive pulmonary disease,[13] region of participant location within the United States (Northeast, Southeast, Midwest, South, Northwest, and Southwest),[15] prior documented positive SARS-CoV-2 PCR, the time of receipt of the second dose,[15] alcohol use as measured by the alcohol use disorders identification test-concise (AUDIT-C) scores,[16,17] alcohol-associated liver disease (either alone, or associated with another etiology),[16,17] BMI,[18] current or former smoking status,[19] and severity of liver disease estimated by electronic Child-Turcotte-Pugh (eCTP) score.[16,17,20] Race and ethnicity were self-reported and captured by a 2-question format, and their use was based on data showing the possible association of race with vaccine hesitancy.[12]

Laboratory values for vaccinated patients and controls were obtained from a date closest to the baseline date, which was defined as the receipt of the third dose of the vaccine or the identical matched assigned date for those who received 2 doses. We obtained BMI, and AUDIT-C scores closest to the baseline date. Tobacco use was classified as current use, former use, or lifetime non-use from the corporate data warehouse, and comorbidities were assessed using the circom, which has been validated in patients with cirrhosis.[14] Alcohol-associated cirrhosis was defined using ICD codes, as described and validated in Veterans, and used in the matching based on data showing the etiology of alcohol as a prognostic marker in patients with cirrhosis and COVID-19.[16,17]

According to population-based genomic surveillance data from the Center for Disease Control, the prevalence of the delta variant increased from <10% in April 2021, to >99% in August 2021, and remained the predominant variant in the United States, until the appearance of the omicron variant in December 2021.[21] The omicron variant was identified in all 50 states in the United States by December 2021 and became the predominant variant in January and February 2022.

Outcomes

The baseline date was defined as the date of the third dose of vaccine for those who received 3 doses. Each matched control (who receive 2 doses) was assigned the same baseline date. Outcomes of participants in both groups were assessed, with a positive SARS-CoV-2 PCR starting 14 days after the baseline date, until the end of the study period or death. Outcomes were aggregated as all cases with symptomatic COVD-19, cases with at least moderate COVID-19, or cases of severe, or critical COVID-19. All outcomes were defined based on the chart review of every participant with a positive SARS-CoV-2 PCR. The severity of COVID-19 was defined using WHO definitions as asymptomatic, mild, moderate, severe, or critical COVID-19. COVID-19-related death was defined as death due to COVID-19 within 60 days of the first positive SARS-CoV-2 PCR.

The time to events was calculated from the baseline date to the event.

Statistical analysis

Propensity score matching was used to ensure comparability of the 3 and 2-dose mRNA vaccine groups. Among the above variables used to calculate propensity scores (PS), an exact match on the variables of age group, sex and the month of administration of the second dose of the mRNA vaccine were included. Based on the derived PS scores, a 1:1 PS matching of the 3- and 2-dose vaccine groups was processed using the nearest neighbor greedy matching algorithm.[22] The groups were evaluated after PS matching for covariate balance using the standardized mean differences, with standardized differences of 0.1 or less between variables for participants in the 3- or 2-dose vaccine groups considered acceptable. Descriptive statistics were compared between the 2 groups for both the matched and full samples, and p values were calculated using Wilcoxon tests comparing the median of continuous variables or Chi-squared tests for binary and categorical variables.

Univariable and multivariable Cox proportional-hazards models were fit for the time from 14 days after the receipt of

the third dose (or after assigned date for the 2-dose group) to positive SARS-COV-2 PCR, to assess the adjusted association of receipt of the third dose of vaccine to outcomes. This was controlled for age,[10] race/ethnicity,[12] alcohol as the etiology of liver disease,[17,18] diabetes mellitus,[13] current or former smoking status, circom, and CTP class.

Cumulative incidence curves were estimated for the 3-dose and 2-dose vaccine groups. Patients were censored at death or the end of study (2/11/22). Vaccine efficacy was calculated as 1-adjusted risk ratio; where the adjusted risk ratio is the ratio of risk of a positive SARS CoV-2 PCR among the 3-dose group, relative to the risk after the baseline date among the 2-dose group.

Statistical significance was defined as p <0.05. Statistical analysis was performed using SAS 9.4 (SAS Inc, Cary NC).

Results

Baseline characteristics

Eligibility criteria included patients with cirrhosis aged 18 years or older who were alive on the date of the first administration of a COVID-19 mRNA vaccine in the VA (n = 65,861). Liver transplant recipients (n = 1,923), unvaccinated or partially vaccinated patients (n = 27,090), and patients who received a COVID-19 vaccine other than an mRNA vaccine (n = 366) were excluded. This resulted in 36,482 participants who received either 2 or 3 doses of either the BNT162b2 mRNA or the 1273 mRNA vaccines between December 18, 2020 and February 11th, 2022 (Fig. 1).

We then performed a PS matching, and 14,264 participants with cirrhosis who received 3 doses were matched with 14,264 who received 2 doses. Participants who died after the second dose of the vaccine and before the date of the assigned third dose were excluded (n = 1,223), along with their matched participants in the 3-dose vaccine group. Thus, 13,041 participants in the 3-dose vaccine group and 13,041 participants in the 2-dose vaccine group were included in the final analytic sample (Fig. 1 and Table 1).

The median age of the PS-matched sample was 63.2 years (IQR 10.1). The cohort was predominantly male (96.6%) and white (59.1%); however, a significant proportion (23.6%) was black. The median BMI was 29.3, and 42% of the cohort had alcohol-associated cirrhosis. The mRNA-1273 vaccine was administered in 50.8% (n = 18,723) of the cohort, while the BNT162b2 was administered to 49.2% (n = 17,759) of participants.

In the overall cohort (before PS matching), participants who received 3 doses of an mRNA vaccine were more likely to have received the mRNA-1273 vaccine (51.6% *vs.* 48.5%, p <0.001). There were differences in the geographical distribution of the participants between the 2 groups, as highlighted in Table 1.

