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Changing Trends in Etiology-Based and Ethnicity-Based Annual Mortality Rates of Cirrhosis and Hepatocellular Carcinoma in the United States

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Abstract

With recent improvements in the treatment of end-stage liver disease (ESLD), a better understanding of the burden of cirrhosis and hepatocellular carcinoma (HCC) is needed in the United States. A population-based study using the US Census and national mortality database was performed. We identified the age-standardized etiology-specific mortality rates for cirrhosis and HCC among US adults ages 20 years or older from 2007 to 2016. We determined temporal mortality rate patterns by joinpoint analysis with estimates of annual percentage change (APC). Age-standardized cirrhosis-related mortality rates increased from 19.77/100,000 persons in 2007 to 23.67 in 2016 with an annual increase of 2.3% (95% confidence interval [CI] 2.0–2.7). The APC in mortality rates for hepatitis C virus (HCV)-cirrhosis shifted from a 2.9% increase per year during 2007 to 2014 to a 6.5% decline per year during 2014 to 2016. Meanwhile, mortality for cirrhosis from alcoholic liver disease (ALD, APC 4.5%) and NAFLD (APC 15.4%) increased over the same period, whereas mortality for hepatitis B virus (HBV)-cirrhosis decreased with an

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average APC of -1.1% . HCC-related mortality increased from 3.48/100,000 persons in 2007 to 4.41 in 2016 at an annual rate of 2.0% (95% CI 1.3–2.6). Etiology-specific mortality rates of HCC were largely consistent with cirrhosis-related mortality. Minority populations had a higher burden of HCC-related mortality.

Conclusion: Cirrhosis-related and HCC-related mortality rates increased between 2007 and 2016 in the United States. However, mortality rates in HCV-cirrhosis demonstrated a significant decline from 2014 to 2016, during the direct-acting antiviral era. Mortality rates for ALD/NAFLD-cirrhosis and HCC have continued to increase, whereas HBV-cirrhosis-related mortality declined during the 10-year period. Importantly, minorities had a disproportionately higher burden of ESLD-related mortality. (Hepatology 2019;69:1064–1074).

Cirrhosis and end-stage liver disease (ESLD) of any etiology are one of leading causes of death and global health burden in the world,^(1,2) with over 1 million deaths in 2010.⁽³⁾ Worldwide cirrhosis-related mortality increased 46% from 1990 to 2013.⁽⁴⁾ In the United States, cirrhosis was the eighth-leading cause of death in 2010 and has demonstrated deteriorating trends in terms of years of life lost from 1990 to 2010.⁽⁵⁾

However, remarkable advances in the management of ESLD including hepatitis C virus (HCV)-related liver disease have been made over the last few years. Therefore, patients with cirrhosis may have benefited from these improvements with a decline in hepatic decompensation and a reduction in the risk of liver cancer. A study based on National Inpatient Sample (NIS) demonstrated that in-hospital mortality from cirrhosis decreased steadily from 9.1% in 2002 to 5.4% in 2010.⁽⁶⁾ However, it is difficult to extrapolate this decline in in-hospital mortality to an improvement in overall cirrhosis-related mortality.⁽⁷⁾ Highly efficacious, safe, and widely tolerable direct-acting antiviral (DAA) agents for the treatment of chronic HCV infection have shifted the paradigm and may have resulted in a decline in mortality in patients with HCV-related cirrhosis.⁽⁸⁾ However, there are few data reporting the trends in cirrhosis-related mortality during the DAA era. On the other hand, the disease burden of ESLD related to alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) continues to rise.⁽⁹⁾ Therefore, an up-to-date estimation of temporal trends in cirrhosis-related mortality in the setting of a population-based study is needed to determine the actual health burden of etiology-specific ESLD in the United States.

Hepatocellular carcinoma (HCC) caused 750,000 deaths in 2012,⁽¹⁰⁾ and is now the third leading cause of cancer-related death in the world.⁽¹¹⁾ Deaths from HCC increased 60% between 1990 and 2013 world-wide, whereas age-standardized mortality rates for HCC slightly decreased by 5%.⁽⁴⁾ Although hepatitis B virus (HBV) is implicated as the most common cause of HCC in the world, HCV is the most common cause of HCC in the United States. Recent studies using the Surveillance, Epidemiology, and End Results (SEER) database, which captures 28% of the US population, reported that the rate of increase has decelerated for the incidence and mortality of HCC around 2007, but overall HCC incidence has continued to increase from 1973 to 2011.^(12,13) More recent data based on the US Cancer Statistics registry demonstrated that HCC incidence increased from 4.4 per 100,000 in 2000 to 6.7 per 100,000 in 2010, with a 4.5% annual increase from 2000 to 2009 and a nonsignificant 0.7% annual increase from 2010 to 2012.⁽¹⁴⁾ However, updated temporal

