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Association of BNT162b2 mRNA and mRNA-1273 Vaccines With COVID-19 Infection and Hospitalization Among Patients With Cirrhosis

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IMPORTANCE Two mRNA-based vaccines against coronavirus disease 2019 (COVID-19) were found to be highly efficacious in phase 3 clinical trials in the US. However, patients with chronic illnesses, including cirrhosis, were excluded from clinical trials. Patients with cirrhosis have immune dysregulation that is associated with vaccine hyporesponsiveness.

OBJECTIVE To study the association of receipt of the Pfizer BNT162b2 mRNA or the Moderna mRNA-1273 vaccines in patients with cirrhosis compared with a propensity-matched control group of patients at similar risk of infection and severe disease from COVID-19.

DESIGN, SETTING, AND PARTICIPANTS We performed a retrospective cohort study of patients with cirrhosis who received at least 1 dose of a COVID-19 mRNA vaccine at the Veterans Health Administration. Patients who received at least 1 dose of the vaccine (n = 20 037) were propensity matched with 20 037 controls to assess the associations of vaccination with new COVID-19 infection and COVID-19 hospitalization and death.

EXPOSURES Receipt of at least 1 dose of the BNT162b2 mRNA or the mRNA-1273 vaccines between December 18, 2020, and March 17, 2021.

MAIN OUTCOMES AND MEASURES COVID-19 infection as documented by a positive result for COVID-19 by polymerase chain reaction, hospitalization, and death due to COVID-19 infection.

RESULTS The median (interquartile range) age of the vaccinated individuals in the study cohort was 69.1 (8.4) years and 19 465 (97.2%) of the participants in each of the vaccinated and unvaccinated groups were male, consistent with a US veteran population. The mRNA-1273 vaccine was administered in 10 236 (51%) and the BNT162b2 mRNA in 9801 (49%) patients. Approximately 99.7% of patients who received the first dose of either vaccine with a follow-up of 42 days or more received a second dose. The number of COVID-19 infections in the vaccine recipients was similar to the control group in days 0 to 7, 7 to 14, 14 to 21, and 21 to 28 after the first dose. After 28 days, receipt of 1 dose of an mRNA vaccine was associated with a 64.8% reduction in COVID-19 infections and 100% protection against hospitalization or death due to COVID-19 infection. The association of reduced COVID-19 infections after the first dose was lower among patients with decompensated (50.3%) compared with compensated cirrhosis (66.8%). Receipt of a second dose was associated with a 78.6% reduction in COVID-19 infections and 100% reduction in COVID-19–related hospitalization or death after 7 days.

CONCLUSIONS AND RELEVANCE This cohort study of US veterans found that mRNA vaccine administration was associated with a delayed but modest reduction in COVID-19 infection but an excellent reduction in COVID-19–related hospitalization or death in patients with cirrhosis.

Supplemental content

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The emergency use authorization (EUA) of 2 mRNA-based vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) heralded a rapid nationwide rollout to slow down the surge of coronavirus disease 2019 (COVID-19) infections. These vaccines have been highly effective in phase 3 clinical trials, offering recipients 94% to 95% protection from infection.[1,2] However, stringent exclusion criteria excluded many individuals with chronic liver disease. For example, the phase 3 trial of the Pfizer BNT162b2 mRNA vaccine against COVID-19 excluded individuals with an anticipated need for immunosuppression, and those with active hepatitis B or C infection.[1] Only 217 (0.6%) of participants had liver disease, with just 3 (<0.01%) with moderate-to-severe liver disease.[3] A similarly low proportion of patients with liver disease were included in the Moderna mRNA-1273 trial with only 196 (0.6%) with liver disease.[2,3]

Patients with cirrhosis have immune dysregulation that is associated with vaccine hyporesponsiveness.[4,5] Therefore, the efficacy of the vaccine in patients with cirrhosis, particularly decompensated cirrhosis, is a significant knowledge gap. Moreover, randomized clinical trials occur in a controlled setting that may not be replicated in a mass vaccination campaign. Patients who are eligible to receive vaccines may experience a delay in the receipt of the second dose. Guidelines recommending COVID-19 vaccination for patients with cirrhosis was based on expert opinion rather than clinical data.[6]

This study aimed to determine the association of receipt of the BNT162b2 mRNA or mRNA-1273 vaccines and COVID-19 infections, hospitalization, and death in patients with cirrhosis compared with a propensity-matched control group of patients at similar risk of infection and severe disease from COVID-19.

Key Points

Question Are COVID-19 mRNA vaccines associated with decrease in COVID-19 infections and death in a real-world setting among patients with cirrhosis of the liver?

