Decreasing Case Fatality Rates for Patients With Cirrhosis Infected With SARS-CoV-2: A National COVID Cohort Collaborative Study

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BACKGROUND & AIMS: **The virulence and severity of SARS-CoV-2 infections have decreased over time in the general population due to vaccinations and improved antiviral treatments. Whether a similar trend has occurred in patients with cirrhosis is unclear. We used the National COVID Cohort Collaborative (N3C) to describe the outcomes over time.**

METHODS: **We utilized the N3C level 3 data set with uncensored dates to identify all patients with chronic liver disease (CLD) with and without cirrhosis who had SARS-CoV-2 infection as of November 2023. We described the observed 30-day case fatality rate (CFR) by month of infection. We used adjusted survival analyses to calculate relative hazard of death by month of infection compared with infection at the onset of the COVID-19 pandemic.**

RESULTS: **We identified 117,811 total patients with CLD infected with SARS-CoV-2 between March 2020 and November 2023: 27,428 (23%) with cirrhosis and 90,383 (77%) without cirrhosis. The observed 30-day CFRs during the entire study period were 1.1% (1016) for patients with CLD without cirrhosis and 6.3% (1732) with cirrhosis. Observed 30-day CFRs by month of infection varied throughout the pandemic and showed a sustained downward trend since 2022. Compared with infection in Quarter 2 of 2020 (at the beginning of the pandemic), the adjusted hazards of death at 30 days for infection in Quarter 3 of 2023 were 0.20 (95% confidence interval [CI], 0.08–0.50) for patients with CLD without cirrhosis and 0.35 (95% CI, 0.18–0.69) for patients with CLD with cirrhosis.**

CONCLUSIONS: **In this N3C study, we found that the observed 30-day CFR decreased progressively for patients with CLD both with and without cirrhosis, consistent with broader trends seen in the general population.**

Keywords: Cirrhosis; Chronic Liver Disease; COVID-19; SARS-CoV-2.

Since its emergence in 2019, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has undergone several rounds of evolution with appearance of new variants.[1,2] These variants have resulted in dramatic shifts in infection virulence, transmissibility, and clinical severity.[3] For instance, infection with the SARS-CoV-2 Omicron variant, which became the most prevalent variant since 2022, has been associated with lower rates of hospitalization and mortality among the general population compared with prior lineages.[4–6] In addition, the introduction of vaccinations and antivirals along with gains in natural immunity have also attenuated the severity of new infections.[7] As total SARS-CoV-2 related hospitalizations and severe outcomes declined throughout 2022 and 2023, the World Health Organization and many countries and jurisdictions have ended public health emergency declarations.[8,9]

Abbreviations used in this paper: AALD, alcohol-associated liver disease; CFR, case fatality rate; CI, confidence interval; CLD, chronic liver disease; EHR, electronic health record; IQR, interquartile range; IRB, institutional review board; MASLD, metabolic dysfunction-associated steatotic liver disease; N3C, National COVID Cohort Collaborative; NCATS, National Center for Advancing Translational Sciences; NIH, National Institutes of Health; OMOP, Observational Medical Outcomes Partnership; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

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Although SARS-CoV-2 infection outcomes in the general population have improved, it is unclear if these trends are also reflected in patients with cirrhosis and severe liver dysfunction. Patients with cirrhosis have worse outcomes associated with SARS-CoV-2 infection.[10–12] At the beginning of the pandemic, the presence of cirrhosis was associated with a greater than 3-fold hazard of 30-day all-cause mortality among patients who tested positive for SARS-CoV-2.[10] Vaccines against SARS-CoV-2 have been shown to be associated with a decreased risk of severe outcomes,[13–15] but patients with cirrhosis often have attenuated responses and deterioration of antibody titers due to impairments in humoral immunity.[14,16,17] Moreover, highly effective antivirals, such as Paxlovid (Niramatrelvir and Ritonavir), are recommended to be used "with caution" in patients with Child-Pugh B cirrhosis and not recommended at all for patients with Child-Pugh C cirrhosis.[18,19] Changes and trends in SARS-CoV-2 outcomes in patients with cirrhosis, therefore, cannot be assumed to be the same as those observed in the general population.

We, therefore, leveraged the National COVID Cohort Collaborative (N3C), which has been previously described in detail in multiple studies,[10,13,20–22,] to answer the above question. As of November 2, 2023, 84 sites had completed data harmonization into the N3C Data Enclave, a central, national repository of electronic health record (EHR) data. We used the N3C Data Enclave to determine whether the all-cause mortality rates for patients with chronic liver disease (CLD) with cirrhosis infected with SARS-CoV-2 have decreased in a similar fashion to patients with CLD without cirrhosis.

What You Need to Know

Background

The virulence and severity of SARS-CoV-2 infections have decreased over time in the general population. Whether a similar trend has occurred in patients with liver diseases and cirrhosis is unclear.

Findings

Thirty-day case fatality rates for patients with chronic liver disease with and without cirrhosis have declined significantly since 2022.

Implications for patient care

Mortality rates and risks from SARS-CoV-2 for patients with cirrhosis have declined dramatically despite concerns about effectiveness of vaccines and treatments in this patient population.

Methods

The N3C is a centralized, harmonized, and nationally representative clinical data resource with embedded analytics.[10,20–23] In brief, the N3C Data Enclave contains EHR data of patients who were tested for SARS-CoV-2 or had related symptoms since 2020 with 2 years of look-back data. All EHR data in the N3C Data Enclave are harmonized in the Observational Medical Outcomes Partnership (OMOP) common data model, version 5.3.1.[24] For all analyses here, we utilized the N3C Data Enclave Level 3 Limited Data Set, version 148, dated November 2, 2023, and accessed on November 2, 2023. As opposed to the de-identified versions of the N3C dataset used in previous analyses,[10,13] Level 3 includes actual geographies and dates of services and is not subjected to date shifting involved in de-identification.[25] This allows for determination of "eras" and "waves" of SARS-CoV-2 infection associated with prevalent variants (eg, Alpha, Delta, and Omicron).[4,7]