trends in HCC-related mortality in population-based studies have not been established. Furthermore, there are accumulating data to suggest that there are ethnic differences in the incidence of cirrhosis and HCC in the United States.⁽¹⁵⁾ A study from the Multiethnic Cohort indicated that HCV was the most common cause of the cirrhosis in blacks, whereas ALD was the leading cause of cirrhosis in whites.⁽¹⁵⁾ However, temporal data are limited on cirrhosis and HCC-related mortality rates stratified by race/ethnicity.

In this study, we used national mortality data from the National Center for Health Statistics to estimate recent temporal trends in cirrhosis-related and HCC-related mortality from 2007 to 2016. The aims of this study were (1) to investigate recent temporal trends in mortality rates for cirrhosis and HCC by etiology; and (2) to determine race/ethnicity-specific trends in cirrhosis-related and HCC-related mortality rates in the United States from 2007 to 2016.

Methods

STUDY DATA

To examine the trends in cirrhosis-related and HCC-related mortality rates for US adults ages 20 years or older, stratified by race/ethnicity, we analyzed de-identified mortality records from the Centers for Disease Control and Prevention's National Vital Statistics System (NVSS), which were extracted from death certificates. This database captures more than 99% of deaths in all 50 states and the District of Columbia. Data for the population under 20 years of age were unreliable due to a small number of events and were therefore excluded from the analysis.

The NVSS used the International Classification of Diseases Tenth Revision (ICD-10) to identify the cause of death documented on death certificates. The NVSS processes mortality records to produce an annual national data set on multiple-cause mortality, which is made available for public use.⁽¹⁶⁾ Each observation in the data set is one death with the decedent's demographic characteristics related to the death.⁽¹⁶⁾ The cause of death based on the death certificate is incorporated into three fields: underlying cause of death, entity axis, and record axis.^(16,17) The underlying cause of death lists the one disease or condition that leads to death. The entity axis includes all causes of death listed on the death certificate. To promote specificity of the data and resolve contradictions, the record axis represents a refined version of the entity axis in which redundant conditions are deleted, related conditions are combined for coding efficiency, and causes violating certain logical checks are eliminated.⁽¹⁷⁾ Because of the higher specificity of the record axis, we analyzed the record axis for underlying or contributing causes of death.⁽¹⁷⁾ Because all data are de-identified and publicly available, the study was not subject to institutional review board review.

DEFINITIONS OF ETIOLOGIES OF CIRRHOSIS AND HCC

ICD-10 codes were used to identify cirrhosis, HCC, and etiologies of underlying disease from the NVSS database. We analyzed subjects with liver cirrhosis complicated by portal hypertension. Eligibility criteria required ICD-10 codes for diagnosis of either liver cirrhosis (K70.3, K74.0, K74.1, K74.3, K74.4, K74.2, and K74.6) or portal hypertension (K76.6), or one of its manifestations: spontaneous bacterial peritonitis (K65.2), hepatic encephalopathy

(K72.11 and K72.91), variceal bleeding (I85.0 and I85.1), or hepatorenal syndrome (K76.7). HCC was defined based on an ICD-10 code (C22.0). Among subjects with cirrhosis and HCC, ICD-10 diagnostic codes were used to identify HCV infection, HBV infection, ALD, and NAFLD (Supporting Table S1). From the information available in this database, we included demographic data (age, race/ethnicity, sex, and education status). Race/ethnicity was categorized into five mutually exclusive groups: non-Hispanic whites, non-Hispanic blacks, non-Hispanic Asian/Pacific Islanders, and Hispanics (who could be of any race).⁽¹⁸⁾ Data for the American Indian and Alaskan native were unreliable due to small number of out-comes and were therefore excluded from final analysis.