Findings In this retrospective cohort study of US veterans with cirrhosis that compared 20 037 patients who received either a Pfizer BNT162b2 mRNA or a Moderna mRNA-1273 COVID-19 vaccine with 20 037 propensity score matched controls, receipt of 1 dose of either vaccine was associated with a 64.8% reduction in COVID-19 infections and 100% reduction in hospitalization or death due to COVID-19 infection after 28 days.

Meaning This cohort study found that mRNA vaccines against COVID-19 were associated with reduced COVID-19 infections in individuals with cirrhosis, despite hyporesponsiveness to other vaccines.

Methods

Study Design

This was a retrospective cohort study using national data from the Veterans Outcomes and Costs Associated with Liver disease (VOCAL) cohort, which consists of over 120 000 Veterans with cirrhosis obtained from the Veterans Health Administration (VHA), and Corporate Data Warehouse (CDW) based on *International Classification of Diseases, Ninth Revision, Clinical Modification (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 March 17, 2021.[7] Dates and type of COVID-19 vaccine administered were identified from the US Department of Veterans Affairs (VA) COVID-19 shared data resource. Institutional review boards at each participating VA medical center approved the study and waived requirement for informed consent.

Inclusion and Exclusion Criteria

Eligibility criteria included patients with cirrhosis aged 18 years or older who received either the BNT162b2 mRNA or the mRNA-1273 vaccines from December 18, 2020, until March 17, 2021. We excluded patients who were not engaged with care in the VA system in the 1 year prior to vaccine availability, those with a history of COVID-19 infection, and those who received a liver transplant or died before the vaccine became available.

Variables

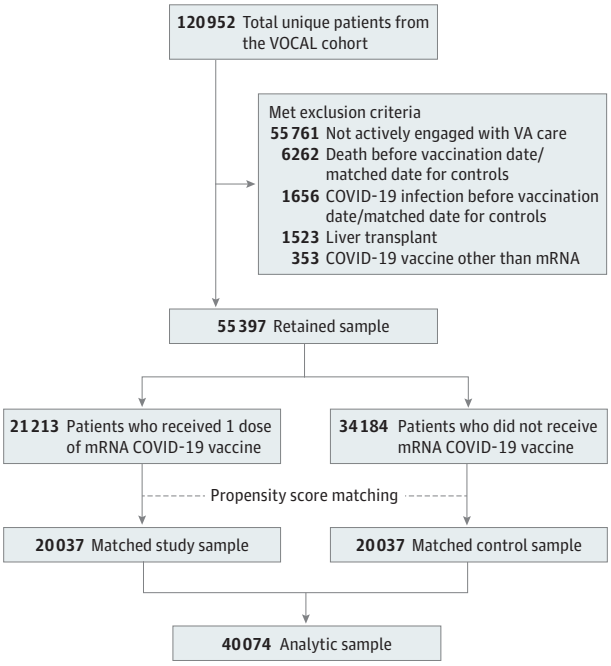
The date of vaccine availability at VA (December 18, 2020) was chosen as the baseline date. The vaccine recipients were matched with controls on a priori–selected baseline factors associated with severe COVID-19 infection, including age group (5 categories),[8] sex,[9] race or ethnicity,[10] duration of follow-up, comorbidities,[11] alcohol-associated liver disease (either alone, or associated with another etiology),[12] and severity of liver disease estimated by Child-Turcotte-Pugh (CTP) score.[12] Race and ethnicity were self-reported and captured by a 2-question format, and its use was based on data showing that severe COVID-19 was more common in Black patients and because of the possible association of race with vaccine hesitancy.[10]

Laboratory values for vaccinated patients and controls were obtained from a date closest to the baseline date (within 90 days). We obtained body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), Alcohol Use Disorders Identification Test-Concise (AUDIT-C) scores, and tobacco use (classified as current use, former use, or lifetime nonuse) from the CDW, closest to the date of vaccine availability. Comorbidities and severity of liver disease were assessed using the previously validated Cirrhosis Comorbidity Index and electronic CTP (eCTP) scores, respectively.[13,14] Alcohol-associated cirrhosis was defined using *ICD* codes, as previously described and validated in a US veteran population.[15]

Outcomes

Index date was defined as the date of vaccination for the vaccinated participants. Each control was assigned the same index date of the vaccinated matched participant. We assessed the association of the receipt of 1 or 2 doses of the vaccine and COVID-19 infection, as well as hospitalization or death related to COVID-19 infection.