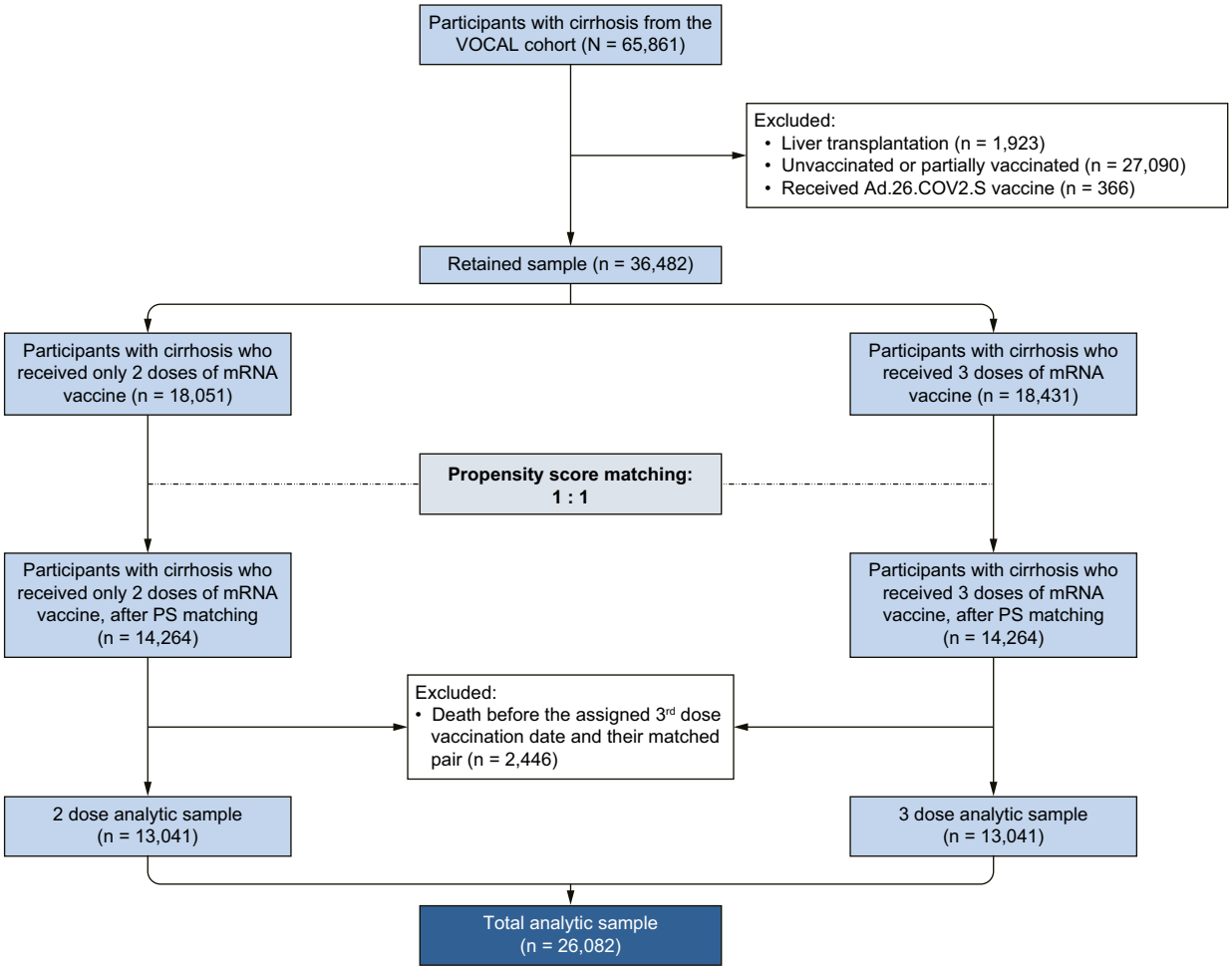


Fig. 1. Study flow chart. PS, propensity score.

Table 1. Descriptive statistics for study patients.

