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Research Article
NAFLD and Alcohol-Related Liver Diseases

JOURNAL
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Impact of the COVID-19 pandemic on liver disease-related mortality rates in the United States

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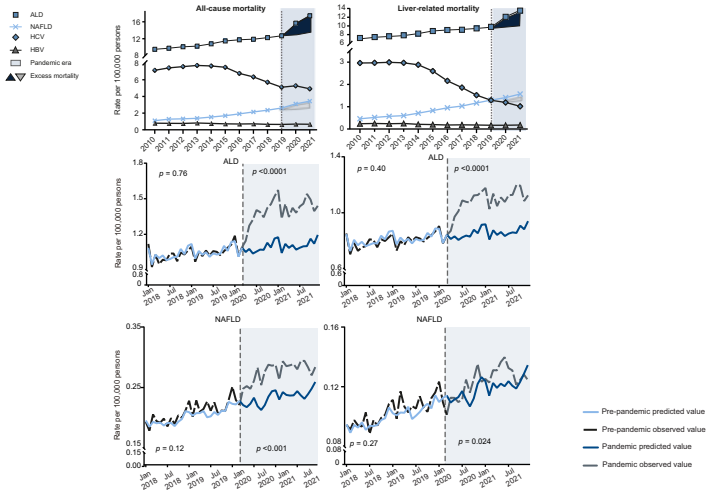
Graphical abstract



Highlights

- All-cause ASMR for ALD increased several fold between 2010–2019 and 2020-2021 (APC 3.5% to 17.6%, p <0.01).
- For NAFLD, all-cause ASMRs also rose steadily across the entire study period but with a sharper rise after 2019.
- ASMR rise for ALD and NAFLD was particularly severe for the 25–44 years age group.
- ASMR rise for ALD was also most pronounced in non-Hispanic Alaska Indians/Native American and White people.

Impact and implications

The pandemic has led to an increase of deaths directly and indirectly related to SARS-CoV-2 infection. As shown in this study, age-standardised mortality rates for alcohol-associated liver disease and non-alcoholic fatty liver disease substantially increased during the COVID-19 pandemic in the USA and far exceeded expected levels predicted from past trends, especially among the young, non-Hispanic White, and Alaska Indian/Native American populations. However, much of this increase was not directly related to COVID-19. Therefore, for the ongoing pandemic as well as its recovery phase, adherence to regular monitoring and care for people with chronic liver disease should be prioritised and awareness should be raised among patients, care providers, healthcare systems, and public health policy makers.

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Impact of the COVID-19 pandemic on liver disease-related mortality rates in the United States

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Background & Aims: The pandemic has resulted in an increase of deaths not directly related to COVID-19 infection. We aimed to use a national death dataset to determine the impact of the pandemic on people with liver disease in the USA, focusing on alcohol-associated liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD).
Methods: Using data from the National Vital Statistic System from the Center for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) platform and ICD-10 codes, we identified deaths associated with liver disease. We evaluated observed *vs.* predicted mortality for 2020–2021 based on trends from 2010–2019 with joinpoint and prediction modelling analysis.
Results: Among 626,090 chronic liver disease-related deaths between 2010 and 2021, Age-standardised mortality rates (ASMRs) for ALD dramatically increased between 2010–2019 and 2020–2021 (annual percentage change [APC] 3.5% to 17.6%, p <0.01), leading to a higher observed ASMR (per 100,000 persons) than predicted for 2020 (15.67 *vs.* 13.04) and 2021 (17.42 *vs.* 13.41). ASMR for NAFLD also increased during the pandemic (APC: 14.5%), whereas the rates for hepatitis B and C decreased. Notably, the ASMR rise for ALD was most pronounced in non-Hispanic Whites, Blacks, and Alaska Indians/Native Americans (APC: 11.7%, 10.8%, 18.0%, all p <0.05), with similar but less critical findings for NAFLD, whereas rates were steady for non-Hispanic Asians throughout 2010–2021 (APC: 4.9%). The ASMR rise for ALD was particularly severe for the 25–44 age group (APC: 34.6%, *vs.* 13.7% and 12.6% for 45–64 and ≥65, all p <0.01), which were also all higher than pre-COVID-19 rates (all p <0.01).
Conclusions: ASMRs for ALD and NAFLD increased at an alarming rate during the COVID-19 pandemic with the largest disparities among the young, non-Hispanic White, and Alaska Indian/Native American populations.

Introduction

Chronic liver disease (CLD) can lead to cirrhosis, which is the 11th most common cause of death globally according to a recent report in 2019.[1,2] In the United States, the incidence of cirrhosis has been increasing steadily with rising mortality, hospitalisation, and costs over the past decades.[3–5] Although highly effective treatment has been available for hepatitis B since 2005 and for hepatitis C virus since 2015, none are currently available for alcohol-associated liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) resulting in increasing burden and mortality for ALD and NAFLD.[3,5,6]

In March of 2020, the World Health Organization declared the world was experiencing a pandemic as the result of SARS-CoV-2 infection, adeptly named, the COVID-19 pandemic. To date, this pandemic has had a dramatic and broad impact on both the physical and mental health of people. A nationwide USA survey demonstrated a 14% increase in alcohol consumption in 2020 compared with 2019.[7,8] Recent studies also showed that ALD was an independent risk factor for death from COVID-19. In fact, individuals with ALD now constitute the majority of those listed for liver transplantation,[9,10] with waiting-list mortality also increasing with the current pandemic.[11]

COVID-19 itself is associated with a 3.5-fold increase in mortality in individuals with known cirrhosis compared with those without cirrhosis, while cirrhosis contributes an additional 70% higher risk of death among those with COVID-19.[12,13] The COVID-19 pandemic has also shattered the many care processes by which we deliver quality care for individuals with cirrhosis. Liver clinic visits, hepatocellular carcinoma surveillance, and diagnostic abdominal imaging have all fallen dramatically as social distancing measures were instituted in 2020.[14,15] Additionally, limited access to primary care provider and mental health services has exacerbated the rise in

Keywords: Alcohol-associated liver disease; Non-alcoholic fatty liver disease; Age-standardised mortality rates; Annual percentage change.
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prevalence and severity of alcohol use disorders as well as other CLDs,[13] especially NAFLD as these individuals tend to have multiple comorbidities, predisposing them to higher risk of care disruption, morbidity, and mortality during the pandemic.

Nationally representative data to guide the optimal allocation of resources and preventive efforts for the most affected populations during the COVID-19 pandemic are limited. Therefore, the aims of this population-based study were to examine the temporal trends and COVID-19 pandemic impact on mortality rates of people with CLD in the USA from January 1, 2010 to December 31, 2021, with a special focus on ALD and NAFLD, the 2 populations likely to be most affected by the pandemic. We also aimed to investigate potential age, sex, and race and ethnicity-related disparities in mortality among people with CLD.

Patients and Methods

Study design and study population

Data were obtained from the National Vital Statistics System (NVSS) dataset through the Center for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) website. This database collected annual death data of >99% of decedents in 50 USA states and the District of Columbia. The data were updated through December 31, 2021. Each record within the database represents the death data of 1 decedent. Demographic data including age, sex, race and ethnicity, and cause of death (all-cause and liver-related) were obtained.

Institutional review board approval was not sought as all data from NVSS are publicly available and completely de-identified. The study is compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Inclusion and exclusion criteria

We included data on deaths associated with a CLD among USA adults aged ≥25 years from January 1, 2010 to December 31, 2021. However, analyses involving race/ethnicity were only up to the end of 2020 because the CDC modified the race/ethnicity categories in 2021 to include a new category of 'multiple-race' people, making the 2021 race/ethnicity data not compatible with data from 2020 and before. All causes of death were recorded using the 10th edition of the International Classification of Diseases (ICD-10). For the purpose of this study, CLD included HCV infection (B17.1, B18.2), HBV infection (B16, B17.0, B18.0, B18.1), ALD (K70), and NAFLD (K75.8, K76.0).

