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Original Article

Multivariable-adjusted trends in mortality due to alcoholic liver disease among adults in the United States, from 1999-2017

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Abstract: Objective: Mortality-trends from alcoholic liver disease (ALD) have recently increased and they differ by various factors in the U.S. However, these trends have only been analyzed using univariate models and in reality they may be influenced by various factors. We thus examined trends in age-standardized mortality from ALD among U.S. adults for 1999-2017, using multivariable piecewise log-linear models. Methods: We collected mortality-data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database, us-ing the Underlying Cause of Death. Results: We identified 296,194 deaths from ALD and 346,386 deaths indirectly attributable to ALD during the period from 1999-2017. The multivariable-adjusted, age-standardized ALD mortality was stable during 1999-2006 (annual percentage change [APC]=-2.24, P=0.24), and increased during 2006-2017 (APC=3.18, P<0.006). Their trends did not differ by sex, race, age or urbanization. Subgroup analyses revealed up-ward multivariable-adjusted, age-standardized mortality-trends in alcoholic fatty liver (APC=4.64, P<0.001), alcohol-ic hepatitis (APC=4.38, P<0.001), and alcoholic cirrhosis (APC=5.33, P<0.001), but downward mortality-trends in alcoholic hepatic failure (APC=-1.63, P=0.006) and unspecified ALD (APC=-0.86, P=0.013). Strikingly, non-alcoholic cirrhosis also had an upward multivariable-adjusted, age-standardized mortality-trend (APC=0.69, P=0.046). By contrast, recent mortality-trends were stable for all cause of deaths (APC=-0.39, P=0.379) and downward for ma-lignant neoplasms excluding liver cancer (APC=-2.82, P<0.001), infections (APC=-2.60, P<0.001), cardiovascular disease (APC=-0.69, P=0.044) and respiratory disease (APC=-0.56, P=0.002). The adjusted mortality with ALD as a contributing cause of death also had an upward trend during 2000-2017 (APC=5.47, P<0.001). Strikingly, common comorbidities of ALD, including hepatocellular carcinoma, cerebrovascular and ischemic heart cardiovascular dis-eases and sepsis, had upward trends during the past 14 to 16 years. Conclusions: ALD had an upward multivariable-adjusted, age-standardized mortality-trend among U.S. adults, without significant differences by sex, race, age or urbanization. Three ALD subtypes (alcoholic fatty liver, alcoholic hepatitis and alcoholic cirrhosis) and non-alcoholic cirrhosis had upward morality-trends, while other ALD subtypes and other causes of death did not.

Keywords: Trend, mortality, alcoholic liver disease, disparity

Introduction

Likely due to increasing alcohol- use, some subtypes of alcoholic liver disease (ALD) have recently increased in prevalence, hospitalization or mortality [1-4]. Prevalence of alcoholic fa-tty liver disease, which is a subtype of ALD, increased [4, 5]. Mortality of alcoholic hepatitis and cirrhosis also had upward trends [6, 7]. Moreover, mortality trends in these causes of death appeared to differ by ethnicity/race, age, sex and urbanization [1- 3]. However, all of these trend analyses used univariate models and could be influenced or biased by confounders.

Thus, multivariable-adjusted trends in ALD-mortality and related factors are much needed to exclude the confounding factors. Moreover, little is known about the multivariable- adjusted age-standardized mortality trends in all sub-types of ALD. We therefore examined trends in age-standardized mortality of ALD and its sub-types among U.S. adults by factors using multi-variable piecewise log- linear models, as well as other common causes of death as the control.

Methods

In this population-based trend study, we collected mortality-data (age-standardized for the 2000 U.S. standard population) from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database (CDC WONDER), using the Underlying Cause of Death Data to identify all deaths from ALD, its subtypes and other common causes of death in the United States from 1999-2017. Rates in WONDER were suppressed when the death count was <20 (or missing data). This study is exempt from approval from an institu-tional review board (IRB) due to the use of de-identified publicly available data on deceased U.S. residents.