	Before PS matching				After PS matching			
	Full (N = 36,842)	3 Dose (n = 18,431)	2 Dose (n = 18,051)	*p* value	Full (N = 26,082)	3 Dose (n = 13,041)	2 Dose (n = 13,041)	*p* value
Vaccination type, n (%)				<0.0001				**<0.0001**
BNT162b2	17,759	9,306 (51.6%)	8,453 (45.9%)		12,978	6,812 (52.2%)	6,166 (47.3%)	
mRNA-1273	18,723	8,745 (48.5%)	9,978 (54.1%)		13,104	6,229 (47.8%)	6,875 (52.7%)	
Location, n (%)				<0.0001				0.8516
Northeast	6,100	2,743 (15.2%)	3,357 (18.2%)		4,271	2,167 (16.6%)	2,104 (16.1%)	
Southeast	6,271	3,275 (18.1%)	2,996 (16.3%)		4,562	2,262 (17.4%)	2,300 (17.6%)	
Midwest	8,184	3,714 (20.6%)	4,470 (24.3%)		5,743	2,884 (22.1%)	2,859 (21.9%)	
South	7,661	3,986 (22.1%)	3,675 (19.9%)		5,502	2,753 (21.1%)	2,749 (21.1%)	
Northwest	2,797	1,560 (8.6%)	1,237 (6.7%)		2,036	1,002 (7.7%)	1,034 (7.9%)	
Southwest	5,469	2,773 (15.4%)	2,696 (14.6%)		3,968	1,973 (15.1%)	1,995 (15.3%)	
Prior COVID-19 infection, n (%)	1,743	828 (4.5%)	915 (5.1%)	0.0098	1,149	578 (4.4%)	571 (4.4%)	0.8327
Etiology, n (%)				<0.0001				0.1106
Autoimmune hepatitis	61	36 (0.2%)	25 (0.1%)		46	27 (0.2%)	19 (0.2%)	
Alcohol	9,489	4,559 (24.7%)	4,930 (27.3%)		6,690	3,454 (26.5%)	3,236 (24.8%)	
HBV	464	247 (1.3%)	217 (1.2%)		334	177 (1.4%)	157 (1.2%)	
HCV	9,351	4,947 (26.8%)	4,404 (24.4%)		6,778	3,372 (25.9%)	3,406 (26.1%)	
HCV + alcohol	5,838	2,821 (15.3%)	3,017 (16.7%)		4,069	2,036 (15.6%)	2,033 (15.6%)	
HFE	61	38 (0.2%)	23 (0.1%)		41	25 (0.2%)	16 (0.1%)	
NAFLD	11,122	5,726 (31.1%)	5,396 (29.9%)		8,040	3,904 (30.0%)	4,136 (31.7%)	
PBC	37	21 (0.1%)	16 (0.1%)		23	14 (0.1%)	9 (0.1%)	
PSC	59	36 (0.2%)	23 (0.1%)		37	20 (0.2%)	17 (0.1%)	
Sex, n (%)				0.2999				1.0000
Male	35,231	17,414 (96.5%)	17,817 (96.7%)		25,290	12,645 (97%)	12,645 (97%)	
Female	1,251	637 (3.5%)	614 (3.3%)		792	396 (3%)	396 (3%)	
Age (years), median (IQR)	63.2 (10.1)	63.1 (10)	63.1 (9.9)	<0.0001	63.1 (10)	62.8 (10.5)	63.5 (9.7)	0.5698
Race, n (%)				<0.0001				0.8969
White	21,551	11,138 (61.7%)	10,413 (56.5%)		15,659	7,748 (59.4%)	7,911 (60.7%)	
Black	8,661	3,797 (21%)	4,864 (26.4%)		5,917	2,882 (22.1%)	3,035 (23.3%)	
Hispanic/Latino	2,964	1,390 (7.7%)	1,574 (8.5%)		2,103	1,059 (8.1%)	1,044 (8%)	
Other	2,893	1,518 (8.4%)	1,375 (7.5%)		2,108	1,185 (9.1%)	923 (7.1%)	
Unknown	413	208 (1.2%)	205 (1.1%)		295	167 (1.3%)	128 (1%)	
BMI, median (IQR)	29.2 (7.8)	29.3 (7.9)	29.2 (7.6)	<0.0001	29.2 (7.7)	29 (7.9)	29.4 (7.8)	0.4311
Diabetes, n (%)	18,809	8,874 (49.2%)	9,935 (53.9%)	<0.0001	13,294	6,644 (51%)	6,650 (51%)	0.9408
Current smoker, n (%)	23,164	11,557 (64%)	11,607 (63%)	0.0375	16,563	8,257 (63.3%)	8,306 (63.7%)	0.5285
Alcohol, n (%)	15,327	7,947 (44%)	7,380 (40%)	<0.0001	10,773	5,267 (40.4%)	5,506 (42.2%)	0.4027
AUDIT-C score, n (%)				<0.0001				0.1535
Low	28,293	13,668 (75.7%)	14,625 (79.4%)		20,256	10,176 (78%)	10,080 (77.3%)	
High	8,189	4,383 (24.3%)	3,806 (20.7%)		5,826	2,865 (22%)	2,961 (22.7%)	
Cirrhosis comorbidity, n (%)				<0.0001				0.1880
0	3,994	2,023 (11.2%)	1,971 (10.7%)		3,000	1,531 (11.7%)	1,469 (11.3%)	
1+0	8,831	4,645 (25.7%)	4,186 (22.7%)		6,418	3,251 (24.9%)	3,167 (24.3%)	
1+1	9,019	4,557 (25.3%)	4,462 (24.2%)		6,495	3,217 (24.7%)	3,278 (25.1%)	
3+0	1,694	796 (4.4%)	898 (4.9%)		1,235	646 (5%)	589 (4.5%)	
3+1	12,754	5,931 (32.9%)	6,823 (37%)		8,833	4,348 (33.3%)	4,485 (34.4%)	
5+0	21	13 (0.1%)	8 (0%)		9	3 (0%)	6 (0.1%)	
5+1	169	86 (0.5%)	83 (0.5%)		92	45 (0.4%)	47 (0.4%)	
CKD, n (%)	9,019	4,813 (26.1%)	4,206 (23.3%)	<0.0001	6,251	3,175 (24.4%)	3,076 (23.6%)	0.1509
eCTP class, n (%)				<0.0001				0.2119
A	29,678	14,485 (80.2%)	15,193 (82.4%)		21,313	10,746 (82.4%)	10,567 (81%)	
B	6,156	3,223 (17.9%)	2,933 (15.9%)		4,310	2,066 (15.8%)	2,244 (17.2%)	
C	648	343 (1.9%)	305 (1.7%)		459	229 (1.8%)	230 (1.8%)	
Baseline lab results, median (IQR)								
Alanine aminotransferase (IU/ml)	41 (46)	41 (47)	41 (46)	0.2864	41 (47)	40.5 (46.5)	41 (46)	0.6283
Platelet count (x10E9/L)	151 (90.8)	151 (91)	150 (88.3)	0.0125	151 (89.7)	150 (92.9)	152 (88.7)	0.1861
Creatinine (mg/dl)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)	<0.0001	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)	0.8336
Total bilirubin (mg/dl)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)	<0.0001	0.8 (0.6)	0.8 (0.7)	0.8 (0.6)	0.3291
International normalized ratio	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	0.0002	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	0.8155
MELD-Na	8 (5)	8 (5)	8 (5)	<0.0001	8 (5)	8 (5)	8 (5)	0.2247

Statistical method/test applied: Chi-Square test (categorical variables); Wilcoxon median test (continuous variables). Values in bold denote statistical significance (p <0.05). AUDIT-C, alcohol use disorders identification test-concise; CKD, chronic kidney disease; eCTP, electronic Child-Turcotte-Pugh; HFE, hemochromatosis; MELD-Na, model for end-stage liver disease-sodium; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PS, propensity score; PSC, primary sclerosing cholangitis.

Participants who received 3 doses of an mRNA vaccine were more likely to be white (61.7 *vs.* 56.5%), smokers (64 *vs.* 63%, p = 0.04), have alcohol-related liver disease (44.0 *vs.* 40.0, p <0.001), have a high AUDIT-C score (24.3 *vs.* 20.7%, p <0.001), and a higher BMI (29.3 *vs.* 29.2, p <0.001). These patients were also less likely to be black (21.0 *vs.* 26.4%, p <0.001), have a prior SARS CoV-2

infection before the second dose of the mRNA vaccine (4.5 *vs.* 5.1%, $p = 0.01$), to be diabetic (49.2 *vs.* 53.9%, $p < 0.001$), or have CTP A cirrhosis (80.2 *vs.* 82.4%, $p < 0.001$).

Both groups were well balanced after PS matching for all the above variables, and laboratory values, including platelet count, total bilirubin, and international normalized ratio (Table 1, Fig. 2). A history of prior COVID-19 was present in 578 (4.4%) participants in the 3-dose, and 571 (4.4%) in the matched 2-dose arm. For participants with prior COVID-19, the time from initial COVID-19 to the second dose of the mRNA vaccine was similar between the 2 groups (141.0 in the 3-dose *vs.* 150.0, $p = 0.06$). Similarly, the time from initial COVID-19 to the second infection in those who were infected twice was also similar between the 2 groups.

Temporal trends of receipt of the third dose of vaccine and development of COVID-19 among study participants

The earliest administration of the third dose of the mRNA vaccine in the study population was July 18th, 2021. Fig. S1 indicates that the number of third dose administrations to the study participants, increased from 7 in July 2021 (partial month) to a peak of 3,989 in November 2021, and then dropped to 976 in January 2022.

Fig. S2 shows the number of participants who developed COVID-19 during each study week. Since only 7 participants received the third dose in July 2021 (matched with 7 in the 2-dose group), and the outcome of COVID-19 was assessed starting 14 days after the third dose, there were no participants with COVID-19 in the first 8 weeks of the study period. Subsequently, the number of participants who developed COVID-19 in the 2-dose group exceeded that among the 3-dose group in every week except one.

