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CLINICAL—LIVER

Trends in Mortality From Extrahepatic Complications in Patients With Chronic Liver Disease, From 2007 Through 2017

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BACKGROUND & AIMS: Trends of mortality associated with extrahepatic complications of chronic liver disease might be changing. We studied trends in mortality from extrahepatic complications of viral hepatitis, alcoholic liver disease (ALD), and nonalcoholic fatty liver disease in the United States. **METHODS:** We performed a population-based study using US Census and the National Center for Health Statistics mortality records from 2007 through 2017. We identified trends in age-standardized mortality using Joinpoint trend analysis with estimates of annual percent change. **RESULTS:** The liver-related mortality among patients with hepatitis C virus (HCV) infection increased from 2007 through 2013 and then decreased once patients began receiving treatment with direct-acting antiviral (DAA) agents, from 2014 through 2017. Among patients with HCV infection, the age-standardized mortality for extrahepatic cancers was 2.6%, for cardiovascular disease was 1.9%, and for diabetes was 3.3%. Among individuals with hepatitis B virus infection, liver-related mortality decreased steadily from 2007 through 2017. During the study, age-standardized mortality from hepatitis B virus–related extrahepatic complications increased by an average of 2.0% each year. Although liver-related mortality from ALD continued to increase, mortality from extrahepatic complications of ALD did not change significantly during the 11-year study. Among patients with nonalcoholic fatty liver disease, the cause of death was most frequently cardiovascular disease, which increased gradually over the study period, whereas liver-related mortality increased rapidly. **CONCLUSIONS:** In an analysis of US Census and the National Center for Health Statistics mortality records, we found that after widespread use of DAA agents for treatment of viral hepatitis, cause-specific mortality from extrahepatic cancers increased, whereas mortality from cardiovascular disease or diabetes increased only among patients with HCV infection. These findings indicate the need to reassess risk and risk factors for extrahepatic cancer, cardiovascular disease, and diabetes in individuals successfully treated for HCV infection with DAA agents.

Keywords: APC; HBV; NAFLD; Epidemiology.

According to the World Health Organization, an estimated 71 million individuals have chronic hepatitis C virus (HCV) infection worldwide.[1] A recent study reported that more than 2 million individuals are chronically infected with HCV in the United States, reflecting a decline in the prevalence of HCV infection associated with the introduction of highly efficacious and curative treatment options.[2] After the US Food and Drug Administration approved sofosbuvir in late 2013, safe and potent direct-acting antiviral (DAA)–based regimens have heralded a revolutionary era in the management of chronic HCV infection. Given the high rates of sustained virologic response (SVR), safety, tolerability, and ease of use achieved with DAA agents across the wide spectrum of patients infected with HCV, from those with mild liver disease to those with end-stage liver disease,[3,4] a significant decrease in national HCV-related mortality have been reported during the DAA era in the United States.[5] Chronic HCV infection is considered a systemic disease with both hepatic and extrahepatic manifestations.[6] In addition to liver-related complications, chronic HCV infection has been associated with extrahepatic complications, such as cardiovascular, metabolic, and immune-mediated conditions including mixed cryoglobulinemia and glomerulonephritis.[7] The overall clinical burden and prognosis associated with chronic HCV infection depend not only on the risk of liver-related complications but also on the trends in the rate and severity of HCV-related extrahepatic complications.[8] A meta-analysis reported that individuals with HCV infection were at a higher risk of extrahepatic manifestations related to immune dysregulation (mixed cryoglobulinemia, lymphoma, etc) and metabolic dysfunction (cardiovascular disease, type 2 diabetes, etc) compared with those without HCV infection.[6] Hence, the

Abbreviations used in this paper: **ALD, alcoholic liver disease; APC, annual percent change; CI, confidence interval; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD-10, International Classification of Diseases, 10th revision; NAFLD, nonalcoholic fatty liver disease; NVSS, national vital statistic system; OR, odds ratio; SVR, sustained virologic response.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Trends of mortality associated with extrahepatic complications of chronic liver disease might be changing.

NEW FINDINGS

After patients with hepatitis C virus (HCV) infection began treatment with direct-acting antiviral agents, cause-specific mortality from extrahepatic cancers increased. Mortality from cardiovascular disease or diabetes increased only among patients with HCV infection.

LIMITATIONS

This was a retrospective analysis of data from one country.

IMPACT

Risk and risk factors for extrahepatic cancer, cardiovascular disease, and diabetes should be reassessed in individuals successfully treated for HCV infection with direct-acting antiviral agents.

risk of overall mortality may be underestimated if extrahepatic complications associated with chronic HCV infection are not accounted for.[7] In terms of cardiovascular disease, a recent meta-analysis showed that patients with HCV infection were at higher risk of developing cerebrocardiovascular events and cardiovascular disease–related mortality compared with their uninfected counterparts.[9]

Furthermore, a growing body of evidence indicates that chronic HCV infection is associated with extrahepatic cancers, such as non-Hodgkin lymphoma, pancreatic cancer, renal cancer, and oropharyngeal cancer,[10,11] without a clear explanation of an HCV-triggered pathogenetic pathway.[11] Recently, increased rates of SVR in patients with chronic HCV infection and successful viral suppression in chronic hepatitis B virus (HBV) infection have favorably altered the clinical course of end-stage liver disease in patients with viral hepatitis. Therefore, trends in mortality from extrahepatic complications may be monitored after following SVR in patients with history of chronic HCV infection. With the introduction of an effective vaccine against HBV) infection followed by approval of increasingly potent antiviral agents with a higher barrier to viral resistance, trends in mortality associated with HBV infection first plateaued from the mid-1990s through 1998 and then steadily declined starting in 1999.[12] Similarly, but lagging behind by several years, mortality associated with chronic HCV infection has started to decrease during the DAA era.[5] A positive impact of therapeutic intervention on the hepatic and extrahepatic complications of HCV or HBV infections has been noted.[13,14] Unfortunately, there have been no significant breakthroughs in the treatment of alcoholic liver disease (ALD) over the last 2 decades, resulting in an increase in estimated global mortality to 3.8%.[15] In the United States, ALD-related age-standardized mortality (per 100,000 persons) increased from 7.8 in 2007 to 10.5 in 2016.[5] Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. The leading cause of death in individuals with NAFLD is cardiovascular disease, followed by extrahepatic malignancies and then liver-related mortality.[16,17] However, recent trends in ALD and NAFLD-related extrahepatic complications compared with those in viral hepatitis have not been studied.

In this study, we analyzed the mortality data from the US National Vital Statistics System (NVSS) to examine the trends in extrahepatic complications of chronic liver disease from 2007 through 2017. The aim of this study was to determine the prevalence and trends of extrahepatic complications for viral hepatitis, ALD, and NAFLD, with mortality stratified by cause of chronic liver disease in the United States.

Methods

Study Data

To investigate the trends in mortality of extrahepatic complications associated with chronic liver disease in US adults aged $\geq$ 20 years, we used deidentified death records from NVSS. The methods used in this study have been described in detail elsewhere.[5,18] Briefly, these mortality records were obtained from death certificates. The NVSS database captures more than 99% of deaths in US residents in all 50 states and the District of Columbia.[19] The NVSS database uses the International Classification of Diseases, 10th revision (ICD-10) to record the cause of death on death certificates. The cause of death based on the death certificate consists of 3 fields: the underlying cause of death, entity axis, and record axis.[20] The underlying cause of death lists the 1 disease or condition that lead to death. All causes of death based on the death certificate are included in the entity axis. To improve the accuracy of the data, the record axis represents a refined version of the entity axis. Because of the higher specificity of the record axis, we used the record axis for underlying or contributing causes of death.[20] Because the NVSS database is deidentified and publicly available, the study was not subject to review by an institutional review board at our institution.

Definitions of Causes of Chronic Liver Disease

We identified chronic HCV infection based on ICD-10 diagnosis codes for HCV infection (B17.1, B18.2, and B19.2). Chronic HBV infection was defined using the HBV infection ICD-10 diagnostic codes (B16, B17.0, B18.0, B18.1, and B19.1). We excluded individuals with HCV and HBV coinfection from both the HBV and HCV infection groups to consistently maintain a mono-infected cohort. Finally, ICD-10 codes for ALD and NAFLD were used to identify ALD (K70.0, K70.1, K70.2, K70.3, K70.4, and K70.9) and NAFLD (K76.0 and K75.81) without evidence of viral hepatitis and ALD. Individuals with chronic HCV infection and ALD were categorized in the HCV infection group. Likewise, we categorized individuals with chronic HBV infection and ALD in the HBV infection group. Cirrhosis was defined by diagnosis codes of liver cirrhosis (K70.3, K74.0, K74.1, K74.2, K74.3, K74.4, and K74.6), portal hypertension (K76.6), or one of its manifestations of cirrhosis/portal hypertension: hepatic encephalopathy (K72.11 and K72.91), spontaneous bacterial peritonitis (K65.2), variceal bleeding (I85.0 and I85.1), or hepatorenal syndrome (K76.7). We identified and defined a cohort without chronic liver disease as individuals without evidence of liver-related death by using ICD-10 codes and excluding individuals with liver-related death in the underlying and contributing cause of death. From

the NVSS database, our analysis included demographic data (age, sex, race/ethnicity, and education status) ascertained with standard methods. We categorized race/ethnicity into 5 mutually exclusive groups: non-Hispanic white, non-Hispanic black, non-Hispanic Asian/Pacific Islander, non-Hispanic American Indian/Alaskan Native, and Hispanic (belonging to any race).