STATISTICAL ANALYSIS

We divided the number of deaths from cirrhosis and HCC by the total US census population for each year to calculate age-specific mortality rates. Age-specific mortality rates per 100,000 persons by age group (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+ years) and age-specific mortality rates by race/ethnicity were calculated. Age-specific mortality rates were standardized to the age distribution of the 2000 US standard population using the direct method. The total population census used to examine the incidence of mortality was derived using the population's estimates from the US Census Bureau. Demographic characteristics of the study population were described as frequencies with percentages for categorical variables. To examine changes in temporal trends over time, we used the National Cancer Institute's joinpoint regression program (version 4.5.0.1). This program fits a series of joined straight lines to trend data, which determine whether age-standardized mortality rates are best explained by a single-trend or multiple-trend segment over time.⁽¹⁹⁾ For each trend segment, the annual percentage change (APC) and the average APC, which is a summary measure of the trend accounting for transitions within each trend segment, were obtained. Joinpoint regression allowing two segments identifies a set of time points at which the change in the slope of the age-standardized mortality rate is statistically significant and calculates the year-to-year percentage change in annual age-standardized mortality rate and the 95% confidence interval (CI) over each trend segment.⁽²⁰⁾ APC was considered statistically significant when the regression line slope differed from zero ($P < 0.05$). This approach determines the year when the slope in mortality rate changes significantly and identifies the magnitude of the change.⁽¹⁹⁾

Results

A total of 25,379,768 deaths among US adults aged 20 years or older between 2007 and 2016 were analyzed in this study. Of these, 534,433 deaths were associated with cirrhosis and 99,753 deaths were attributed to HCC. The demographic characteristics are presented in Table 1. Deaths from cirrhosis and HCC were mostly from males. Regarding racial distributions, although the proportion of non-Hispanic whites was the highest in both cirrhosis and HCC, HCC among non-Hispanic blacks (15.8% for HCC versus 9.6% for cirrhosis) and non-Hispanic Asians (7.4% for HCC versus 2.1% for cirrhosis) represented more deaths compared with cirrhosis. The proportion of cirrhosis-related deaths was highest in non-Hispanic whites, followed by Hispanics, followed by non-Hispanic blacks, and

Asians. The proportion of HCC-related deaths was comparable to those of cirrhosis, except for non-Hispanic blacks (second) and Hispanics (third).

TRENDS IN AGE-STANDARDIZED MORTALITY FOR CIRRHOSIS

Deaths from cirrhosis steadily increased from 43,876 in 2007 to 63,770 in 2016. As shown in Fig. 1, the age-standardized mortality increased from 19.77 per 100,000 persons in 2007 to 23.67 per 100,000 persons in 2016. As given in Table 2, we observed a statistically significant increase in average APC of 2.3% (95% CI 2.0–2.7). In terms of etiologies of cirrhosis, age-standardized HCV cirrhosis-related mortality rates reached a plateau in 2014 and markedly declined from 2014 to 2016 (Fig. 2A). The age-standardized mortality rates for HCV cirrhosis increased initially from 3.06 per 100,000 persons in 2007 to 3.68 per 100,000 persons in 2014. However, a steep decline after the introduction of DAA agents was observed from 3.68 per 100,000 persons in 2014 to 3.20 per 100,000 persons in 2016. As indicated in Table 2, there was an initial increase in HCV-related cirrhosis at an annual rate of 2.9% (95% CI 2.3–3.5) from 2007 to 2014, followed by a decrease from 2014 to 2016 at a rate of 6.5% per year (95% CI –10.3 to –2.6) using joinpoint analysis. In contrast, there was a linear increase in the age-standardized ALD and NAFLD cirrhosis-related mortality rates, whereas the HBV cirrhosis-related mortality rates steadily declined over 10 years. The age-standardized ALD cirrhosis-related mortality rates increased annually by 4.5% (95% CI 3.8–5.3) during the study period. For NAFLD cirrhosis, age-standardized mortality rates increased annually with an average APC of 15.4% (95% CI 14.1–16.7) during the 10-year period. Regarding HBV cirrhosis, age-standardized mortality rates declined annually 1.1% (95% CI –2.0 to –0.2) between 2007 and 2016.

