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The impact of COVID-19 on the clinical course and outcome of patients with cirrhosis: An observational study

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Abstract

Background and Aims: Severe outcomes of COVID-19 are associated with advancing age and comorbidities. The specific aim of our study was to determine the impact of COVID-19 on the clinical course and outcome of patients with cirrhosis.

Methods: We retrieved data from VA national repository and identified patients tested for SARS-CoV-2 RNA who had cirrhosis. Each virus positive patient was propensity-matched with virus negative subjects by demographics and comorbidities. Primary endpoint was death within 30 days of COVID-19 diagnosis and secondary endpoint was hospitalization within 14 days.

Results: Among 1,115,037 individuals tested for SARS-CoV-2 RNA, 31,680 had cirrhosis. Of those patients, 4456 virus positive patients were propensity-matched with 8752 virus negative subjects. In this cohort of 13,208, median age was 67 years and 95% were male. Most had multiple comorbidities. Alcohol use, hepatitis C and MASH were the dominant etiologies of cirrhosis. At baseline, median MELD was 6% and 21% had hepatic decompensation. Advanced age was the most significant determinant of hospitalization and mortality. Comorbidities, alcohol use and MELD increased the likelihood of hospitalization whereas SARS-CoV-2 positivity had lower Day-14 hospitalization hazard. MELD was associated with higher mortality hazard whereas vaccination reduced the hazard of hospitalization and death. SARS-CoV-2 positivity increased the hazard of death at Day-30 by 72% and at Day-90 by 26%.

Conclusion: Although patients with cirrhosis who developed COVID-19 were less likely to be hospitalized, they were more likely to die within 30 days compared to their virus negative counterparts. Vaccination was effective in reducing both hospitalization and death.

KEYWORDS

COVID vaccination, data analysis, SARS-CoV-2, veterans

1 | INTRODUCTION

COVID-19 pandemic resulted in significant morbidity and mortality around the world. In the early phase of the pandemic, around 20% of infected individuals progressed to develop severe or critical illness.[1] However, increased testing and early identification of cases, improvement in management, widespread use of highly effective vaccines, and emergence of less aggressive viral strains led to improved disease prognosis.[2] Several factors have been associated with worse outcomes, principally advancing age and co-morbid conditions including cardiovascular disease, chronic pulmonary disease and diabetes.[3,4] COVID-19 has been commonly associated with acute liver injury with the degree of injury related to the severity of disease.[5,6] Patients with cirrhosis were particularly affected by COVID-19, and were reported to have a higher mortality rate compared to those with cirrhosis who remained uninfected.[7–10] Most studies were undertaken during the earlier phase of the pandemic. A reassessment of the interaction between COVID-19 and advanced liver disease may therefore be warranted.

The Veterans Health Administration (VHA) is the largest integrated healthcare system in the United States (US). It provides care to 9 million veterans each year at its 1298 facilities including 171 medical centers.[11] Veterans Affairs patient data is stored at a central repository and is available to researchers. Additional data resources were established in response to COVID-19 pandemic. The VA patient data therefore provided unique opportunities to assess the impact of COVID-19 on the natural history of patients with cirrhosis.[7,12] The specific aim of our study was to determine the effect of COVID-19 on the clinical course and outcome of patients with cirrhosis. Our objectives were to characterize patients with cirrhosis who underwent testing for SARS-CoV-2 infection, to determine the hospitalization and survival rates of patients with or without COVID-19, and to determine factors that influenced the hospitalization and survival rates of such patients.

Key points

- BACKGROUND: Using data from Veterans Affairs national repository, we identified patients with cirrhosis who were tested for SARS-CoV-2, to determine the impact of COVID-19 on the outcome of such patients.
- FINDINGS: In the study cohort of 13,208 patients with 4456 SARS-CoV-2 positive patients propensity matched to virus negative subjects, SARS-CoV-2 infection was associated with 9% lower hazard of 14-day hospitalization but 72% increased hazard of 30-day mortality.
- IMPLICATIONS FOR PATIENT CARE: The study confirmed prior observations that COVID-19 increased the mortality risk of patients with cirrhosis. It also validated the effectiveness of vaccination in reducing both hospitalization and death among patients with cirrhosis.

2 | PATIENTS AND METHODS

2.1 | Study population

The Veterans Affairs (VA) Corporate Data Warehouse (CDW) is the national repository for VA patient data, and the linked COVID-19 Shared Data Resource contains validated information of all veterans with a confirmed diagnosis of SARS-CoV-2 infection.[13] We extracted data from the CDW and the COVID-19 resource of patients evaluated during the period between January 2020 and May 2022. We determined diagnoses using International Statistical Classification of Diseases and Related Health Problems-9-Clinical Modification (ICD-9-CM) and ICD-10-CM codes. Among all veterans tested for SARS-CoV-2 RNA during this period, we identified those with a diagnosis of cirrhosis based on the presence of at least one inpatient or two outpatient diagnostic codes. Patients with a history of organ transplantation and those with hepatic or extrahepatic malignancies, except resected non-melanoma skin cancers, were excluded. We defined the study baseline date as the date of the first positive test for SARS-CoV-2 RNA. Each SARS-CoV-2 positive patient was propensity-matched with up to two SARS-CoV-2 negative patients for demographics and comorbidities.