Figure 1. Study Flowchart



VA Indicates the US Department of Veterans Affairs; VOCAL, Veterans Outcomes and Costs Associated with Liver disease.

The primary outcome was COVID-19 infection as documented by a positive COVID-19 result by polymerase chain reaction (PCR) assay 28 days after the first dose of either the BNT162b2 mRNA or the mRNA-1273 vaccine. This cutoff was chosen because the benefit of a single dose of both mRNA vaccines were anticipated by this time point. Secondary outcomes included COVID-19 infection as documented by a positive COVID-19 result by PCR 7 days after the second dose of either vaccine, hospitalization, or death from SARS-CoV2 infection 28 days after the first dose of either the BNT162b2 mRNA or mRNA-1273 vaccine, or after 7 days of the second dose of either vaccine.

Outcomes were validated by medical chart review for all patients who developed a positive COVID-19 result by PCR during the study period, to confirm the date of infection, and reason for hospitalization or death. The time to events was calculated as the number of days from index date to the date of the event.

Statistical Analysis

Propensity score (PS) matching was used to ensure comparability of the vaccinated sample to the unvaccinated sample. The propensity score was calculated as the probability of being vaccinated by regressing vaccinated on the baseline characteristics (age at the baseline date, age group, sex, race, alcohol use, BMI at baseline date, BMI class, diabetes, smoking history, AUDIT-C, CirCom, eCTP, and MELD-Na). Patients were matched exactly by (age group, sex, race, alcohol use, eCTP, and cirrhosis comorbidity score) and the Greedy method was used to select the nearest PS neighbor among the possible exactly matched patients. The 2 groups were evaluated after PS matching for covariate balance using the standardized mean differences, and the comparison was presented using Love plots. Standardized differences of 0.1 or less between variables for vaccinated and unvaccinated groups were considered acceptable. Descriptive statistics were compared between the vaccinated and unvaccinated matched and full samples, and *P* values were calculated using *t* tests comparing means of continuous variables, Brown-Mood test to compare the medians, or χ^2 tests for binary and categorical variables.

Cox proportional hazards models were fit for time to COVID-19 infection or COVID-19–related death of the matched pairs. Unadjusted and adjusted hazard ratios controlling for potential baseline confounders were estimated. Cumulative incidence curves were estimated for the vaccine and control groups.[8,12,16,17] Patients were censored at end of study (March 17, 2021).

The vaccine efficacy was calculated as 1 minus risk ratio; where risk ratio is the ratio of risk after 28 days among vaccinated to risk after 28 days among unvaccinated.

Statistical significance was defined as $P < .05$. Statistical analysis was performed using SAS statistical software (version 4.9; SAS Institute, Inc).

Results

Baseline Characteristics

Of the 120 952 patients in the VOCAL cohort, we excluded patients who were not engaged in care in the VA system in the year prior to vaccine availability (n = 55 761), those who died (n = 6262), developed COVID-19 infection (n = 1656), or were transplanted (n = 1523) prior to vaccine availability, and those who received a non-mRNA COVID-19 vaccine (n = 353) (**Figure 1**).

We identified 55 397 individuals with cirrhosis who met inclusion criteria, of whom 21 213 received at least 1 dose of a COVID-19 vaccine. We matched 20 037 patients who received at least 1 dose of vaccine with 20 037 controls (**Table 1**). The median (interquartile range) age of the PS-matched sample was 69.1 (8.4) years in the vaccinated and 69 (8.8) years in the unvaccinated group; the older age consistent with the age-based prioritization for vaccination. Though the cohort was predominantly male (19 465 [97.3%]) and white (12 135 [60.6%]), consistent with a veteran cohort, a considerable proportion (4646 [23.2%]) was Black.

Vaccine recipients and controls were exactly matched 1:1 with respect to age group, sex, race or ethnicity, alcohol as the etiology for cirrhosis, CirCom scores, and eCTP scores. Also, both groups remained well balanced after PS matching with respect to median age, BMI, baseline AUDIT-C score, current or prior smoking history, as well as laboratory values, including platelet count, total bilirubin, and INR (Table 1) (**Figure 2**) (eFigure 1 in the Supplement).

Vaccine Administration

Figure 3 shows the weekly administration of both vaccines over time. The BNT162b2 mRNA vaccine had an earlier roll out by a few days but the mRNA-1273 vaccine became the more common vaccine administered in the later part.