Definitions of Liver-Related and Extrahepatic Mortality

The liver-related death as underlying cause of death was defined among individuals with chronic liver disease as having viral hepatitis (ICD-10 codes B15-B19); malignant neoplasms of liver (C22, except intrahepatic bile ducts cancer [C22.1]); chronic liver disease, toxic liver disease, and cirrhosis (K70-K77); sequelae of viral hepatitis (B94.2); ascites (R18); and bleeding esophageal varices (I85.0). Based on the previous study,[21,22] we used ICD-10 diagnostic codes to ascertain mortality rates of liver-related extrahepatic complications from this database. Among individuals with chronic liver disease (listed as underlying or contributing cause of death), we defined cardiovascular disease-related mortality as ICD-10 I00-I99, extrahepatic cancer–related mortality as ICD-10 C00-C97 (except C22.0, C22.2, C22.4, C22.7, C22.8, and C22.9), and diabetes-related mortality as ICD-10 E10-E14 using the underlying cause of death. To determine the robustness of our results, we performed sensitivity analyses based on the presence or absence of cirrhosis. Among individuals with chronic liver disease who died with extrahepatic cancer, we used ICD-10 codes to identify each extrahepatic cancer (Supplementary Table 1). For further analyses, all extrahepatic cancers were classified as solid cancers and hematologic cancers.

Statistical Analysis

We used a previously described method for statistical analyses.[5,18] To calculate age-standardized mortality, we divided the count of hepatic or extrahepatic deaths among individuals with HCV, HBV, ALD, and NAFLD by the total US census population for each year. We calculated age-standardized mortality per 100,000 persons by age group (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and ≥80 years), adjusted to the age distribution of the 2010 US standard population using the direct method. We retrieved the total population census and used it to calculate the incidence of mortality from the census population estimates from the US Census Bureau. We presented baseline demographic characteristics as frequencies with percentages. We used the Joinpoint regression program, version 4.7.0.0 (National Cancer Institute, Bethesda, MD), to investigate temporal changes over time. This program uses a piecewise linear regression approach to examine whether a single segment or multiple linear segments explain the best mortality during the study period.[23] We provided each trend segment by annual percent change (APC) and the trend for the entire study period by the average APC,[24] which determines the year when the trend in age-standardized mortality changed significantly and estimates the magnitude of the change.

Results

Patient Characteristics

We analyzed a total of 27,903,198 deaths among US adults aged ≥20 years from 2007 through 2017 in this study. The baseline characteristics for chronic liver disease–related mortality are shown in Supplementary Table 2. Deaths associated with chronic liver disease were mostly observed in men except NAFLD. Individuals with NAFLD and viral hepatitis died more frequently at age ≥60 years than those with ALD. Although the proportion of non-Hispanic whites was the most prevalent in all causes of chronic liver disease, Hispanics with HCV infection, ALD, and NAFLD; non-Hispanic blacks with HCV infection and HBV infection; and non-Hispanic Asians with HBV infection each represented more than 10% of the deaths in the respective causes of chronic liver disease.

Age-Standardized Mortality Rates for Chronic Liver Disease

As shown in Table 1 and Supplementary Figure 1, age-standardized mortality for HCV infection reached a plateau in 2013 and markedly declined from 2014 to 2017. The age-standardized HCV-related mortality increased from 2007 to 2014 (APC, 2.2%; 95% confidence interval [CI], 1.7–2.7) and decreased from 2014 to 2017 (APC, −6.5%; 95% CI, −8.3 to −4.7). In contrast, age-standardized mortality for ALD and NAFLD increased in an accelerated fashion over time, whereas the HBV-related mortality decreased steadily during the 11 years (Tables 2–4 and Supplementary Figure 1).

Age-Standardized Liver-Related and Extrahepatic Mortality Rates for Chronic Liver Disease

Figure 1*A*, Table 1, and Supplementary Figure 2 show hepatic and extrahepatic mortality among individuals with HCV infection. The age-standardized mortality due to HCV-related liver disease decreased significantly from 2014 through 2017 (APC, −9.8%; 95% CI, −11.5 to −8.1). In contrast, the age-standardized mortality for cardiovascular disease increased annually by 1.9% (95% CI, 1.2–2.5). Similarly, diabetes-related mortality showed a steady increase with an average APC of 3.3%. In contrast, the age-standardized extrahepatic cancer–related mortality among individuals with HCV infection increased significantly during the pre-DAA era from 2007 to 2014 (APC, 4.6%; 95% CI, 3.2–6.1) and remained stable thereafter (APC, −2.1%; 95% CI, −7.1 to 3.2). Table 2, Figure 1*B* and Supplementary Figure 2 show the age-standardized mortality for cause-specific mortality among individuals with ALD. As an accelerated increase in age-standardized mortality for all-cause and liver-related deaths, age-standardized mortality for extrahepatic cancer pari passu increased with statistical significance during the 11 years. Regarding cardiovascular disease, the age-standardized mortality rates remained stable from 2007 to 2009 and increased from 2009 to 2017 (APC, 3.5%; 95% CI, 2.6–4.4). Despite a steady decline at a rate of −2.4% in HBV liver-related mortality rates, the extrahepatic cancer-related mortality rates showed a steady increase during the study period, with an average APC of 2.0% (95% CI, −0.1 to 4.2) (Table 3 and Figure 1*C*). We conducted a sensitivity analysis by comparing mortality in

Table 1. Age-Standardized Mortality Due to Chronic HCV Infection, Cause-Specific Mortality Among Individuals With HCV Infection, and APC Among US Adults ≥20 years, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
All-cause mortality							
	6.911	6.583	–0.5 (–1.0 to 0.0)	2007–2014	2.2 (1.7 to 2.7)[a]	2014–2017	–6.5 (–8.3 to –4.7)[a]
Cause-specific death among individuals with HCV							
Age-standardized mortality rate							
Liver disease	4.506	3.703	–2.0 (–2.5 to –1.5)[a]	2007–2014	1.5 (1.0 to 2.0)[a]	2014–2017	–9.8 (–11.5 to –8.1)[a]
Cardiovascular disease	0.589	0.678	1.9 (1.2 to 2.5)[a]				
Cancer	0.478	0.630	2.6 (1.0 to 4.1)[a]	2007–2014	4.6 (3.2 to 6.1)[a]	2014–2017	–2.1 (–7.1 to 3.2)
Diabetes	0.115	0.152	3.3 (2.0 to 4.7)[a]				
Proportion, %							
Liver disease	65.2	56.1	–1.5 (–1.8 to –1.1)[a]	2007–2013	–0.4 (–0.9 to 0.1)	2013–2017	–3.0 (–3.9 to –2.0)[a]
Cardiovascular disease	8.5	10.3	2.1 (1.3 to 3.0)[a]	2007–2013	–1.2 (–2.2 to –0.1)[a]	2013–2017	7.4 (5.3 to 9.5)[a]
Cancer	6.9	9.8	3.2 (2.6 to 3.9)[a]				
Diabetes	1.7	2.3	3.4 (2.2 to 4.5)[a]				

[a]$P < .05$.

individuals with and without chronic liver disease. In contrast to decreasing trends in age-standardized extrahepatic mortality among individuals without liver-related death from 2007 through 2017 (cardiovascular disease: APC, –1.6%; 95% CI, –1.9 to –1.2; extrahepatic cancer: APC, –1.8%; 95% CI, –1.9 to –1.7; diabetes: APC, –0.9%; 95% CI, –1.5 to –0.2) (Figure 1*E* and Supplementary Table 3), the age-standardized extrahepatic mortality due to HCV infection increased from 2007 to 2017. We performed additional sensitivity analyses excluding individuals with viral hepatitis who were coinfected with HIV, and the results remained identical (Supplementary Tables 4 and 5). As shown in Table 4 and Figure 1*D*, the age-standardized mortality for cause-specific mortality among individuals with NAFLD increased steadily. Compared with other chronic liver diseases, the cause of death in NAFLD was more likely to be cardiovascular disease (approximately 20%), which increased at a gradual rate (APC, 2.0%; 95% CI, 0.6–3.4), whereas liver-related mortality increased rapidly (APC, 12.6%; 95% CI, 11.7–13.5). The age-standardized mortalities for extrahepatic cancer (APC, 15.1%) and diabetes (APC, 9.7%) compared with cardiovascular disease (APC 2.0%) showed a more pronounced increase in APC.