2.2 | Study variables

We studied patient demographics including age, sex, race and geographic location of testing site, the latter in lieu of patient's location. We evaluated liver disease etiologies and laboratory studies. SARS-CoV-2 infection was determined by the detection of viral RNA. Diagnoses for alcohol use disorder (AUD) and comorbid conditions including diabetes, hypertension, cardiovascular disease, chronic pulmonary disease, and acute and chronic kidney disease were noted within 2 years of the baseline date. Additionally, Charlson Comorbidity Index (CCI) score was calculated.[14] Data regarding COVID-19 vaccines, hepatic decompensation, hospitalization, intensive care unit (ICU) admission, respiratory support, renal replacement therapy, and death, were also retrieved.

2.3 | Severity of illness

We regarded illness to be mild if there was no hospitalization or death. It was considered moderate if a patient was hospitalized. Severe or critical illness was characterized by either admission to ICU, or respiratory support, or death.

2.4 | Study endpoints

The primary endpoint of the study was defined as death from any cause within 30 days of COVID-19 diagnosis. The secondary endpoint was defined as hospitalization within 14 days of COVID-19 diagnosis.

2.5 | Statistical analysis

Descriptive statistics including measures of central tendency (median) and dispersion (interquartile range) were computed for continuous data. Frequency distributions were calculated for categorical variables. The two groups of patients and matched controls were compared by Wilcoxon rank sum test for continuous variables, and chi-square test for categorical variables. Kaplan Meier plots were generated to assess hospitalization and survival rates, and Fine-Gray model was used to perform competing risk analysis for hospitalization and death. We used Cox proportional hazards modeling to determine factors associated with study endpoints. Multivariable Cox analysis was performed by including factors noted to be significant on univariable analysis. Statistical analyses were performed with SAS® (version 9.4, SAS Institute Inc.).

2.6 | Ethical considerations

The study was approved by the Institutional Review Board at the VA Pittsburgh Healthcare System. A waiver of informed consent was granted for the study.

3 | RESULTS

3.1 | Study cohort

(Figure 1) Among 1,115,037 veterans tested for SARS-CoV-2 RNA, 31,680 (2.8%) were noted to have cirrhosis. We excluded 10,962 patients, all except twelve because of a history of organ transplantation or hepatic or extrahepatic malignancies. In the residual cohort of 20,718, we identified 4456 (21.5%) patients who were positive for SARS-CoV-2 RNA. Each SARS-CoV-2 positive patient was propensity-matched to virus negative patients in a ratio of 1:2 except 160 who were matched in a ratio of 1:1 due to lack of a suitable second match. Thus, 4456 SARS-CoV-2 positive patients were matched to 8752 virus negative patients to constitute a study cohort of 13,208.

3.2 | Demographics & baseline features

(Table 1) The median age was 67 years, 95% were male, two-thirds were white, and one quarter were black. The distribution of SARS-CoV-2 RNA testing was similar in the five geographic regions. Excessive weight/obesity were commonly noted with the median body mass index (BMI) of 29.5. The majority of subjects had multiple comorbidities, principally hypertension, dyslipidemia, cardiovascular disease, diabetes, chronic pulmonary disease, chronic kidney disease, and acute kidney injury. Comorbidities were of moderate severity as indicated by the median CCI score of 3.[14] (Table 2) Many patients had more than one etiology of cirrhosis as evidenced by AUD in 55%, hepatitis C in 47% and nonalcoholic steatohepatitis (MASH) in 33%. SARS-CoV-2 positive patients were more likely to have MASH or autoimmune hepatitis but less likely to have AUD. Although laboratory values were largely within the normal range, relatively higher serum ALT and sodium levels and lower alkaline phosphatase level and white cell count were noted in the SARS-CoV-2 positive patients. Serum creatinine level was also lower among virus positive patients which was reflected in the lower MELD-Na score (Table 3).