Table 1. Descriptive Statistics for Patients by Vaccine

Variable	Unmatched			Matched		
	No. (%)			No. (%)		
	Vaccine	Control	*P* value	Vaccine	Control	*P* value
No.	21 213	34 184		20 037	20 037	
Patient who received the first dose						
BNT162b2 mRNA vaccine	10 409 (49.1)	NA	NA	9801 (48.9)	NA	NA
mRNA-1273 vaccine	10 804 (50.9)	NA	NA	10 236 (51.1)	NA	NA
Patients who received the second dose						
BNT162b2 mRNA vaccine	6906 (52.2)	NA	NA	6539 (52.0)	NA	NA
mRNA-1273 vaccine	6317 (47.8)	NA	NA	6029 (48.0)	NA	NA
Sex						
Male	20 525 (96.8)	32 859 (96.1)	<.001	19 465 (97.2)	19 465 (97.2)	>.99
Female	688 (3.2)	1325 (3.9)		572 (2.9)	572 (2.9)	
Age, median (IQR), y	69.2 (8.5)	66.9 (10.1)	<.001	69.1 (8.4)	69 (8.8)	.09
Age group, y						
<50	384 (1.8)	1727 (5.1)	<.001	349 (1.7)	349 (1.7)	>.99
50-59.9	1944 (9.2)	5071 (14.8)		1844 (9.2)	1844 (9.2)	
60-69.9	9289 (43.8)	15 493 (45.3)		8932 (44.6)	8932 (44.6)	
70-85	9164 (43.2)	11 269 (33)		8534 (42.6)	8534 (42.6)	
≥85	432 (2)	624 (1.8)		378 (1.9)	378 (1.9)	
Race/ethnicity						
White	12 619 (59.5)	21 462 (62.8)	<.001	12 135 (60.6)	12 135 (60.6)	>.99
Black	5072 (23.9)	6881 (20.1)		4646 (23.2)	4646 (23.2)	
Other[a]	1593 (7.5)	2881 (8.4)		1505 (7.5)	1505 (7.5)	
Hispanic/Latino	1699 (8)	2483 (7.3)		1556 (7.8)	1556 (7.8)	
Unknown	230 (1.1)	477 (1.4)		195 (1)	195 (1)	
Alcohol-associated cirrhosis						
No	12 393 (58.4)	18 617 (54.5)	<.001	11 629 (58)	11 629 (58)	>.99
Yes	8820 (41.6)	15 567 (45.5)		8408 (42)	8408 (42)	
BMI, median (IQR)[b]	29.2 (7.9)	28.7 (8)	<.001	29.2 (7.9)	29 (7.9)	.31
Class						
Overweight	7203 (34)	11 574 (33.9)	<.001	6829 (34.1)	6804 (34)	.32
Class 1 obesity (BMI 30.0-34.9)	5471 (25.8)	8336 (24.4)		5182 (25.9)	5070 (25.3)	
Class 2 obesity (BMI 35.0-39.9)	2630 (12.4)	3787 (11.1)		2500 (12.5)	2390 (11.9)	
Class 3 obesity (BMI >40.0)	1274 (6)	2024 (5.9)		1207 (6)	1167 (5.8)	
Diabetes						.07
No	9879 (46.6)	18 079 (52.9)	<.001	9329 (46.6)	9675 (48.3)	.07
Yes	11 334 (53.4)	16 105 (47.1)		10 708 (53.4)	10 362 (51.7)	
Tobacco use						.09
Current smoker	7992 (37.7)	14 563 (42.6)	<.001	7569 (37.8)	7760 (38.7)	.09
Former smoker	6828 (32.2)	9931 (29.1)		6471 (32.3)	6338 (31.6)	
Never smoker	6393 (30.1)	9690 (28.4)		5997 (29.9)	5939 (29.6)	
AUDIT-C score						
Low	16 655 (78.5)	25 612 (74.9)	<.001	15 677 (78.2)	15 577 (77.7)	.23
High	4558 (21.5)	8572 (25.1)		4360 (21.8)	4460 (22.3)	
Cirrhosis comorbidity index score[c]						
0	3292 (15.5)	5668 (16.6)	<.001	3121 (15.6)	3121 (15.6)	>.99
1 + 0	5081 (24)	9808 (28.7)		4880 (24.4)	4880 (24.4)	
1 + 1	4860 (22.9)	8185 (23.9)		4661 (23.3)	4661 (23.3)	
3 + 0	1184 (5.6)	1574 (4.6)		1071 (5.4)	1071 (5.4)	
3 + 1	6618 (31.2)	8734 (25.6)		6175 (30.8)	6175 (30.8)	
5 + 0	38 (0.2)	38 (0.1)		20 (0.1)	20 (0.1)	
5 + 1	140 (0.7)	177 (0.5)		109 (0.5)	109 (0.5)	