SARS-CoV-2 positivity status, vaccination status and type (based on the first administered dose), CLD etiologies, and cirrhosis definitions were based off OMOP concept identifiers used in previous works utilizing the N3C Data Enclave.[10,13] We attempted to capture initial SARS-CoV-2 infections; therefore, positivity status was isolated at the first instance/recording of a positive test, and we did not consider repeat infections. Decompensated cirrhosis was defined based on the presence of decompensation symptoms per OMOP concept identifiers, which largely correspond with International Classification of Diseases codes, in previous publications.[10,13] We excluded all patients who had undergone orthotopic liver transplantation and included only adults (documented age $\geq$18 years). The outcome of death was centrally defined based on N3C shared logic.[10,20,21] We defined the timeline of predominant SARS-CoV-2 variants in the United States based on data provided by the Centers for Disease Control, specifically "Alpha" between January 2021 and June 2021, "Delta" between July 2021 and November 2021, and "Omicron" since December 2021 through September 2023.[7,26]

Baseline Characteristics

Baseline demographic characteristics extracted from N3C Data Enclave included age, sex, race/ethnicity, height, weight, body mass index, and state and region of origin.[27] We utilized a "Modified Charlson Index" based on the Charlson Comorbidity Index excluding "mild liver disease" and "severe liver disease."[10] We utilized N3C shared logic sets and definitions for the international normalized ratio to extract laboratory results.[10] We calculated the Model for End-stage Liver Disease 3.0 (MELD 3.0) score closest to, but within 30 days before to 7 days after the date of the earliest positive SARS-CoV-2 test (for infected patients) or latest negative test (for non-infected patients).[28]

Study Questions

We focused on 2 study questions: (1) How did the observed 30-day case fatality rates (CFR) of patients with CLD with cirrhosis and without cirrhosis evolve throughout the pandemic?; and (2) Has the protection of vaccinations in patients with CLD with cirrhosis remained durable with evolving variants and changes in therapeutics throughout the pandemic?

For the first question regarding the evolution of CFR throughout the pandemic, we calculated and compared the monthly observed all-cause 30-day CFRs among patients with CLD with and without cirrhosis (regardless of vaccination status) who tested positive for SARS-CoV-2. We then used Cox proportional hazard models to compare the quarterly hazard of 30-day mortality (eg, Quarter 3 of 2023) vs Quarter 2 of 2020 at the onset of the pandemic for patients with CLD without cirrhosis and with cirrhosis. Cox regression models were adjusted for age, sex, race/ethnicity, CLD etiology, modified Charlson Index, and region of origin. We did not include vaccination status and type in this set of Cox modeling due to vaccines not largely available to the general public until after Quarter 1 of 2021.

In the second study question regarding the durability of vaccinations, we used Cox proportional hazard models to compare the quarterly hazard of 30-day mortality seen in patients with CLD with cirrhosis with vaccination ("+cirrhosis/+vaccination") and without vaccination ("+cirrhosis/−vaccination") vs a control population, defined as non-vaccinated patients with CLD without cirrhosis ("−cirrhosis/−vaccination"). In addition to our analyses for the entire cirrhosis population, we also conducted analyses for the subset of patients with decompensated cirrhosis ("+decompensated cirrhosis/+vaccination" and "+decompensated cirrhosis/−vaccination") compared with the reference population of "−cirrhosis/−vaccination." All Cox regression models here were also adjusted for age, sex, race/ethnicity, CLD etiology, modified Charlson Index, and region of origin.

Statistical Analyses

Clinical characteristics and laboratory data were summarized by medians and interquartile ranges (IQRs) for continuous variables, frequencies, or percentages (%) for categorical variables. Comparisons between groups were performed using Kruskal-Wallis and χ^2 tests where appropriate. All patients were followed until their last visit, procedure, measurement, observation, or condition occurrence in the N3C Data Enclave. Two-sided *P*-values $< .05$ were considered statistically significant in all analyses. All extractions, transformations, and analyses were conducted using the Palantir Foundry implementations of Spark-Python, version 3.6, and Spark-SQL, version 3.0. Statistical analyses were performed using the Palantir Foundry implementation of Spark-R, version 3.5.1 "Feather Spray" (R Core Team).[29]

Institutional Review Board Oversight

Submissions of data from individual centers to N3C are governed by a central institutional review board (IRB) protocol #IRB00249128 hosted at Johns Hopkins University School of Medicine via the SMART IRB40 Master Common Reciprocal reliance agreement. This central IRB covers data contributions and transfer to N3C but does not cover research using N3C data. If elected, individual sites may choose to exercise their own local IRB agreements instead of utilizing the central IRB. As the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) is the steward of the repository, data received and hosted by NCATS on the N3C Data Enclave, its maintenance, and its storage are covered under a central NIH IRB protocol to make EHR-derived data available for the clinical and research community to use for studying COVID-19. Our institution has an active data transfer agreement with N3C. This specific analysis of the N3C Data Enclave was approved by N3C under Data Use Agreements titled "[RP-E77B79] COVID-19 Outcomes in Vaccinated Patients with Liver Diseases." The use of N3C data for this study was authorized by the IRB at the University of California, San Francisco under Study #21-35861.

Results

Characteristics of Patients With CLD Infected With SARS-CoV-2

The full baseline characteristics are presented in Table 1. We identified 117,811 total patients with CLD who tested positive for SARS-CoV-2 between March 2020 and November 2023. Of these 117,811 total patients with CLD with SARS-CoV-2, 90,383 (77%) did not have cirrhosis and 27,428 (23%) had cirrhosis. Thirty-six percent (42,561) of all patients with CLD received at least one dose of SARS-CoV-2 vaccine with a relative rate that was higher in patients without cirrhosis (38% or 34,007 patients) vs that in those with cirrhosis (31% or 8,554). In general, patients with cirrhosis were more likely to be men (52% vs 43%), older (median age, 60 vs 51 years), non-Hispanic White (62% vs 61%), have alcohol-associated liver disease as their etiology (27% vs 6%), and have higher modified Charlson scores (median, 3 vs 1). Patients with decompensated cirrhosis comprised 71% (19,600) of the total patients with cirrhosis. The baseline characteristics of patients with CLD both with and without cirrhosis by different infection waves are presented in Supplementary Tables 1 and 2. These demonstrated that although there were minor shifts in the characteristics of the cohort throughout the pandemic with a greater predominance of female and older populations.