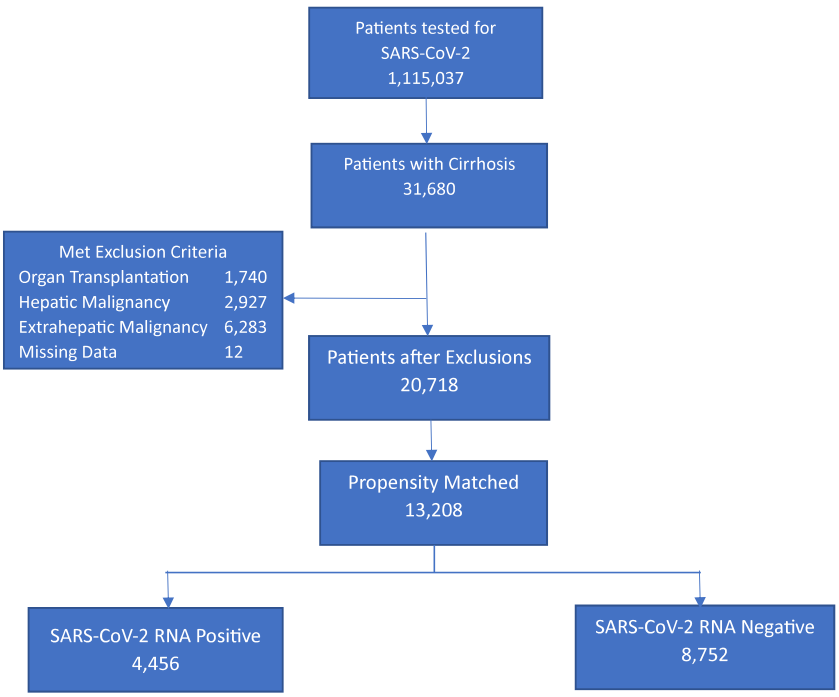

FIGURE 1 Composition of the study cohort.

TABLE 1 Baseline demographics and comorbidities included in propensity matching of SARS-CoV-2 RNA positive and negative patients with cirrhosis.

	All Patients with cirrhosis (*n* = 13208)	SARS-CoV-2 positive (*n* = 4456)	SARS-CoV-2 negative (*n* = 8752)	SMD
Age, y	67 (61,72)	67 (61,72)	67 (61,71)	0.0007
Male sex	12,609 (95.46%)	4246 (95.29%)	8363 (95.56%)	−0.0128
Race:				0
White	8833 (66.88%)	2999 (67.3%)	5834 (66.66%)	
Black	3310 (25.06%)	1102 (24.73%)	2208 (25.23%)	
Other	1065 (8.06%)	355 (7.97%)	710 (8.11%)	
Geographic location at testing:				0.0321
Continental	2190 (16.58%)	749 (16.81%)	1441 (16.46%)	
Midwest	2529 (19.15%)	849 (19.05%)	1680 (19.2%)	
North Atlantic	3113 (23.57%)	1045 (23.45%)	2068 (23.63%)	
Pacific	2378 (18%)	808 (18.13%)	1570 (17.94%)	
Southeast	2998 (22.7%)	1005 (22.55%)	1993 (22.77%)	
Body mass index, kg/m^2	29.5 (25.5,34.2)	29.8 (25.8,34.2)	29.4 (25.4,34.2)	0.0152
Co-morbidities:				
Diabetes	7058 (53.44%)	2407 (54.02%)	4651 (53.14%)	0.0175
Dyslipidemia	8255 (62.5%)	2790 (62.61%)	5465 (62.44%)	0.0035
Hypertension	10759 (81.46%)	3639 (81.67%)	7120 (81.35%)	0.008
Cardiovascular disease	7396 (56%)	2494 (55.97%)	4902 (56.01%)	−0.0008
Chronic pulmonary disease	4203 (31.82%)	1441 (32.34%)	2762 (31.56%)	0.0167
Chronic kidney disease	3308 (25.05%)	1145 (25.7%)	2163 (24.71%)	0.0226
Acute Kidney Failure	2951 (22.34%)	1047 (23.5%)	1904 (21.76%)	0.0416
Charlson comorbidity index score	3 (2,5)	3 (2,5)	3 (2,5)	0.0317

Note. Data summarized as medians and interquartile range for continuous variables, and numbers and proportions for categorical variables.
Abbreviation: SMD, standardized mean difference.

3.3 | Disease severity and endpoints

(Table 3) Our cohort had mild liver disease at baseline as median MELD was 6 and a minority of 21% had hepatic decompensation, with similar proportions in the two groups. However, SARS-CoV-2 positive patients had lower MELD score and lower rate of transition to hepatic decompensation. With competing risk analysis, we found SARS-CoV-2 positive patients to have lower probability of hospitalization at both Day-14 (Figure 2) and Day-90 of diagnosis (Figure 3). However, following hospitalization, which was required in 37% of the cohort, virus positive patients more often required intensive care and had longer hospital stay. Most patients had mild severity of illness with moderate severity in 20% and severe/critical illness in another 20%. We found SARS-CoV-2 positive patients to be more likely to develop severe/critical illness. Overall, 20% of our cohort died with the 30-day mortality rate of 5.7%. Despite lower overall mortality, SARS-CoV-2 positive patients had a higher 30-day mortality rate of 7% compared to 5% in the virus negative patients (Figure 4). However, that difference dissipated by Day-90 resulting in similar mortality rates in the two groups (Figure 5). The majority of patients received at least one dose of a COVID-19 vaccine; however, a substantial minority (31%) remained unvaccinated (Table 4). A higher proportion of SARS-CoV-2 positive patients were unvaccinated compared to their matched virus negative counterparts. Almost 15% of patients who received at least one dose of vaccine developed breakthrough infections.