(continued)

Table 1. Descriptive Statistics for Patients by Vaccine (continued)

Variable	Unmatched No. (%) Vaccine	Unmatched No. (%) Control	Unmatched P value	Matched No. (%) Vaccine	Matched No. (%) Control	Matched P value
eCTP class						
A	17 884 (84.3)	26 513 (77.6)	<.001	16 895 (84.3)	16 895 (84.3)	>.99
B	3197 (15.1)	7244 (21.2)		3028 (15.1)	3028 (15.1)	
C	132 (0.6)	427 (1.3)		114 (0.6)	114 (0.6)	
Lab results at baseline date, median (IQR)						
Alanine aminotransferase, IU/ml	24.0 (17.0)	24.0 (19.0)	.002	24.0 (17.5)	24.0 (18.0)	.32
Platelet count, $\times 10^9$/L	161.0 (94.0)	160.0 (101.0)	.08	161 (94)	162 (98)	.39
Creatinine, mg/dL	1.00 (0.35)	1.00 (0.47)	<.001	1.00 (0.41)	1.00 (0.44)	.40
Total bilirubin, mg/dL	0.70 (0.55)	0.70 (0.60)	<.001	0.70 (0.60)	0.70 (0.60)	.07
International normalized ratio	1.10 (0.15)	1.10 (0.20)	<.001	1.10 (0.20)	1.10 (0.20)	.06
MELD-Na score	8.0 (6.0)	8.0 (5.0)	<.001	8.0 (5.0)	8.0 (5.0)	.07

Abbreviations: BMI, body mass index; AUDIT-C, Alcohol Use Disorders Identification Test-Concise; eCTP, electronic Child Pugh Turcotte; IQR, interquartile range; MELD-Na, Model for Endstage Liver Disease-Sodium; NA, not applicable.

[a] Other includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and more than 1 race.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] The Cirrhosis comorbidity index assesses the presence of 1 of 9 of the following comorbidities: chronic obstructive pulmonary disease, acute myocardial infarction, peripheral arterial disease, epilepsy, substance abuse, heart failure, nonmetastatic cancer, metastatic cancer, and chronic kidney disease.

A high proportion (99.7%) of individuals who received a first dose of either vaccine and had a follow-up of at least 42 days, received a second dose within this CDC-recommended period.

Association of Receipt of 1 Dose of BNT162b2 or mRNA-1273 Vaccines and COVID-19 Infection

We analyzed each mRNA vaccine separately and in combination, and found that the findings were similar between the 2 vaccines. Therefore, we chose to present the data by combining the 2 vaccines to improve the power (**Table 2**).

Following the first dose of either the BNT162b2 or the mRNA-1273 vaccines, 83 patients in the vaccine group and 105 patients in the control group developed COVID-19 infection. The number of COVID-19 infections in the vaccine and control groups was similar in days 0 to 7, days 7 to 14, days 14 to 21, and days 21 to 28 after administering the first dose. However, after the first 28 days, receipt of 1 dose of either vaccine was associated with a 64.8% reduction in COVID-19 infections (Table 2).

Twenty-eight patients who received either vaccine developed COVID-19–related hospitalization compared with 29 controls. After 28 days from the first dose, none of the vaccinated individuals were hospitalized for COVID-19–related infection compared with 3 controls. Vaccine administration was associated with a 100% reduction in COVID-19–associated hospitalization after 28 days. The secondary outcome of COVID-19 related death was not observed in any patients who received a COVID-19 vaccine, compared with 2 controls, indicating a 100% association with decrease in COVID-19–related death.

Association of Receipt of 2 Doses of BNT162b2 or mRNA-1273 Vaccine and COVID-19 Infection

Following 7 days after the second dose of either the BNT162b2 or the mRNA-1273 vaccine, 3 patients in the vaccine group and 14 patients in the control group developed COVID-19 infection (eTable 1 in the Supplement). Receipt of a second dose of either vaccine was associated with a 78.6% reduction in COVID-19 infections after 7 days. No patient who received the second dose of either vaccine developed COVID-19–related hospitalization or death, compared with 2 hospitalizations and 1 death in the control group, indicating an association of 100% reduction in COVID-19–related hospitalization or death after 7 days of the second dose of either vaccine.