Table 1. Baseline Characteristics of the 117,811 Patients With CLD Who Were Infected With SARS-CoV-2

	Patients with CLD without cirrhosis (n = 90,383)	Patients with CLD with cirrhosis (n = 27,428)	*P*-value
Female	51,826 (57)	13,274 (48)	< .01
Age, *years*	51 (39–61)	60 (50–68)	< .01
18–49	41,803 (46)	6735 (25)	
50–64	32,033 (35)	10,997 (40)	
65+	16,547 (18)	9696 (35)	
Race/ethnicity			< .01
White	54,980 (61)	17,007 (62)	
Black/African American	12,529 (14)	5118 (19)	
Hispanic	14,518 (16)	3167 (12)	
Asian/unknown	2699 (3)	539 (2)	
Unknown/other	5657 (6)	1597 (6)	
Height, *cm*	168 (160-175)	168 (161-178)	< .01
Weight, *kg*	94 (77–115)	86 (70–107)	< .01
BMI, kg/m^2	33 (28–38)	30 (25–36)	< .01
Liver disease etiology			< .01
MASLD	67,616 (75)	11,401 (42)	
Hepatitis C	13,168 (15)	4922 (18)	
AALD	5085 (6)	7542 (27)	
Hepatitis B	3453 (4)	1199 (4)	
Cholestatic	237 (0)	1509 (6)	
Autoimmune	824 (1)	855 (3)	
Decompensated cirrhosis	0 (0)	19,600 (71)	
Modified Charlson Index[a]	1 (0–3)	3 (1–6)	< .01
Region			< .01
Northeast	4988 (6)	1593 (6)	
Midwest	9502 (11)	3581 (13)	
South	13,343 (15)	4372 (16)	
West	4929 (5)	1004 (4)	
Other	57,626 (64)	16,878 (62)	
Initial vaccine type			< .01
BNT162b2	18,379 (20)	4357 (16)	
mRNA-1273	12,338 (14)	3260 (12)	
JNJ-784336725 and Other[b]	3051 (3)	786 (3)	
Outcome			< .01
Death	2302 (3)	5102 (19)	< .001
Death in 30 days	1016 (1)	1732 (6)	< .001
Death in 90 days	1337 (1)	2598 (9)	< .001

Note: Continuous variables are described as medians with interquartile ranges in parentheses, ordinal and categorical variables are described as counts with percentages in parentheses.
AALD, Alcohol-associated liver disease; BMI, body mass index; CLD, chronic liver diseases; MASLD, metabolic dysfunction-associated steatotic liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Modified Charlson Index was calculated based on the original Charlson Comorbidity Score excluding weights for "mild liver disease" and "severe liver disease."
[b]Categories were consolidated to adhere to N3C rules that small cells with n <20 must be obfuscated.

Observed CFRs Over Time and Era of Infection

The overall observed 30-day CFR during the entire study period was 1.1% (1016) for patients with CLD without cirrhosis and 6.3% (1731) for those with cirrhosis. The observed 30-day CFR by month of infection along with annotations by eras/waves of infection ("Alpha," "Delta," and "Omicron") is displayed in Figure 1*A*. At the start of the pandemic in March 2020, observed CFRs were estimated to be 4.2% for patients without cirrhosis and 12.0% for patients with cirrhosis. These rates gradually declined throughout 2020 and the beginning of 2021 with the introduction of vaccinations. In the summer of 2021, however, observed CFRs surged to as a high as 1.9% for patients without cirrhosis and 10.8% for patients with cirrhosis during the late "Alpha" and early "Delta" surge. These CFRs gradually declined throughout 2022 and 2023, reaching an average of 0.7%