Compared with other race/ethnic groups, non-Hispanic whites had a higher mortality rate for cirrhosis (24.61 per 100,000 versus 20.34 for Hispanics and 15.86 for non-Hispanic blacks in 2016) (Fig. 2B). Table 2 indicates that age-standardized cirrhosis-related mortality increased across all race/ethnic groups. Trends in cirrhosis-related mortality rates were highest among non-Hispanic whites (APC 2.9%, 95% CI 2.5–3.2), followed by Hispanics (1.0%, 95% CI 0.6–1.4) and non-Hispanic blacks (0.9%, 95% CI 0.3–1.6), and lowest among non-Hispanic Asians (–0.5%, 95% CI –0.9 to –0.1) from 2007 to 2016. When we analyzed mortality rates by sex, cirrhosis-related mortality rates in men were 1.9-fold higher than those in women (Fig. 2C). However, increasing trends in cirrhosis-related mortality rates were slightly higher in women (APC 2.9%, 95% CI 2.4–3.3) than in men (2.0%, 95% CI 1.6–2.3) (Table 2).

TRENDS IN AGE-STANDARDIZED MORTALITY FOR HCC

Death from HCC steadily increased from 7,692 deaths in 2007 to 12,469 in 2016. As shown in Fig. 1, the age-standardized HCC-related mortality rate increased from 3.48 per 100,000 persons in 2007 to 4.41 per 100,000 persons in 2016. As indicated in Table 3, joinpoint analysis showed a statistically significant average APC increase of 2.0% (95% CI 1.3–2.6) without any trend segments. Regarding etiologies of HCC (Fig. 3A), age-standardized HCC-related mortality rates for HCV reached a plateau in 2012 (APC 7.0%, 95% CI 5.5–8.6) and remained stable between 2012 and 2016 (APC 0.4%, 95% CI –1.6 to 2.5). Consistent with cirrhosis-related mortality, there was a linear increase in the age-

standardized HCC-related mortality rates for ALD and NAFLD (7.4% [95% CI 6.1–8.7] for ALD and 19.1% [95% CI 14.0–24.5] for NAFLD). The HCC-related mortality rates for HBV remained stable with a marginal decline of –2.2% annually (95% CI –5.0 to 0.7, $P=0.07$) between 2010 and 2016.

As shown in Fig. 3B, non-Hispanic Asians had higher mortality rates (4.96 per 100,000 versus 4.03 for non-Hispanic blacks and 3.01 for non-Hispanic whites) in 2007. However, non-Hispanic blacks surpassed non-Hispanic Asians as the highest mortality group for HCC from 2013 onward. In 2016, compared with the other groups, non-Hispanic blacks had higher mortality rates for HCC (5.12 per 100,000 versus 4.31 for non-Hispanic Asians and 3.87 for non-Hispanic whites). Age-standardized HCC-related mortality increased annually by 2.4% (95% CI 1.9–2.8) in non-Hispanic whites. Mortality rates among non-Hispanic blacks and Hispanics remained stable during the study period, whereas the mortality rate among non-Hispanic Asians decreased annually by 2.0% (95% CI –3.6 to –0.5), with an annual 3.5% (95% CI –4.6 to –2.4) decline from 2009 to 2016. When we analyzed mortality rates by sex, HCC-related mortality rates in men were 3.4-fold higher than those in women (Fig. 3C). Increasing trends in HCC-related mortality rates were similar between women (APC 2.1%, 95% CI 1.4–2.8) and men (APC 2.1%, 95% CI 0.6–3.5).

Discussion

In this population-based study using nationally representative mortality data, we demonstrated that the age-standardized cirrhosis and HCC-related mortality rate increased by 2% annually during a 10-year period from 2007 to 2016 (average APC 2.3% for cirrhosis and 2.0% for HCC). However, since the introduction DAA agents, there has been a significant decline in the nationwide mortality due to HCV-associated cirrhosis. In contrast, mortality rates for ALD-associated and NAFLD-associated cirrhosis and HCC continued to increase during the 10-year study period, whereas mortality rates for HBV-associated cirrhosis and HCC steadily declined.

Advances in medical care and therapeutic interventions to eliminate or control the etiology of chronic liver disease resulting in cirrhosis, ESLD, and HCC may provide survival benefits. According to a study using NIS data, mortality during hospitalization decreased continuously from 9.1% in 2002 to 5.4% in 2010, whereas hospitalizations for cirrhosis increased steadily.⁽⁶⁾ However, this decline in inpatient mortality may not be representative of improvement in the overall survival of patients with cirrhosis.⁽⁷⁾ A recent Veterans Affairs study reported that 30-day mortality in patients with cirrhosis increased from 9.3% in 2004 to 10.1% in 2013, whereas inpatient mortality decreased from 11.4% in 2004 to 7.6% in 2013.⁽²¹⁾ Another study showed that over 50% of patients with decompensated cirrhosis experienced at least one early readmission and the proportion of readmission increased from 35% in 2010 to 40% in 2014.⁽²²⁾ Early readmission is associated with a 66% increase in 90-day mortality.⁽²²⁾ These results suggest that recent changes in the health delivery system have shifted the burden of mortality to the outpatient setting without having a substantial effect on over-all survival in patients with cirrhosis.⁽²¹⁾ Indeed, the prevalence and mortality associated with cirrhosis within the veterans' population increased nearly 2-fold and 1.5-fold, respectively, from 2001 to 2013, whereas the incidence and mortality associated with