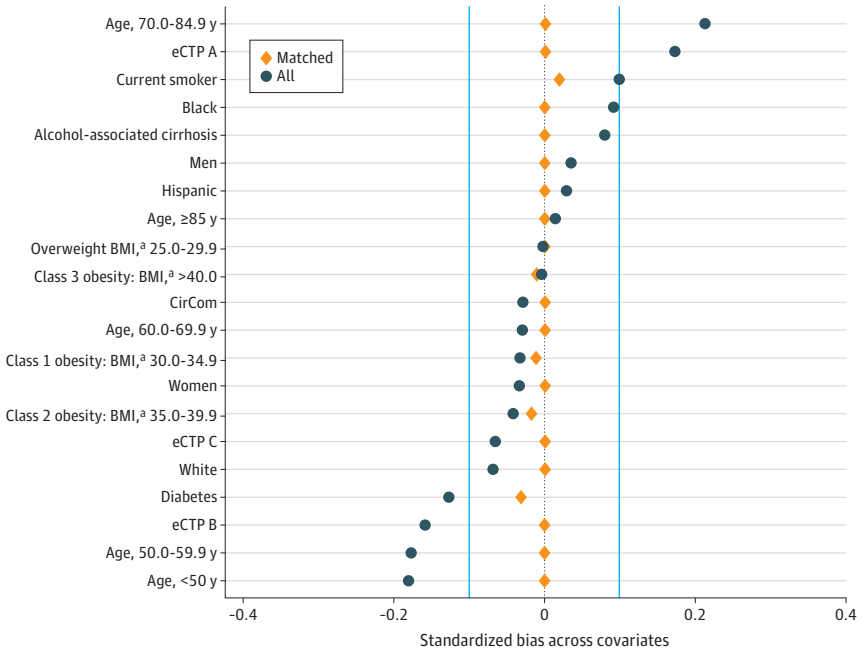
Association of Receipt of mRNA Vaccine and COVID-19 Infections Among Patients With Decompensated Cirrhosis

A total of 3142 patients with decompensated cirrhosis received at least 1 dose of a COVID-19 mRNA vaccine. Within 28 days of the first dose of either vaccine, 17 patients in the vaccine group and 16 patients in the control group developed COVID-19 infection. However, after the first 28 days, 1 patient in the vaccine group and 2 in the control group developed COVID-19 infection, indicating a 50.3% reduction in COVID-19 infections in patients with decompensated cirrhosis after 28 days of one dose of either vaccine (eTable 2 in the Supplement). No patient in the vaccine group and one patient in the control group developed COVID-19 related hospitalization and death, indicating an association of a 100% reduction in COVID-19 related hospitalization or death.

Association of Receipt of mRNA Vaccine and COVID-19 Infections Among Patients With Compensated Cirrhosis

A total of 16 895 patients with compensated cirrhosis received the first dose of either mRNA vaccine. After the first 28 days, 5 patients in the vaccine group and 15 patients in the control group developed COVID-19 infection, indicating a 66.8% reduction in COVID-19 infections in patients with compensated cirrhosis (eTable 3 in the Supplement). No patient in the vaccine group developed COVID-19–related hospitalization or

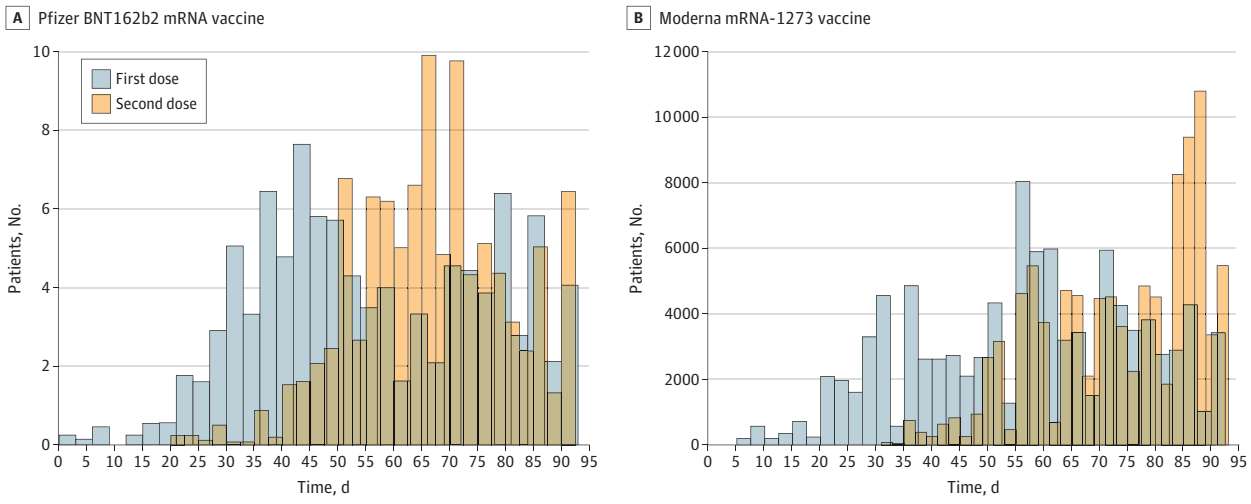
Figure 2. Standardized Variable Differences Plot Between Patients With Vaccine and Controls, Before and After Propensity Score Matching