Table 2. Age-Standardized Mortality Due to ALD, Cause-Specific Mortality Among Individuals With ALD, and APC Among US Adults ≥20 years, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
All-cause mortality							
	7.756	10.638	3.4 (2.8 to 3.9)[a]	2007–2012	2.1 (1.2 to 3.1)[a]	2012–2017	4.6 (3.6 to 5.5)[a]
Cause-specific death among individuals with ALD							
Age-standardized mortality rate							
Liver disease	6.445	8.724	3.3 (2.6 to 3.9)[a]	2007–2012	2.0 (0.9 to 3.1)[a]	2012–2017	4.6 (3.5 to 5.8)[a]
Cardiovascular disease	0.428	0.519	2.1 (0.7 to 3.5)[a]	2007–2009	–3.4 (–10.6 to 4.4)	2009–2017	3.5 (2.6 to 4.4)[a]
Cancer	0.138	0.203	3.6 (1.9 to 5.4)[a]				
Diabetes	0.043	0.046	2.2 (–1.0 to 5.5)				
Proportion, %							
Liver disease	83.2	81.8	–0.1 (–0.2 to –0.0)[a]				
Cardiovascular disease	5.5	5.0	–0.4 (–1.1 to 0.3)				
Cancer	1.7	2.0	1.1 (–0.4 to 2.7)				
Diabetes	0.6	0.4	–0.9 (–3.9 to 2.2)				

[a]$P < .05$.

Table 3. Age-Standardized Mortality Due to HBV Infection, Cause-Specific Mortality Among Individuals With HBV Infection, and APC Among US Adults ≥20 years, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
All-cause mortality							
	0.606	0.530	–1.2 (–2.0 to –0.3)[a]				
Cause-specific death among individuals with HBV							
Age-standardized mortality rate							
Liver disease	0.392	0.303	–2.4 (–3.2 to –1.5)[a]				
Cardiovascular disease	0.040	0.037	0.3 (–1.7 to 2.3)				
Cancer	0.057	0.066	2.0 (–0.1 to 4.2)				
Diabetes	0.009	0.012	1.3 (–1.7 to 4.4)				
Proportion, %							
Liver disease	64.6	56.7	–1.3 (–1.5 to –1.0)[a]				
Cardiovascular disease	6.5	7.2	1.7 (–0.0 to 3.5)				
Cancer	9.3	12.8	3.5 (2.0 to 5.1)[a]				
Diabetes	1.5	2.4	2.8 (–0.7 to 6.5)				

[a]$P < .05$.

As shown in Supplementary Tables 6 through 9 and Supplementary Figure 3, annual trends in liver-related mortality among individuals with HCV markedly decreased from 2013 to 2014, irrespective of the presence or absence of cirrhosis. Extrahepatic cancer–related death increased more steeply in HCV-related cirrhosis than in the absence of cirrhosis in early years, which was followed by stabilization afterward. Cardiovascular disease–related death in the HCV subcohort with cirrhosis increased more steadily than in HCV counterparts without cirrhosis (Supplementary Table 6). In terms of ALD, annual trends in liver-related and extrahepatic mortality in individuals with ALD were identical to mortality in the overall ALD population with and without cirrhosis. However, liver-related and extrahepatic mortality in ALD without cirrhosis decreased more or less during the study period (Supplementary Table 7). Annual trends in extrahepatic mortalities among individuals with HBV were consistent with previous results in the overall population with HBV infection irrespective of presence or absence of cirrhosis, whereas liver-related death decreased more noticeably among individuals without cirrhosis than among those with cirrhosis (Supplementary Table 8). Although stratification was based on the presence or absence of cirrhosis, the trends for hepatic and extrahepatic mortalities remained comparable in individuals with NAFLD, except that hepatic and extrahepatic mortality rates in NAFLD-related cirrhosis were more pronounced

Table 4. Age-Standardized Mortality Due to NAFLD, Cause-Specific Mortality Among Individuals With NAFLD, and APC Among US Adults ≥20 years, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
All-cause mortality							
	0.892	1.962	8.1 (6.8 to 9.4)[a]	2007–2013	6.1 (4.4 to 7.8)[a]	2013–2017	11.2 (7.9 to 14.5)[a]
Cause-specific death among individuals with NAFLD							
Age-standardized mortality rate							
Liver disease	0.341	1.126	12.6 (11.7 to 13.5)[a]				
Cardiovascular disease	0.252	0.337	2.0 (0.6 to 3.4)[a]				
Cancer	0.013	0.059	15.1 (13.0 to 17.2)[a]				
Diabetes	0.032	0.077	9.7 (7.3 to 12.2)[a]				
Proportion, %							
Liver disease	37.6	58.9	4.7 (4.1 to 5.5)[a]				
Cardiovascular disease	28.5	16.2	–6.1 (–7.1 to –5.1)[a]				
Cancer	1.4	3.1	7.3 (6.1 to 8.5)[a]				
Diabetes	3.5	4.0	2.0 (–0.2 to 4.2)				

[a]$P < .05$.

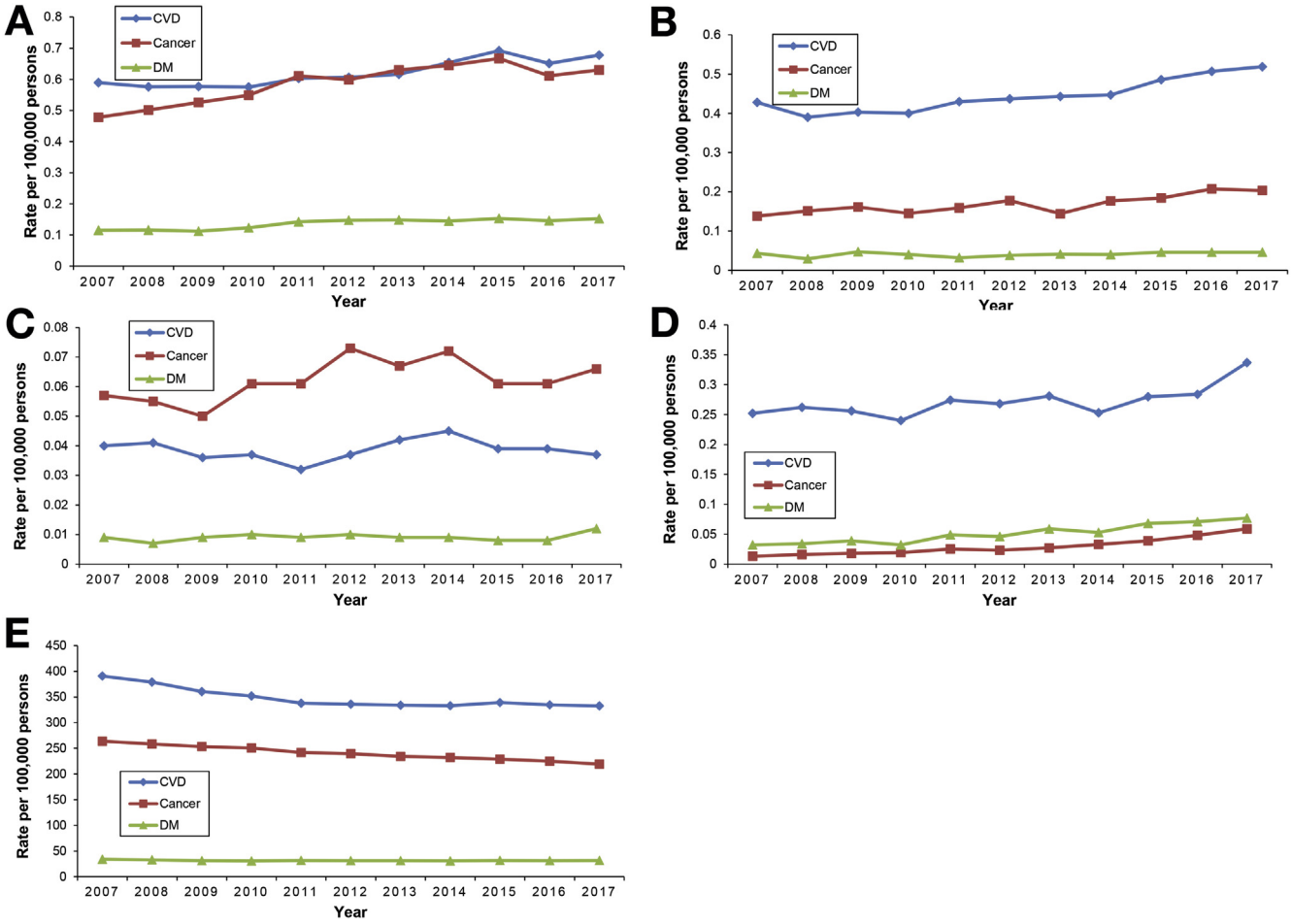

Figure 1. Annual age-standardized extrahepatic mortality among individuals with chronic liver disease in the United States between 2007 and 2017: (*A*) HCV infection, (*B*) ALD, (*C*) HBV infection, (*D*) NAFLD, and (*E*) the cohort without chronic liver disease. CVD, cardiovascular disease; DM, diabetes mellitus.

than in NAFLD without cirrhosis subcohort (Supplementary Table 9).