Statistical analysis

Demographic characteristics of decedents with CLD were presented as frequencies with percentages. The crude mortality rate (per 100,000 persons) was computed by dividing the number of deaths of each CLD by the total USA population of the corresponding year. Age-standardised mortality rates (ASMRs, per 100,000 persons) were developed using the age structure (25–85+ years) from the 2000 USA Census Standard Population and the direct standardisation method (by multiplying the age-specific mortality rates of the study population to the number of persons in each age group of the standard population).

First, to determine the nationwide trend of mortality in people with CLD, we conducted joinpoint regression analysis (a piecewise linear regression that utilises the grid search method).[16] We then used this method combined with the Monte Carlo Permutation test to determine whether the overall trend was best depicted by one or more segments to determine the annual percentage change (APC) with 95% CI of each segment and their associated *p* values. The positivity/negativity and magnitude of APCs denote the direction and steepness of trends. To compare APCs among the subgroups during the pandemic, we set the subgroup with the lowest APC as reference and analysed the difference between each subgroup to the referent subgroup by permutation test and pairwise comparison.[16]

Next, to determine the predicted mortality rates in 2020 and 2021 based on the mortality rates from 2010 to 2019 to compare with observed rates, we performed predictive analysis using constructed linear regression models between the study years and ASMR. The changing trends of ASMR during 2010–2019 were fitted to the model to predict mortality rates in 2020 and 2021 for ALD, NAFLD, and HBV. For HCV, the changing trend of ASMR was fitted with 2016–2019 data to coincide with the availability of direct antiviral agents in 2015. The predicted value was compared with the observed value and assessed whether the observed value falls within the 95% CI of the fitting model. Linear regression coefficients and 95% CI were calculated with the ordinary least squares method.

Additionally, we performed subgroup analyses by using the following preplanned groups: age (25–44, 45–64, and ≥65 years), sex (male and female), race and ethnicity (Hispanic, non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic Asians (including Pacific Islanders), and non-Hispanic American Indian/Alaska Natives). We elected to perform subgroup analysis by age, sex, and race/ethnicity, as these factors may be clinically meaningful and have been reported to associate with mortality for many conditions including liver disease.[17–19] Subgroups with ≤20 deaths may produce unreliable estimates for mortality rates and were excluded.

All-cause mortality is defined as mortality of any cause – liver related or non-liver related. Liver-related mortality is defined as mortality caused by liver complications as the primary underlying cause of death. We calculated the ASMR of all-cause mortality and liver-related mortality for the overall analysis. For subgroup analysis of ASMR, calculations were based on all-cause mortality as all-cause mortality can better reflect the overall health and vital status of people. This is especially relevant in this setting when many downstream effects on disease and health were expected with the COVID-19 pandemic, which has brought on much economic and social change that can lead to both liver and non-liver consequences for people with CLD. All calculations were performed using the National Cancer Institute's joinpoint regression (Joinpoint Trend Analysis Software version

4.9.0.0; National Cancer Institute, Bethesda, MD), R 4.0.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria), and PyCharm 3.9.0. A 2-sided *p* value with the threshold of significance at 0.05 was used.

Results

Decedent population and characteristics

A total of 626,090 deaths among adults aged 25 years and older with CLD were documented from 2010 to 2021. ALD was the most common, accounting for 55% of deaths, followed by HCV (33%), NAFLD (9%), and HBV (3%) (Table S1). Although the majority of decedents with ALD were male (71%) or between 45 and 64 years of age (62%) at the time of death, the majority of those with NAFLD were females (55%) or ≥65 years old (52%). The majority of decedents with HCV or HBV were male (71–73%) and in the middle age group (53–66%). Decendents with ALD or NAFLD were overwhelmingly non-Hispanic Whites (71% and 80%) followed by Hispanics (16% and 11%), respectively. Although non-Hispanic Blacks and Asians only made up 8% and 1% of decedents with ALD, 5% and 2% for NAFLD, they made up 18% and 2% of decedents with HCV and 19% and 26% for HBV, respectively.

There was significant heterogeneity in the distribution of mortality among the states, with also some shifting in the density of mortality before and during the pandemic (Fig. 1A and B). States including Alaska, Montana, Wyoming, Colorado, New Mexico, and South Dakota experienced the highest ALD-related deaths during the COVID-19 pandemic (Fig. 1A).

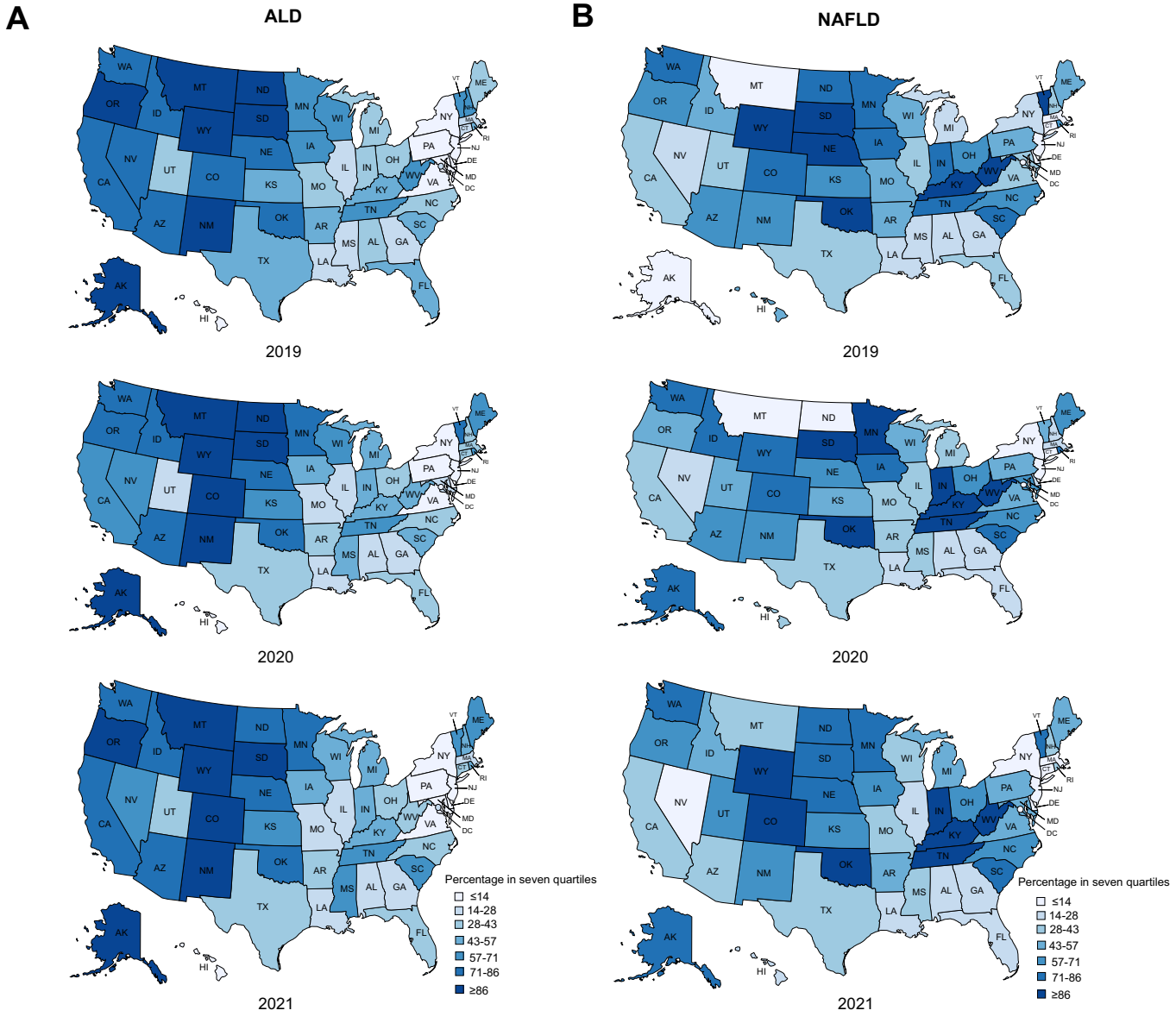

Fig. 1. All-cause age-standardised mortality rate by states in United States adults with ALD and NAFLD during the pandemic. ALD, alcohol-associated liver disease; NAFLD, non-alcoholic fatty liver disease.