Subjects were included if they were aged 25 years or older and had ALD (International Classification of Diseases, 10_{th} edition [ICD-10] code, K70) as the underlying cause of death on their death certificates. The subtypes of ALD were classified using the ICD-10 system, for alcoholic fatty liver (ICD-10 code, K70.0), alcoholic hepatitis (ICD-10 code, K70.1), alcoholic fibrosis and sclerosis of liver (ICD-10 code, K70.2), alcoholic cirrhosis of liver (ICD-10 code, K70.3), alcoholic hepatic failure (ICD-10 code, K70.4), and unspecified alcoholic liver disease (ICD-10 code, K70.9). We also extracted the mortality data of other common causes of death by their ICD-10 codes, including all causes, malignant neoplasms excluding HCC (ICD-10 code, C00-C21 and C23-C48), infections (ICD-10 code, A00-B99), cardiovascular disease (ICD-10 code, I00-I99), and respiratory disease (ICD-10 code, J00-J98) [8]. Furthermore, we examined whether the trends of ALD mortality correlated with those of common comorbidity in ALD patients. Specifically, we extracted mor-tality data on deceased adults in the U.S.A. who had the common comorbidity of ALD as the underlying cause of death and ALD as a contributing cause of death (up to 20 contributing causes of death are allowed). The common comorbidities included sepsis (A41, A40), cerebrovascular and ischemic heart disease (I60-I69, I25), trauma (V01-Y89), hepatocellular carcinoma (C22.0), gastrointestinal bleeding (K25-K28, K92.0-K92.2, I85.0), peritonitis (K65.9) and hepatorenal syndrome (K76.7) [9].

Data were also extracted by the following variables: Sex (female/male), 20-year age group (25-44 years, 45-64 years, and 65+ years), race (White/non-White), urbanization (metro/non-metro, based on the 2006 NCHS Urban-Rural Scheme for Counties). Institutional Review Board approval was not required because this was not human- subject research (all subjects were deceased at the time of study) and we used de-identified, publicly available data.

Trends in mortality over time were explored using the National Cancer Institute's join point regression software (version 4.7.0.0) to determine the possible presence of 1 trend change-point. We then used multivariable piecewise log-linear models to adjust covariables (Stata, version 15) as described before [5, 10-14]. Specifically, trends in age -standardized mortality were further adjusted for sex, race (White/non-White), 3-tier age groups and urbanization, except when the variable was used as the major factor. The years with death-count fewer than 20 were excluded due to unreliable data. Bas-ed on the multivariable piecewise linear model and adjusted to sex, race and urbanization, we predicted the age-standardized mortality among U.S. adults during 1999-2040 by age-group, using the age-standardized mortality ratios of male/female, White/non-White and Metropolitan/Non-Metropolitan in 2017. Given a recently-reported change-point of trends in ALD mortality during 2007-2017 [7], we analyzed the trend and its potential change-point using a similar multivariable piece-wise log-linear model. All *P* values were 2-sided, and only $P<0.05$ was considered statistically signifi-cant.

Results

We identified 296,194 deaths due to ALD dur-ing the period of 1999-2017 and found a recent upward trend in multivariable-adjusted, age-standardized mortality of AFD from 2006-2017

Table 1. Multivariable-adjusted trends in age-standardized mortality of alcoholic liver disease among U.S. adults aged 25+ years, 1999-2017