Association of receipt of 3 *vs.* 2 dose BNT162b2 or mRNA-1273 vaccines and COVID-19

A total of 68 participants had a positive SARS-CoV-2 PCR 14 days or more after receiving the third dose (or the assigned 3rd dose among controls). The incidence of a positive SARS-CoV-2 PCR was 0.08% (11 out of 13,041) in the 3-dose group, compared to 0.44% in the 2-dose vaccine group (57 out of 13,041, $p < 0.001$). This translated to an 80.7% reduction in the 3-dose group (95% CI 39.2-89.1, $p < 0.001$). Similar differences were noted with symptomatic COVID-19, with 9 participants developing symptomatic COVID-19 in the 3-dose compared to 46 in the 2-dose group, translating to an 80.4% reduction in the 3-dose group (95% CI 36.8-88.9%, $p < 0.0001$) (Table 2).

The associations with moderate, severe or critical COVID-19 were also similar. Three participants in the 3-dose group fell into this category, compared to 15 in the 2-dose group. This equated to an 80.0% reduction in the 3-dose group (95% CI 34.5-87.6%, $p = 0.005$). No vaccinated individual in the 3-dose group developed severe or critical COVID-19, compared to 7 in the 2-dose group. Receipt of the third dose of an mRNA COVID-19 vaccine was associated with a 100% reduction in severe or critical COVID-19 (95% CI 99.2-100.0, $p = 0.01$).

COVID-19-related death was a rare event in both groups, with only 2 deaths in the 2-dose arm and none among those who received 3 doses. One participant died 207 days after the second dose of the mRNA-1273 and the second 251 days after the second dose of the BNT162b2 vaccine, respectively. Both patients had compensated cirrhosis, were treated with the standard of care at the time of infection (remdesivir and dexamethasone), and died following critical COVID-19. Receipt of the third dose of an mRNA vaccine was associated with a 100% reduced hazard of COVID-19-related death (95% CI 99.8-100.0, $p = 0.007$).

Adjusted analysis

On a multivariable analysis using Cox proportional-hazard models, factors associated with a positive SARS-CoV-2 PCR included race other than non-Hispanic white (adjusted hazard ratio [aHR] 1.51, 95% CI 1.29-1.88, $p = 0.02$). After adjusting for potential confounders, receiving 3 doses of a COVID-19 mRNA vaccine was associated with an 81% reduction in COVID-19 (aHR 0.19, 95% CI 0.10-0.36, $p < 0.001$) compared to participants who received 2 doses (Table 3 and Fig. 3).

Receipt of 3 doses of a COVID-19 mRNA vaccine was also associated with an 81% reduction in symptomatic COVID-19 (aHR 0.19, 95% CI 0.09-0.39, $p < 0.001$), an 80% reduction in moderate, severe or critical COVID-19 (aHR 0.20, 95% CI 0.06-0.70, $p = 0.01$), and a 100% reduction in severe or critical COVID-19 (aHR 0.0, 95% CI 0.0-0.08, $p = 0.01$) compared to participants who received 2 doses (Table 3 and Fig. 3).

Comparison of BNT162b2 *vs.* mRNA-1273 vaccines

To investigate whether the type of mRNA vaccine and the receipt of the third dose is associated with the development of COVID-19 (or varying severities of it), we added to the model an interaction term of vaccine effectiveness by type of vaccine (Table 4). This model demonstrates a statistically significant interaction between vaccine effectiveness of the third dose and the type of vaccine. Therefore, the null hypothesis that the hazard ratios for the BNT162b2 and mRNA-1273 vaccines are similar was rejected (since p value of the interaction term was <0.05).

The receipt of 3 doses of the BNT 162b2 mRNA vaccine was associated with a highly significant 96% reduction in COVID-19 infection (aHR 0.04, 95% CI 0.01-0.27, $p = 0.001$), a 91% reduction in symptomatic COVID-19 (aHR 0.01-0.71, $p = 0.02$), a 100% reduction in moderate, severe or critical COVID-19 (aHR 0.00, 95% CI 0.00-0.04, $p < 0.001$), and a 100% reduction in severe or critical COVID-19 (aHR 0.0, 95% CI 0.00-0.02, $p < 0.001$) compared to participants who received 2 doses (Table 4).

The differences between 3- and 2-dose regimens were less pronounced with the mRNA-1273 vaccine; receiving 3 doses of the mRNA-1273 vaccine was associated with a 61% reduction in COVID-19 (aHR 0.39, 95% CI 0.18-0.84, $p = 0.002$), but not with symptomatic COVID-19 (aHR 0.44, 95% CI 0.16-1.21, $p = 0.11$), or moderate, severe or critical COVID-19 (aHR 0.62, 95% CI 0.11-3.48, $p = 0.58$). However, like the BNT162b2 vaccine, receiving a third dose of the mRNA-1273 vaccine was associated with a 100% reduction in severe or critical COVID-19 (aHR 0.00, 95% CI 0.00-0.07, $p < 0.001$) compared to participants who received 2 doses.

Association of receipt of mRNA vaccine and COVID-19 infections among patients with compensated and decompensated cirrhosis

To investigate whether the association of receipt of the third dose and COVID-19 (or varying severities of it) was different among patients with compensated and decompensated cirrhosis, we added to the model an interaction term of vaccine effectiveness by hepatic compensation status (Table 4). This model demonstrates a statistically significant interaction between vaccine effectiveness of the third dose and hepatic compensation,