3.4 | Variables associated with hospitalization and mortality

(Tables 5 and 6) (Supporting Information S1: Tables S1 and S2 include all variables) We found advanced age to be the most significant determinant of hospitalization. Patients 80 years of age or older had 59% higher hazard of hospitalization at Day-14% and 51% higher hazard at Day-90. In addition to age, at both Day-14 and Day-90, CCI score, AUD and MELD were associated with higher hazard of

TABLE 2 Etiology and baseline laboratory values of SARS-CoV-2 RNA positive and negative patients with cirrhosis.

	All Patients with Cirrhosis (*n* = 13,208)	SARS-CoV-2 positive (*n* = 4456)	SARS-CoV-2 negative (*n* = 8752)	pValue (positive vs. negative)
Etiology of cirrhosis:				
MASH	4341 (32.87%)	1574 (35.32%)	2767 (31.62%)	<0.001
Autoimmune	86 (0.65%)	39 (0.88%)	47 (0.54%)	0.02
PBC/PSC	308 (2.33%)	107 (2.4%)	201 (2.3%)	0.71
Hepatitis C	6168 (46.7%)	2083 (46.75%)	4085 (46.68%)	0.94
Hepatitis B	2082 (15.76%)	721 (16.18%)	1361 (15.55%)	0.35
Alcohol use disorder	7232 (54.75%)	2356 (52.87%)	4876 (55.71%)	0.002
Laboratory Features:				
Total bilirubin, mg/dL	0.6 (0.4,1)	0.6 (0.4,1)	0.6 (0.4,1)	0.38
ALT, IU/L	24 (17,36)	25 (17,37)	24 (16,36)	0.01
Alkaline phosphatase, IU/L	89 (69,119)	88 (68,117)	90 (70,121)	0.01
Albumin, g/dL	3.8 (3.4,4.2)	3.8 (3.4,4.2)	3.9 (3.4,4.2)	0.11
White cell count, 10^9/L	6.3 (4.9,8)	6.1 (4.8,7.8)	6.4 (5,8)	<0.001
Hemoglobin, g/dL	13.4 (11.7,14.7)	13.4 (11.8,14.7)	13.3 (11.7,14.6)	0.42
Platelets, 10^9/L	167 (120,221)	168 (120,220)	167 (120,222)	1.00
INR	1.1 (1,1.2)	1.1 (1,1.2)	1.1 (1,1.2)	0.22
Sodium, mmol/L	138 (136,140)	139 (137,140)	138 (136,140)	0.01
Creatinine, mg/dL	1 (0.8,1.3)	1 (0.8,1.3)	1 (0.8,1.3)	0.03

Note. Data summarized as medians and interquartile range for continuous variables, and numbers and proportions for categorical variables.

hospitalization whereas nonblack race, and complete COVID-19 vaccination were associated with lower hazard. SARS-CoV-2 positivity was associated with lower hazard of hospitalization at Day-14, but it had no association at Day-90.

Mortality was predominantly influenced by advancing age as the 30-day mortality hazard increased by 229% with age 65–79 and by 432% with age 80 and older. Whereas, the 90-day mortality hazard increased by 207% and 418% for those age groups, respectively. In addition to age, MELD score and SARS-CoV-2 positivity were associated with increased hazard of death at both Day-30 and Day-90 whereas Black race and vaccination were associated with reduced hazard of death. The CCI score was associated with increased hazard of death at Day-90 but not at Day-30. SARS-CoV-2 positivity increased the hazard of death at Day-30 by 72% and at Day-90 by 26%. COVID-19 vaccination was associated with reduced hazard of death.

4 | DISCUSSION

To assess the impact of COVID-19, we identified patients with cirrhosis and compared those positive for SARS-CoV-2 RNA with a propensity matched group of negative patients. We found a 72% increase in 30-day mortality risk and a 26% increase in 90-day mortality risk associated with SARS-CoV-2 positivity. Age was the most significant determinant of both hospitalization and death. Additionally, MELD score was associated with higher hazards whereas COVID-19 vaccination was associated with reduced hazards of both hospitalization and mortality.

The median age of 67 years in our cohort of US veterans was considerably higher than the median age of 58 years among patients with newly diagnosed cirrhosis in the US general population.[15] Additionally, 95% of our patients were male which is a much larger proportion than the reported 55% male among patients with cirrhosis in the United States.[15,16] We noted a high burden of comorbidities that was manifested by a median CCI score of three that was much higher than the norm of 1.2 in the general population.[17] Despite matching for comorbidities including diabetes, dyslipidemia and hypertension that constitute metabolic syndrome, we found a higher prevalence of MASH among SARS-CoV-2 positive patients. Metabolic syndrome and MASH have been linked to the severity, progression, and prognosis of COVID-19.[18,19] Our study suggested an independent predisposition of MASH induced cirrhosis to COVID-19. One notable finding was the lower frequency of AUD among SARS-CoV-2 positive patients. Alcohol consumption increased

TABLE 3 Disease severity and outcome of SARS-CoV-2 RNA positive and negative patients with cirrhosis.