HCC increased approximately 3-fold.⁽²³⁾ These trends were dominated by a rise in HCV-associated cirrhosis and HCC, with a much smaller contribution from NAFLD and ALD.⁽²³⁾ Another recent study from Europe demonstrated a reduction in mortality rate associated with achieving sustained virologic response among patients with HCV-related cirrhosis.⁽²⁴⁾ In our study, a steep decline in the HCV-related mortality rate was observed during the DAA era from 3.68 per 100,000 persons in 2014 to 3.2 per 100,000 persons in 2016, with a rate of 6.5% decline per year. If current trends continue, our data suggest that HCV-cirrhosis-related mortality rates will decline in the future. However, the disease burden and mortality associated with ALD-associated and NAFLD-associated cirrhosis will continue to rise with no approved therapeutic interventions.

The most recent data from the US Cancer Statistics registry suggested that a maximum peak in the rate of increase in the incidence of HCC may not have been reached yet (up until 2012) in all 50 US states,⁽¹⁴⁾ whereas studies from the SEER database reported that the incidence rate of HCC from 2007 to 2010 has slowed down.^(12,13) Our study demonstrates that the age-standardized HCC mortality rate increased from 3.48 per 100,000 persons in 2007 and 4.00 per 100,000 persons in 2011 to 4.41 in 2016. Although the SEER data are broadly representative of the US population, there are temporal differences in geographic regions with a significant effect of racial diversity due to the higher proportion of the US Native Hawaiian/Pacific Islander, Asian, American Indian/Alaska Native, and Hispanic populations compared with non-Hispanic white and non-Hispanic black populations. These race/ethnicity-based differences in HCC-related mortality explain the inconsistencies observed between the SEER and NVSS data sets. The persistent increase in the HCC-related mortality rates was largely driven by increasing trends in ALD and NAFLD. The magnitude and timing of anticipated changes in mortality rates in patients with HCV-associated HCC may vary with linkage to care and access to DAA agents, especially among minorities (non-Hispanic blacks and Hispanics) who have disproportionally higher HCC-related mortality rates.⁽²⁵⁾

Regarding HBV infection, potent and effective antiviral agents may have resulted in a significant reduction in HBV-associated cirrhosis and HCC mortality.⁽²⁶⁾ Specifically, a decline in cirrhosis and HCC mortality among non-Hispanic Asians is indirect evidence that effective antiviral agents are already having a favorable effect on the mortality rates in patients with HBV-associated cirrhosis and HCC. Consistent with prior studies,⁽¹²⁾ non-Hispanic blacks with HCC had the worst mortality rates compared with other races/ethnicities. The continuing increase in the HCC-related mortality rates was largely driven by increasing trends among non-Hispanic blacks, non-Hispanic whites, and Hispanics.

The strength of this study lies in capturing longitudinal trends at the national level over a 10-year period. This allowed us to compare population-wide mortality data and gain unique insight into cirrhosis and HCC-related mortality based on a wide range of etiologies. We used recently updated, nationally representative mortality data, which enabled us to capture up-to-date trends for cirrhosis and HCC. Additionally, we defined cirrhosis based on the diagnosis of cirrhosis and/or portal hypertension-related complications, such as spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding, or hepatorenal syndrome, all known complications of cirrhosis that may lead to death. Current annual estimates from the