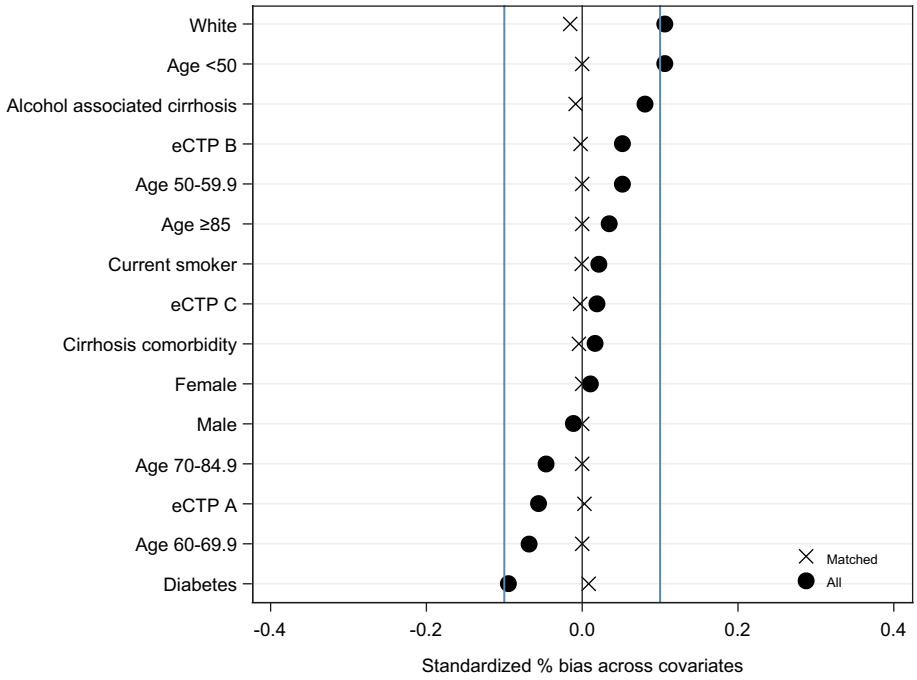


Fig. 2. Standardized variable differences plot between patients who received 3 *vs.* 2 doses of a COVID-19 mRNA vaccine before (o) and after (x) PS matching. Area between the vertical redlines represents the accepted observed standardized bias (-0.1-0.1) between the matched vaccinated and control groups. eCTP, electronic Child-Turcotte-Pugh; PS, propensity score.

and the null hypothesis that the hazard ratios for compensated and decompensated cirrhosis are similar was rejected (since *p* value of the interaction term was <0.05). This supports that vaccine effectiveness between the 3- and 2-dose regimen is different among participants with compensated and decompensated cirrhosis.

Among 21,313 participants with compensated cirrhosis, receipt of the third dose of an mRNA vaccine was associated with a significant reduction in COVID-19 (aHR 0.05, 95% CI 0.01-0.17, *p* <0.0001), symptomatic COVID-19 (aHR 0.08, 95% CI 0.02-0.28, *p* <0.0001), moderate, severe or critical COVID-19 (aHR 0.15, 95% CI 0.06-0.27, *p* <0.0001), and a 100% reduction in severe or critical COVID-19 (aHR 0.0, 95% CI 0.00-0.08, *p* <0.0001) compared to controls (Table 4).

A total of 4,769 participants with decompensated cirrhosis received 3 or 2 doses of a COVID-19 mRNA vaccine. Among

Table 2. Number of participants with COVID-19, and severity of COVID-19, after administration of 3 *vs.* 2 doses of an mRNA vaccine.

BNT162b2/mRNA-1273 Vaccine	3 Dose	2 Dose	Comparative efficacy of 3 Dose *vs.* 2 Dose COVID-19 mRNA vaccine, % (95% CI)	*p* value
COVID-19 infection				
No.	68		80.7 (39.2–89.1)	
Event, no.	11	57		<.0001
No. at risk	13,041	13,041		
Incidence, %	0.08	0.44		
Symptomatic				
No.	55		80.4 (36.8–88.9)	
Event, no.	9	46		<.0001
No. at risk	13,041	13,041		
Incidence, %	0.07	0.35		
Moderate + severe + critical				
No.	18		80.0 (34.5–87.6)	
Event, no.	3	15		0.0047
No. at risk	13,041	13,041		
Incidence, %	0.02	0.12		
Severe + critical				
No.	7		100.00 (99.2–100.0)	
Event, no.	0	7		0.0081
No. at risk	13,041	13,041		
Incidence, %	0.00	0.05		
COVID-19-related death				
No.	2		100.00 (99.8–100.0)	
Event, no.	0	2		0.0072
No. at risk	13,041	13,041		
Incidence, %	0.00	0.02		

Statistical method/test applied: Fisher`s exact test.

Table 3. Predictors of COVID-19 after full vaccination among participants who received 3 *vs.* 2 doses of an mRNA vaccine.

	Number of events		Number of events: COVID-19 severity based on chart review					
	COVID-19		Symptomatic		Moderate + severe + critical		Severe + critical	
	aHR (95% CI)	*p* value	aHR (95% CI)	*p* value	aHR (95% CI)	*p* value	aHR (95% CI)	*p* value
Total number of patients	26,082		26,082		26,082		26,082	
Number of events	68		55		18		7	
2 Dose mRNA vaccine	57 (0.44%)		46 (0.35%)		15 (0.12%)		7 (0.05%)	
3 Dose mRNA vaccine	11 (0.08%)		9 (0.07%)		3 (0.02%)		0 (0.00%)	
Vaccine								
2 Dose mRNA vaccine	REF		REF		REF		REF	
3 Dose mRNA vaccine	0.19 (0.10–0.36)	**<0.0001**	0.19 (0.09–0.39)	**<0.0001**	0.20 (0.06–0.70)	**0.0113**	0.00 (0.00–0.00)	**<0.0001**
Age	1.03 (0.99–1.06)	0.1128	1.02 (0.99–1.06)	0.2007	1.07 (1.02–1.12)	**0.0058**	1.07 (1.01–1.13)	**0.0193**
Race other than non-Hispanic white	1.51 (1.29–1.88)	**0.0150**	1.55 (0.31–2.01)	0.0905	1.35 (0.10–2.20)	0.0946	1.30 (0.35–2.54)	0.2677
Alcohol-associated cirrhosis	1.15 (0.55–1.62)	0.8387	1.13 (0.51–1.70)	0.8131	1.54 (0.18–2.58)	0.2575	1.36 (0.14–2.12)	0.2251
Diabetes	1.30 (0.80–2.11)	0.2852	1.33 (0.77–2.28)	0.3035	2.80 (0.88–8.92)	0.0815	1.98 (0.83–11.81)	0.4546
Current/former smoker	1.84 (0.51–2.37)	0.4774	1.84 (0.49–2.44)	0.5190	1.89 (0.33–2.41)	0.8170	1.83 (0.43–2.61)	0.9667
Cirrhosis comorbidity								
0	REF		REF		REF		REF	
1+0	1.34 (0.11–2.03)	0.0574	1.23 (0.06–1.89)	0.0330	n.a.	n.a.	n.a.	n.a.
1+1	1.78 (0.78–4.06)	0.1696	1.54 (0.65–3.64)	0.3217	2.44 (0.52–11.47)	0.2599	2.35 (0.23–24.37)	0.4736
3+0	1.35 (0.43–4.21)	0.6058	1.56 (0.49–4.98)	0.4558	2.85 (0.45–17.95)	0.2644	1.97 (0.13–30.07)	0.6261
3+1	1.91 (0.40–3.10)	0.8307	1.92 (0.39–3.15)	0.8393	1.09 (0.21–5.70)	0.9227	n.a.	n.a.
eCTP class								
A	REF		REF		REF		REF	
B or C	1.58 (0.88–2.85)	0.1267	1.48 (0.75–2.93)	0.2547	1.04 (0.31–3.49)	0.9468	1.14 (0.34–4.04)	0.9929

Values in bold denote statistical significance.
Statistical method/test applied: Cox proportional-hazards model.
References were: race (non-Hispanic white); no alcohol-associated cirrhosis; no diabetes; non-smoker/former smoker.
aHR, adjusted hazard ratio; eCTP, electronic Child-Turcotte-Pugh.

participants with decompensated cirrhosis, receipt of 3 doses of an mRNA vaccine was not associated with a statistically significant decrease in COVID-19 (aHR 0.30, 95% CI 0.08-1.09, $p = 0.07$) or symptomatic COVID-19 (aHR 0.52, 95% CI 0.10-2.63, $p = 0.43$), but was associated with a 79% reduction in moderate, severe or critical COVID-19 (aHR 0.21, 95% CI 0.09-0.41, $p = 0.0001$), and a 100% reduction in severe or critical COVID-19 among participants with decompensated cirrhosis (aHR 0.00, 95% CI 0.00-0.04, $p < 0.0001$).