	1999-2017	1999		2017		Trend segment 1			Trend segment 2			*P* for Parallelism (2006-2017)
	Deaths, n	Deaths, n	ASM	Deaths, n	ASM	*Years*	*APC# (95% CI)*	*P for trend*	*Years*	*APC# (95% CI)*	*P for trend*	
Overall	296194	11948	6.71	22231	9.17	1999-2006	-2.24 (-5.94, 1.47)	0.24	2006-2017	3.18 (0.92, 5.45)	0.006	
Sex												
Male	83681	3034	3.25	6673	5.58	1999-2009	-1.76 (-5.11, 1.59)	0.30	2009-2017	3.92 (-0.01, 7.85)	0.051	0.70
Female*	212513	8914	10.64	15458	13.09	1999-2006	-1.18 (-6.62, 4.25)	0.67	2006-2017	3.69 (0.42, 6.97)	0.027	Reference
Age, yr												
25-44	44496	2445	2.89	3019	3.77	1999-2006	-3.56 (-8.95, 1.83)	0.19	2006-2017	3.87 (1.48, 6.25)	0.005	0.59
45-64	189129	6661	11.03	13912	15.90	1999-2005	-1.04 (-4.60, 2.52)	0.57	2005-2017	3.41 (1.83, 4.99)	<0.001	0.92
65+*	62569	2842	8.14	5300	10.09	1999-2010	-1.38 (-2.91, 0.14)	0.07	2010-2017	5.37 (2.95, 7.80)	<0.001	Reference
Race												
White	257224	10034	6.63	19400	9.94	1999-2011	1.36 (-0.74, 3.46)	0.20	2011-2017	6.26 (-0.51, 13.04)	0.07	0.40
Non-White*	38970	1914	7.25	2831	6.00	1999-2006	-5.13 (-10.89, 0.63)	0.08	2006-2017	1.84 (-0.65, 4.34)	0.147	Reference
Urbanization (2006)												
Metropolitan	241854	9794	6.81	18055	8.94	1999-2006	-3.55 (-7.97, 0.87)	0.12	2006-2017	3.13 (0.40, 5.86)	0.025	0.88
Non-metropolitan*	54340	2154	6.58	4176	10.51	1999-2009	0.17 (-2.73, 3.06)	0.92	2009-2017	3.86 (-0.76, 8.48)	0.106	Reference

ASM, Age-standardized mortality (per 100,000); APC, annual percentage change; CI, confidence intervals. #All APC were adjusted for sex, race, age (3 groups), and urbanization, except when as the factor. *There were suppressed/unreliable data for females, aged 65+, Non-White and Non-Metropolitan for several years (1999-2008, 2010, 2011, 2013). Urbanization was defined using the 2006 version of the NCHS (National Center for Health Statistics) Urban-Rural Classification Scheme for Counties.

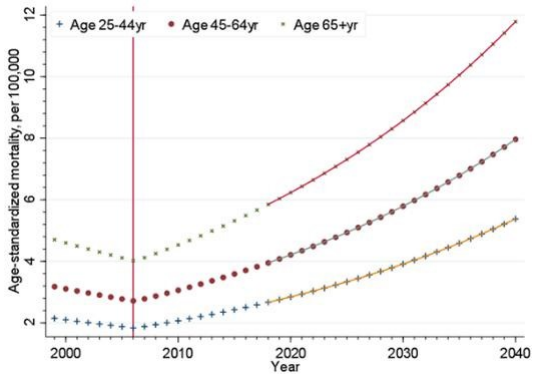

Figure 1. Multivariable-adjusted trends in sex-, race- and urbanization-adjusted age-standardized mortal-ity of alcoholic liver disease among U.S. adults by age group during 1999-2017 and beyond. There was a changing point of the trends in all age groups (verti-cal line, 2006) during 1999-2017. For data points in the years after 2017 (dash line), the ratios of male/female, white/non-white and metropolitan/non-metropolitan were assumed similar to those in 2017, and used for respective mortality prediction. Analysis was limited to adults aged 25+ years.

(**Table 1**, annual percentage change [APC] =3.18, P=0.006). Trends in multivariable -adjusted, age-standardized mortality did not differ by sex, race, age or urbanization (**Table 1**).

No change-points were identified from 2007-2017 (*P*=0.482). Strikingly, our multivariable model showed that subjects aged 65+ years had the highest and the fastest growing mortality in the 3 age-groups, despite the trend similar to those of other age groups. The age-standardized mortality ratios of male/female, White/non-White and Metropolitan/Non-Metropolitan were 2.346, 1.657 and 0.851 in 2017, respectively. Based on these ratios and models, we predicted the sex-, race- and urbanization-adjusted age-standardized mortality due to ALD from 1999-2040 (**Figure 1**). If no effective interventions are made, the predicted ALD mortality would double by 2040 and become 12 per 100,000 in adults 65+ years.