Table 1. ASMR and APC in mortality in United States adults with liver disease, by liver disease aetiology for all-cause mortality and liver-related mortality, 2010–2021.

	Deaths (age-standardised rate per 100,000)			Average APC (95% CI)	Trend segment		
	2010 (Pre-pandemic referent epoch)	2020 (Pandemic epoch 1)	2021 (Pandemic epoch 2)	2010–2021	Year	APC (95% CI)	*p* value
All-cause mortality							
ALD	20,983 (9.49)	38,603 (15.67)	42,666 (17.42)	5.9 (5.1 to 6.7)	2010–2019	3.5 (3.0 to 3.9)	<0.001
					2019–2021	17.6 (12.2 to 23.2)	<0.001
NAFLD	2,367 (1.1)	8,145 (3.11)	8,940 (3.44)	10.7 (8.2 to 13.3)	2010–2014	7.6 (3.5 to 11.9)	0.007
					2014–2019	11.8 (7.5 to 16.2)	0.001
					2019–2021	14.5 (1.1 to 29.6)	0.039
HCV	16,520 (7.14)	14,733 (5.28)	13,654 (4.92)	-3.3 (-4.0 to -2.5)	2010–2014	2.5 (1.1 to 3.8)	0.007
					2014–2019	-7.8 (-9.0 to -6.6)	<0.001
					2019–2021	-2.8 (-6.8 to 1.4)	0.138
HBV	1,777 (0.8)	1,738 (0.69)	1,725 (0.67)	-1.9 (-2.6 to -1.2)	2010–2021	-1.9 (-2.6 to -1.2)	<0.001
Liver-related mortality							
ALD	15,905 (7.22)	29,399 (12.1)	32,756 (13.53)	6.1 (5.2 to 7.1)	2010–2019	3.7 (3.2 to 4.2)	<0.001
					2019–2021	17.8 (11.4 to 24.6)	<0.001
NAFLD	987 (0.46)	3,852 (1.41)	4,251 (1.57)	12.0 (10.4 to 13.7)	2010–2018	12.6 (11.3 to 14.0)	<0.001
					2018–2021	10.3 (4.3 to 16.7)	0.004
HCV	6,807 (2.96)	3,227 (1.19)	2,838 (1.02)	-9.2 (-9.9 to -8.4)	2010–2014	0.1 (-1.3 to 1.5)	0.882
					2014–2019	-15.1 (-16.3 to -13.9)	<0.001
					2019–2021	-11.4 (-15.2 to -7.4)	0.002
HBV	585 (0.24)	410 (0.17)	408 (0.18)	-3.8 (-4.9 to -2.7)	2010–2021	-3.8 (-4.9 to -2.7)	<0.001

The temporal trend analysis was performed using joinpoint analysis. APCs and *p* values were estimated using the Monte Carlo permutation test.
ALD, alcohol-associated liver disease; APC, annual percentage change; ASMR, age-standardised mortality rate; NAFLD, non-alcoholic fatty liver disease.

Oklahoma, Indiana, Kentucky, Tennessee, and West Virginia experienced the highest NAFLD-related deaths in 2020–2021 (Fig. 1B). State-level ASMR data for ALD and NAFLD from 2019 to 2021 are provided in Fig. S1.

Impact of COVID-19 pandemic on ASMR for CLD

Overall analysis for all-cause and liver-related ASMR

All-cause ASMR (per 100,000) for ALD increased from 9.49 in 2010 to 17.42 in 2021 yielding an average APC of 5.9% for 2010–2021 (95% CI 5.1–6.7) (Table 1 upper panel and Fig. 2A). However, on trend segment analysis, we found accelerated APC from 3.5% (95% CI 3.0–3.9) for 2010–2019 to 17.6% (95% CI 12.2–23.2) for 2019–2021. As a result, the observed ASMRs of 15.67 for ALD in 2020 and 17.42 in 2021 were much higher than the predicted values of 13.04 (95% CI 12.65–13.43) for 2020 and 13.41 (95% CI 13.0–13.82) for 2021 (Fig. 2C and D).

For NAFLD, all-cause ASMR also rose steadily across the entire study period but with sharper rise after 2019, yielding an APC of 14.5% (95% CI 1.1–29.6) during pandemic (Table 1 upper panel and Fig. 2A). Similar to ALD, the observed ASMR of 3.11 in 2020 to 3.44 in 2021 were both higher than the predicted rates of 2.64 (95% CI 2.33–2.95) in 2020 and 2.80 (95% CI 2.48–3.13) in 2021 (Fig. 2E). As shown in Fig. 3, we also found consistent changes when we analysed the observed *vs.* predicted monthly mortality from January 2018 to December 2021 based on trends from 2010 to 2017 monthly with prediction modelling analysis for all-cause and liver-related mortality in both ALD and NAFLD.

In contrast, the all-cause ASMR trend for viral hepatitis was either stable or declining (Table 1 upper panel and Fig. 2A). For HBV, ASMR decreased from 2010 to 2021 at an average APC of -1.9% (95% CI, -2.6 to -1.2, p <0.01) and without significant segmental variation. For HCV, the ASMR increased from 2010 to 2014 then decreased from 2014 onwards, yielding APC percentages of -7.8% for 2014–2019 (95% CI -9.0 to -6.6) but this decreasing trend slowed down by almost 3-fold at -2.8% for 2019–2021 (95% CI -6.8 to 1.4). However, the observed ASMRs for 2020 and 2021 were still higher than predicted levels for HCV (5.28 *vs.* 4.58 for 2020, 4.92 *vs.* 4.02 for 2021) (Fig. 2G).

Data for liver-related ASMRs followed similar trends for all liver aetiologies (Table 1 lower panel and Fig. 2B), with an even more dramatic decline in liver-related ASMRs for viral hepatitis in more recent years.

Subgroup analysis for all-cause ASMR

By race and ethnicity. As shown in Table S2 and Fig. 4A and B, all-cause ASMR for ALD and NAFLD increased steadily across all races and ethnicities during the study period, but the most dramatic APC rise was for ALD and during 2018–2020 in non-Hispanic American Indians/Alaska Natives (18.0%, 95% CI 6.1–31.4, p <0.05) followed by non-Hispanic Whites (11.7%, 95% CI 6.9–16.6, p <0.01), and non-Hispanic Blacks (10.8%, 95% CI 1.8–20.7, p <0.05), with a much more modest rise during the same time period in non-Hispanic Asians (APC 4.9%). For NAFLD, the racial ethnic groups with the steepest all-cause ASMR rise during the pandemic with APCs of 11.9%,11.9%, 12.9%, 13.1% and 10.9% in non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic Asians, Hispanics and American Indians/Alaska Natives, respectively. As a result, the observed ASMRs in 2020 were much higher than rates predicted from 2010 to 2019 trends for both ALD and NAFLD for all race and ethnicities (Fig. 4CC–L). The observed *vs.* predicted ASMRs for ALD in 2020 were 88.42 *vs.* 63.72 for non-Hispanic American Indians/Alaska Natives, 16.52 *vs.* 13.75 non-Hispanic Whites, and 10.30 *vs.* 8.62 for non-Hispanic Blacks, respectively. For NAFLD, the observed *vs.* predicted ASMRs in 2020 were 8.31 *vs.* 6.15 for non-Hispanic American Indians/Alaska Natives, 3.44 *vs.* 2.97 non-Hispanic Whites, and 1.34 *vs.* 1.03 for non-Hispanic