	All Patients with cirrhosis (*n* = 13208)	SARS-CoV-2 positive (*n* = 4456)	SARS-CoV-2 negative (*n* = 8752)	pValue (positive vs. negative)
MELD-Na	6 (6,10.5)	6 (6,10.2)	6 (6,10.6)	0.01
Hepatic decompensation	2727 (20.65%)	912 (20.47%)	1815 (20.74%)	0.72
Variceal bleeding	670 (5.07%)	238 (5.34%)	432 (4.94%)	0.32
Ascites	1873 (14.18%)	606 (13.6%)	1267 (14.48%)	0.17
Encephalopathy	1153 (8.73%)	406 (9.11%)	747 (8.54%)	0.27
Transition to Decompensation	530 (4.01%)	124 (2.78%)	406 (4.64%)	<0.001
Hospitalization	4829 (36.56%)	1562 (35.05%)	3267 (37.33%)	0.01
Intensive care admission	1685 (12.76%)	657 (14.74%)	1028 (11.75%)	<0.001
Respiratory support	1035 (7.84%)	322 (7.23%)	713 (8.15%)	0.06
Length of hospitalization, d	5 (2,10)	6 (3,13)	4 (2,8)	<0.001
Disease Severity:				<0.001
Mild Disease	7825 (59.24%)	2706 (60.73%)	5119 (58.49%)	
Moderate Disease	2740 (20.75%)	811 (18.2%)	1929 (22.04%)	
Severe Critical Disease	2643 (20.01%)	939 (21.07%)	1704 (19.47%)	
Death	2641 (20%)	731 (16.4%)	1910 (21.82%)	<0.001
Death within 30 days of diagnosis	753 (5.7%)	309 (6.93%)	444 (5.07%)	<0.001
Vaccinated	9098 (68.88%)	2944 (66.07%)	6154 (70.3%)	<0.001

Note. Data summarized as medians and interquartile range for continuous variables, and numbers and proportions for categorical variables.

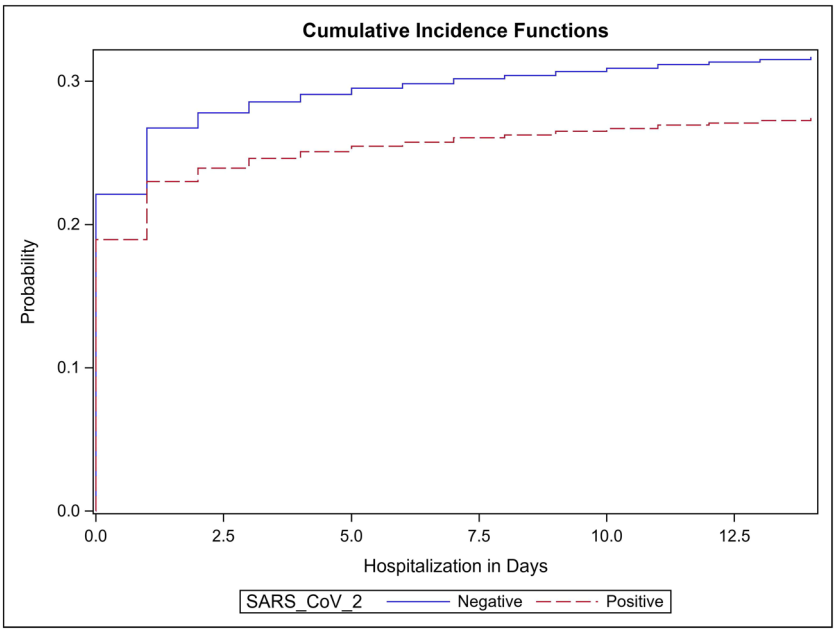

FIGURE 2 Cumulative incidence function for hospitalization within 14 days.