National Center for Health Statistics⁽²⁷⁾ are based on the diagnosis called “chronic liver disease and cirrhosis,” which may underestimate the complications and mortality observed in patients with cirrhosis and its complications, ESLD and HCC.⁽²⁸⁾ Finally, mortality rates are a less biased method for tracking improvements in the management of disease. Commonly observed forms of bias noted in survival analyses, including length time or lead time bias, do not affect mortality rate.⁽¹²⁾ The present study has several limitations. First, the underlying cause of death based on death certificate may be subject to misclassification and underestimation. However, the method has been constant over time, which would likely not explain these temporal trends in cirrhosis and HCC. Second, age-standardized mortality rates may not represent actual mortality rates, but these rates were appropriate for comparisons across the population and over time as population distributions change. Third, the increase in mortality rates for cirrhosis and HCC, particularly related to NAFLD, could in part be attributed to improved reporting because of increased awareness and improvements in diagnostic imaging modalities during the study period. Finally, the ICD-10 code for NAFLD captured only a small subset of NAFLD, which may be subject to underestimation. Additionally, we could not capture all etiologies among the deceased with cirrhosis and HCC due to the limitation of this database being based on death certificates. Moreover, these limitations prevented us from separating the effect of hepatitis D virus among patients harboring HBV, even though it has been well documented that HDV co-infection is associated with higher rates of HCC and mortality. However, such problems may be mitigated when analyzing trends in which underestimation has been assumed to be relatively constant over the study period.

In conclusion, cirrhosis-related and HCC-related mortality continued to increase between 2007 and 2016 in the United States. Mortality rates for ALD-associated and NAFLD-associated cirrhosis and HCC have increased, whereas HBV-cirrhosis-related mortality has constantly decreased during the recent 10-year study period. After the introduction of DAA-based treatments, HCV-cirrhosis-related mortality has decreased compared with the pre-DAA era. In addition, minorities in the United States have a disproportionately higher burden of HCC-related mortality, suggesting that disparities in linkage to care and access to new treatments should be studied further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

ALD alcoholic liver disease

APC	annual percentage change
CI	confidence interval
DAA	direct-acting antiviral
ESLD	end-stage liver disease
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
ICD-10	International Classification of Diseases Tenth Revision
NAFLD	nonalcoholic fatty liver disease
NVSS	National Vital Statistic System
SEER	Surveillance, Epidemiology, and End Results

REFERENCES

- 1). Bosetti C, Levi F, Lucchini F, Zatonski WA, Negri E, La Vecchia C. Worldwide mortality from cirrhosis: an update to 2002. *J Hepatol* 2007;46:827–839. [PubMed: 17336419]
- 2). Zhang Y, Ren JS, Shi JF, Li N, Wang YT, Qu C, et al. International trends in primary liver cancer incidence from 1973 to 2007. *BMC Cancer* 2015;15:94. [PubMed: 25879744]
- 3). Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med* 2014;12:145. [PubMed: 25242656]
- 4). GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385:117–171. [PubMed: 25530442]
- 5). Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, et al. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA* 2013;310:591–608. [PubMed: 23842577]
- 6). Schmidt ML, Barritt AS, Orman ES, Hayashi PH. Decreasing mortality among patients hospitalized with cirrhosis in the United States from 2002 through 2010. *Gastroenterology* 2015;148:967–977, e962. [PubMed: 25623044]
- 7). Kanwal F. Decreasing mortality in patients hospitalized with cirrhosis. *Gastroenterology* 2015;148:897–900. [PubMed: 25805421]
- 8). Panel AIHG. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015;62:932–954. [PubMed: 26111063]
- 9). Cholanteril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol* 2018;16:1356–1358. [PubMed: 29199144]
- 10). Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–E386. [PubMed: 25220842]
- 11). El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142:1264–1273, e1261. [PubMed: 22537432]