Our analyses on subtypes of ALD (**Table 2**) showed upward mortality-trends in alcoholic fatty liver (APC=4.64, P<0.001), alcoholic hepatitis (APC=4.38, P<0.001), and alcoholic cirrhosis of liver (APC=5.33, P<0.001) during the past 5-10 years, but downward mortality-trends in alcoholic hepatic failure (APC=-1.63, P=0.006) and unspecified alcoholic liver diseases (APC=-0.86, P=0.013). Strikingly, the multivariable- adjusted age- standardized mortality-trend of non-alcoholic cirrhosis was also upward (APC=0.69, P=0.046). By contrast, recent multivariable-adjusted age-standardized mortality-trends were stable for all causes (APC=- 0.39, P=0.379), but decreasing for malignant neoplasm excluding liver cancer (APC=-2.82, P<0.001), infections (APC=-2.60, P< 0.001), cardiovascular disease (APC=-0.69, P=0.044) and respiratory disease (APC=-0.56, P=0.002) during the past 8-15 years.

Among the 346,386 deaths with ALD as a contributing cause of death in U.S. adults from 1999 -2017, 269,634 (77.8%) had another ty-pe of ALD as the underlying cause of death. Consistent with the trend in age- , race- and sex-adjusted mortality with ALD as the underlying cause of death, those with ALD as a contribut-ing cause of death were also in an upward trend during the period of 2000-2017 (APC=5.47, P<0.001, **Table 3**) and this may have begun 2 years earlier for the beginning of the upward trend in ALD as the underlying cause of death. Strikingly, all common comorbidities of ALD, except trauma (V01-Y89), had an upward trend during the past 14 to 16 years (**Table 3**) which was different from the downward or stable trends in the general population (**Table 1**) [8].

Discussion

Age- standardized mortality due to ALD among U.S. adults decreased during 1999-2006, but has continued increasing ever since. There were no significant differences in ALD-morta-lity trends by sex, race, age and urbanization. Therefore, the mortality disparities of ALD by these factors [6, 7, 15] will continue increasing. These findings are somewhat alarming and highlight the need for awareness of ALD bur-dens and continued health disparities.

Our subgroup analyses demonstrate that alcoholic cirrhosis of the liver had the fastest growing and the largest proportion of multivariable-adjusted age-standardized mortality among all ALD subtypes. Alcoholic fatty liver and alcoholic hepatitis too had an upward trend in their mortality rates, which was in part supported by previous studies [6, 9, 16, 17]. These 3 subtypes of ALD thus would mostly likely contribute to the overall upward trends of ALD. These observations were further augmented by the down-

Table 2. Multivariable-adjusted trends in age-standardized mortality of subtypes of alcoholic liver disease and other causes among U.S. adults aged 25+ years, 1999-2017

Cause, ICD-10 code(s)	1999		2017		Trend segment 1			Trend segment 2		
	No. Deaths	ASM	No. Deaths	ASM	Years	APC* (95% CI)	P	Years	APC* (95% CI)	P
ALD (K70)										
Alcoholic fatty liver (K70.0)**	303	0.20	469	0.19	1999-2002	-17.31 (-32.93, -1.70)	0.03	2002-2017	4.64 (2.77, 6.51)	<0.001
Alcoholic hepatitis (K70.1)	804	0.47	1396	0.60	1999-2005	-6.64 (-9.63, -3.66)	<0.001	2005-2017	4.38 (3.08, 5.69)	<0.001
Alcoholic cirrhosis of liver (K70.3)	7260	4.09	16547	6.73	1999-2009	-0.41 (-1.69, 0.87)	0.528	2009-2017	5.33 (3.83, 6.83)	<0.001
Alcoholic hepatic failure (K70.4)	1564	0.88	1545	0.66	1999-2005	-5.32 (-9.02, -1.62)	0.005	2005-2017	-1.63 (-2.78, -0.48)	0.006
ALD, unspecified (K70.9)	2014	1.13	2263	0.95	1999-2017	-0.86 (-1.54, -0.19)	0.013			
Other underlying causes of death										
Cirrhosis (K74.3 to K74.6) excluding alcoholic cirrhosis (K70.3)	13809	7.78	19397	8.76	1999-2008	-1.78 (-2.58, -0.98)	<0.001	2008-2017	0.69 (0.01, 1.38)	0.046
All causes	2319606	1314.25	2749563	1098.72	1999-2012	-2.02 (-2.29, -1.75)	<0.001	2012-2017	-0.39 (-1.25, 0.48)	0.379
Malignant neoplasm excluding liver cancer	534316	301.70	569440	224.11	1999-2011	-1.91 (-2.23, -1.59)	<0.001	2011-2017	-2.82 (-3.86, -1.77)	<0.001
Infections (A00-B99)	58447	32.94	68303	27.25	1999-2005	-0.39 (-2.58, 1.79)	0.72	2005-2017	-2.60 (-3.57, -1.64)	<0.001
Cardiovascular disease (I00-I99)	951686	540.97	856964	338.16	1999-2011	-4.07 (-4.27, -3.86)	<0.001	2011-2017	-0.69 (-1.36, -0.02)	0.044
Respiratory disease (J00-J98)	227985	129.37	277101	109.63	1999-2007	-1.59 (-2.03, -1.15)	<0.001	2007-2017	-0.56 (-0.91, -0.21)	0.002