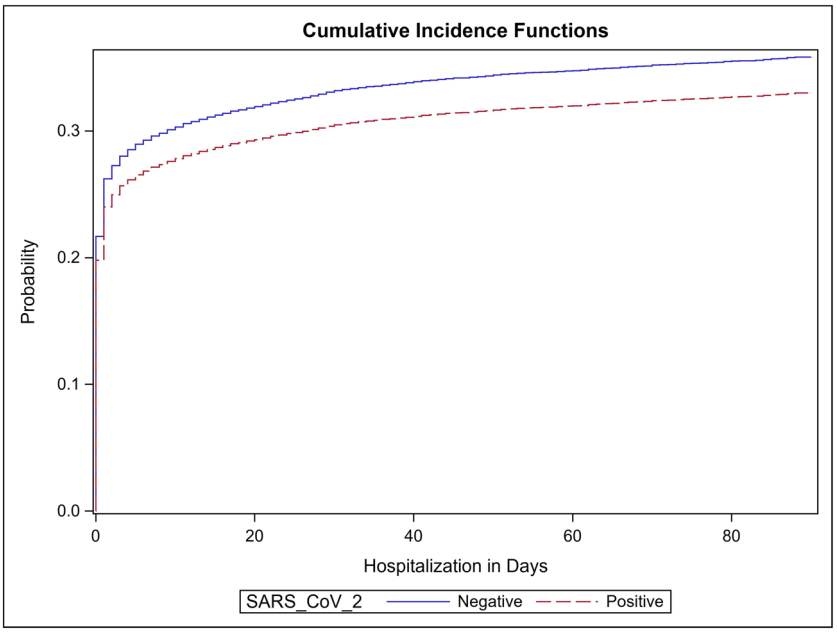

FIGURE 3 Cumulative incidence function for hospitalization within 90 days.

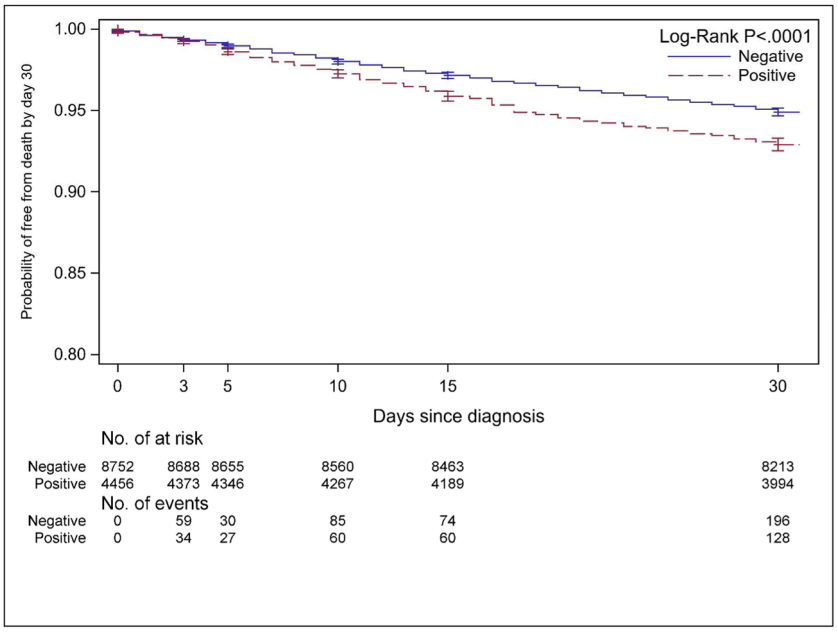

FIGURE 4 Kaplan-Meier curve for 30-day survival.

during the COVID-19 pandemic particularly among females and young to middle aged adults.[20,21] Our patient population was older, and we did not examine the change in alcohol consumption during the study period. We speculate that patients with cirrhosis and AUD had reduced exposure to SARS-CoV-2 due to behavioral change and risk avoidance. We also noted SARS-CoV-2 positive patients to have milder disease compared to virus negative patients as indicated by lower MELD and lower rate of transition to hepatic decompensation and hospitalization. One plausible explanation for this finding might be the greater mobility and social contact among patients with less severe liver disease resulting in higher rate of viral exposure. However, once hospitalized, SARS-CoV-2 positive patients were sicker with higher rate of intensive care admission and severe critical illness, longer duration of hospitalization, and higher mortality rate within the first 30 days of diagnosis. One discordant finding was the lower rate of respiratory support among virus positive patients which may be related to improved management of COVID pneumonia. Whereas, in virus negative patients respiratory support was needed for non-COVID reasons. We found COVID-19 vaccination to be protective against infection, hospitalization, and death in our cohort of patients with cirrhosis. Unfortunately, one-third of our patients remained unvaccinated.

We determined factors that influenced our primary endpoint of 30-day mortality. The most important determinant of death was advanced age. That was expected as patient's age is an

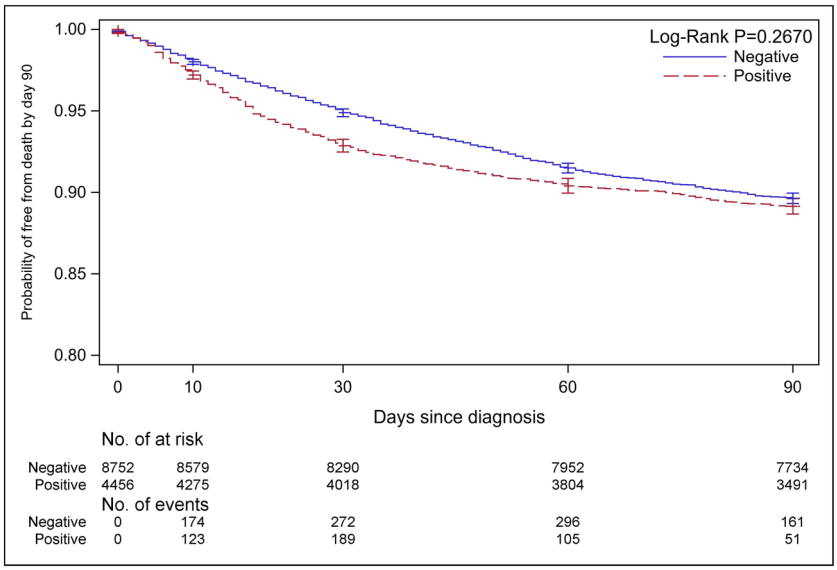

FIGURE 5 Kaplan-Meier curve for 90-day survival.