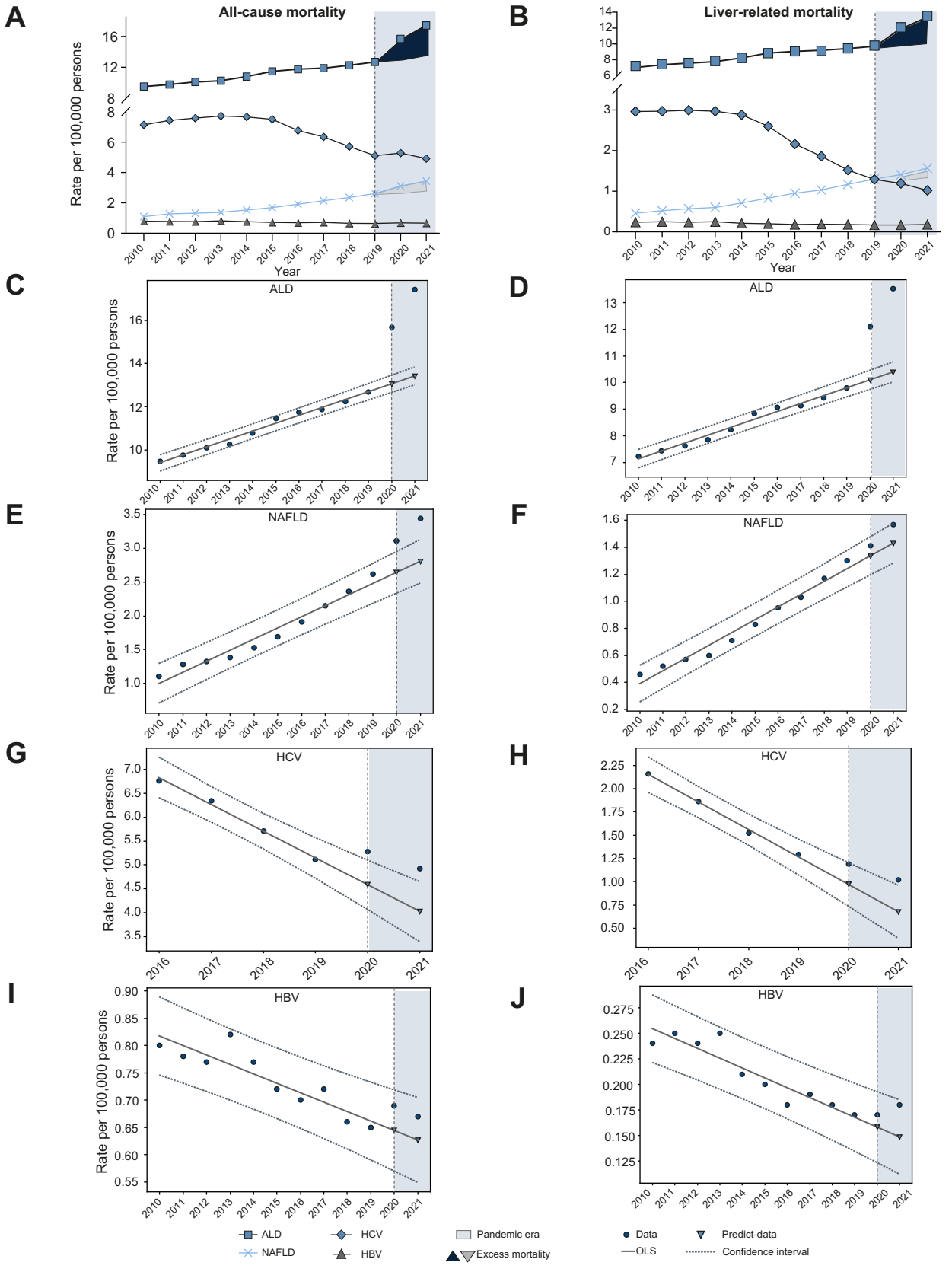

Fig. 2. Age-standardised mortality rates for liver disease in the United States in 2010–2021 by liver disease aetiology, with comparisons between observed (blue dot) *vs.* predicted (blue arrow) mortality for 2020–2021 based on 2010–2019 trends for each liver disease aetiology. The prediction of mortality rates in 2020 and 2021 were performed using linear regression using ordinary least squares according to the mortality rates in 2012-2019. ALD, alcohol associated liver disease; NAFLD, non-alcoholic fatty liver disease; OLS, ordinary least squares.

Blacks, respectively. With the Hispanics group with the lowest APC as a reference, the APC of all-cause mortality and liver-related mortality for non-Hispanic White and Alaska Indian/Native American populations trends were higher but without statistically meaningful in ALD (Table S3). However, there was a 6.3 times increased APC in non-Hispanic White in NAFLD, compared with that in non-Hispanic Blacks (Table S4). The effect of the COVID-19 pandemic on NAFLD and mortality in Hispanic and non-Hispanic Asians were relatively small.

For HCV and HBV, the effect of the COVID-19 pandemic on mortality was fairly consistent across the different racial ethnic groups (Table S2 and Fig. S2).

By age group. Subgroup analysis by age found significant ASMR rise throughout the entire study period 2010–2021 among the youngest group (25–44 years) for ALD and among the older groups (45–64 and ≥65 years) for NAFLD; however, significant rise was also observed for ALD for the older groups since 2019 and for the youngest group with NAFLD since 2019 (Table 2 and Fig. 5A and B). As a result, the 2019–2021 A PCs for ASMR in ALD showed a significant increase for all age groups with the highest change (34.6%) for the youngest group aged 25–44 years for ALD (*vs.* 13.7% and 12.6% for 45–64 and ≥65 years age groups, respectively, all p <0.01), which were also all higher than pre-COVID-19 rates (all p <0.05).

For NAFLD, although a significant change in trend was observed mainly for the youngest group (2019–2021 APC 28.1%), the older groups have had steady rise since 2010 with the ≥65 years age group having the highest ASMR change (2010–2021 average APC 16.0, 95% CI 14.2–17.9, p <0.05) (Table 2). There were also differences by age for HCV and HBV,