Discussion

Due to the limited inclusion of participants with cirrhosis and chronic liver disease in clinical trials, data on the effectiveness of COVID-19 vaccination rely on post-approval real-world data. Our data suggests that receipt of a third dose of an mRNA vaccine is associated with an 80% decrease in overall COVID-19, an 80% decrease in symptomatic COVID-19, and an 80% decrease in moderate, severe or critical COVID-19, with a 100% decrease in severe or critical COVID-19. This decrease is notable, particularly because the comparison group is those who received 2 doses; therefore, the overall decrease in COVID-19 when comparisons are made with unvaccinated or partially vaccinated participants is likely to be even greater. Notably, receiving a third dose of an mRNA vaccine was associated with a 100% reduction in severe or critical COVID-19. Most importantly, only 2 COVID-19-related deaths were noted in the study (both in the 2-dose arm), highlighting the high efficacy of both 2- and 3-dose vaccination in preventing COVID-19-related death in patients with cirrhosis.

Although we did not have healthy individuals to compare in the VOCAL database, the reduction in SARS-CoV-2 infection associated with the third dose in this study is greater than that described in the healthy population. A study by Accorsi *et al.* found that the likelihood of vaccination with 3 mRNA vaccine doses (*vs.* 2 doses) was significantly lower among both omicron (odds ratio, 0.34) and delta (odds ratio, 0.16) cases than in SARS-CoV-2–negative controls.[23] Although not a head-to-head comparison, this suggests that the third dose of the vaccine in cirrhosis exceeds the effectiveness described in the literature among healthy participants and may be able to overcome vaccine hyporesponsiveness in cirrhosis, similar to that observed among recipients of the hepatitis B vaccine.

We observe interesting differences between compensated and decompensated cirrhosis. The third dose of an mRNA vaccine is associated with a highly significant difference in overall and symptomatic COVID-19 in those with compensated cirrhosis. However, the protection associated with the 3-dose regimens was lower among participants with decompensated cirrhosis, probably reflecting the greater degree of vaccine hyporesponsiveness in this population. However, the findings are reassuring in that the third dose was associated with a significant reduction in severe and critical COVID-19 among both patients with compensated and decompensated cirrhosis. Although not a head-to-head comparison, the data suggests that the decrease in COVID-19 with the third dose appears to be greater for the Pfizer BNT 162b2 vaccine than the Moderna mRNA-1273 vaccine. This cannot be explained by the higher effectiveness of a 2-dose regimen of the mRNA-1273 vaccine because the infection rate among participants who received 2 doses of the Pfizer BNT 162b2 was 9.10 per 100 person-month, while that for those who received the Moderna 1273-mRNA vaccine was 11.97 per 100 person-month.[8]

