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Short Communication

Trends of Cirrhosis-related Mortality in the USA during the COVID-19 Pandemic

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Abstract

Immunocompromised status and interrupted routine care may render patients with cirrhosis vulnerable to the coronavirus disease 2019 (COVID-19) pandemic. A nationwide dataset that includes more than 99% of the decedents in the U.S. between April 2012 and September 2021 was used. Projected age-standardized mortality during the pandemic were estimated according to prepandemic mortality rates, stratified by season. Excess deaths were determined by estimating the difference between observed and projected mortality rates. A temporal trend analysis of observed mortality rates was also performed in 0.83 million decedents with cirrhosis between April 2012 and September 2021 was included. Following an increasing trend of cirrhosis-related mortality before the pandemic, with a semiannual percentage change (SAPC) of 0.54% [95% confidence interval (CI): (0.0–1.0%), p=0.036], a precipitous increase with seasonal variation occurred during the pandemic (SAPC 5.35, 95% CI: 1.9–8.9, p=0.005). Significantly increased mortality rates were observed in those with alcohol-associated liver disease (ALD), with a SAPC of 8.44 (95% CI: 4.3–12.8, p=0.001) during the pandemic. All-cause mortality of nonalcoholic fatty liver disease rose steadily across the entire study period with a SAPC of 6.79 (95% CI: 6.3–7.3, p<0.001). The decreasing trend of HCV-related mortality was reversed during the pandemic, while there was no significant change in HBV-related deaths. While there was significant increase in COVID-19-related deaths, more than 55% of the excess deaths were the indirect impact of the pandemic. We observed an alarming increase in cirrhosis-related deaths during the pandemic especially for ALD, with evidence in both direct and indirect impact. Our findings have implications on formulating policies for patients with cirrhosis.

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Abbreviations: AILD, autoimmune liver disease; ALD, alcohol-associated liver disease; COVID-19, coronavirus disease 2019; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; SAPC, semi-annual percentage change.

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Introduction

Cirrhosis has a high mortality rate and represents a global health threat.[1] A previous study reported an increasing trend of cirrhosis-related mortality in the USA from 2009 to 2016.[2] During the pandemic, routine care for patients with cirrhosis was severely interrupted.[3] Patients with cirrhosis are at high risk for severe COVID-19 infection because of their compromised immune system, and have 2.5 times increased risk of death.[4] However, data from the USA were limited by a small sample size and covering a short period of the pandemic.

Recent data show an increase of cirrhosis-related mortality in the USA between January 2017 and September 2020, covering only the first 6 months of the pandemic and including only cirrhosis-related deaths when cirrhosis was the primary cause of death.[5] In this study, we analyzed cirrhosis-related deaths whether cirrhosis was the primary or secondary cause of death and analyzed data up to September 2021 to cover 18 months of the pandemic. We also aimed to quantify the number of excess deaths among decedents with cirrhosis by forecasting mortality rates based on prior trend and comparing those with observed rates during the pandemic.