The Proportion of the Liver-Related vs Extrahepatic Mortality Rates Among Chronic Liver Disease

Consistent with age-standardized mortality, annual trends in the proportion of liver-related mortality among individuals with HCV markedly decreased from 2013 to 2017, with an annual decline of 3.0% (95% CI, −3.9 to −2.0) (Table 1), whereas annual trends in the proportion of liver-related mortality among those with ALD did not change considerably during the study period (Table 2). Comparable with previous results, yearly trends in liver-related mortality among individuals with HBV infection decreased steadily from 2007 to 2017 (APC, −1.3%; 95% CI, −1.5 to −1.0) (Table 3). Although there was a marked decrease in HCV liver-related deaths from 2013 onward, annual trends in the proportion of cardiovascular disease–related deaths among individuals with HCV increased from 2013 to 2017, with an APC of 7.4% (Table 1 and Figure 2*A*). Yearly trends in a portion of extrahepatic cancer– and diabetes-related mortality among individuals with HCV infection or extrahepatic cancer in HBV infection increased steadily (Tables 1 and 3 and Figures 2*A* and *C*), whereas annual trends in the proportion of cardiovascular-, extrahepatic cancer–, and diabetes-related mortality among individuals with ALD did not change during the same period (Table 2 and Figure 2*B*). We then conducted sensitivity analyses classifying cirrhosis and non-cirrhosis (Supplementary Tables 6–9 and Supplementary Figure 4). As expected, the proportion of liver-related deaths among individuals with cirrhosis was higher than among those without cirrhosis, irrespective of cause of chronic liver disease. In contrast, proportions of extrahepatic deaths were more pronounced among individuals without cirrhosis than among those with cirrhosis. In terms of viral hepatitis, the results remained similar (Supplementary Tables 6 and 8). Interestingly, the proportion of extrahepatic cancer–related mortality in ALD-related cirrhosis increased steadily in contrast to decreasing extrahepatic cancer–related mortality in ALD without cirrhosis (Supplementary Table 7). Among individuals with NAFLD, proportions of extrahepatic cancer– and diabetes-related mortality increased significantly in the absence of cirrhosis, whereas diabetes-related mortality decreased in

individuals with NAFLD in the setting of cirrhosis (Supplementary Table 9).

Extrahepatic Cancer Mortality in Chronic Liver Disease

We analyzed the extrahepatic cancer data by categorizing cancers as solid cancers and hematologic cancers (Supplementary Table 10). We noted that the hematologic cancer in individuals with viral hepatitis remained stable during the study period, but we noted increasing trends in extrahepatic cancer–related deaths in individuals with solid cancers in the setting of chronic liver disease. In contrast, hematologic cancer– and solid cancer–related mortality among individuals with ALD or NAFLD increased significantly during the study period. Detailed results of the proportion of extrahepatic cancer in individuals with chronic liver disease during the 11 years from 2007 through 2017 are provided in Figure 3. Differences in extrahepatic cancer–related mortality for chronic liver disease varied by cause. Compared with individuals with ALD, those with HCV infection had a higher proportion (divided by total cancer for each etiology) and number of non-Hodgkin lymphoma (6.4%, n = 982 for HCV infection; 2.7%, n = 119 for ALD; and 3.6% for cohort without liver-related death [control]); and intrahepatic cholangiocarcinoma (4.3%, n = 659 vs 3.4%, n = 150 vs 0.9% for control). Compared with individuals with HCV infection, those with ALD had a higher proportion of digestive tract cancer: colon cancer (7.7% for ALD, 5.4% for HCV infection, and 7.5% for control); esophagus cancer (5.8% vs 3.0% vs 2.6%, respectively); and oropharyngeal cancer (4.8% vs 3.1% vs 1.4%, respectively). Compared with HCV infection, the proportions of non-Hodgkin lymphoma (16.6% for HBV, 6.4% for HCV, 2.7% for ALD, and 3.6% for control), intrahepatic cholangiocarcinoma (6.2% vs 4.3% vs 3.4% vs 0.9%); and leukemia (7.5% vs 3.1% vs 2.1% vs 4.0%) were more prevalent in the individuals with HBV infection.

Discussion

In this nationally representative population-based US study, although the introduction of potent antiviral agents against HBV and HCV infections have been credited for the significant decline in overall liver-related mortality, lack of improvement in the management of ALD has contributed to an ongoing increase in liver-related deaths. Our data suggest that potent antiviral agents have favorably influenced liver-related mortality rates in the United States. However, more intriguing are the rising trends in the rates of extrahepatic mortality associated with viral hepatitis and, in particular, among individuals with HCV infection. Consistent with a previous study,[25] death due to cardiovascular disease increased more steadily in individuals with HCV-related cirrhosis than in those without. In contrast, the proportions of ALD-related extrahepatic mortality have remained relatively unchanged, except for an increase in the trend for extrahepatic cancer–related death in the presence of cirrhosis during the 11-year study. The disparate trends in the hepatic and extrahepatic mortality of viral hepatitis may be explained by the introduction of potent antiviral agents and the increased life expectancy of individuals with HBV and HCV infections after successful treatment.

In terms of HCV infection, the recent introduction of second-generation DAA agents with markedly higher cure rates has favorably affected liver-related outcomes with reduction in mortality.[26] In a previous population-based study, we reported a significant reduction in HCV-related mortality after the introduction of DAA agents in the United States.[5] Data presented in this study have shown a widening gap in mortality between ALD and HCV infection from 2016 to 2017. Although there was a significant decrease in liver-related mortality due to an observed benefit of SVR in individuals with HCV infection, the age-standardized rates or proportions of extrahepatic cardiovascular disease–, cancer-, and diabetes-related mortality steadily increased in this population. Economically, individuals with HCV infection incurred relatively higher medical costs from extrahepatic complications but showed cost savings from all-cause medical expenses that were largely associated with the eradication of HCV infection by DAA-based regimens.[27] A recent study reported that patients with viral hepatitis have a 30% higher risk of extrahepatic cancer compared with the general population.[28] With the expected decline in liver-related complications during the era of antiviral agents, the improved longevity in individuals with viral hepatitis has been marred by rising mortality from extrahepatic complications, now representing the fourth most common cause of death in the overall cohort and the leading cause in patients with viral eradication (HCV infection) or adequate viral suppression (HBV infection).[28] Several studies have suggested that chronic HCV infection or chronic HBV infection increases the risk of hematologic malignancy, particularly non-Hodgkin lymphoma and myelodysplastic syndrome.[11,29–31] HCV or HBV infections may cause hematologic malignancy through chronic antigenic stimulation and viral replication in pluripotent hematopoietic stem cells.[11,31] We noted that the age-standardized extrahepatic cancer–related mortality remained stable after the introduction of DAA agents from 2014 through 2017, which was consistent with a recent review regarding the protective effect of DAA therapy on extrahepatic cancer.[32] In several studies, the eradication of HCV infection was closely associated with a reduction in hematologic cancer, a better response to chemotherapy, and an improvement in overall survival.[31–33] A recent meta-analysis showed that the risk of non-Hodgkin lymphoma declined significantly among individuals with SVR compared with those without SVR (hazard ratio, 0.64; 95% CI, 0.43–0.95).[13] Our findings also showed that mortality from hematologic malignancy remained stable during the interferon and DAA eras in individuals with HCV infection and oral nucleoside- or nucleotide-based antiviral therapy among individuals with HBV infection. These observations can be conceptually explained by the fact that viral antigenic stimulation was substantially reduced after the eradication of HCV and adequate suppression of HBV replication with potent