TABLE 4 Vaccination status of SARS-CoV-2 RNA positive and negative patients with cirrhosis.

	All Patients with Cirrhosis (*n* = 13,208)	SARS-CoV-2 positive (*n* = 4456)	SARS-CoV-2 negative (*n* = 8752)	p-Value
Vaccine received:				<0.001
Pfizer-BioNTech	4864 (36.83%)	1626 (36.49%)	3238 (37%)	
Moderna	4108 (31.1%)	1272 (28.55%)	2836 (32.4%)	
Janssen[a]	126 (0.95%)	46 (1.03%)	80 (0.91%)	
None	4110 (31.12%)	1512 (33.93%)	2598 (29.68%)	
SARS-CoV-2 breakthrough[b]	1324/9098 (14.6%)	–	–	

[a]Janssen COVID-19 vaccine (Ad26. COV2.S).

[b]Defined as SARS-CoV-2 RNA positivity at least 14 days after receiving one or two doses of the vaccine.

established risk factor for COVID-19 related mortality.[22] COVID-19 caused considerable loss of life-expectancy in the US and that loss was particularly prominent among blacks and Hispanics.[23,24] In contrast, we found black race to be associated with reduced hazard of death. This variance may have resulted from a difference in the duration of follow-up in our study compared to the earlier studies. Not surprisingly, MELD score was associated with increased hazard of mortality given that MELD was developed to predict short term mortality risk among patients with cirrhosis.[25] Most interestingly, SARS-CoV-2 RNA positivity was associated with 72% increase in the hazard of 30-day mortality and a 26% increase in 90-day mortality. Such an effect possibly resulted from the immune dysregulation induced by SARS-CoV-2.[26]

Our study had some limitations. We used ICD-CM codes to determine diagnoses. As those are manually entered by health care providers or coding specialists, inaccurate assignment or omission remained a possibility. However, the impact of such errors was likely minimized given the size of our data set. The application of our findings to the general population might be limited by the composition of our study cohort that primarily included older men. Our study spanned over several phases of COVID-19 pandemic that witnessed an evolution in vaccination and management. That might have impacted case matching and interpretation of results. Another limitation was the lack of availability of cause of death. Such information would have provided a better understanding of the interaction between advanced chronic liver disease and COVID-19.

In conclusion, our study provided further evidence of the negative impact of COVID-19 on the clinical course and outcome of patients with cirrhosis. We outlined variables that influenced the frequency of hospitalization of such patients and their risk of death. Additionally, we highlighted the effectiveness of COVID-19 vaccination in reducing both hospitalization and death. We recommend universal application of COVID-19 vaccination, further development of strategies to facilitate early identification of cases, and effective intensive care management of such patients.

TABLE 5 Cox regression analysis to determine factors associated with hospitalization.

	Hospitalization by Day-14				Hospitalization by Day-90			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (comparator: <50 years)								
50–64	1.05(0.91,1.21)	0.54	0.99(0.85,1.14)	0.85	1.04(0.9,1.18)	0.62	0.97(0.85,1.12)	0.71
65–79	1.13(0.98,1.3)	0.09	1.04(0.9,1.21)	0.57	1.11(0.98,1.27)	0.11	1.02(0.89,1.16)	0.81
80 +	1.74(1.46,2.09)	<0.001	1.59(1.32,1.91)	<0.001	1.7(1.43,2.01)	<0.001	1.51(1.27,1.8)	<0.001
Male sex	1.31(1.12,1.54)	0.001	1.08(0.92,1.27)	0.35	1.33(1.15,1.55)	<0.001	1.1(0.94,1.28)	0.22
Race								
Black	1.03(0.96,1.1)	0.46	0.96(0.89,1.03)	0.26	1.02(0.95,1.09)	0.63	0.95(0.89,1.02)	0.15
Other	0.84(0.75,0.95)	0.004	0.84(0.75,0.95)	0.005	0.88(0.78,0.98)	0.02	0.88(0.78,0.98)	0.02
Charlson co-morbidity index	1.1(1.09,1.11)	<0.001	1.07(1.05,1.08)	<0.0001	1.11(1.1,1.12)	<0.001	1.08(1.06,1.09)	<0.001
Alcohol use disorder	1.31(1.23,1.39)	<0.001	1.37(1.29,1.46)	<0.0001	1.31(1.24,1.39)	<0.001	1.37(1.29,1.46)	<0.001
MELD	1.05(1.05,1.06)	<0.001	1.04(1.03,1.04)	<0.0001	1.05(1.05,1.06)	<0.001	1.04(1.03,1.04)	<0.001
SARS-CoV-2 positive	0.84(0.79,0.9)	<0.001	0.91(0.85,0.97)	0.005	0.91(0.86,0.96)	0.002	0.95(0.89,1.02)	0.14
Vaccination: (comparator-unvaccinated)								
Primary series incomplete	0.95(0.81,1.1)	0.47	0.94(0.81,1.09)	0.39	0.94(0.82,1.09)	0.42	0.92(0.8,1.06)	0.24
Primary series completed	0.84(0.76,0.93)	0.001	0.84(0.75,0.92)	0.001	0.91(0.83,0.99)	0.04	0.88(0.8,0.97)	0.01
Primary series plus booster	0.58(0.47,0.71)	<0.001	0.57(0.46,0.7)	<0.0001	0.74(0.62,0.88)	0.001	0.7(0.58,0.84)	0.001