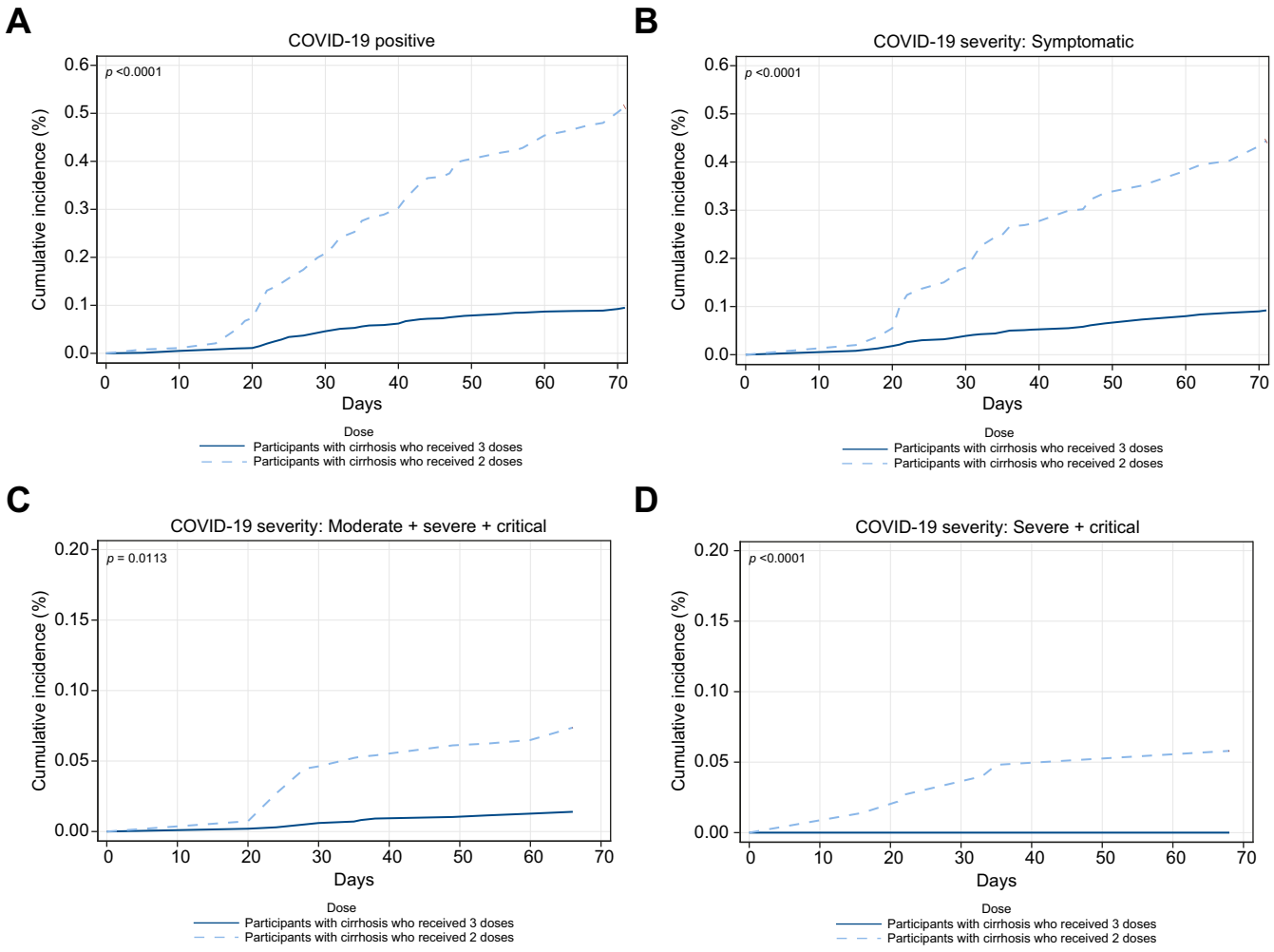


Fig. 3. Adjusted time from the receipt of 3rd dose (or assigned date of 3rd dose) of a COVID-19 mRNA vaccine to a COVID-19-related endpoint. (A) COVID-19 infection, (B) symptomatic COVID-19, (C) moderate, severe, or critical COVID-19, (D) severe or critical COVID-19 in participants with cirrhosis. Statistical method/test applied: Cox proportional-hazards model (with interaction terms).

Our data add to the growing body of literature on COVID-19 vaccines in chronic liver disease.[1,2,24,25] Although patients with cirrhosis and liver transplant recipients do not consistently generate antibodies to spike protein, the real-world efficacy appears to be higher, suggesting a potential role of T cell-mediated responses.[2,9]

The data also supports recommendations from experts and liver societies on vaccinating patients with cirrhosis.[26–28]

We acknowledge the following limitations of our observational study. First, the study may be affected by residual confounding due to differences between participants who received 3 *vs.* 2 doses, especially regarding the differential risk of COVID-19 exposure. Second, while our study was able to capture data on vaccine administration outside the VA system, this could be incomplete. It is also possible that patients were diagnosed with COVID-19 outside the VA system. Since we included only patients who were actively engaged with VA care, we believe that the likelihood of these events would be low and similar among the 2 groups. A third limitation is that our Veteran cohort is limited in the proportion of females; however, no sex-based differences in vaccine efficacy have been described. Fourth, though the VOCAL cohort has been well characterized, participants may have unrecognized comorbidities, including exposure to immunosuppressive drugs, that were not captured using ICD codes. Fifth, we acknowledge the lack of measurement of anti-spike antibodies or T-cell response to COVID-19. Sixth, while mRNA vaccines have been predominantly administered in the West, most participants in developing countries have received viral vector vaccines that have demonstrated effectiveness in patients with cirrhosis.[29] Because we excluded participants who received the Janssen Ad.26.COV2.S vaccine, we cannot make recommendations regarding boosters after viral vector vaccines. Finally, because of the recent introduction of the third dose of the vaccine, we had a relatively short follow-up. A longer follow-up is needed to assess if this association is sustained for the omicron BA.5 variant, which has limited cross-reactivity to prior strains, and whether additional COVID-19 mRNA vaccine boosters are needed in the future.

The data we present also has relative strengths. This is a large cohort of participants with cirrhosis who have been well characterized. By assigning a date of the third dose to each matched participant in the 2-dose arm and including the date of receipt of the second dose and patient location in the PS matching, the study was able to balance the exposure of participants in the 2

Table 4. Adjusted hazard ratio of COVID-19 infection after full vaccination among those who received 3 *vs.* 2 doses by type of vaccine (BNT162b2/mRNA-1273) and by compensation status.

		Number of events		Number of events: COVID-19 severity based on chart review					
		COVID-19		Symptomatic		Moderate + severe + critical		Severe + critical	
Total number of patients		**26,082**		**26,082**		**26,082**		**26,082**	
Number of events		**68**		**55**		**18**		**7**	
		aHR (95% CI)	***p* value**	**aHR (95% CI)**	***p* value**	**aHR (95% CI)**	***p* value**	**aHR (95% CI)**	***p* value**
Compensated cirrhosis									
3 Dose mRNA vaccine	HR1	0.05 (0.01,0.17)	**<0.0001**	REF		REF		REF	
2 Dose mRNA vaccine		REF		0.08 (0.02,0.28)	**<0.0001**	0.15 (0.06,0.27)	**<0.0001**	0.00 (0.00,0.08)	**<0.0001**
Decompensated cirrhosis									
3 Dose mRNA vaccine	HR2	0.30 (0.08,1.09)	0.0672	0.52 (0.10,2.63)	0.4316	0.21 (0.09,0.41)	**<.0001**	0.00 (0.00,0.04)	**<.0001**
2 Dose mRNA vaccine		REF		REF		REF		REF	
Null hypothesis: HR1 = HR2		***p* = 0.0110**		***p* = 0.0377**		*p* = 0.2066		***p* <0.0001**	
		aHR (95% CI)	***p* value**	**aHR (95% CI)**	***p* value**	**aHR (95% CI)**	***p* value**	**aHR (95% CI)**	***p* value**
Vaccination: BNT162b2									
2 Dose mRNA vaccine		REF		REF		REF		REF	
3 Dose mRNA vaccine	HR3	0.04 (0.01,0.27)	**0.0011**	0.09 (0.01,0.71)	**0.0217**	0.00 (0.00,0.06)	**<0.0001**	0.00 (0.00,0.03)	**<0.0001**
Vaccination: mRNA-1273									
2 Dose mRNA vaccine		REF		REF		REF		REF	
3 Dose mRNA vaccine	HR4	0.39 (0.18,0.84)	**0.0163**	0.44 (0.16,1.21)	0.1125	0.62 (0.11,3.48)	0.5849	0.00 (0.00,0.08)	**<0.0001**
Null hypothesis: HR3 = HR4		***p* = 0.0308**		*p* = 0.1713		***p* <0.0001**		*p* = 0.9559	

Values in bold denote statistical significance.
Statistical method/test applied: Cox proportional-hazards model (with interaction terms).
HR1: aHR of 3 doses *vs.* 2 doses for patients with compensated cirrhosis.
HR2: aHR of 3 doses *vs.* 2 doses for patients with decompensated cirrhosis.
HR3: aHR of 3 doses *vs.* 2 doses for patients who received BNT162b2.
HR4: aHR of 3 doses *vs.* 2 doses for patients who received mRNA-1273.
aHR, adjusted hazard ratio.

arms to similar variants and ensure similar follow-up time. The study sample was more diverse, with a higher proportion of black individuals (23%). The study was performed at a point in time where there were comparable numbers of participants in the 3- and 2-dose groups and when the community prevalence of variants of concern including the B.1.617.2 (delta) and B.1.1.529 (omicron) variants, were high.