- 12). Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology* 2015;61:191–199. [PubMed: 25142309]
- 13). Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. *Am J Gastroenterol* 2014;109:542–553. [PubMed: 24513805]
- 14). White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology* 2017;152:812–820,e815. [PubMed: 27889576]
- 15). Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: the multiethnic cohort. *Hepatology* 2016;64:1969–1977. [PubMed: 27301913]
- 16). Bureau USC. The nation's older population is still growing, Census Bureau reports. Published June 22, 2017. Available at <https://www.census.gov/newsroom/press-releases/2017/cb17-100.html>. Accessed at January 10, 2017.
- 17). Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012;156:271–278. [PubMed: 22351712]
- 18). Yang Q Tong X, Schieb L, Vaughan A, Gillespie C, Wiltz JL, et al. Vital signs: recent trends in stroke death rates—United States, 2000–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:933–939. [PubMed: 28880858]
- 19). Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19:335–351. [PubMed: 10649300]
- 20). Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med* 2009;28:3670–3682. [PubMed: 19856324]
- 21). Kanwal F, Tansel A, Kramer JR, Feng H, Asch SM, El-Serag HB. Trends in 30-day and 1-year mortality among patients hospitalized with cirrhosis from 2004 to 2013. *Am J Gastroenterol* 2017;112:1287–1297. [PubMed: 28607480]
- 22). Scaglione SJ, Metcalfe L, Kliethermes S, Vasilyev I, Tsang R, Caines A, et al. Early hospital readmissions and mortality in patients with decompensated cirrhosis enrolled in a large national health insurance administrative database. *J Clin Gastroenterol* 2017;51:839–844. [PubMed: 28383303]
- 23). Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001–2013. *Gastroenterology* 2015;149:1471–1482 e1475; quiz e1417–e1478. [PubMed: 26255044]
- 24). Hallager S, Brehm Christensen P, Ladelund S, Rye Clausen M, Lund Laursen A, Moller A, et al. Mortality rates in patients with chronic hepatitis C and cirrhosis compared with the general population: a Danish cohort study. *J Infect Dis* 2017;215:192–201. [PubMed: 27803168]
- 25). Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology* 2017;65:804–812. [PubMed: 28012259]
- 26). Kim WR. Epidemiology of hepatitis B in the United States. *Hepatology* 2009;49:S28–S34. [PubMed: 19399791]
- 27). Heron M Deaths: leading causes for 2015. *Natl Vital Stat Rep* 2017;66:1–76.
- 28). Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. *Gastroenterology* 2013;145:375–382,e371–372. [PubMed: 23583430]

FIG. 1.

Annual age-standardized mortality rates for cirrhosis and HCC in the United States from 2007 to 2016. Age-standardized mortality rates are displayed per calendar year of death with lines/graphs plotted using the joinpoint analysis. A positive slope indicates an increasing risk/rate of mortality, whereas a negative slope indicates a decline in the risk/rate of mortality. The lines on the graphs represent APC trends for each period as designated. * $P < 0.05$.

Fig. 2.

Annual age-standardized mortality rates for cirrhosis stratified by etiology (A), race/ethnicity (B), and sex (C) in the United States from 2007 to 2016. Age-standardized mortality rates are displayed per calendar year of death with lines/graphs plotted using the joinpoint analysis. A positive slope indicates an increasing risk/rate of mortality, whereas a negative slope indicates a decline in the risk/ rate of mortality. The lines on the graphs represent APC trends for each period as designated. * $P < 0.05$.

FIG. 3.

Annual age-standardized mortality rates for HCC stratified by etiology (A), race/ethnicity (B), and sex (C) in the United States from 2007 to 2016. Age-standardized mortality rates are displayed per calendar year of death with lines/graphs plotted using the joinpoint analysis. A positive slope indicates an increasing risk/rate of mortality, whereas a negative slope indicates a decline in the risk/ rate of mortality. The lines on the graphs represent APC trends for each period as designated. * $P < 0.05$.

TABLE 1.

Characteristics of Deaths in the United States for Cirrhosis and HCC as a Cause of Death in 2007–2016

	Cirrhosis (n = 534,433)	HCC (n = 99,753)
Age (years)		
20–39	14,839 (2.8)	903 (0.9)
40–49	62,592 (11.7)	4,029 (4.0)
50–59	165,772 (31.0)	27,451 (27.5)
60–69	147,128 (27.5)	32,689 (32.8)
70–79	89,660 (16.8)	20,886 (20.9)
80	54,440 (10.2)	13,795 (13.8)
Ethnicity		
White, non-Hispanic	382,169 (71.8)	61,911 (62.2)
Black, non-Hispanic	51,287 (9.6)	14,766 (15.8)
American Indian or Alaskan Native, non-Hispanics	9,901 (1.9)	1,059 (1.1)
Asians or Pacific Islanders, non-Hispanics	10,967 (2.1)	7,363 (7.4)
Hispanics	77,972 (14.7)	13,485 (13.5)
Sex		
Men	347,245 (65.0)	77,873 (77.9)
Women	187,188 (35.0)	22,039 (22.1)
Education		
Less than high school	100,821 (23.8)	18,526 (23.4)
Completed high school	185,397 (43.8)	34,143 (43.2)
Some college	59,460 (14.1)	10,953 (13.9)
Completed college or beyond	77,589 (18.3)	15,441 (19.5)
Etiology		
Hepatitis C	87,248 (32.1)	25,014 (70.1)
ALD	165,919 (61.1)	6,677 (18.7)
Hepatitis B	7,068 (2.6)	3,262 (13.0)
NAFLD	11,354 (4.2)	745 (2.1)

Note: Data are presented as number (percent).