eCTP Indicates Cirrhosis Comorbidity Index and electronic Child-Turcotte-Pugh system score. The area between the vertical blue lines represents the accepted observed standardized bias (−0.1 to 0.1) between the matched vaccinated and control groups.

[a] Body mass index, calculated as weight in kilograms divided by height in meters squared.

Figure 3. Number of Patients With Cirrhosis Who Received the First and Second Doses of BNT162b2 and mRNA-1273 Vaccines Since Rollout in the Veterans Health Administration



death, compared with 2 hospitalizations and 1 death in the control group, indicating a 100% reduction in COVID-19-related hospitalization or death.

Adjusted Analysis

On multivariable analysis using competing risk models, receipt of a COVID-19 mRNA vaccine was associated with a 25% reduction in COVID-19 infection or death from the time of vaccination, after adjusting for age, diabetes mellitus, tobacco use, AUDIT-C score, and MELD-Na (adjusted hazard ratio [aHR], 0.75; 95% CI, 0.61-0.93; *P* = .008) (eTable 4 and eFigure 2 in the Supplement). The association was significant for patients with compensated cirrhosis (aHR, 0.69; 95% CI, 0.54-0.89; *P* = 005) but not for decompensated cirrhosis (aHR, 0.90; 95% CI, 0.62-1.30; *P* = .57). We performed a stratified analysis among women, combining the 2 vaccines. There were 1144 women with cirrhosis included in the study, who developed 6 events (COVID-19 infection or death). On multivariable analysis, receipt of 1 dose of a COVID-19 vaccine was not associated with COVID-19 infection or death in women (aHR, 0.53; 95% CI, 0.10-2.89; *P* = .46) (eTable 5 in the Supplement).

Table 2. COVID-19 Infection, Hospitalization for COVID-19, and COVID-19–Related Death After Administration of First Dose of the Pfizer BNT162b2 mRNA or the Moderna mRNA-1273 Vaccines

	Day 0-7		Day 7-14		Day 14-21		Day 21-28		Day 28-onward		Vaccine efficacy day 28 onward, % (95% CI)[a]	*P* value
Vaccine and control	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control		
COVID-19 infection												
No.	183										64.8 (10.9-86.1)	
Events, no.	25	36	21	32	17	12	14	8	6	17		
Cumulative events, no.	25	36	46	68	63	80	77	88	83	105		.03
No. at risk	20037	20037	18109	18073	15991	15935	13731	13678	12059	12012		
Cumulative incidence, %	0.12	0.18	0.25	0.38	0.39	0.50	0.56	0.64	0.69	0.87		
Hospitalization for COVID												
No.	57										100.0 (99.3-100.0)	
Events, no.	4	8	8	7	6	5	10	6	0	3		
Cumulative events, no.	4	8	12	15	18	20	28	26	28	29		.20
No. at risk	20037	20037	18109	18073	15991	15935	13731	13678	12059	12012		
Cumulative incidence, %	0.02	0.04	0.07	0.08	0.11	0.13	0.20	0.19	0.23	0.24		
COVID-19–related death												
No.	13										100.0 (99.3-100.0)	
Events, no.	1	3	2	1	0	2	1	1	0	2		
Cumulative events, no.	1	3	3	4	3	6	4	7	4	9		.20
No. at risk	20037	20037	18109	18073	15991	15935	13731	13678	12059	12012		
Cumulative incidence, %	0	0.01	0.02	0.02	0.02	0.04	0.03	0.05	0.03	0.07		

[a] Vaccine efficacy (VE) = 1-(IRv/IRc) where IR is the incidence rate of the event in vaccinated at risk(v) and controls at risk(c). *P* values: testing the null hypothesis that incidence rates are the same in both groups using Fisher exact test.