ALD, alcoholic liver disease; ASM, Age-standardized mortality (per 100,000); APC, annual percentage change; CI, confidence intervals; ICD-10, International classification of diseases, 10th edition. *Adjusted for sex and race (white/nonwhite). Alcoholic fibrosis and sclerosis of liver (K70.2) did not have enough deaths to compute trends even without adjusting for any groups. **Contained some unreliable values for age adjusted rate in selected years.

Table 3. Multivariable-adjusted trends in age-standardized leading mortality in U.S. adults with alcoholic liver disease as contributing cause of death, 1999-2017

Cause, ICD-10 code(s)	1999		2017		Trend segment 1			Trend segment 2		
	No. Deaths	ASM	No. Deaths	ASM	Years	APC* (95% CI)	P	Years	APC* (95% CI)	P
All	11022	6.21	29199	11.95	1999-2000	-26.06 (-45.50, -6.62)	0.009	2000-2017	5.47 (4.79, 6.15)	<0.001
Sepsis (A41, A40)	55	0.01	285	0.12	1999-2001	-12.52 (-69.15, 44.11)	0.655	2001-2017	6.98 (5.50, 8.45)	<0.001
Cerebrovascular and ischemic heart disease (I60-I69, I25)	228	0.10	623	0.25	1999-2001	-31.34 (-72.81, 10.13)	0.136	2001-2017	6.98 (5.50, 8.45)	<0.001
Trauma (V01-Y89)	143	0.07	979	0.42	1999-2011	19.80 (15.41, 24.20)	<0.001	2011-2017	-0.63 (-8.95, 7.69)	0.880
Hepatocellular carcinoma (C22.0)	112	0.07	830	0.28	1999-2003	-0.76 (-31.75, 30.23)	0.960	2003-2017	11.58 (8.69, 14.47)	<0.001

ALD, alcoholic liver disease; ASM, Age-standardized mortality (per 100,000); APC, annual percentage change; CI, confidence intervals; ICD-10, International classification of diseases, 10th edition. *Adjusted for sex and race (white/nonwhite); adults defined as being 25+ years of age. Gastrointestinal bleeding (K25-K28, K92.0-K92.2, I85.0), Peritonitis (K65.9) and Hepatorenal syndrome (K76.7) each had too few cases for reliable trend analyses.

ward mortality trends in all causes, malignant neoplasm excluding liver cancer, infections, cardiovascular disease and respiratory disease (as compared with upward trends in subtypes of ALD) which may serve as a population con-trol for the study period. It is noteworthy that the trends in common causes of death in this study are consistent with a previous report on short-term trends [8]. Therefore, the 3 subtypes of ALD with upward trends should be consid-ered as a research topic and as a priority for disease prevention and treatment.