Methods

The study was performed in accordance with the STROBE

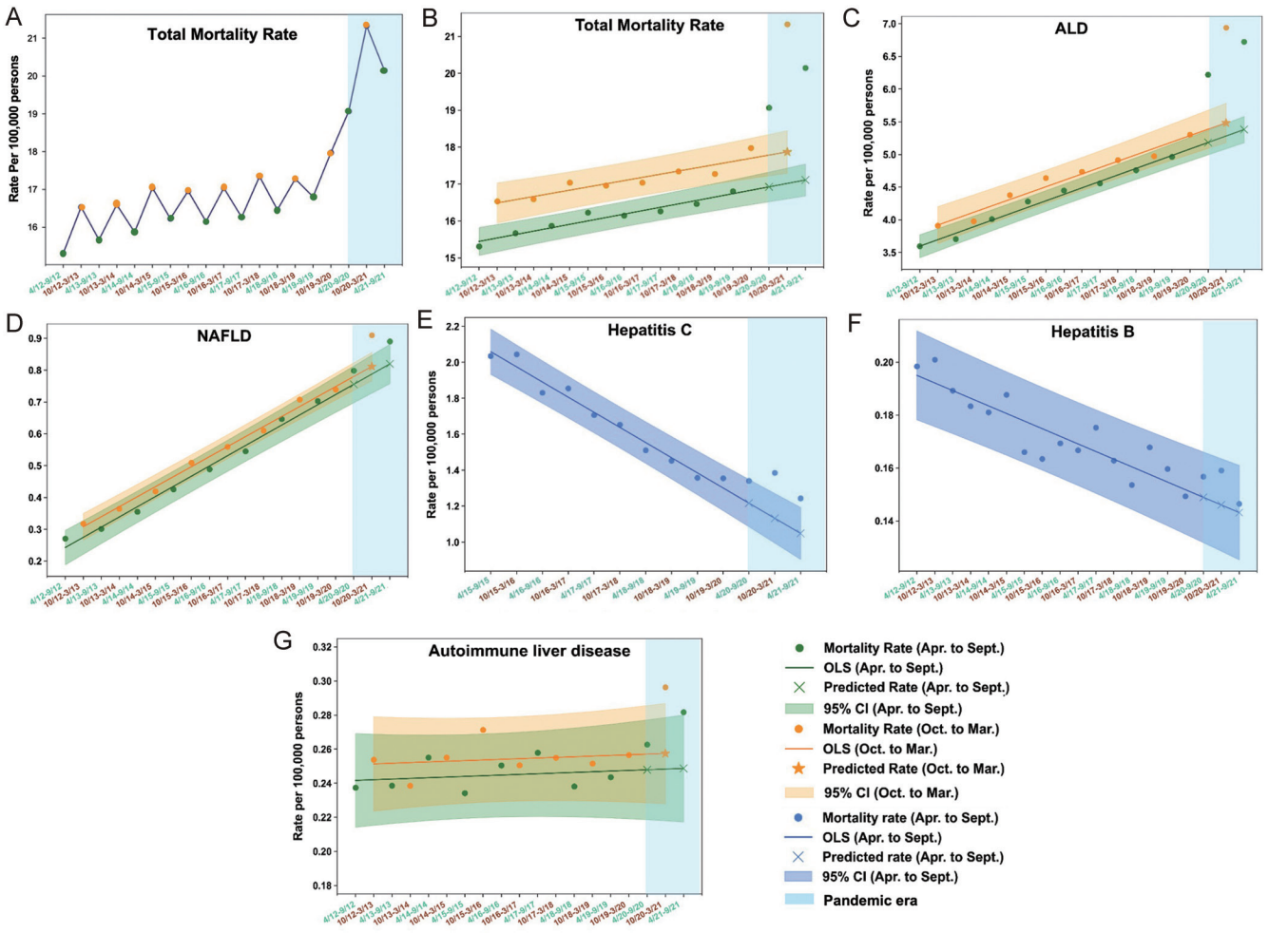

Fig. 1. Age-standardized mortality rate (ASMR) for cirrhosis in the USA between 2012 and 2021. (A) Temporal trend of ASMR between 2012 and 2021, divided by 6 months; (B) Overall cirrhosis: comparison between predicted and observed mortality rates in 4/2020–9/2020 (green cross vs. green dot), 10/2020–3/2021 (orange star vs. orange dot), and 4/2021–9/2021 (green cross vs. green dot); (C) ALD; (D) NAFLD; (E) Hepatitis C; (F) Hepatitis B; (G) Autoimmune liver disease. *Only one linear regression was fitted to the trends in (E) and (F) as there were no significant seasonal variations observed in these two panels. **R square for predictive models: (B) 4–9/2020: 0.935, 10/2020–3/2021: 0.858; (C) 4–9/2020: 0.987, 10/2020–3/2021: 0.966; (D) 4–9/2020: 0.988, 10/2020–3/2021: 0.993; (E) 0.971; (F) 0.802; (G) 4–9/2020: 0.046, 10/2020–3/2021: 0.043. ***The trend for hepatitis C in (E) started from 4/2015 to coincide with availability of new antivirals for HCV. CI, confidence interval; OLS, ordinary least squares.

checklist for cross-sectional studies. Institutional review board review was not required according to the common rule, as the data were de-identified and publicly available. We obtained de-identified death records from the National Vitals Statistics System (NVSS) from the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) database.[6] The NVSS registered more than 99% of decedents in the USA through April 16, 2022. Death data associated with cirrhosis among adults in the USA from April 1, 2012 to September 30, 2021 who were 25 years of age and above were collected. Cirrhosis and chronic liver disease etiologies, liver cancer, cardiovascular disease, metabolic disease, respiratory disease, renal disease, COVID-19 related mortality, and other causes of mortality, were defined using International Classification of Diseases tenth revision (ICD-10) codes (Supplementary Table 1).[7] Age was stratified as 25–44, 45–64, and ≥65 years, and race/ethnicity was recorded as non-Hispanic Alaska Indians/American Natives, non-Hispanic Asians, non-Hispanic Blacks, Hispanics, and non-Hispanic Whites.