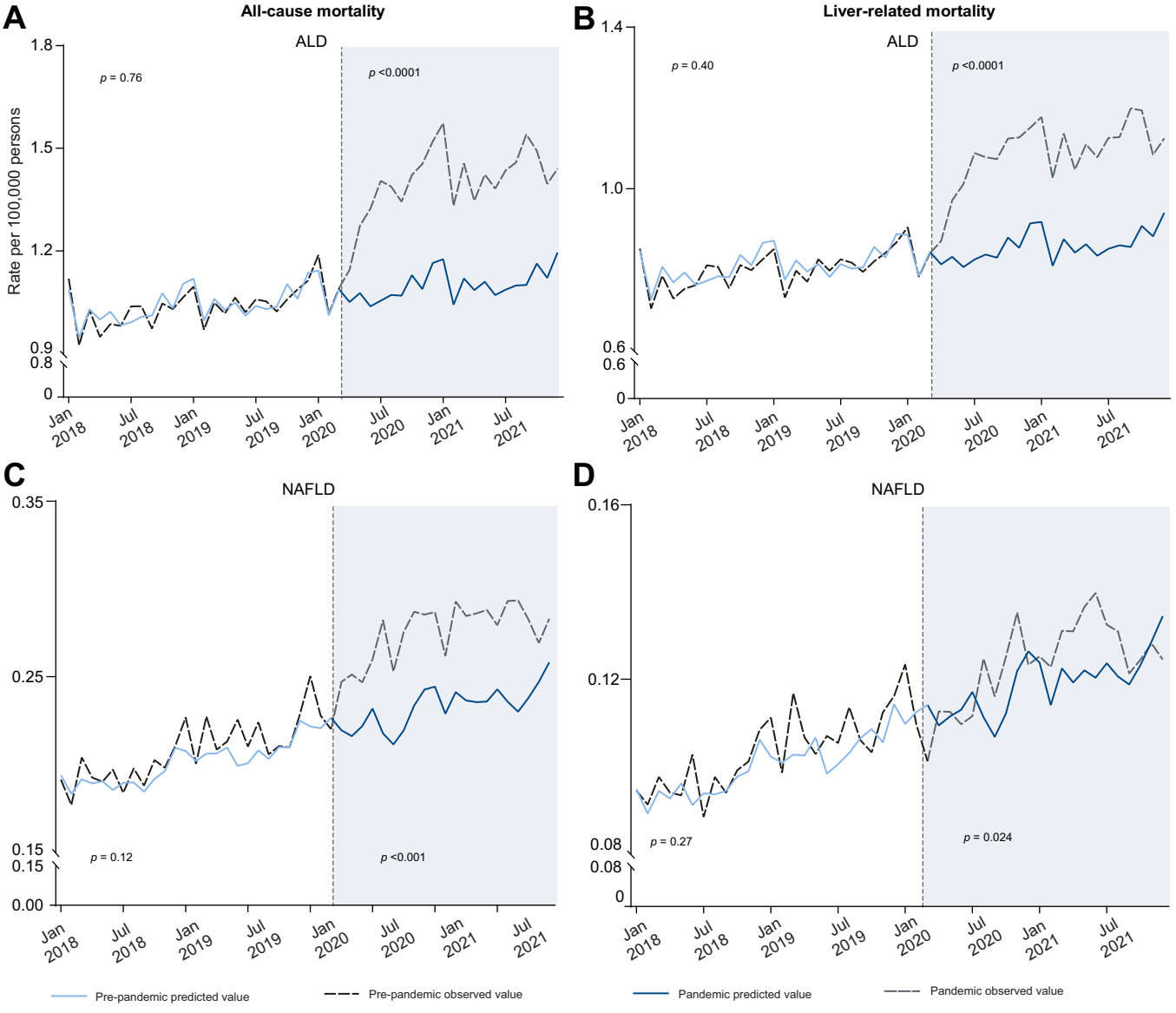

Fig. 3. Age-standardised mortality for ALD and NAFLD in the United States in 2018–2021 by month. (A) All-cause mortality for ALD, (B) liver-related mortality for ALD, (C) all-cause mortality for NAFLD, (D) liver-related mortality for NAFLD. The prediction of mortality rates in 2020 and 2021 were performed using linear regression using ordinary least squares according to the mortality rates in 2012–2019. Pairwise comparison between trends was performed to assess the difference between observed and predicted mortality. ALD, alcohol-associated liver disease; NAFLD, non-alcoholic fatty liver disease.

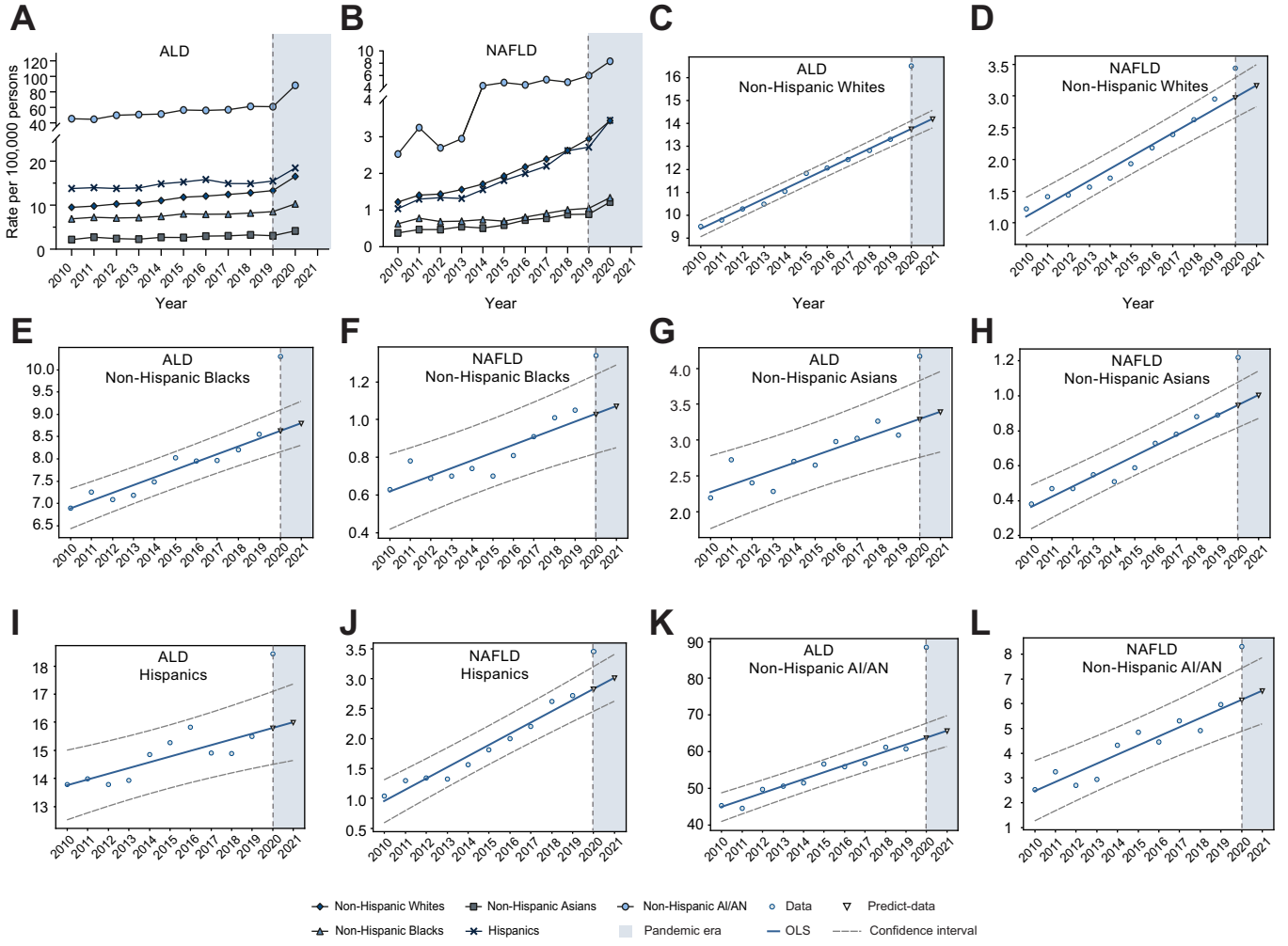

Fig. 4. All-cause age-standardised mortality for ALD and NAFLD in the United States in 2010–2020 by race and ethnicity, with comparisons between observed (blue dot) *vs.* predicted (black arrow) mortality for 2020 based on 2010–2019 trend for each race and ethnicity. The prediction of mortality rates in 2020 and 2021 were performed using linear regression using OLS according to the mortality rates in 2012–2019. ALD, alcohol-associated liver disease; NAFLD, non-alcoholic fatty liver disease; non-Hispanic AI/AN, non-Hispanic American Indian/Alaska Native; OLS, ordinary least squares.

with significant decline observed mainly for the 45–64 years age group since 2013 for HBV and since 2014 for HCV (Table 2).

When used the older group (aged ≥65 years) as a reference, the APC of all-cause mortality and liver-related mortality in the young group (aged 25–44 years) saw a 17.1 and 16.9 times difference in ALD (Table S5); and 12.1 times increased APC of all-cause mortality in NAFLD (Table S6 upper panel).