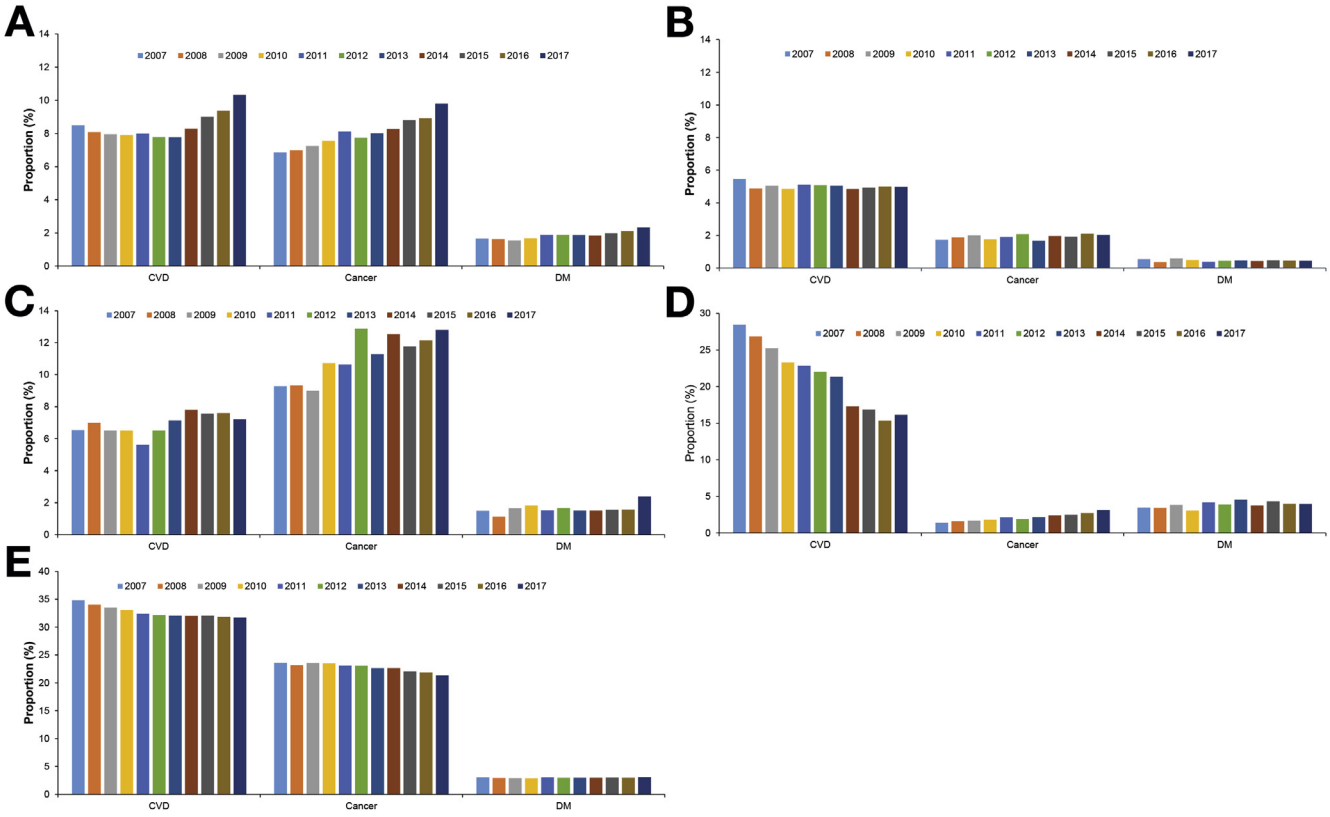

Figure 2. Annual trends in the proportion of extrahepatic mortality among individuals with chronic liver disease in the United States between 2007 and 2017: (*A*) HCV infection, (*B*) ALD, (*C*) HBV infection, (*D*) NAFLD, and (*E*) the cohort without chronic liver disease. CVD, cardiovascular disease; DM, diabetes mellitus.

antiviral therapy.[32] We noted a relatively higher proportion of non-Hodgkin lymphoma in individuals with HBV infection compared with HCV infection. Although a consistent modest association between chronic HCV infection and non-Hodgkin lymphoma has been reported, there is growing evidence of an association of chronic HBV infection with non-Hodgkin lymphoma.[34–36] A study based on half a million individuals from the Korean Cancer Prevention Study reported that individuals who tested positive for hepatitis B surface antigen had a 74% increased risk of non-Hodgkin lymphoma.[34] Recently, a Taiwanese population cohort study showed that HBV infection was an independent risk factor for the development of non-Hodgkin lymphoma (hazard ratio, 2.18; 95% CI, 1.80–2.65), specifically with an increased risk of diffuse large B-cell lymphoma and other B-cell lymphomas.[36] A case-control study using the Surveillance, Epidemiology, and End Results (SEER) Medicare database in US adults determined that HBV infection was associated with diffuse large B-cell lymphoma (adjusted odds ratio [OR], 1.24; 95% CI, 1.06–1.46).[35] Although the mechanism remains unclear, chronic immune activation and B-cell proliferation have been suspected as a potential mechanism for HBV-related lymphomagenesis.[37] In addition, several studies reported that HCV infection was associated with a 3-fold higher incident intrahepatic cholangiocarcinoma.[11,38,39] Whether viral hepatitis mediates a direct oncogenic action in the extrahepatic target organ by modulating the cell-signaling pathways or mediates indirect effects by promoting chronic antigenic stimulation or inflammation remains unclear.[11,39] Our study showed that individuals with chronic HBV or HCV infection had a higher rate of extrahepatic cancer–related deaths from non-Hodgkin lymphoma and intrahepatic cholangiocarcinoma compared with those with ALD. Consistent with a previous study,[40] we found that individuals with ALD had a higher risk of extrahepatic mortality from oropharyngeal cancer, pancreatic cancer, and digestive system cancers such as esophageal and colon cancer. A recent study showed that patients who achieved SVR with interferon-based therapy had higher rates of incident extrahepatic cancer.[41] In our study, the age-standardized mortality for extrahepatic cancer in the setting of HCV infection increased significantly during the pre-DAA era from 2007 through 2013 and remained stable during the DAA era. Therefore, whether effective DAA-based antiviral therapy for HCV infection reduces the risk of extrahepatic cancer is still unclear because of the competing nature of liver-related vs extrahepatic deaths in this population. Marked reduction in liver-related deaths after treatment in individuals with HCV infection may increase life expectancy and, thus, place these individuals at higher risk of developing non–liver-related extrahepatic complications such as cancer and cardiovascular disease. Therefore, we must re-evaluate the

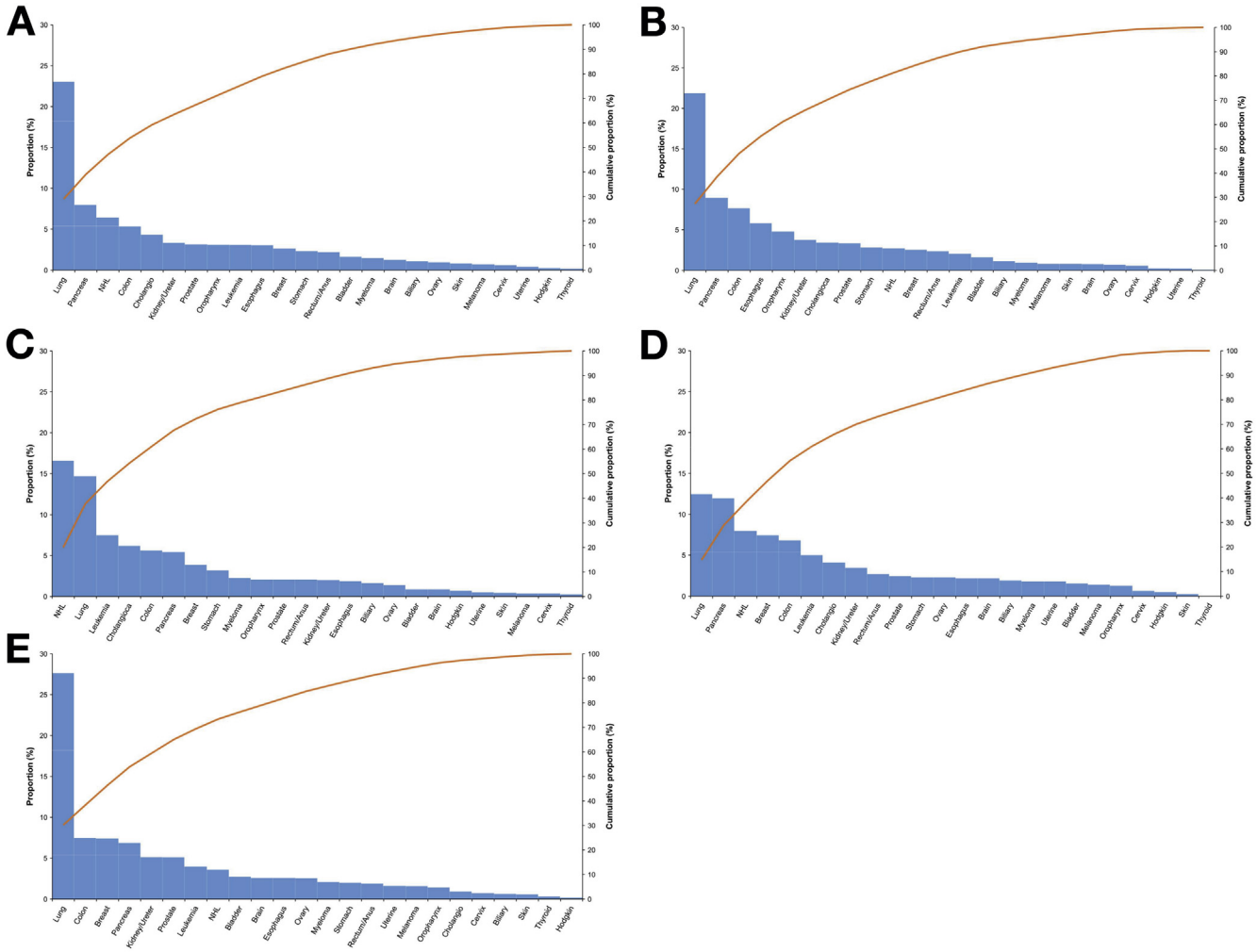

Figure 3. Proportion of cause-specific underlying causes of death for extrahepatic cancer among individuals with chronic liver disease in the United States between 2007 and 2017: (*A*) HCV infection, (*B*) ALD, (*C*) HBV infection, (*D*) NAFLD, and (*E*) the cohort without chronic liver disease.

surveillance programs and adjust the modeling algorithms for individuals previously infected with HCV who have developed SVR.