Statistical analysis

We estimated age-standardized mortality per 100,000 persons using the direct method, referring to the 2000 USA Census.[8] To determine the impact of the pandemic on cirrhosis-related mortality, we performed a forecast analysis to predict mortality rates during the pandemic based on trend during 2012–2019. We selected the linear regression forecast model according to the distribution of the data and model fitness. To account for seasonal variation in mortality, we divided the study period into 6-month blocks (April–September and October–March, Fig. 1). In addition, we determined the temporal trend of mortality using joinpoint regression analysis.[9] Analysis by liver disease etiology for hepatitis C (HCV) decedents started in 2015 to coincide with availability of new antivirals for HCV.

We reported mortality data by cause of deaths. COVID-19-related mortality denoted deaths with COVID-19 listed as the primary cause. The statistical analysis was done with the Joinpoint Regression Program (4.9.0.0, National Institutes of Health, Bethesda, MD, USA), R software 4.0.2, and Pycharm

Table 1. Characteristics of liver cirrhosis-related all-cause death in the USA overall, by age, sex, race, and etiology, from April 2012 to September 2021 and during the pandemic

	Deaths, *n* [%] (4/2012–9/2021)	Deaths, *n* [%] (4/2020–9/2020)	Deaths, *n* [%] (10/2020–3/2021)	Deaths, *n* [%] (4/2021–9/2021)
Overall	828,923 [100]	50,483 [100]	56,350 [100]	53,029 [100]
Age				
25–44 years	55,857 [6.74]	4,274 [8.47]	4,726 [8.39]	4,715 [8.89]
45–64 years	391,736 [47.26]	22,074 [43.72]	24,009 [42.61]	22,737 [42.88]
≥65 years	381,330 [46.00]	24,135 [47.81]	27,615 [49.00]	25,577 [48.23]
Sex				
Male	508,808 [61.38]	30,722 [60.86]	34,257 [60.79]	31,896 [60.15]
Female	320,115 [38.62]	19,761 [39.14]	22,093 [39.21]	21,133 [39.85]
Race/Ethnicity#				
Non-Hispanic Whites	514,574 [71.52]	35,284 [69.89]	NA	NA
Non-Hispanic Blacks	71,100 [9.88]	4,770 [9.45]	NA	NA
Non-Hispanic Asians	17,431 [2.42]	1,320 [2.62]	NA	NA
Non-Hispanic AI/AN	13,305 [1.85]	1,131 [2.24]	NA	NA
Hispanics	103,134 [14.33]	7,978 [15.80]	NA	NA

#Race and ethnicity data available through 2020. NA, not applicable.

3.9.0. A two-sided *p*-value <0.05 considered as the threshold of significance.

Results

Study population and characteristics

There were 828,923 deaths associated with cirrhosis diagnosis between April 2012 and September 2021 (Table 1). Middle-aged and elderly groups accounted for more than 90% of the population and male decedents (61.38%) outnumbered females. The proportion of the younger group 25–44 years of age increased and the middle-aged group decreased during the pandemic epochs. Non-Hispanic Whites constituted the highest proportion of decedents (71.52%), followed by Hispanics (14.33%), non-Hispanic Blacks (9.88%), and non-Hispanic Asians (2.42). Non-Hispanic Alaskan and American/Native Indians represented the smallest proportion (1.85%).

Overall analysis of all-cause cirrhosis-related mortality

Before the pandemic, prior to 4/2020, there was a slightly increasing trend in cirrhosis-related mortality per 100,000 persons overall at a semiannual percentage change (SAPC) of 0.54% (95% CI 0.0–1.0%, p=0.036), with seasonal variation (Fig. 1A, B and Table 2). However, during the pandemic from April 2020 onwards (light blue shade), overall cirrhosis-related mortality increased dramatically at a SAPC of 5.35% (95% CI: 1.9–8.9%, p=0.005, Fig. 1A, B, Table 2). Between October 2019 and March 2020 and April 2020 to September 2020, cirrhosis-related mortality surged from 17.98 to 19.07, then to 21.33 between October 2020 and March 2021, and to 20.15 between April 2021 and September 2021. The observed mortality rates were 12.6%, 19.4%, and 17.8% higher than the predicted values estimated from prepandemic data in the pandemic stages 1, 2, and 3, respectively.