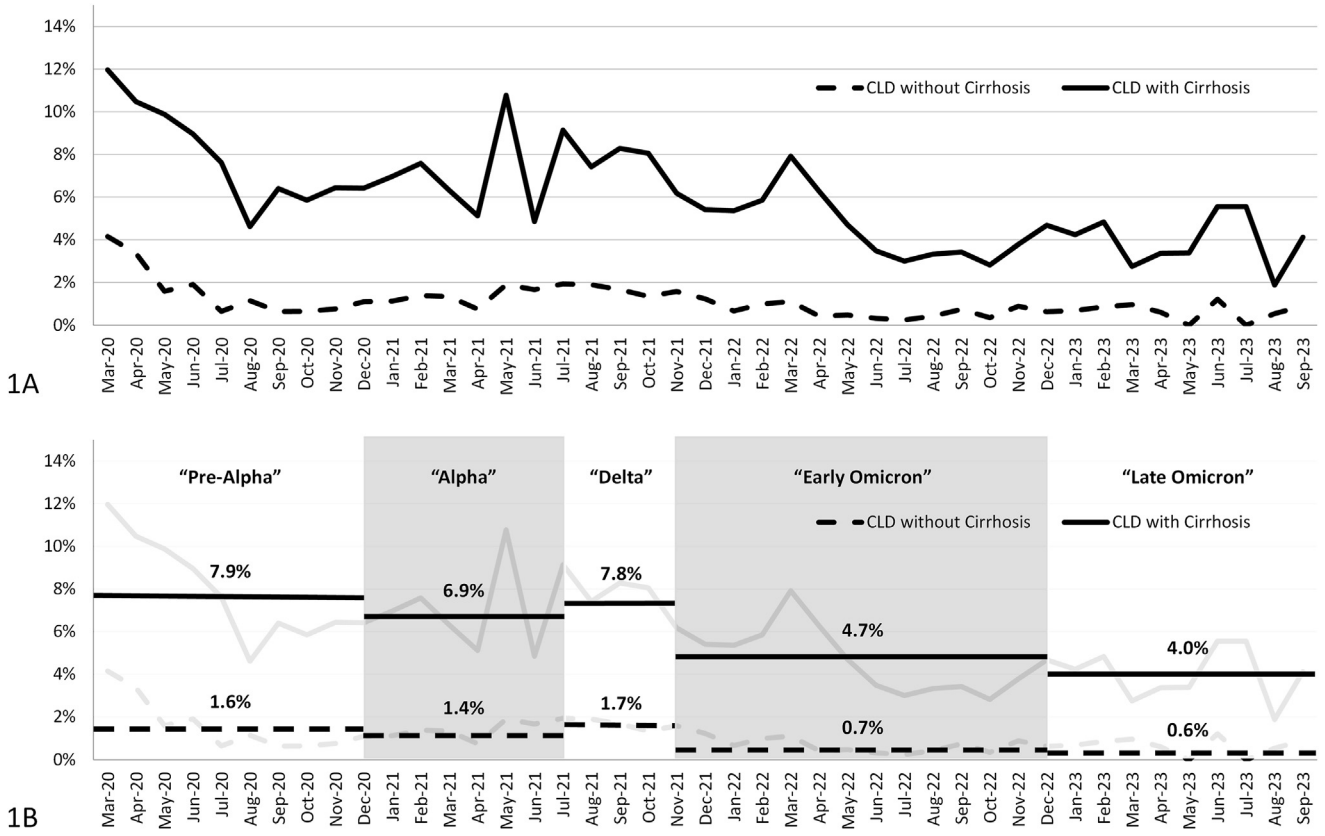

Figure 1. (*A*) Observed 30-day CFR for patients with CLD with SARS-CoV-2 by month of infection. (*B*) Average 30-day CFR for patients with CLD with SARS-CoV-2 by infection era/wave.

and 4.7% in the early "Omicron" era (November 2021 through December 2022) and 0.6% and 4.0% in the late "Omicron" era (January 2023 through September 2023), for patients without cirrhosis and with cirrhosis, respectively. Average CFRs by eras/waves of infection are superimposed in Figure 1*B*.

Relative Hazard of 30-Day Mortality at Each Quarter vs at the Onset of the Pandemic

The relative hazards of 30-day mortality at each quarter of infection vs Quarter 2 of 2020 as a reference are presented in Table 2 for patients with CLD without cirrhosis and Table 3 for patients with CLD with cirrhosis. In adjusted analyses for patients with CLD both with and without cirrhosis, the relative hazards of 30-day mortality in all quarters after Quarter 2 of 2020 were less than that at the onset of the pandemic. Compared with infection in Quarter 2 of 2020, the relative hazard of 30-day mortality for infection in Quarter 3 of 2021 was 0.69 (95% confidence interval [CI], 0.55–0.87; $P < .01$) for patients with CLD without cirrhosis and 0.79 (95% CI, 0.65–0.97; $P < .01$) for patients with CLD with cirrhosis. This time period of Quarter 3 of 2021 corresponded with the Delta era between July 2021 and November 2021.[7,26] Compared with infection in Quarter 2 of 2020, the relative hazard of 30-day mortality for infection in Quarter 3 of 2023 was 0.20 (95% CI, 0.08–0.50; $P < .01$) for patients with CLD without cirrhosis and 0.35 (95% CI, 0.18–0.69; $P < .01$) for patients with CLD with cirrhosis. In the evaluation of the contributions of CLD etiology for patients with cirrhosis – compared to patients with metabolic dysfunction-associated liver disease (MASLD), patients with alcohol-associated liver disease (AALD) had a relative hazard of 30-day mortality of 1.19 (95% CI, 1.06–1.34; $P < .01$). In contrast, compared with patients with cirrhosis due to MASLD, patients with cirrhosis due to cholestatic liver disease had a relative hazard of 30-day mortality of 0.76 (95% CI, 0.59–0.98; $P = .04$).

Impact of Vaccination on Observed CFRs

To determine the impact of vaccinations on CFRs over time, we calculated the relative hazards of mortality for patients with cirrhosis with vaccinations ("+cirrhosis/+vaccination") and without vaccinations ("+cirrhosis/−vaccination") vs patients with CLD without cirrhosis and without vaccinations ("−cirrhosis/−vaccination") at each quarter time-period. This data is displayed in Figure 2*A*. With the introduction of vaccinations in Quarter 1 of 2021, there was an initial mortality benefit associated with vaccination in the remainder of 2021; compared to the reference population of −cirrhosis/−vaccination, the

Table 2. Relative Hazards of 30-day Mortality at Each Quarter of Infection for Patients With CLD Without Cirrhosis

	Univariable Cox regression			Multivariable Cox regression		
	HR	95% CI	*P*-value	aHR	95% CI	*P*-value
Quarter of infection						
2020-Q2	1 [Reference]			1 [Reference]		
2020-Q3	0.29	0.21–0.41	< .01	0.34	0.24–0.48	< .01
2020-Q4	0.33	0.26–0.40	< .01	0.35	0.28–0.44	< .01
2021-Q1	0.45	0.36–0.57	< .01	0.42	0.33–0.53	< .01
2021-Q2	0.46	0.33–0.64	< .01	0.46	0.33–0.64	< .01
2021-Q3	0.67	0.54–0.84	< .01	0.69	0.55–0.87	< .01
2021-Q4	0.49	0.39–0.61	< .01	0.52	0.41–0.65	< .01
2022-Q1	0.27	0.21–0.34	< .01	0.25	0.20–0.32	< .01
2022-Q2	0.15	0.09–0.26	< .01	0.12	0.07–0.21	< .01
2022-Q3	0.16	0.09–0.26	< .01	0.11	0.07–0.19	< .01
2022-Q4	0.24	0.14–0.40	< .01	0.15	0.09–0.26	< .01
2023-Q1	0.30	0.17–0.53	< .01	0.18	0.10–0.32	< .01
2023-Q2	0.21	0.05–0.86	.03	0.11	0.03–0.45	< .01
2023-Q3	0.32	0.13–0.78	.01	0.20	0.08–0.50	< .01
Age, *years*	1.00	1.00–1.00	< .01	1.00	1.00–1.00	<0.01
Female	0.53	0.47–0.60	< .01	0.62	0.54–0.70	<0.01
Race/ethnicity						
White	1 [Reference]			1 [Reference]		
Black/African American	1.21	1.02–1.44	.03	0.75	0.63–0.90	< .01
Hispanic	0.71	0.58–0.87	< .01	0.70	0.57–0.87	< .01
Asian	1.30	0.94–1.80	.11	1.31	0.93–1.84	.12
Unknown/other	1.06	0.82–1.36	.66	1.07	0.83–1.38	.59
Etiology of liver disease						
MASLD	1 [Reference]			1 [Reference]		
Hepatitis C	1.88	1.62–2.18	< .01	1.54	1.32–1.80	< .01
AALD	1.26	0.97–1.64	.08	1.11	0.84–1.46	.47
Hepatitis B	1.61	1.22–2.13	< .01	1.10	0.81–1.47	.55
Cholestatic	0.43	0.06–3.09	.41	0.48	0.07–3.43	.47
Autoimmune	1.76	1.04–2.99	.04	1.72	1.01–2.92	.05
Modified Charlson Index[a] (per point)	1.23	1.21–1.25	< .01	1.23	1.21–1.25	<0.01
Region						
Northeast	1 [Reference]			1 [Reference]		
Midwest	0.52	0.40–0.67	< .01	0.69	0.53–0.90	< .01
South	0.56	0.45–0.71	< .01	0.88	0.67–1.13	.32
West	0.21	0.14–0.32	< .01	0.37	0.24–0.58	< .01
Other	0.39	0.32–0.48	< .01	0.58	0.47–0.72	< .01