A link between HCV infection, but not HBV infection, and type 2 diabetes has been reported, suggesting that HCV infection is associated with an increased risk of diabetes.[7,42] Recent literature suggests that SVR among patients after the eradication of HCV reduces the risk for incident type 2 diabetes and diabetic complications.[43] In contrast, our study showed an increasing trend in diabetes-related mortality in the setting of HCV infection during the DAA era from 2014 through 2017, and we believe that the trends in the mortality of chronic disease such as diabetes need a relatively longer follow-up period than that presented in our study. Regarding cardiovascular disease, a recent meta-analysis showed that patients with HCV infection had a higher risk of cardiovascular mortality (OR, 1.65), carotid plaques (OR, 2.27), and cerebrocardiovascular events (OR, 1.30) compared with uninfected individuals.[9] The mechanism associating HCV infection with cardiovascular disease and diabetes is multifactorial and implicates as the likely culprits viral replication in extrahepatic cells, proinflammatory cytokine/chemokine release, insulin resistance, endothelial damage, and oxidative stress, which induce a profibrogenic and proinflammatory milieu, leading to systemic effects.[7,42,44] Successful eradication of HCV with interferon-based treatment was suggestive of improvement in overall extrahepatic mortality from complications including cryoglobulinemia, insulin resistance, diabetes, and cerebrovascular accident.[7,13,44] A recent study showed a survival benefit of DAA agents for HCV-associated cryoglobulinemia and vasculitis with a decline in mortality (2.8%).[45] Recent data showed that individuals with SVR after treatment for HCV infection had a 58% lower risk of cardiovascular events during the era of interferon-based therapy.[41] A cohort study in HCV-infected veterans (ERCHIVES) reported that DAA treatment was associated with 43% reduced risk and interferon-based therapy with 22% reduced risk for incident cardiovascular events.[46] DAA therapy most likely resulted in further improvements in the outcomes from extrahepatic complications, particularly diabetes and cardiovascular disease, which suggests that

HCV infection may be a modifiable cardiovascular risk factor.[47] A study from Italy reported that HCV eradication by DAA-based treatment improved carotid atherosclerosis, suggesting beneficial effects of SVR by DAA agents on cardiovascular disease.[8] However, a study with a longer follow-up period is needed to clearly and accurately show the impact of DAA-based treatment on mortality due to chronic diseases such as cardiovascular disease and diabetes.

Currently, there are no approved pharmacologic treatment options for individuals with NAFLD. Therefore, it can be argued that the unabated increase in age-standardized and proportions of liver-related mortalities for individuals with NAFLD, along with extrahepatic cancer–related mortality, are due to the lack of an approved pharmacologic agent for a liver disease with a rapidly increasing prevalence. More noticeably, the proportions of extrahepatic cancer– and diabetes-related mortality showed a significantly higher increase in NAFLD without cirrhosis compared with counterparts with cirrhosis, which may be partially explained by nonalcoholic steatohepatitis–associated metabolic abnormalities.

The strengths of this study include longitudinal trends and examination of individual-level data in a national database over 11 years. This study allowed us to compare trends in national mortality and gain a unique insight into hepatic and extrahepatic mortality in the setting of chronic liver disease. Additionally, we used updated national data, which enabled us to capture current trends in the mortality of extrahepatic complications of viral hepatitis, NAFLD, and ALD. There are several weaknesses of this study. First, the underlying cause of death based on the death certificate may be subject to misclassification and result in underestimation or overestimation. There may be a systematic coding of the cause known to be the most common and, conversely, undercoding of causes known to be less frequent. In addition, this systematic miscoding may have varied over time and skewed the observed trends. Second, age-standardized mortality rates might not represent actual mortality rates, but these rates were appropriate to compare across the population and over time as population distributions change or age. Third, the NVSS data were not collected in a prospective longitudinal fashion; rather, the NVSS database was created by recoding the underlying and contributing causes of death by extracting this information from the death records each year. Therefore, we are unable to perform a competitive risk analysis, which is appropriate for and can be applied only to a longitudinal cohort, to investigate the real impact of antiviral therapy on hepatic and extrahepatic risks. Future prospective cohort studies are needed to perform competitive risk analysis. Fourth, we were not able to account for the effect of antiviral therapy on an individual level because of limitations of this database. Fifth, individuals with HCV infection or ALD have a higher prevalence of smoking and alcohol use than the general population. Therefore, there could be an increased risk of extrahepatic complication, such as cancer and cardiovascular disease, not only because of the pathogenesis of the virus but also because of higher exposure to risk factors.[39] Hypothetically, the increase in extrahepatic mortality among individuals with viral hepatitis can in part be attributed to a resumption or increase in alcohol consumption and impairment of metabolic risk profile after achieving virologic eradication or suppression. However, these longitudinal data are not available in the NVSS database. Because of the limitations of the NVSS database and our study design, we were unable to investigate the impact of temporal change in alcohol consumption and metabolic risk factors on increasing mortality due to extrahepatic complications in individuals with viral hepatitis. Future studies with longitudinal prospective cohort are warranted to evaluate this hypothesis. Sixth, the relatively short-term follow-up after the introduction of DAA agents is a limitation to this analysis. These caveats may partly explain the increase in extrahepatic cancer after the introduction of potent, clinically efficacious, and tolerable antivirals agents for HBV infection (entecavir in 2005 and tenofovir disoproxil fumarate in 2008). A future study with a longer follow-up after the introduction of DAA agents for HCV infection is needed. Although the results of our study may be generalizable to Western populations that share similar social and health behavioral patterns as those of the United States, the conclusions may not be generalizable to other populations.

In conclusion, after the introduction of potent antiviral agents for HBV and HCV infections, there has been a significant decrease in liver-related mortality among individuals with viral hepatitis. However, mortality from extrahepatic complications increased in individuals with viral hepatitis during the widespread use of DAA agents from 2014 through 2017, particularly in the setting of HCV infection. In the absence of improved treatment options for ALD during the 11-year study period, liver-related mortality for ALD increased and continues to maintain a steep upward trajectory, whereas mortality associated with the extrahepatic complications in individuals with ALD has remained unchanged. Therefore, the quest for newer therapies must remain the cornerstone in our efforts to improve the care of individuals with ALD.

Even more intriguing are the contrasting trends in liver-related and extrahepatic mortality among individuals with HCV infection and ALD and their temporal relationship to the advent of highly efficacious DAA-based therapy in the case of HCV infection versus the static state of management options with no substantial improvement in the treatment of ALD over the last 2 decades. Despite the temporal relationship, these observations should not be interpreted as a causal link between DAA agents and extrahepatic mortality after the eradication of HCV. The widespread use of, higher efficacy of, and durable response to DAA agents in individuals with HCV infection may have resulted in a paradigm shift in the clinical progression of coexisting disease entities after response to DAA agents in the virus-free environment. These findings suggest assessment and identification of risk and risk factors for extrahepatic cancer, cardiovascular disease, and diabetes in individuals who have been successfully treated and cured of HCV infection. If our findings are reproduced, then surveillance programs and forecasting models will need re-evaluation and revision

with a focus on an ongoing need for risk assessment and risk factor modification for extrahepatic cancer, cardiovascular disease, and diabetes in individuals with HCV infection after treatment with DAA agents.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.06.026.