Previous univariate modelling revealed that age-standardized mortality trends in ALD and its subtypes appeared to differ by age, sex, ethnicity/race, and urbanization [1-3]. Strikingly, the multivariable modelling used here did not reveal any trend differences by these factors. Thus, the previously reported trend difference might be influenced or biased by confounding factors. The further efforts may focus on the overall population rather than a single group by one of these factors. However, the lack of trend difference in mortality of ALD and some of its subtypes by age, sex, ethnicity/race and urbanization should not negate the importance of public health measures and health policies that are effective in selected populations (e.g., screening males for hepatocellular carcinoma) [18]. Similarly, the fastest growing mortality in older adults shown here are very concerning, and seems to deserve attention among primary care providers, hepatologists and public health workers.

It is noteworthy that non-alcoholic cirrhosis of the liver had an upward multivariable-adjusted mortality trend during 2008-2017 (APC=0.69), after 9 years of a downward trend. This trend contrasts the overall downward mortality in all causes and other causes of death as shown here. The other trend analysis, albeit using a univariate model, confirms the upward trend in non-alcoholic cirrhosis of the liver and stable trends in mortality of liver malignancies [8]. Further studies and interventions are warranted to confirm our findings and reverse the upward mortality trend in non-alcoholic cirrhosis of the liver. Indeed, various guidelines and scholars have focused on this subject and more research would effectively reverse the upward mortality-trend soon [18-21].

We also showed the correlation of ALD with its common comorbidities, such as hepatocellular carcinoma, cerebrovascular and ischemic heart cardiovascular diseases and sepsis via adjusted trend analyses. These findings are consistent with previous reports on the subject [22, 23]. Our works also highlights a bigger adjusted mortality trend in hepatocellular carcinoma among the subjects with ALD than the overall mortality trend among these subjects (ACP=11.58 versus 5.47). Additional studies and measures are warranted to attenuate and reverse those very pressing upward trends.

Limitations of this study include potential misclassification of causes on death certificates, which were used before [7, 15] and not being highly specific for underlying causes of death other than pneumonia [24]. Owing to a long study-period, we might have underestimated the number of trend change-points. To address this issue, we conducted a sensitivity analysis for 2007-2017, but did not identify any addition-al change-points, which were shown in a univariable model [7]. The difference might be attributable to multivariable versus univariable model and aged 25+ versus 20+ years in this and the prior studies, respectively.

In summary, we here show the continuation of upward multivariable-adjusted trends in ALD mortality, without significant tend difference in age, sex, ethnicity/race, and urbanization. Three ALD subtypes appear to significantly contribute to the overall upward-trends of ALD mor-tality, including alcoholic fatty liver, alcoholic hepatitis and alcoholic cirrhosis, while other ALD subtypes and other causes of death did not have an upward mortality trend. Further research is warranted to validate and delineate the associated factors.

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Disclosure of conflict of interest

None.

Abbreviations

ALD, alcoholic liver disease; APC, annual percentage change; CDC WONDER, Centers for Disease Control and Prevention Wide-ranging

Online Data for Epidemiologic Research database; ICD-10, International Classification of Diseases, 10th edition.

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References

[1] Shirazi F, Singal AK and Wong RJ. Alcohol-asso-ciated cirrhosis and alcoholic hepatitis hospi-talization trends in the United States. J Clin Gastroenterol 2021; 55: 174-179.

[2] Paik JM, Golabi P, Biswas R, Alqahtani S, Venkatesan C and Younossi ZM. Nonalcoholic fatty liver disease and alcoholic liver disease are major drivers of liver mortality in the United States. Hepatol Commun 2020; 4: 890-903.

[3] Moon AM, Yang JY, Barritt AS 4th, Bataller R and Peery AF. Rising mortality from alcohol-as-sociated liver disease in the United States in the 21st century. Am J Gastroenterol 2020; 115: 79-87.

[4] Wong T, Dang K, Ladhani S, Singal AK and Wong RJ. Prevalence of alcoholic fatty liver dis-ease among adults in the United States, 2001-2016. JAMA 2019; 321: 1723-1725.

[5] Zhang J, Lin Y and Zhang L. Trends in alcoholic fatty liver disease. JAMA 2019; 322: 979-980.

[6] Jinjuvadia R and Liangpunsakul S; Translation-al Research and Evolving Alcoholic Hepatitis Treatment Consortium. Trends in alcoholic hepatitis-related hospitalizations, financial burden, and mortality in the United States. J Clin Gastroenterol 2015; 49: 506-511.