In addition, we found the observed all-cause ASMRs to be significantly higher than predicted levels for all age groups for both ALD and NAFLD (Fig. 5C–H). For ALD, the observed *vs.* predicted all-cause ASMRs were 7.69 *vs.* 5.26, 25.18 *vs.* 21.86, and 17.81. *vs.* 15.91 for age groups 25–44, 45–64, and ≥65 years for 2020, and 8.96 *vs.* 5.47, 27.60 *vs.* 22.29, and 19.48 *vs.* 16.54 for 2021. Meanwhile, although the overall impact of COVID-19 pandemic on the ASMR for viral hepatitis was relatively mild, the observed ASMRs were still higher than predicted for the 45–64 years age group for HCV (7.89 *vs.* 6.76 in 2020, 7.00 *vs.* 5.26 in 2021) and the ≥65 years age group for HBV (1.54 *vs.* 1.33 in 2020, 1.52 *vs.* 1.33 in 2021) (Table 2 and Fig. S3A–H).

By sex. The sharp rise during the 2019–2021 period was observed for both males and females for ALD (2019–2021 APC 16.7% for males, 19.1% for females, both p <0.01), whereas the ASMR increase was steady throughout the whole study period 2010–2021 for both sexes for NAFLD, and there was no significant increase for HCV and HBV (Table S7). As a result, for ALD, the observed ASMRs were significantly higher than expected for both males (22.30 *vs.* 18.85 in 2020, 24.92 *vs.* 19.31 in 2021) and females (9.58 *vs.* 7.74 in 2020, 10.52 *vs.* 8.01 in 2021) (Fig. S4). Similarly, for NAFLD, the observed ASMR was higher than predicted for males (3.02 *vs.* 2.52 in 2020, 3.29 *vs.* 2.67 in 2021) and females (3.16 *vs.* 2.71 in 2020, 3.56 *vs.* 2.88 in 2021). Furthermore, we found consistent sharp rise with the highest APC in 2019–2021 compared with earlier

Table 2. All-cause ASMR and APC in mortality in U.S. adults with liver disease, by liver disease aetiology and by age, 2010–2021.

	Deaths (age-standardised rate per 100,000)			Average APC (95% CI)	Trend segment		
Age	2010 (Pre-pandemic referent epoch)	2020 (Pandemic epoch 1)	2021 (Pandemic epoch 2)	2010–2021	Year	APC (95% CI)	*p* value
ALD							
25–44	2,656 (3.44)	6,358 (7.69)	7,367 (8.96)	10.2 (8.2 to 12.2)	2010–2019	5.3 (4.3 to 6.4)	<0.001
					2019–2021	34.6 (20.5 to 50.5)	<0.001
45–64	14,227 (17.23)	21,945 (25.18)	23,980 (27.60)	4.3 (3.8 to 4.8)	2010–2019	2.3 (1.8 to 2.9)	<0.001
					2019–2021	13.7 (7.3 to 20.5)	0.001
≥65	4,100 (10.15)	10,300 (17.81)	11,319 (19.48)	6.5 (5.1 to 7.9)	2010–2019	5.2 (4.5 to 6.0)	<0.001
					2019–2021	12.6 (3.9 to 22.0)	0.010
NAFLD							
25–44	453 (0.57)	720 (0.83)	840 (1.04)	5.5 (1.8 to 9.3)	2010–2019	1.0 (-1.0 to 3.0)	0.275
					2019–2021	28.1 (3.0 to 59.4)	0.032
45–64	1,158 (1.36)	2,622 (2.95)	2,848 (3.19)	7.4 (6.1 to 8.8)	2010–2021	7.4 (6.1 to 8.8)	<0.001
≥65	756 (1.91)	4,803 (8.78)	5,252 (9.58)	16.0 (14.2 to 17.9)	2010–2019	16.9 (15.9 to 18.0)	<0.001
					2019–2021	12.0 (1.5 to 23.6)	0.029
HCV							
25–44	810 (1.06)	753 (0.94)	737 (0.95)	-0.5 (-3.2 to 2.3)	2010–2019	-2.9 (-4.3 to -1.3)	0.003
					2019–2021	11.0 (-6.3 to 31.5)	0.188
45–64	12,532 (14.86)	7,556 (7.89)	6,675 (7.00)	-6.7 (-7.5 to -5.8)	2010–2014	1.6 (-0.1 to 3.3)	0.053
					2014–2019	-11.8 (-13.3 to -10.4)	<0.001
					2019–2021	-9.1 (-13.7 to -4.3)	0.007
≥65	3,178 (7.91)	6,424 (10.93)	6,242 (10.63)	3.0 (1.7 to 4.3)	2010–2015	6.6 (5.0 to 8.2)	<0.001
					2015–2019	-1.9 (-5.1 to 1.4)	0.182
					2019–2021	4.1 (-2.6 to 11.2)	0.167
HBV							
25–44	184 (0.21)	138 (0.21)	150 (0.21)	-0.4 (-1.5 to 0.8)	2010–2021	-0.4 (-1.5 to 0.8)	0.495
45–64	1,050 (1.28)	749 (0.86)	741 (0.80)	-4.2 (-5.6 to -2.8)	2010–2013	-0.4 (-5.9 to 5.3)	0.855
					2013–2021	-5.5 (-6.7 to -4.4)	<0.001
≥65	543 (1.36)	851 (1.54)	834 (1.52)	1.0 (-0.0 to 2.0)	2010–2021	1.0 (-0.0 to 2.0)	0.056

The temporal trend analysis was performed using joinpoint analysis. APCs and *p* values were estimated using the Monte Carlo permutation test.
ALD, alcohol-associated liver disease; APC, annual percentage change; ASMR, age-standardised mortality rate; NAFLD, non-alcoholic fatty liver disease.

time periods in all age groups in both males and females for ALD (Table 3).

Discussion

In this study, we assessed the temporal trends of mortality for 4 major CLDs (namely ALD, NAFLD, HCV, and HBV) from 2010 to 2021 to determine the effect of the COVID-19 pandemic on mortality of people with these CLDs. We found alarming rise in both all-cause and liver-related mortality among people with ALD and NAFLD during the 2019–2021 time period that were significantly higher than levels predicted from pre-pandemic trend, whereas the impact on HCV and HBV was fortunately none to mild. Importantly, we also found that the pandemic effect on ALD and NAFLD mortality spans across the sex, age, and racial and ethnic spectrum. However, there were marked disparities.

For ALD, the most affected groups were the young population (aged 25–44 years), with a 17.1 and 16.9 times increase in APC of all-cause and liver-related mortality compared with older group aged ≥65 years (Table S5), non-Hispanic American Indian/Alaska Natives, and non-Hispanic Whites. In fact, the APC during 2019–2021 was 34.6% for the young population, about 3 times the rate for those ≥45 years of age. The racial disparity was also stark, with the APC during pandemic for non-Hispanic American Indian/Alaska Natives topped at 18.0% (compared with the next group, non-Hispanic Whites at 11.7%), despite lack of statistical significance (Table S3). In 2020, the observed ASMR in American Indian/Alaska Natives with ALD was 40% higher than the pre-pandemic predicted level (89 *vs.* 64 per 100,000 persons). The disparity was smaller between females (19.1%) and males (16.7%) but notable because ALD historically has affected males more than females. The disparities in ASMRs for NAFLD were less pronounced and affected more of the middle-aged and elderly populations, as well as females and non-Hispanic American Indian/Alaska Natives and Whites more than the other groups. Noteworthy, there was 12.1 times increased APC of all-cause mortality in NAFLD compared with the older group aged ≥65 years (Table S6).