Discussion

Despite 2 large phase 3 randomized clinical trials that demonstrated the efficacy of the BNT162b2 mRNA and mRNA-1273 vaccines in the general population, the effectiveness of the vaccine in patients with cirrhosis and the uptake of the vaccine are important knowledge gaps. These data show that a very high proportion of patients with cirrhosis who are engaged in the VA health care system received the available COVID-19 vaccines according to guidelines, with more than 99.7% of patients receiving a second dose within 42 days of the first dose per US Centers for Disease Control guidelines.[18]

Chronic liver disease, particularly decompensated cirrhosis, is associated with vaccine hyporesponsiveness to several commonly used vaccines, including hepatitis B,[19] pneumococcal, and influenza vaccines.[20] The data demonstrates that receipt of either mRNA vaccine was not associated with a reduction in COVID-19 infection in the first 28 days after the first dose, indicating a slow immune response. However, after 28 days of the first dose, and 7 days after a second dose, receipt of either mRNA vaccine was associated with a significant reduction in COVID-19 infection. More importantly, receipt of either vaccine was associated with a 100% reduction in hospitalization or death due to COVID-19 infection. The association of receipt of mRNA vaccines and COVID-19 infection seemed to be lower in decompensated compared with compensated cirrhosis. However, this needs to be confirmed in future studies because the number of patients and events among patients with decompensated cirrhosis were low. Although not a head-to-head comparison, the data suggest that there were no significant differences between the 2 mRNA vaccines among patients with cirrhosis.

The association of receipt of mRNA vaccines and reduction in COVID-19 infection in this study was lower than that described in some randomized clinical trials.[1,2] A study from Israel[21] suggested that the receipt of 1 dose of the BNT162b2 mRNA vaccine was associated with a 95% reduction in COVID-19 infection, and this was noted as early as 14 days after the first dose. Findings of this study suggest that the receipt of either mRNA vaccine was not associated with reduction in COVID-19 infection among patients with cirrhosis until 28 days after the first dose. This may be because humoral immunity is impaired or delayed in patients with cirrhosis.[3] An alternative explanation may be the emergence of variants in the US, including B.1.1.7 (often referred to as the UK variant) and B.1.351 (also called the South African variant).[22] These variants are considerably more infectious than the wild-type coronavirus, and may be associated with reduced vaccine efficacy.[23,24] Though the phase 3 randomized clinical trials for the initial mRNA vaccines showed 94% to 95% efficacy, the more recently published data on the Janssen vaccine showed only 72% efficacy against COVID-19 infection in the US.[18,25,26] This difference has been postulated to be primarily dowing to the emergence of the variants rather than differences in vaccine efficacy. The data suggest that receipt of 1 dose of vaccine was not associated with a reduction in COVID-19 infection in the first 28 days; therefore, strict preventive measures should be continued until full vaccination is achieved. Also, vaccinated patients with cirrhosis can still be infected with COVID-19 infection, albeit with milder symptoms, and contribute to the spread of COVID-19 among contacts.

Limitations

We acknowledge the following limitations with this observational study. The study may have been affected by residual confounding due to differences between vaccinated persons and unvaccinated controls, especially in terms of differential risk to COVID-19 exposure. Patients who received the COVID-19 vaccine may be less likely to receive COVID-19 PCR testing in the presence of symptoms. However, the fact that the associations held up for COVID-19–related hospitalization and death strengthens the findings. In addition, our veteran cohort is limited in the proportion of women; however, to our knowledge, no sex-based differences in vaccine efficacy have been described. Our stratified analysis by sex was likely underpowered owing to the small number of patients and events among women. Furthermore, although this 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 infection or hospitalized outside the VA system. Because 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 vaccine recipients and controls. Finally, because of the recent rollout of the vaccine, we had relatively small numbers of individuals and events, particularly after 28 days. Longer follow-up is needed to assess if this association is sustained.

Strengths

The data presented herein have relative strengths. We reported a large cohort of well-characterized patients with cirrhosis who were not represented in the pivotal clinical trials. The study cohort was derived from patients in an integrated health care system located throughout the US.[27] The study sample was more diverse, with a higher proportion of Black participants (23% vs 10%) compared with randomized clinical trials. The study was performed at a point in time where there were comparable numbers of vaccinated patients and controls. As more patients receive the vaccine, it will become difficult to have large enough number of controls in future studies.

Conclusions

This study found that the BNT162b2 mRNA and mRNA-1273 vaccines were associated with a 64.8% decrease in the development of COVID-19 infection after the first dose and a 78.6% decrease after the second dose. Although these associations suggest lower benefit in this cohort with cirrhosis compared with randomized clinical trials, they appear to be highly associated with a reduction in hospitalization and death due to COVID-19. These findings strengthen the hope that these vaccines may mitigate the effects of the COVID-19 pandemic on individuals with cirrhosis in the US.

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