Subgroup analysis for all-cause cirrhosis-related mortality by etiology

Additionally, there was considerable heterogeneity in the trends of cirrhosis-associated mortality by liver disease etiology. Notably, both nonalcoholic fatty liver disease (NAFLD) and ALD saw upward trends in mortality both before and during the pandemic (Fig. 1C, D). Significantly increased mortality rates were observed in ALD with a SAPC of 8.44 (95% CI: 4.3–12.8, p=0.001) during the pandemic (Fig. 1C and Table 2), which increased gradually from 3.60 between April 2012 and September 2012 to 5.30 between October 2019 and March 2020, and then soared to 6.22, 6.94, and 6.72 in pandemic epochs 1, 2, and 3, respectively (Table 2). Compared with predicted values projected from prepandemic data, mortality was 20.1%, 26.6%, and 24.9% higher. Although less dramatic and more delayed, the observed versus predicted pandemic era mortality increase for NAFLD and HCV were also considerable. All-cause cirrhosis-related mortality of NAFLD rose steadily across the entire study period with a SAPC of 6.79 (95% CI: 6.3–7.3, p<0.001). HCV-related mortality saw a significant decrease between October 2014 and September 2019 (SAPC −5.07, 95% CI: −6.1 to −4.1), followed by a non-significant change between April 2019 and September 2021 (Fig. 1E). In contrast, HBV-related deaths consistently decreased throughout, and the difference between the observed versus predicted levels during the pandemic was not significant (Fig. 1F). For autoimmune liver disease, all-cause mortality also increased steadily across the entire study period, but with a sharper rise during the pandemic, yielding a SAPC of 3.66 (95% CI: −0.5 to 8.0). Joinpoint regression analysis revealed consistent findings.

Causes of cirrhosis-related mortality

Furthermore, the increased cirrhosis-related mortality during the pandemic appears largely the result of increasing liver-related mortality, with 10.59%, 16.73%, and 17.46% larger

Table 2. Age-standardized mortality rates and semiannual percentage change (SAPC) in mortality of adults in the USA with liver cirrhosis in 2012–2021, total and subgroups stratified by etiology

	Age-standardized mortality rate per 100,000 persons							Joinpoint regression	
	April–September 2012	April 2020–September 2020 (Pandemic epoch 1)		October 2020–March/2021 (Pandemic epoch 2)		April 2021––September 2021 (Pandemic epoch 3)		Trend segment(s)	SAPC, % (95% CI)
	Observed (*N*=35,916)	Predicted, *n* (95% CI)	Observed (*N*=50,483, Δ, %)	Predicted, *n* (95% CI)	Observed (*N*=56,350, Δ, %)	Predicted, *n* (95% CI)	Observed (*N*=53,029, Δ, %)		
Total	15.31	16.93 (16.53–17.33)	19.07 (+12.6%)	17.87 (17.30–18.45)	21.33 (+19.4%)	17.11 (16.68–17.54)	20.15 (+17.8%)	4/12–9/12 to 4/19–9/19; 4/19–9/19 to 4/21–9/21	0.54* (0.0 to 1.0); 5.35* (1.9 to 8.9)
ALD	3.60	5.18 (5.00–5.37)	6.22 (+20.1%)	5.48 (5.18–5.78)	6.94 (+26.6%)	5.38 (5.18–5.58)	6.72 (+24.9%)	4/12–9/12 to 4/19–9/19; 4/19–9/19 to 4/21–9/21	2.29* (1.7 to 2.9); 8.44* (4.3 to 12.8)
NAFLD	0.27	0.76 (0.70–0.81)	0.80 (+5.3%)	0.81 (0.77–0.86)	0.91 (+12.3%)	0.82 (0.76–0.88)	0.89 (+8.5%)	4/12–9/12 to 4/21–9/21	6.79* (6.3 to 7.3)
AILD	0.24	0.25 (0.22–0.28)	0.26 (+4.0%)	0.26 (0.23–0.29)	0.30 (+15.4%)	0.25 (0.22–0.28)	0.28 (+12.0%)	4/12–9/12 to 4/19–9/19; 4/19–9/19 to 4/21–9/21	0.14 (−0.5 to 0.8); 3.66 (−0.5 to 8.0)
HCV#	2.09	1.22 (1.09–1.35)	1.34 (+9.8%)	1.13 (0.99–1.27)	1.38 (+22.1%)	1.05 (0.90–1.19)	1.24 (+18.1%)	4/12–9/12 to 10/14–3/15; 10/14–3/15 to 4/19–9/19; 4/19–9/19 to 4/21–9/21	0.78 (−1.4 to 3.0); −5.07* (−6.1 to −4.1); −1.74 (−4.7 to 1.3)
HBV##	0.20	0.15 (0.13–0.17)	0.16 (+6.7%)	0.15 (0.13–0.16)	0.16 (+6.7%)	0.14 (0.13–0.16)	0.15 (+7.1%)	4/12–9/12 to 4/21–9/21	−1.40* (−1.8 to −1.0)