In summary, our findings show that the receipt of the third dose of either the BNT162b2 mRNA or the mRNA-1273 vaccines is associated with an 80% decrease in the development of COVID-19, symptomatic COVID-19, and moderate, severe or critical COVID-19, and a 100% reduction in severe or critical COVID-19 and COVID-19-related death, compared to participants with cirrhosis who received only 2 doses. These findings support recommendations for administering the third dose of an mRNA COVID-19 vaccine in patients with cirrhosis and suggest that a third dose can overcome the vaccine hyporesponsiveness in these patients.

Abbreviations

aHR, adjusted hazard ratio; AUDIT-C, alcohol use disorders identification test-concise; Circom, cirrhosis comorbidity index; eCTP, electronic Child-Turcotte-Pugh; PS, propensity score; VA, Veterans Affairs; VOCAL, Veterans Outcomes and Costs Associated with Liver disease.

Financial support

Services supporting this analysis and interpretation of the data of this research project were generated by the VCU Massey Cancer Center Biostatistics Shared Resource, supported, in part, with funding from NIH-NCI Cancer Center Support Grant P30 CA016059.

Conflict of interest

Dr John received institutional research support from BMS, Exelixis, Exact Sciences, GSK, Glycotest, Inc, H3B biosciences, Viking therapeutics. Dr Kaplan received institutional research support from Gilead Sciences, Glycotest, Inc, Astra Zeneca, Bayer and Exact Sciences. None of the other authors have personal or financial conflicts of interests to declare concerning this publication.

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

Authors' contributions

Binu V. John and Bassam Dahman had full access to all the data in the study and are responsible for the integrity of the data and the accuracy of the data analysis. Concept and design: John. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: John, Dahman. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: John, Deng, and Dahman. Obtained funding: John, Dahman. Administrative, technical, or material support: All authors. Supervision: John, Dahman.

Data availability statement

The United States Department of Veterans Affairs (VA) places legal restrictions on access to Veterans' healthcare data, which includes both identifying data and sensitive patient information. The analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement. This limitation is consistent with other studies based on VA data. However, VA data are freely available to researchers behind the VA firewall with an approved VA study protocol. For more

information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center (VIReC) at Virec@Va.gov.

Acknowledgment
We acknowledge data and support from the VA COVID-19 shared data resource.

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.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.036.

References
[1] 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 Oct 1;181(10):1306–1314.
[2] Thuluvath PJ, Robarts P, Chauhan M. Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases. J Hepatol 2021 Dec;75(6):1434–1439.
[3] Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta KD, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nat Med 2021;27:2127–2135.
[4] Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. N Engl J Med 2021 Dec 9;385(24):e83.
[5] McCashland TM, Preheim LC, Gentry MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. J Infect Dis 2000;181:757–760.
[6] Aggeletopoulou I, Davoulou P, Konstantakis C, Thomopoulos K, Triantos C. Response to hepatitis B vaccination in patients with liver cirrhosis. Rev Med Virol 2017 Nov;27(6).
[7] 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 Aug;74(2):879–891.
[8] John BV, Deng Y, Schwartz KB, Taddei TH, Kaplan DE, Martin P, et al. Postvaccination COVID-19 infection is associated with reduced mortality in patients with cirrhosis. Hepatology 2022 Jul;76(1):126–138.
[9] 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 Nov 7. S0016-5085(21)03722-03727.
[10] Davies NG, Klepac P, Liu Y, Prem K, Jit M, CMMID COVID-19 working group, Eggo RM. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020 Aug;26(8):1205–1211.
[11] Bwire GM. Coronavirus: why men are more vulnerable to covid-19 than women? SN Compr Clin Med 2020:1–3.
[12] Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King Jr JT, Skanderson M, 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.
[13] 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):1833–1839.
[14] Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. Gastroenterology 2014;146(1). 147-e16.
[15] Galloway SE, Paul P, MacCannell DR, Johansson MA, Brooks JT, MacNeil A, et al. Emergence of SARS-CoV-2 B.1.1.7 Lineage - United States, December 29, 2020-January 12, 2021. MMWR Morb Mortal Wkly Rep 2021 Jan 22;70(3):95–99.
[16] Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. J Hepatol 2021;74(3):567–577.
[17] 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 multicenter study. Clin Gastroenterol Hepatol 2021 Jul;19(7):1469–1479.e19.
[18] Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucosky MS, Lange SJ, 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 Mar 12;70(10):355–361.
[19] Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis 2020 Mar 20;18:20. https://doi.org/10.18332/tid/119324.
[20] Kaplan DE, Dai F, Aytaman A, Baytarian M, Fox R, Hunt K, 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 Dec;13(13):2333–2341.
[21] COVID data tracker-Variant proportions. https://covid.cdc.gov/covid-data-tracker/#variant-proportions Accessed 5/14/22.
[22] Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci 2010 Feb 1;25(1):1–21.
[23] Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 Omicron and Delta variants. JAMA 2022 Feb 15;327(7):639–651.
[24] Ruether DF, Schaub GM, Duengelhoef PM, Haag F, Brehm TT, Fathi A, et al. SARS-CoV2-specific humoral and T-cell immune response after second vaccination in liver cirrhosis and transplant patients. Clin Gastroenterol Hepatol 2022 Jan;20(1):162–172.e9.
[25] Wang J, Hou Z, Liu J, Gu Y, Wu Y, Chen Z, et al. Safety and immunogenicity of COVID-19 vaccination in patients with non-alcoholic fatty liver disease (CHESS2101): a multicenter study. J Hepatol 2021 Aug;75(2):439–441.
[26] Fix OK, Blumberg EA, Chang KM, Chu J, Chung RT, Goacher EK, et al., AASLD COVID-19 Vaccine Working Group. American Association for the Study of Liver Diseases expert panel consensus statement: vaccines to prevent coronavirus disease 2019 infection in patients with liver disease. Hepatology 2021 Aug;74(2):1049–1064.
[27] Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. J Hepatol 2021 Apr;74(4):944–951.
[28] Marjot T, Webb GJ, Barritt AS, Ginès P, Lohse AW, Moon AM, et al. SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question. Lancet Gastroenterol Hepatol 2021;6(3):156–158.
[29] John BV, Barritt 4th AS, Moon A, Taddei TH, Kaplan DE, Dahman B, Contributors as part of the VOCAL COVID-19 investigators, Doshi A, Deng Y, Mansour N, Ioannou G, Martin P, Chao HH. Effectiveness of COVID-19 viral vector Ad.26.COV2.S vaccine and comparison with mRNA vaccines in cirrhosis. Clin Gastroenterol Hepatol 2022 Jun 15. https://doi.org/10.1016/j.cgh.2022.05.038. S1542-3565(22)00566-3.