Note: Multivariable Cox regression model was adjusted for sex, age, race/ethnicity, liver disease etiology, modified Charlson score, and region.
AALD, Alcohol-associated liver disease; aHR, adjusted hazard ratio; CI, confidence interval; CLD, chronic liver diseases; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease.
[a]Modified Charlson Index was calculated based on the original Charlson Comorbidity Score excluding weights for "mild liver disease" and "severe liver disease."

relative hazard of 30-day mortality was 0.72 to 1.49 for +cirrhosis/+vaccination vs 2.39 to 3.42 for +cirrhosis/−vaccination. The relative hazards of mortality for +cirrhosis/+vaccination and +cirrhosis/−vaccination in comparison to −cirrhosis/−vaccination both increased throughout 2022 and 2023, peaking in Quarter 3 of 2022. Despite this, the comparative mortality advantage associated with vaccination (hazard ratio for +cirrhosis/+vaccination being smaller than +cirrhosis/−vaccination) largely remained present throughout the entire study period. Our analyses of the subset of patients with decompensated cirrhosis demonstrated a similar pattern in Figure 2*B*.

Discussion

In this retrospective study utilizing the National COVID Cohort Collaborative Data Enclave, we found that the observed 30-day CFRs decreased progressively for patients with CLD. Specifically, in our cohort of 27,428 patients with CLD with cirrhosis, 30-day mortality rates declined from 12.0% at the beginning of the COVID-19 pandemic and 10.8% during the Delta era to around 3% in the late Omicron era (corresponding to late 2022 through 2023). These decreases in observed CFRs are largely consistent with those seen in the general population. Moreover, our Cox proportional modeling

Table 3. Relative Hazards of 30-day Mortality at Each Quarter of Infection for Patients With CLD With Cirrhosis

	Univariable Cox regression			Multivariable Cox regression		
	HR	95% CI	*P*-value	aHR	95% CI	*P*-value
Quarter of infection						
2020-Q2	1 [Reference]			1 [Reference]		
2020-Q3	0.59	0.47–0.76	< .01	0.59	0.46–0.76	< .01
2020-Q4	0.60	0.50–0.71	< .01	0.62	0.52–0.74	< .01
2021-Q1	0.67	0.55–0.80	< .01	0.66	0.54–0.79	< .01
2021-Q2	0.65	0.50–0.84	< .01	0.67	0.51–0.86	< .01
2021-Q3	0.77	0.63–0.94	< .01	0.79	0.65–0.97	.02
2021-Q4	0.58	0.47–0.70	< .01	0.60	0.49–0.73	< .01
2022-Q1	0.53	0.45–0.63	< .01	0.53	0.44–0.63	< .01
2022-Q2	0.44	0.32–0.60	< .01	0.40	0.29–0.55	< .01
2022-Q3	0.31	0.22–0.43	< .01	0.27	0.20–0.38	< .01
2022-Q4	0.37	0.27–0.53	< .01	0.32	0.23–0.46	< .01
2023-Q1	0.40	0.27–0.58	< .01	0.33	0.22–0.49	< .01
2023-Q2	0.37	0.17–0.78	< .01	0.32	0.15–0.67	< .01
2023-Q3	0.43	0.22–0.84	.01	0.35	0.18–0.69	< .01
Age, *years*	1.00	1.00–1.00	<2e-16	1.00	1.00–1.00	< .01
Female	0.81	0.73–0.89	< .01	.87	0.79–0.96	< .01
Race/ethnicity						
White	1 [Reference]			1 [Reference]		
Black/African-American	0.92	0.81–1.04	.18	0.76	0.66–0.86	< .01
Hispanic	1.01	0.87–1.17	.92	0.93	0.80–1.09	.37
Asian	1.32	0.98–1.78	.07	1.25	0.92–1.71	.15
Unknown/other	1.17	0.96–1.41	.12	1.16	0.96–1.42	.13
Etiology of liver disease						
MASLD	1 [Reference]			1 [Reference]		
Hepatitis C	1.04	0.91–1.18	.61	1.04	0.90–1.19	.61
AALD	1.12	1.00–1.25	.06	1.19	1.06–1.34	< .01
Hepatitis B	1.01	0.80–1.28	.93	0.91	0.71–1.16	.46
Cholestatic	0.69	0.54–0.89	< .01	0.76	0.59–0.98	.04
Autoimmune	0.98	0.74–1.30	.90	1.11	0.84–1.47	.48
Modified Charlson Index[a] (per point)	1.07	1.06– 1.08	< .01	1.08	1.07–1.09	< .01
Region						
Northeast	1 [Reference]			1 [Reference]		
Midwest	0.81	0.66–0.99	.04	0.92	0.75–1.14	.44
South	0.70	0.58–0.85	< .01	0.90	0.73–1.11	.31
West	0.41	0.29–0.58	< .01	0.49	0.35–0.70	< .01
Other	0.59	0.50–0.70	< .01	0.69	0.58–0.83	< .01