In addition, for liver-related mortality associated with NAFLD, the time segments were unchanged with a slightly smaller upward trend for the period involving the pandemic. This observation suggested that liver-related mortality contributed a relatively lower proportion of death burden to the overall death burden during the pandemic as compared with non-liver causes. Indeed, cardiovascular deaths are well known to be the most common cause of mortality, and diabetes and cardiovascular deaths have also been reported to increase disproportionately during the pandemic,[20–22] likely attributable to disruption of routine care for related illnesses that normally require intensive monitoring such as diabetes, hypertension, hyperlipidaemia, chronic kidney disease, angina, and congestive heart disease.[18,19,23] In addition, individuals with NAFLD are frequently obese, and obese individuals are known to have higher risk of cancer in general. Thus, delay in cancer diagnosis and treatment during the pandemic may also increase the death burden by cancer causes in this population.[23–25]

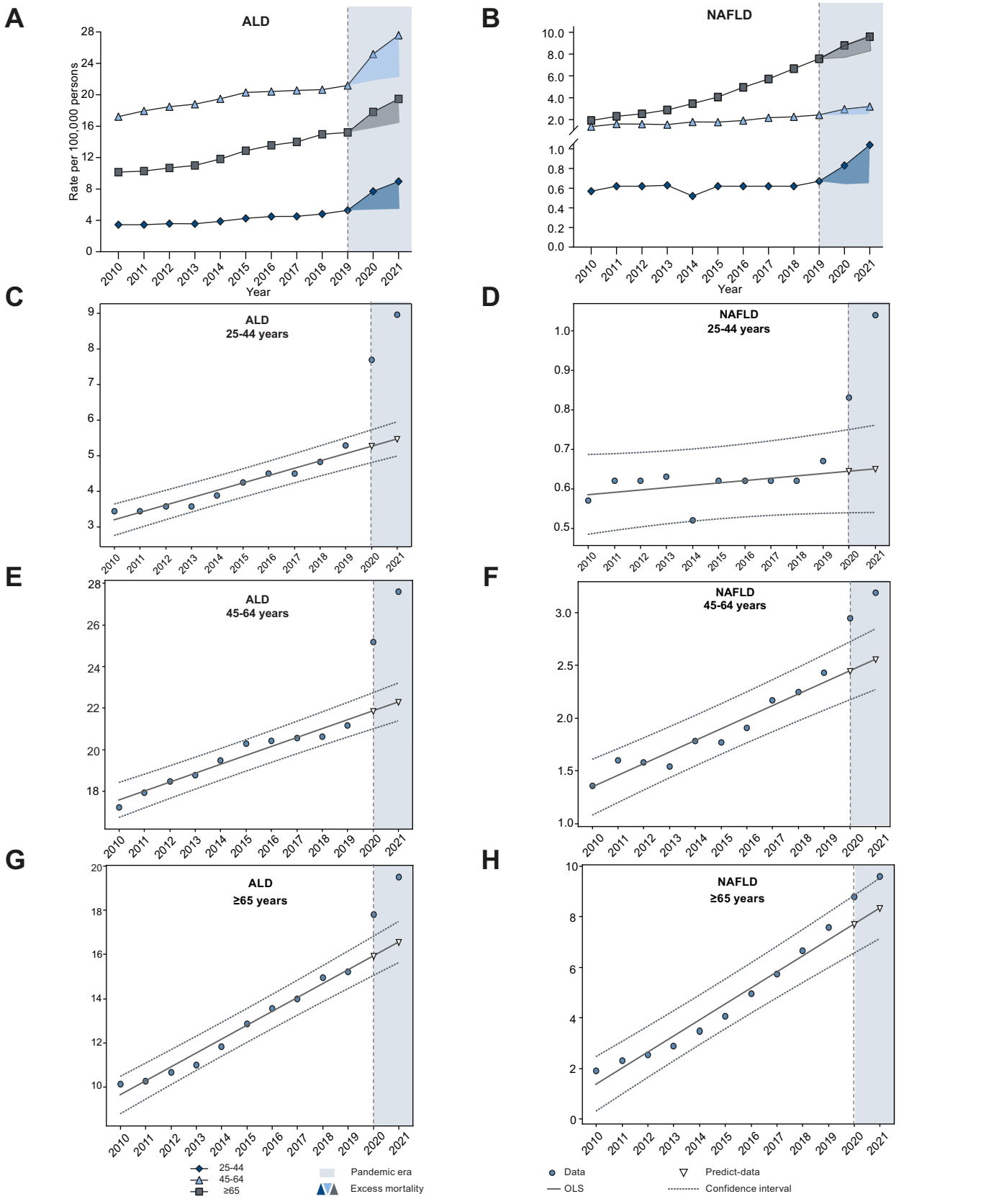

Fig. 5. All-cause age-standardised mortality for ALD and NAFLD in the United States in 2010–2021 by age group, with comparisons between observed (blue dot) *vs.* predicted (black arrow) mortality for 2020–2021 based on 2010–2019 trends for each age group. The prediction of mortality rates in 2020 and 2021 were performed using linear regression using OLS according to the mortality rates in 2012–2019. ALD, alcohol-associated liver disease; NAFLD, non-alcoholic fatty liver disease; non-Hispanic AI/AN, non-Hispanic American Indian/Alaska Native; OLS, ordinary least squares.

Table 3. All-cause age- and sex-standardised mortality rate and APC in mortality in United States adults with ALD, by age, 2010–2021.

ALD	Deaths (age-standardised rate per 100,000)			Average APC (95% CI)	Trend segment		
	2010 (Pre-pandemic referent epoch)	2020 (Pandemic epoch 1)	2021 (Pandemic epoch 2)	2010–2021	Year	APC (95% CI)	*p* value
Female							
25–44	884 (2.26)	2,305 (5.60)	2,630 (6.43)	10.9 (8.1 to 13.7)	2010–2019	6.7 (5.2 to 8.3)	<0.001
					2019–2021	31.5 (12.5 to 53.8)	0.004
45–64	3,802 (9.12)	6,853 (15.63)	7,416 (16.80)	5.7 (4.2 to 7.2)	2010–2019	3.9 (3.0 to 4.7)	<0.001
					2019–2021	14.2 (4.6 to 24.7)	0.009
≥65	981 (4.40)	2,632 (8.34)	2,899 (9.16)	7.7 (5.6 to 9.8)	2010–2019	5.5 (4.3 to 6.6)	<0.001
					2019–2021	18.3 (4.9 to 33.4)	0.013
Male							
25–44	1,772 (4.61)	4,053 (9.84)	4,737 (11.55)	9.3 (8.1 to 10.6)	2010–2014	2.3 (0.4 to 4.3)	0.030
					2014–2019	6.2 (4.2 to 8.2)	0.001
					2019–2021	34.4 (26.4 to 42.8)	<0.001
45–64	10,425 (25.81)	15,092 (35.14)	16,564 (38.85)	3.7 (2.8 to 4.6)	2010–2019	1.7 (1.2 to 2.2)	<0.001
					2019–2021	13.3 (7.4 to 19.5)	0.001
≥65	3,119 (17.32)	7,668 (29.14)	8,420 (31.98)	5.8 (4.3 to 7.2)	2010–2012	2.4 (-4.5 to 9.9)	0.395
					2012–2019	5.5 (4.2 to 6.7)	<0.001
					2019–2021	10.2 (2.7 to 18.2)	0.018

The temporal trend analysis was performed using joinpoint analysis. APCs and *p* values were estimated using the Monte Carlo permutation test.
ALD, alcohol-associated liver disease; APC, annual percentage change.