*$p<0.05$ or a significant upward or downward trend. AILD, Autoimmune liver disease; ALD: alcohol-associated liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease. #Predicted mortality rate of hepatitis C estimated from April 2015 to March 2020 data and from April 2012 to March 2020 for all other etiologies. ##Given no significant seasonal variation in the trend of HBV-related mortality, the predicted mortality rates in all epochs were calculated using prepandemic data without separation by season. Δ%=100% (observed mortality – predicted mortality)/predicted mortality.

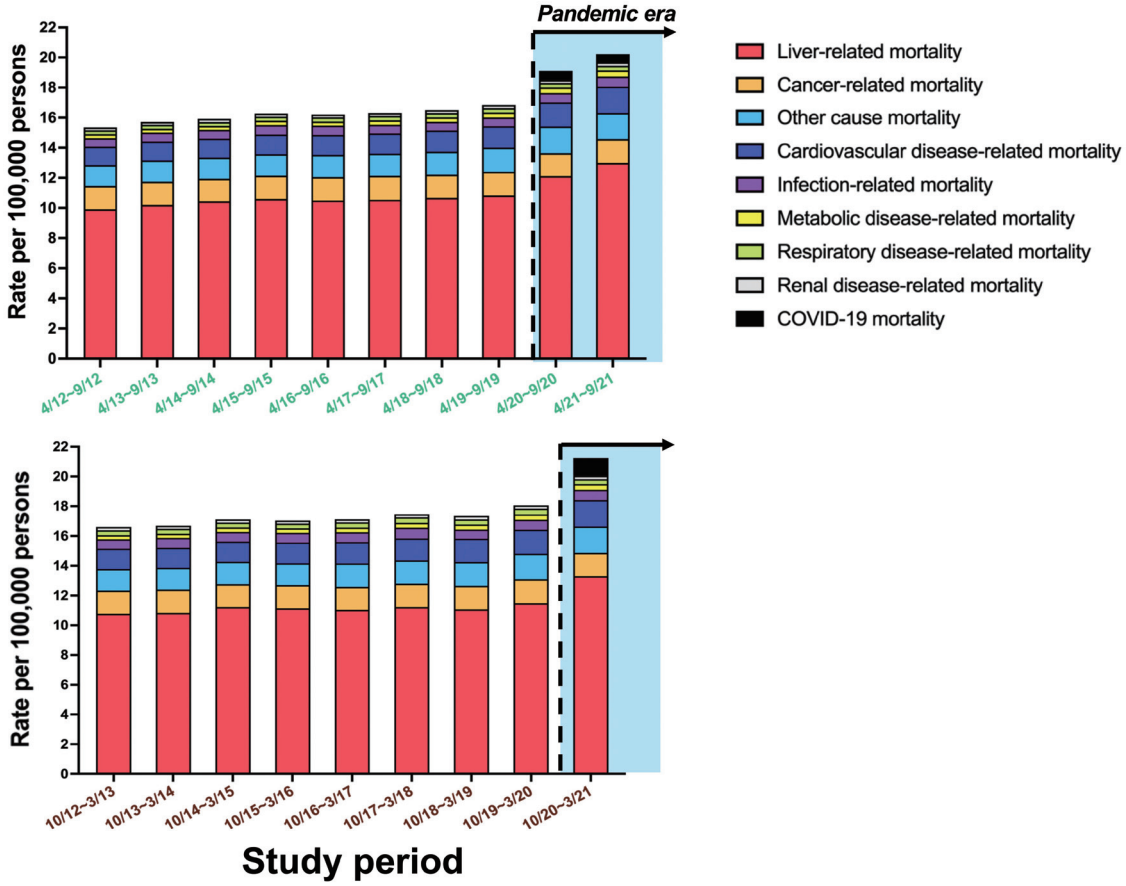

Fig. 2. Trend of cause of death of people with cirrhosis. (A) Between April and September and (B) between October and March of the following year. The trend was stratified by season to allow better visualization.

than predicted liver-related mortality during pandemic epochs 1, 2, and 3, and corresponding to 52.89%, 53.49%, and 54.37%, respectively, of the excess mortality during three pandemic epochs (Fig. 2). COVID-19 infection was another contributor. COVID-19-related mortality constituted 36.14%, 45.07%, and 22.09% of the excess cirrhosis-related mortality during the pandemic epochs 1, 2 and 3, respectively. Most causes of death stayed at the same mortality rates as seen in 2019, except for a slight increase in cardiovascular disease and other causes during the COVID-19 pandemic (Fig. 2).