TABLE 6 Cox regression analysis to determine factors associated with mortality.

	30-day Mortality				90-day mortality			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (comparator: <50 years)								
50–64	1.35(0.86,2.13)	0.19	1.41(0.89,2.21)	0.14	1.26(0.91,1.74)	0.16	1.26(0.91,1.75)	0.16
65–79	2.24(1.45,3.48)	<0.001	2.29(1.47,3.58)	<0.001	2.1(1.54,2.87)	<0.001	2.07(1.51,2.85)	<0.001
80 +	5.05(3.12,8.17)	<0.001	4.32(2.64,7.07)	<0.001	4.99(3.53,7.06)	<0.001	4.18(2.93,5.96)	<0.001
Male sex	1.46(0.97,2.19)	0.07	0.95(0.63,1.43)	0.80	1.45(1.07,1.96)	0.02	0.92(0.68,1.25)	0.59
Race								
Black	0.77(0.65,0.92)	0.004	0.73(0.61,0.88)	0.001	0.75(0.65,0.85)	<0.001	0.69(0.6,0.79)	<0.001
Other	0.84(0.64,1.11)	0.22	0.85(0.65,1.13)	0.26	0.92(0.75,1.12)	0.38	0.93(0.76,1.13)	0.47
Charlson co-morbidity index	1.16(1.13,1.19)	<0.001	1.03(1,1.06)	0.06	1.18(1.16,1.2)	<0.001	1.06(1.04,1.08)	<0.001
Alcohol use disorder	0.9(0.78,1.04)	0.15	1.02(0.88,1.18)	0.79	0.97(0.87,1.07)	0.51	1.11(1,1.24)	0.06
MELD	1.1(1.09,1.11)	<0.001	1.09(1.08,1.1)	<0.001	1.1(1.1,1.11)	<0.001	1.08(1.08,1.09)	<0.001
SARS-CoV-2 positive	1.41(1.22,1.62)	<0.001	1.72(1.48,2)	<0.001	1.07(0.95,1.19)	0.27	1.26(1.12,1.41)	0.001
Vaccination: (comparator-unvaccinated)								
Primary series incomplete	0.64(0.42,0.97)	0.04	0.52(0.34,0.8)	0.003	0.7(0.52,0.94)	0.02	0.61(0.45,0.83)	0.002
Primary series completed	0.61(0.46,0.79)	0.002	0.45(0.34,0.59)	<0.001	0.62(0.51,0.75)	<0.001	0.5(0.41,0.61)	<0.001
Primary series PLUS booster	0.41(0.23,0.74)	0.003	0.23(0.13,0.42)	<0.001	0.38(0.24,0.61)	<0.001	0.26(0.16,0.42)	<0.001

AUTHOR CONTRIBUTIONS

Obaid S. Shaikh conceived the research idea, developed the project, reviewed, and interpreted the results, and wrote the manuscript. Peng Yan collected the data, verified analytical methods, and performed the analyses. Shari Rogal contributed to the research idea, and critically reviewed and interpreted the results. Adeel A. Butt contributed to the research idea, verified analytical methods, and critically reviewed and interpreted the results. All authors provided feedback, helped shape the analysis and contributed to the final version of the manuscript. All authors have read and approved the final version of the manuscript. Obaid Shaikh MD had full access to all the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. Obaid Shaikh MD affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

This study used data created and maintained by the Veterans Health Administration, Department of Veterans Affairs. These data are freely available to approved individuals after fulfilling the specified requirements. Requests for data must be directed to the Veterans Health Administration at the Department of Veterans Affairs. Any request must fulfil all requirements for data sharing according to the existing laws, regulations, and policies of the Department of Veterans Affairs.

TRANSPARENCY STATEMENT

The lead author Obaid S. Shaikh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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