Factors that could potentially help to explain the increases in ASMRs in general include access to medical care, vulnerability to COVID-19 infection, rate of liver transplant referral, loss of insurance coverage, and severity of the pandemic in local areas. A multinational, multicentre study showed that during the pandemic there was significantly less follow-up care for those with CLD to include less laboratory testing to detect the presence of liver disease, fewer endoscopies for oesophageal varices as well as less hepatocellular carcinoma surveillance for liver cancer.[15] Another study highlighted the decrease in liver transplantation and the increased waiting-list deaths that have occurred during the pandemic.[11]

We showed that, although ALD mortality has been increasing in a linear fashion during the past decade, ALD has had a higher mortality increase during the pandemic. This is a distressing finding but not surprising given a recent report on the escalation in alcoholic beverage sales and alcohol use during the COVID-19 pandemic which may be outcomes related to increased depression, mounting stress from economic uncertainty, social isolation, disturbance of inpatient medical resources, deferral of outpatient visit, as well as the closure of resources for alcohol treatment that have occurred during the pandemic.[26] Adding to this confluence of factors is a prior study reporting that patients with ALD constituted the majority of the population listed for transplantation during the pandemic, adding to the burden of those already waiting for a transplant given that some transplant centres continue to maintain a mandatory 6-month sobriety for individuals with ALD before liver transplantation.[9]

Meanwhile, the mortality of individuals with viral hepatitis appears to be less affected by the pandemic when compared with ALD because their mortality has been decreasing for the past decades with the advent of effective antiviral therapy. The increased HCV-related mortality could be attributed to the decrease in HCV surveillance and treatment in the United States during the first few months of the pandemic, as well as the ongoing opioid crisis occurring in the United States at this same time.[27] However, with the increased use of telemedicine during the pandemic, challenges in delayed appointments and access to chronic use of antiviral medications is now being addressed.

NAFLD has been associated with higher mortality in those with COVID-19 which could also have contributed to an increase in their mortality rate.[28] Among decedents with NAFLD, the major causes of death included cardiovascular disease, metabolic disease, and end-stage liver disease.[3] These conditions were reported to be disproportionally vulnerable to COVID-19 infection and with distorted cascade of care during the pandemic.[22,29]

Regarding our findings suggesting that the young and middle-aged populations had steeper upward mortality trends when compared with those above the age of 65 years old especially for those with ALD and NAFLD, the cause can be multifactorial with multiple potential reasons already discussed above. However, understanding the increase in mortality related to NAFLD may require more research but, as noted in a recent study,[28] those with NAFLD were at an increased risk for mortality if they contracted COVID-19. In addition, because morbid obesity has also been found to be an independent risk factor for COVID-19 mortality, this risk factor also places persons with NAFLD and obesity at high risk for mortality. Together, these risk factors may also help to explain the increase in NAFLD related mortality at least at the beginning of the pandemic.

We showed that females had a steeper increasing trend of mortality for all 4 CLDs than males during the pandemic. A recent meta-analysis showed that females are at higher risk for developing cirrhosis than males with the same amount of alcohol consumption,[30] which may explain the higher APC between 2019 and 2021 in females. In addition, the COVID-19 pandemic has posed a greater socioeconomic impact on females than males, which includes disruption of access to medical resources and loss of employment opportunities along with increased childcare burden with closure of schools and childcare facilities.[31] Less access to life-saving interventions such as liver transplantation most likely also played an important role in the increased deaths among females with CLD. It has long been known that females have a lower likelihood of

receiving liver transplantation owing to differences in MELD exception points, anthropometric, and liver measurements (body surface area, liver volume, and liver weight).[32] A nationwide study showed that during the first period of the COVID-19 pandemic, March to November 2020, female candidates on the liver transplant waiting-list had a significantly reduced liver transplant rate when compared with pre-pandemic era.[33]

Our findings also indicated a disparate impact of the pandemic across different racial/ethnic groups. During the COVID-19 pandemic, non-Hispanic Blacks sustained the highest percentage of excess deaths when compared with other races and ethnicities in general.[34] Non-Hispanic American Indian/Alaska Natives and non-Hispanic Whites suggested the highest ALD-related mortality rates and the steepest upward trend during pandemic. Despite these findings, a recent study noted that ethnic and racial minorities experienced a disproportionally lower chance of undergoing liver transplantation.[24] We showed that American Indian/Alaska Natives had the mildest downward trend for HCV-related deaths and the highest NAFLD-related mortality rate. The social determinants, access to care, and the quality of care should be targeted to improve the health of these populations.[35] The surging HCV-related deaths in 2020 was more dramatic in non-Hispanic Whites. Given the widespread use of curative therapy, decedents from HCV-related deaths were likely those with recent infection through intravenous drug use or high-risk sexual behaviour or those who did not have access to curative antiviral therapy. Either population subgroup was highly vulnerable to the pandemic. Non-Hispanic Asians and Pacific Islanders was the only racial group which saw significant increase in HBV-related deaths in 2020. This is likely a result of the high disease prevalence among Asians and Pacific Islanders.[36] The death rate fell back to the predicted range in 2021, which was consistent with a recent finding that Asians had fewer excess deaths among all racial and ethnic groups.[37]

The strength of our study was that we used a dataset that captures >99% of deaths in the USA which allowed us to provide trends in mortality both yearly and monthly with minimal selection bias. Leveraging the trend from 2010 to 2019, we were able to estimate the predicted mortality rates of CLD with high accuracy which provided the latest information on the impact of the COVID-19 pandemic on CLD-related mortality. However, we also acknowledge several limitations with this study. Firstly, the CDC assume that the numbers of the total United States population in 2021 and 2020 were same, so further analyses when the total population in 2021 is available from the CDC will be needed. Secondly, socioeconomic status and health coverage which, to some extent, could explain the observed disparities was not available and thus not assessed. Thirdly, our study provided mortality data for people with CLD and not the overall health status of the population with CLD who were still living. Fourthly, our study is an observational study and we reported all-cause and liver-related mortality in people with CLD, and the data do not infer a causal relationship between specific CLD and mortality. Lastly, there can be miscoding in the cause of death with large administrative databases such as the WONDER database. During the pandemic, especially early on, there could also be underreporting of COVID-19 related deaths owing to lack of testing and other logistic problems with early public health response.

Conclusions

The current study provided updated and comprehensive data to include both liver-related and all-cause mortality rates for people with liver disease. The study found a decreasing trend in mortality for viral hepatitis but rising mortality for NAFLD and ALD in the United States. However, with the COVID-19 pandemic, the progress for viral hepatitis has slowed down, while the increasing mortality trend for ALD and NAFLD became accelerated. The study also found widened gaps in the disparities among the different racial and ethnic groups. Our findings can inform medical practice and public health intervention to address the observed mortality trends and associated inequities for the USA. We also encourage future studies to examine these trends for other geographic regions to inform local practice and policy makers for the ongoing pandemic and during its recovery phase.

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Abbreviations

ALD, alcohol-associated liver disease; APC, annual percentage change; ASMR, age-standardized mortality rates; CDC WONDER, Center for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research; CLD, chronic liver disease; ICD-10, International Classification of Diseases – 10th edition; NAFLD, non-alcoholic fatty liver disease; NVSS, National Vital Statistics System.

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Conflicts of interest

FJ: Speaker: Gilead Sciences, MSD, and Ascletis. Consulting/advisory board: Gilead, MSD. MHN: Grants: Gilead, Pfizer, Enanta, Vir, Glycotest, National Cancer Institute, B.K. Kee Foundation, Exact Sciences; Helio Health; Consulting or advisory board: Intercept, Gilead, Exact Sciences, Laboratory of Advanced Medicine, Bayer, Eisai, GSK, Novartis. All other authors do not have any conflicts of interest.

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

Authors' contributions

Study design and data analysis: XG, FL, XH, JZ, YHY, FJ, MHN. Drafting of the manuscript: XG, FL, YHY, FJ. Critical review of the manuscript: JZ, YHY, FJ,

MHN. Critical revision of the manuscript: MHN. Study conception and study supervision: JZ, FJ, MHN. Data interpretation and approval of the manuscript: all authors.

Data availability statement

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

Supplementary data

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