Age-Standardized Cirrhosis-Related Mortality Rate and APC Among Adults 20 Years Or Older in the United States From 2007 to 2016

TABLE 2.

	Age-Standardized Rate		Average APC (95% CI)		Trend Segment 1		Trend Segment 2	
	2007	2016	2007–2016		Year	APC (95% CI)	Year	APC (95% CI)
Cirrhosis	19.77	23.67	2.3 (2.0, 2.7)*		2007–2016	2.3 (2.0, 2.7)*		
Etiology								
Hepatitis C	3.06	3.20	0.7 (–0.1, 1.5)		2007–2014	2.9 (2.3, 3.5)*	2014–2016	–6.5 (–10.3, –2.6)*
ALD	5.68	8.23	4.5 (3.8, 5.3)*		2007–2013	3.4 (2.6, 4.2)*	2013–2016	6.8 (4.3, 9.3)*
Hepatitis B	0.29	0.26	–1.1 (–2.0, –0.2)*		2007–2016	–1.1 (–2.0, –0.2)*		
NAFLD	0.22	0.82	15.4 (14.1, 16.7)*		2007–2016	15.4 (14.1, 16.7)*		
Race/ethnicity								
Non-Hispanic whites	19.63	24.61	2.9 (2.5, 3.2)*		2007–2016	2.9 (2.5, 3.2)*		
Non-Hispanic blacks	15.36	15.86	0.9 (0.3, 1.6)*		2007–2016	0.9 (0.3, 1.6)*		
Non-Hispanic Asians	7.38	7.00	–0.5 (–0.9, –0.1)*		2007–2016	–0.5 (–0.9, –0.1)*		
Hispanics	19.15	20.34	1.0 (0.6, 1.4)*		2007–2016	1.0 (0.6, 1.4)*		
Sex								
Men	26.25	30.42	2.0 (1.6, 2.3)*		2007–2016	2.0 (1.6, 2.3)*		
Women	13.63	17.09	2.9 (2.4, 3.3)*		2007–2016	2.9 (2.4, 3.3)*		

* $P < 0.05$.

TABLE 3.
Age-Standardized HCC-Related Mortality Rate and APC Among Adults 20 Years or Older in the United States From 2007 to 2016

	Age-Standardized Rate		Average APC (95% CI)		Trend Segment 1		Trend Segment 2	
	2007	2016	2007–2016		Year	APC (95% CI)	Year	APC (95% CI)
HCC	3.48	4.41	2.0 (1.3, 2.6)*		2007–2016	2.0 (1.3, 2.6)*		
Etiology								
Hepatitis C	0.72	1.03	4.0 (3.1, 5.0)*		2007–2012	7.0 (5.5, 8.6)*	2012–2016	0.4 (–1.6, 2.5)
ALD	0.18	0.35	7.4 (6.1, 8.7)*		2007–2016	7.4 (6.1, 8.7)*		
Hepatitis B	0.12	0.12	0.5 (–2.1, 3.2)		2007–2010	6.3 (–2.5, 15.9)	2010–2016	–2.2 (–5.0, 0.7)
NAFLD	0.012	0.06	19.1 (14.0, 24.5)*		2007–2016	19.1 (14.0, 24.5)*		
Race/ethnicity								
Non-Hispanic whites	3.01	3.87	2.4 (1.9, 2.8)*		2007–2016	2.4 (1.9, 2.8)*		
Non-Hispanic blacks	4.03	5.12	2.1 (–0.3, 4.5)		2007–2009	8.4 (–4.4, 22.8)	2009–2016	0.4 (–1.3, 2.1)
Non-Hispanic Asians	4.96	4.31	–2.0 (–3.6, –0.5)*		2007–2009	3.3 (–5.0, 12.2)	2009–2016	–3.5 (–4.6, –2.4)*
Hispanics	2.99	3.64	1.2 (–0.1, 2.4)		2007–2016	1.2 (–0.1, 2.4)		
Sex								
Men	5.41	6.77	2.1 (0.6, 3.5)*		2007–2009	5.3 (–2.4, 13.7)	2009–2016	1.1 (0.1, 2.2)*
Women	1.62	2.06	2.1 (1.4, 2.8)*		2007–2016	2.1 (1.4, 2.8)*		

* $P < 0.05$.