Note: Multivariable Cox regression model was adjusted for sex, age, race/ethnicity, liver disease etiology, modified Charlson score, and region.
AALD, Alcohol-associated liver disease; aHR, adjusted hazard ratio; CI, confidence interval; CLD, chronic liver diseases; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease.
[a]Modified Charlson Index was calculated based on the original Charlson Comorbidity Score excluding weights for "mild liver disease" and "severe liver disease."

indicated that the decreases in mortality rates persisted even after adjusting for demographic factors, CLD etiologies, and comorbid conditions (as summarized by the Modified Charlson Index).

Our calculations of CFR and survival modeling did reveal several findings about the overall trajectory of the pandemic. First, while mortality rates and hazards steadily declined throughout the pandemic (highest CFRs being in Quarter 2 of 2020), there was a significant local peak during the Delta era of infection, corresponding to Quarter 3 of 2021. Although increases in mortality rates were seen in both patients with CLD without and with cirrhosis, they never exceeded the rates seen at the beginning of the pandemic – thereby most likely indicating effects of vaccinations blunting the impact of the Delta variant at the time. Second, mortality rates and hazards declined all throughout the Omicron era, with the trough occurring in Quarter 2 of 2023, likely the result of Omicron's relatively mild clinical course compared with previous variants in combination with the impact of vaccinations.[4,5]

Moreover, in our survival analyses, we found that the etiology of liver disease may have had a differential

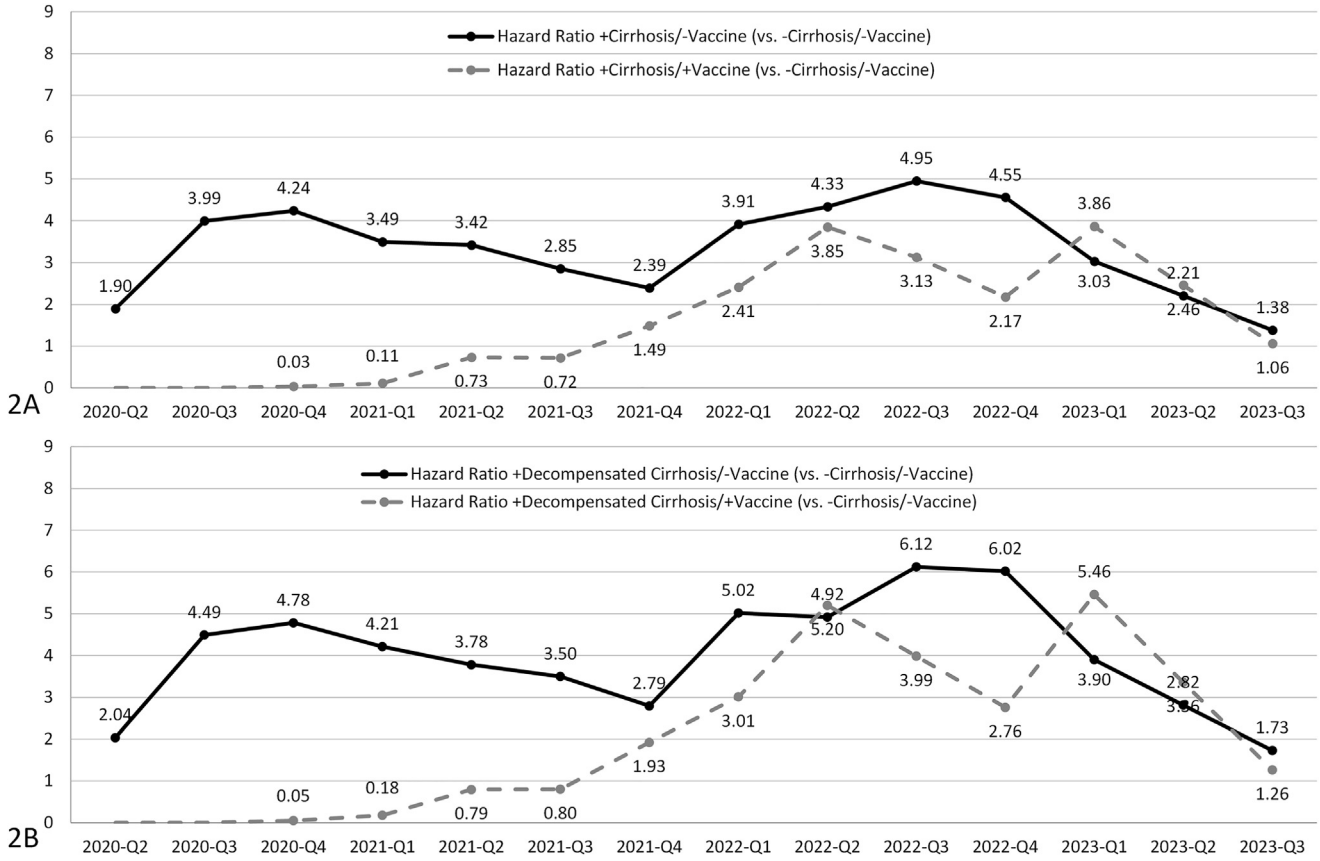

Figure 2. (*A*) Comparisons of the impact of cirrhosis and vaccination status on relative hazard of mortality by quarter of infection. (*B*) Comparisons of the impact of decompensated cirrhosis and vaccination status on relative hazard of mortality by quarter of infection.

impact of mortality risks: patients with cirrhosis with AALD had a higher risk of mortality, whereas those with cholestatic liver disease had a lower risk of mortality compared with the reference population of MASLD. It is interesting, however, that we did not find statistical associations in the comparisons of patients with cirrhosis with hepatitis C, hepatitis B, and autoimmune liver disease vs the reference population of MASLD. These results indicate that MASLD and its associated comorbid conditions resulting from metabolic syndrome may not have been as strong as a risk for poor outcomes for SARS-CoV-2 infection in the latter parts of the pandemic. Overall, concerns regarding a differential finding in patients with CLD with cirrhosis (eg, COVID-19 outcomes did not improve with vaccinations and treatments) throughout the pandemic were not supported by the findings of this study. Our data demonstrated that vaccinations were associated with a durable mortality advantage that largely persisted throughout the pandemic and into late 2023.