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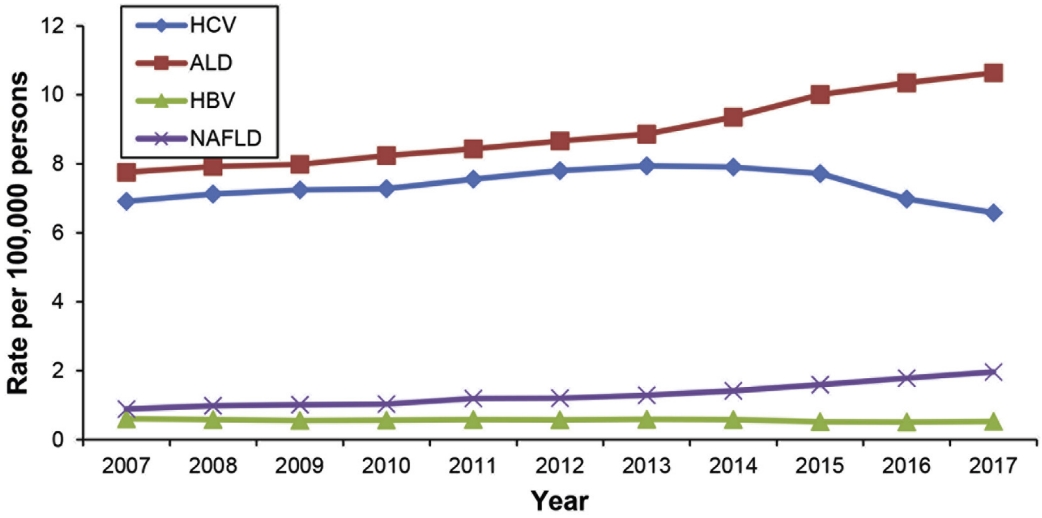
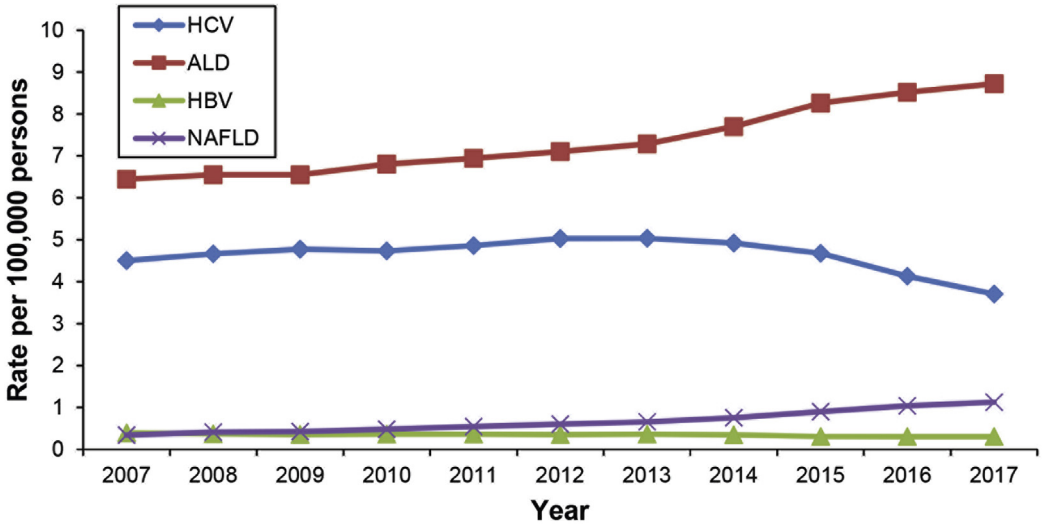
Acknowledgments
Author contributions: Donghee Kim and Aijaz Ahmed were responsible for the study concept and design, acquisition of data, statistical analysis, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approval of the final draft manuscript. All authors were responsible for interpretation of data, critical revision of the manuscript for important intellectual content, and approval of the final manuscript and have agreed to be accountable for all aspects of the work.

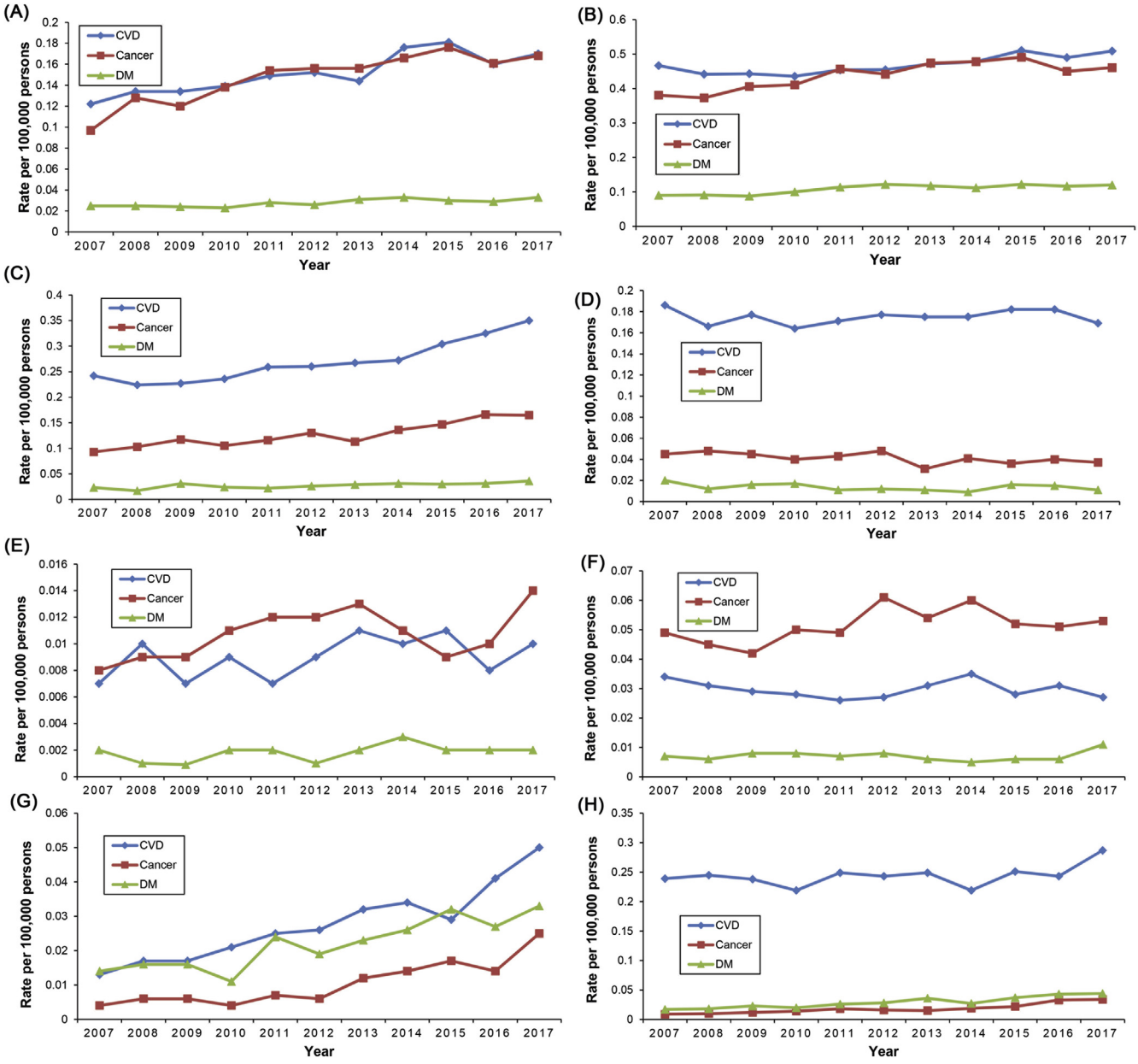
Conflicts of interest
The authors disclose no conflicts.



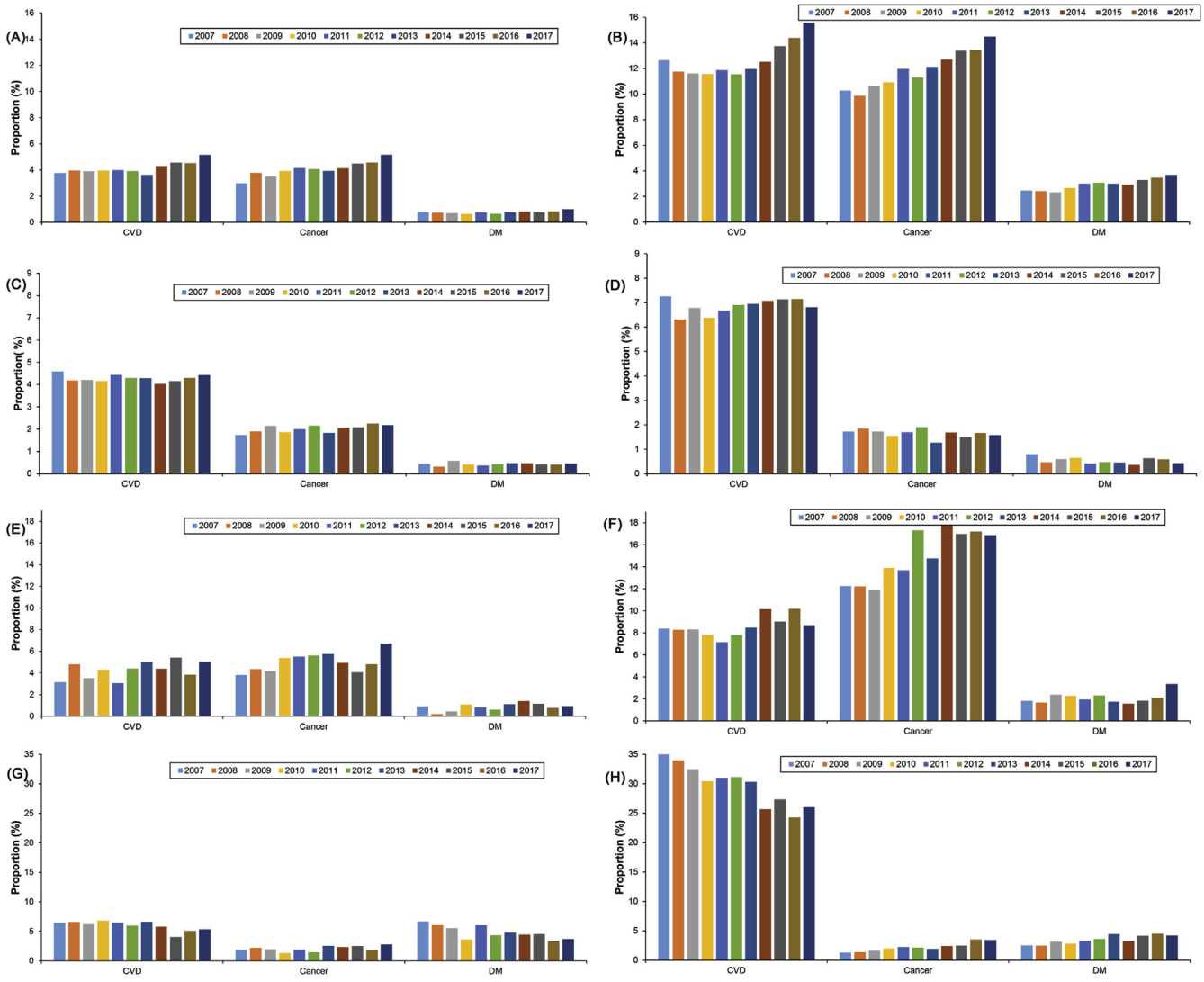
Supplementary Figure 1. Annual age-standardized mortality for chronic liver disease in the United States between 2007 and 2017.