[7] Kim D, Li AA, Gadiparthi C, Khan MA, Cholankeril G, Glenn JS and Ahmed A. Changing trends in etiology-based annual mortality from chronic liver disease, from 2007 through 2016. Gastroenterology 2018; 155: 1154-1163, e1153.

[8] Hu X, Lin Y, Qin G and Zhang L. Underlying causes of death among adults in the United States, 2013-2017. Explor Res Hypothesis Med 2020; 5: 122-128.

[9] Tapper EB and Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 2018; 362: k2817.

[10] Yuan X, Xu J, Hussain S, Wang H, Gao N and Zhang L. Trends and prediction in daily new cases and deaths of COVID-19 in the United States: an internet search-interest based mod-el. Explor Res Hypothesis Med 2020; 5: 1-6.

[11] Xu J, Lin Y, Yang M and Zhang L. Statistics and pitfalls of trend analysis in cancer research: a review focused on statistical packages. J Can-cer 2020; 11: 2957-2961.

[12] Xu J, Hussain S, Lu G, Zheng K, Wei S, Bao W and Zhang L. Associations of stay-at-home or-der and face-masking recommendation with trends in daily new cases and deaths of labora-tory-confirmed COVID-19 in the United States. Explor Res Hypothesis Med 2020; 1-10.

[13] Yuan X, Song F and Zhang L. Methodological considerations in trend analysis of diabetic mortality. Lancet 2019; 393: 1931-1932.

[14] Wang J, Xia HH, Zhang Y and Zhang L. Trends in treatments for prostate cancer in the United States, 2010-2015. Am J Cancer Res 2021; 11: 2351-2368.

[15] Kim D, Li AA, Perumpail RB, Cholankeril G, Gonzalez SA, Kim W and Ahmed A. Disparate trends in mortality of etiology-specific chronic liver diseases among hispanic subpopulations. Clin Gastroenterol Hepatol 2019; 17: 1607-1615, e1602.

[16] Szabo G, Kamath PS, Shah VH, Thursz M and Mathurin P; EASL-AASLD Joint Meeting. Alcohol-related liver disease: areas of consensus, unmet needs and opportunities for further study. Hepatology 2019; 69: 2271-2283.

[17] Kim D, Li AA, Perumpail BJ, Gadiparthi C, Kim W, Cholankeril G, Glenn JS, Harrison SA, Younossi ZM and Ahmed A. Changing trends in etiology-based and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2019; 69: 1064-1074.

[18] Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, Kawaguchi T, Kurosaki M, Sakaida I, Shimizu M, Taniai M, Terai S, Nishikawa H, Hiasa Y, Hidaka H, Miwa H, Chayama K, Enomoto N, Shimosegawa T, Takehara T and Koike K. Evidence-based clinical practice guidelines for liver cirrhosis 2020. J Gastroen-terol 2021; 56: 593-619.

[19] Younossi ZM, Corey KE and Lim JK. AGA clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: expert review. Gastroenterology 2021; 160: 912-918.

[20] Singal AG and El-Serag HB. Rational HCC screening approaches for patients with NAFLD. J Hepatol 2022; 76: 195-201.

[21] Foerster F, Gairing SJ, Müller L and Galle PR. NAFLD-driven HCC: Safety and efficacy of current and emerging treatment options. J Hepatol 2022; 76: 446-457.

[22] Celli R and Zhang X. Pathology of alcoholic liver disease. J Clin Transl Hepatol 2014; 2: 103-109.
[23] Parikh N, Martel-Laferriere V, Zhang X, Diet-erich D, Fiel MI and Perumalswami P. Hepato-cellular carcinoma in a noncirrhotic patient with HIV: a case report and review of the litera-ture. Semin Liver Dis 2012; 32: 186-192.
[24] Mieno MN, Tanaka N, Arai T, Kawahara T, Kuchiba A, Ishikawa S and Sawabe M. Accura-cy of death certificates and assessment of fac-tors for misclassification of underlying cause of death. J Epidemiol 2016; 26: 191-198.