One curious finding was that while absolute mortality decreases were greater for patients with CLD with cirrhosis, the relative mortality decreases were greater for those without cirrhosis. This led to a paradoxical finding that patients with cirrhosis (regardless of vaccination status) had a higher relative hazard of mortality in the latter parts of the pandemic (2022 and 2023) than in the earlier parts of the pandemic (prior to 2022) in comparison to unvaccinated patients without cirrhosis. The explanation for this finding is likely multifactorial due to our use of unvaccinated patients without cirrhosis as the comparison population. First, there is likely a significant amount of post-infection immunity as infection with SARS-CoV-2, especially in the latter parts of the pandemic, often went unreported and may not be apparent to health systems. Second, a similar misclassification may have occurred with regards to vaccination status as the N3C Data Enclave only includes vaccination information for patients who had received their vaccines in hospitals and health systems – and does not necessarily include vaccinations administered at other venues (eg, pharmacies, mass vaccination sites, and other non-traditional sites). The "non-vaccination" state that we observed, therefore, may be more accurately noted and classified as "lack of recorded vaccination." These findings also likely reflect an underestimate of the benefit of vaccinations in both the cirrhosis and non-cirrhosis populations at the end of the pandemic. Third, we did not analyze the specific contributions of vaccine types (eg, mRNA-1273 vs BNT162b2) or the number of vaccinations. This is because as patients were encouraged to mix and match vaccination types throughout the

pandemic,[30] it became technically challenging to disaggregate and ascertain this information from the N3C Enclave.

Finally, in addition to the limitations noted above, there are also limitations with regards to case ascertainment. In the latter part of the pandemic, diagnosis of SARS-CoV-2 infection shifted from tests administered at health care facilities to those done at home and in nontraditional health care settings. This means that the population that we isolated from the N3C Enclave is likely only a sample of the full population of patients who were infected with SARS-CoV-2. In fact, our reliance upon a diagnosis of SARS-CoV-2 infection at a health care facility means that the quality of data from the early pandemic is higher than those from the latter parts of the pandemic. It follows that estimates for the later dates (2022 and 2023) may be less accurate, and there were fewer SARS-CoV-2 infection cases ascertained by the N3C Data Enclave (Supplementary Tables 1 and 2).

Despite these limitations, our study is one of the largest studies of the longitudinal evolution of the COVID-19 pandemic in patients with liver diseases. Overall, our data indicates that patients with cirrhosis have benefited from improved efficacies of treatments and vaccinations as indicated by declining CFRs mirroring those seen in general population. This is despite concerns regarding effectiveness of vaccinations and limitations on direct oral antiviral use. Although our data showed that, while patients with cirrhosis remains higher risk of poor outcomes compared with patients without cirrhosis when infected with SARS-CoV-2, this likely is an artifact of the baseline clinical risk associated with cirrhosis. These results imply that patients with cirrhosis should continue to follow updated vaccination, treatment, and personal protective equipment guidance designed for the general population – and similarly, may have a degree of "return to normalcy" given CFR trends.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.07.028.

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Conflicts of interest

The authors disclose no conflicts.

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Data Availability

The N3C Data Enclave (covid.cd2h.org/enclave) houses fully reproducible, transparent, and broadly available limited and de-identified datasets (HIPAA definitions: https://www.hhs.gov/hipaa/for-professionals/privacy/specialtopics/de-identification/index.html). Data is accessible by investigators at institutions that have signed a Data Use Agreement with the National Institutes of Health who have taken human subjects and security training and attest to the N3C User Code of Conduct. Investigators wishing to access the limited dataset must also supply an institutional review board protocol. All requests for data access are reviewed by the National Institutes of Health Data Access Committee. A full description of the N3C Enclave governance has been published; information about how to apply for access is available on the NCATS website: https://ncats.nih.gov/n3c/about/applying-for-access. Reviewers and health authorities will be given access permission and guidance to aid reproducibility and outcomes assessment. A Frequently Asked Questions about the data and access has been created at: https://ncats.nih.gov/n3c/about/program-faq The data model is OMOP 5.3.1, specifications are posted at: https://ncats.nih.gov/files/OMOP_CDM_COVID.pdf.

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Supplementary Table 1. Baseline Characteristics of Patients With CLD Without Cirrhosis by "Era" of SARS-CoV-2 Infection