Discussion

We found a surge in cirrhosis-related mortality during the COVID-19 pandemic, most of which was from liver-related and COVID-19 infection, and was significantly higher than predicted rates of ALD, NAFLD, and HCV. The early surge in ALD suggests an increased ALD incidence, while the delayed surge in NAFLD and HCV suggests pandemic-associated disruption of routine care, as previously reported.[3] Taken together, while there were deaths directly related to COVID-19, much of the dramatic surge and excess in cirrhosis-related mortality during the pandemic may have been an indirect consequence of various social, economic, and medical upheavals experienced by people with cirrhosis during the pandemic.

Using population-based data that span a decade, we showed a mortality trend before and during the pandemic with minimal selection bias. By separating the trends by seasonal variation, we were able to show a highly linearized relationship of the prepandemic trend and to estimate the predicted mortality rates with high accuracy. The predicted mortality rates represent the disease burden as if there were no COVID-19 pandemic. The percentage difference between the observed and predicted values helps to quantify the overall impact of the pandemic on people with cirrhosis and to identify the most vulnerable groups (e.g., those with ALD and NAFLD).

The early surge of cirrhosis-related ALD mortality is consistent with prior reports of increased alcohol sales and use during the initial period of the pandemic and increased ALD-associated hospitalization.[10–13] Recent studies showed that alcohol abuse was independently associated with severe COVID-19 and COVID-19-related death.[14] Another recent study showed an increase in both COVID-19-related and non-COVID-19-related mortality of patients with ALD.[15] Enhanced mental health service and alcohol treatment programs are urgently needed. Meanwhile, the delayed surge in NAFLD and ALD call for additional provider and patient education to maintain best practice monitoring and treatment despite the pandemic. Consistent with findings from a recent study reporting widened care gaps for HCV during the pandemic, with delayed treatment and diagnosis, we found the decline of HCV mortality during the pandemic was only one-third that in the prepandemic level.[3,16]

The increase in non-COVID-19 related mortality reflects

the indirect impact of the pandemic on patients with cirrhosis. Patients with cirrhosis require highly coordinated care to prevent, diagnose, and manage the sequalae of cirrhosis. Readmission rates secondary to esophageal variceal bleeding, fluid overload, and hepatic encephalopathy are high in patients with decompensated cirrhosis. Therefore, disrupted healthcare delivery, shifted medical resources, and delayed presentation of disease during the pandemic increased the risk of preventable major complications and mortality.

We acknowledge the following limitations. First, given that ICD-10 codes were used to identify patients, the study may by subject to classification bias and under-reporting bias during the pandemic. However, that would only underestimate the increasing trend and would not change the conclusion. Second, sample size in hepatitis B and autoimmune liver disease subgroups are small, limiting the statistical power to determine a trend. Finally, predictors of cirrhosis-related death were not included in the analysis. Additional studies are needed. Nevertheless, our study adds to the existing literature in several ways. First, prior reports were limited by using deaths directly caused by chronic liver disease and cirrhosis without accounting for mortality by other causes in people with cirrhosis. Second, our study provided comprehensive mortality data for patients with cirrhosis whether cirrhosis was primary or secondary cause of death. Third, previous articles only evaluated the short early pandemic period, but our study evaluated data obtained up to September 2021.[5,17] Lastly, we provided forecast data predicting mortality rates during the pandemic based on a prior trend from 2012 to 2019 and compared forecasted data with observed rates, thereby helping to quantify the impact of the pandemic on cirrhosis-related mortality.

As the pandemic continues to march on, healthcare providers/systems and patients should be even more committed to routine preventive care and chronic disease management to mitigate poor outcomes. Strategic plans for the "new normal" for people with cirrhosis should also focus on populations most affected by the pandemic.

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Author contributions

Study conception and supervision (FJ, MN), data collection and analysis (YHY, XH, FL, FJ); drafting the manuscript (YHY, MN), data interpretation and critical review of the manuscript (all authors).

Data sharing statement

The NVSS can be accessed at: https://wonder.cdc.gov/mcd-icd10-provisional.html.

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