	Pre-Alpha (n = 29,655)	Alpha (n = 13,232)	Delta (n = 12,772)	Early Omicron (n = 31,844)	Late Omicron (n = 2,880)
Female	16,392 (55)	7315 (55)	7256 (57)	19,011 (60)	1852 (64)
Age, *years*	51 (40-61)	52 (40-62)	50 (38-61)	51 (39-61)	56 (43-65)
18–49	13,649 (46)	5845 (44)	6311 (49)	14,953 (47)	1045 (36)
50–64	10,653 (36)	4951 (37)	4277 (33)	11,107 (35)	1045 (36)
65+	5353 (18)	2436 (18)	2184 (17)	5784 (18)	790 (27)
Race/ethnicity					
White	16,182 (55)	7711 (58)	9322 (73)	20,047 (63)	1718 (60)
Black/African American	3910 (13)	1925 (15)	1472 (12)	4664 (15)	558 (19)
Hispanic	6580 (22)	2110 (16)	1247 (10)	4185 (13)	396 (14)
Asian/unknown/other[a]	2983 (10)	1486 (11)	731 (6)	2948 (9)	208 (7)
Height, *cm*	168 (160-175)	168 (160-175)	168 (160-176)	168 (160-175)	166 (160-175)
Weight, *kg*	95 (79-117)	94 (76-114)	95 (78-117)	94 (77-114)	93 (77-111)
BMI, kg/m^2	32 (28-38)	33 (28-38)	33 (28-39)	33 (28-38)	33 (28-39)
Liver disease etiology					
MASLD	22,332 (75)	9665 (73)	9277 (73)	24,075 (76)	2267 (79)
Hepatitis C	3690 (12)	1973 (15)	2288 (18)	4831 (15)	386 (13)
AALD	2071 (7)	891 (7)	715 (6)	1308 (4)	100 (3)
Hepatitis B	1232 (4)	548 (4)	342 (3)	1237 (4)	94 (3)
Cholestatic and autoimmune[a]	330 (1)	155 (1)	150 (1)	393 (1)	33 (1)
Modified Charlson Index[b]	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-3)	2 (1-5)
Region					
Northeast	2071 (7)	1223 (9)	296 (2)	1284 (4)	114 (4)
Midwest	4115 (14)	1541 (12)	1137 (9)	2475 (8)	234 (8)
South	3027 (10)	1471 (11)	1634 (13)	6121 (19)	1090 (38)
West	1974 (7)	803 (6)	545 (4)	1444 (5)	158 (5)
Other	18,468 (62)	8194 (62)	9160 (72)	20,520 (64)	1284 (45)
Initial vaccine type					
BNT162b2	6071 (20)	2527 (19)	2081 (16)	6966 (22)	734 (25)
mRNA-1273	4623 (16)	1585 (12)	1133 (9)	4483 (14)	514 (18)
JNJ-784336725 and Other[a]	935 (3)	451 (3)	449 (4)	1126 (4)	90 (3)
Outcome					
Death	834 (3)	391 (3)	405 (3)	632 (2)	40 (1)
Death in 30 days	377 (1)	163 (1)	216 (2)	240 (1)	20 (1)
Death in 90 days	479 (2)	207 (2)	272 (2)	346 (1)	33 (1)

Note: Continuous variables are described as medians with interquartile ranges in parentheses, ordinal and categorical variables are described as counts with percentages in parentheses.

AALD, Alcohol-associated liver disease; BMI, body mass index; CLD, chronic liver diseases; MASLD, metabolic dysfunction-associated steatotic liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Categories were consolidated to adhere to N3C rules that small cells with n <20 must be obfuscated.

[b]Modified Charlson Index was calculated based on the original Charlson Comorbidity Score excluding weights for "mild liver disease" and "severe liver disease."

Supplementary Table 2. Baseline Characteristics of Patients With CLD With Cirrhosis by "Era" of SARS-CoV-2 Infection

	Pre-Alpha (n = 8231)	Alpha (n = 4341)	Delta (n = 3606)	Early Omicron (n = 10,073)	Late Omicron (n = 1177)
Female	3760 (46)	2079 (48)	1815 (50)	5021 (50)	599 (51)
Age, *years*	60 (51-68)	60 (50-68)	59 (48-67)	60 (49-68)	62 (53-71)
18–49	1852 (23)	1038 (24)	1012 (28)	2599 (26)	234 (20)
50–64	3378 (41)	1792 (41)	1413 (39)	3979 (40)	435 (37)
65+	3001 (36)	1511 (35)	1181 (33)	3495 (35)	508 (43)
Race/ethnicity					
White	4593 (56)	2581 (59)	2627 (73)	6475 (64)	731 (62)
Black/African American	1533 (19)	853 (20)	549 (15)	1907 (19)	276 (23)
Hispanic	1366 (17)	520 (12)	245 (7)	912 (9)	124 (11)
Asian/unknown/other[a]	739 (9)	387 (9)	185 (5)	779 (8)	46 (4)
Height, *cm*	169 (161-178)	168 (160-178)	169 (162-178)	168 (161-178)	170 (163-178)
Weight, *kg*	87 (72-108)	86 (70-105)	86 (72-107)	86 (70-106)	86 (70-104)
BMI, kg/m^2	30 (25-36)	29 (25-36)	30 (25-36)	30 (25-36)	30 (26-36)
Liver disease etiology					
MASLD	3310 (40)	1734 (40)	1550 (43)	4251 (42)	556 (47)
Hepatitis C	1440 (17)	750 (17)	713 (20)	1820 (18)	199 (17)
AALD	2348 (29)	1296 (30)	934 (26)	2661 (26)	303 (26)
Hepatitis B	379 (5)	200 (5)	129 (4)	444 (4)	47 (4)
Cholestatic and autoimmune[a]	754 (9)	361 (8)	280 (8)	897 (9)	72 (6)
Decompensated cirrhosis	5641 (69)	3142 (72)	2600 (72)	7334 (73)	883 (75)
Modified Charlson Index[b]	2 (1-5)	3 (1-6)	3 (1-6)	3 (1-7)	5 (3-8)
Region					
Northeast	666 (8)	365 (8)	68 (2)	440 (4)	54 (5)
Midwest	1312 (16)	633 (15)	427 (12)	1114 (11)	95 (8)
South	879 (11)	569 (13)	498 (14)	2011 (20)	415 (35)
West	386 (5)	145 (3)	117 (3)	309 (3)	47 (4)
Other	4988 (61)	2629 (61)	2496 (69)	6199 (62)	566 (48)
Initial vaccine type					
BNT162b2	1133 (14)	588 (14)	532 (15)	1850 (18)	254 (22)
mRNA-1273	1017 (12)	424 (10)	334 (9)	1290 (13)	195 (17)
JNJ-784336725 and other[a]	184 (2)	120 (3)	115 (3)	335 (3)	32 (3)
Outcome					
Death	1714 (21)	942 (22)	715 (20)	1619 (16)	112 (10)
Death in 30 days	604 (7)	302 (7)	277 (8)	504 (5)	45 (4)
Death in 90 days	847 (10)	439 (10)	403 (11)	827 (8)	82 (7)

Note: Continuous variables are described as medians with interquartile ranges in parentheses, ordinal and categorical variables are described as counts with percentages in parentheses.

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