Supplementary Figure 2. Annual age-standardized liver-related mortality in the United States between 2007 and 2017.



Supplementary Figure 3. Annual age-standardized extrahepatic mortality among individuals with chronic liver disease according to the presence of absence of cirrhosis in the United States between 2007 and 2017: (*A*) HCV–related cirrhosis, (*B*) HCV without cirrhosis, (*C*) ALD-related cirrhosis, (*D*) ALD without cirrhosis, (*E*) HBV–related cirrhosis, (*F*) HBV without cirrhosis, (*G*) NAFLD-related cirrhosis, and (*H*) NAFLD without cirrhosis. CVD, cardiovascular disease; DM, diabetes mellitus.



Supplementary Figure 4. Annual trends in the proportion of extrahepatic mortality among individuals with chronic liver disease according to the presence or absence of cirrhosis in the United States between 2007 and 2017: (*A*) hepatitis C–related cirrhosis, (*B*) hepatitis C without cirrhosis, (*C*) ALD-related cirrhosis, (*D*) ALD without cirrhosis, (*E*) hepatitis B–related cirrhosis, (*F*) hepatitis B without cirrhosis, (*G*) NAFLD-related cirrhosis, and (*H*) NAFLD without cirrhosis. CVD, cardiovascular disease; DM, diabetes mellitus.

Supplementary Table 1.ICD-10 Codes for Extrahepatic Cancer

Extrahepatic cancer	ICD-10 codes
Solid cancer	
Oral cavity/pharynx	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14
Digestive system	
Esophagus	C15
Stomach	C16
Colon	C18
Rectum/anus	C19, C20, C21
Intrahepatic bile duct	C22.1
Biliary tract	C23, C24
Pancreas	C25
Other digestive organs	C26
Lung and bronchus	C34
Melanoma	C43
Other skin cancer	C44
Breast	C50
Prostate	C61
Urinary bladder	C67
Kidney/ureter	C64, C65. C66
Brain	C70, C71
Thyroid	C73
Cervix	C53
Uterine	C54, C55
Ovary	C56
Hematologic cancer	
Hodgkin lymphoma	C81
Non-Hodgkin lymphoma	C82, C83, C84, C85
Myeloma	C90
Leukemia	C91, C92, C93, C94, C95
Other	C96

Supplementary Table 2. Characteristics of Deaths in the United States for Chronic Liver Disease as a Cause of Death, 2007–2017 (N = 27,903,198)

Characteristics	HCV (n = 189,013)	ALD (n = 226,541)	HBV (n = 14,317)	NAFLD (n = 33,945)
Age at death, *y*				
20–39	3460 (1.8)	15,306 (6.8)	770 (5.4)	3431 (10.1)
40–49	20,259 (10.7)	43,322 (19.1)	1990 (13.9)	4819 (14.2)
50–59	81,005 (42.9)	80,821 (35.7)	3959 (27.7)	7335 (21.6)
60–69	59,920 (31.7)	58,172 (25.7)	3787 (26.5)	8842 (26.1)
70–79	16,091 (8.5)	22,143 (9.8)	2305 (16.1)	6699 (19.7)
≥80	8278 (4.4)	6777 (3.0)	1506 (10.5)	2819 (8.3)
Race/ethnicity				
White, non-Hispanic	119,590 (63.7)	163,184 (72.4)	6068 (42.6)	27,171 (80.2)
Black, non-Hispanic	33,907 (18.1)	17,286 (7.7)	2618 (18.4)	1853 (5.5)
American Indian or Alaskan Native, non-Hispanic	2792 (1.5)	7829 (3.5)	80 (0.6)	554 (1.6)
Asian or Pacific Islander, non-Hispanic	4369 (2.3)	2843 (1.3)	4441 (31.2)	659 (2.0)
Hispanic	27,210 (14.5)	34,333 (15.2)	1044 (7.3)	3627 (10.7)
Sex				
Men	133,957 (70.9)	162,126 (71.6)	10,318 (72.1)	16,009 (47.2)
Women	55,056 (29.1)	64,415 (28.4)	3999 (27.9)	17,936 (52.8)
Education				
Less than high school	39,179 (25.5)	38,712 (20.5)	2886 (24.8)	4760 (16.7)
Completed high school	72,526 (47.3)	81,667 (43.2)	4465 (38.3)	12,031 (42.2)
Some college	21,691 (14.1)	30,309 (16.0)	1447 (12.4)	4730 (16.6)
Completed college or beyond	20,046 (13.1)	38,569 (20.4)	2851 (24.5)	7008 (24.6)

NOTE. Data are presented as n (%).

Supplementary Table 3. Age-Standardized Mortality Due to Individuals Without Chronic Liver Disease, Cause-Specific Mortality, and APC Among US Adults ≥20 Years, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
Age-standardized mortality rate							
All-cause mortality	1117.5	1050.4	–0.7 (–0.9 to –0.4)[a]	2007–2011	–1.8 (–2.5 to –1.1)[a]	2011–2017	0.1 (–0.3 to 0.5)
Cardiovascular disease	390.7	332.6	–1.6 (–1.9 to –1.2)[a]	2007–2011	–3.7 (–4.5 to –2.8)[a]	2011–2017	–0.2 (–0.6 to 0.3)
Cancer	263.9	219.3	–1.8 (–1.9 to –1.7)[a]				
Diabetes	34.1	31.7	–0.9 (–1.5 to –0.2)[a]	2007–2009	–4.5 (–7.9 to –0.9)[a]	2009–2017	1.1 (–0.3 to 0.5)
Proportion, %							
Cardiovascular disease	34.8	31.7	–0.9 (–1.0 to –0.8)[a]	2007–2011	–1.8 (–2.1 to –1.5)[a]	2011–2017	–0.3 (–0.5 to –0.2)[a]
Cancer	23.6	21.3	–0.8 (–1.3 to –0.4)[a]	2007–2010	0.2 (–1.4 to 1.8)	2010–2017	–1.3 (–1.7 to –0.9)[a]
Diabetes	3.0	3.1	0.2 (–0.1 to 0.6)				

[a]$P < .05$.

Supplementary Table 4. Age-Standardized Mortality Due to Chronic HCV Infection Without Coinfection With HIV, Cause-Specific Mortality Among Individuals With HCV Infection, and APC Among US Adults ≥20 years, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
All-cause mortality							
	6.725	6.430	–0.5 (–1.0 to 0.1)	2007–2014	2.2 (1.7 to 2.8)[a]	2014–2017	–6.5 (–8.4 to –4.7)[a]
Cause-specific death among individuals with HCV							
Age-standardized mortality rate							
Liver disease	4.499	3.694	–2.0 (–2.6 to –1.5)[a]	2007–2014	1.5 (1.0 to 2.1)[a]	2014–2017	–9.8 (–11.6 to –8.0)[a]
Cardiovascular disease	0.586	0.668	1.8 (1.1 to 2.6)[a]				
Cancer	0.478	0.613	2.5 (1.2 to 3.8)[a]	2007–2013	4.8 (3.0 to 6.5)[a]	2013–2017	–0.8 (–3.9 to 2.3)
Diabetes	0.114	0.150	3.4 (2.0 to 4.9)[a]				
Proportion, %							
Liver disease	67.0	57.3	–1.6 (–2.0 to –1.2)[a]	2007–2014	–0.7 (–1.1 to –0.3)[a]	2014–2017	–3.6 (–4.9 to –2.2)[a]
Cardiovascular disease	8.7	10.4	2.1 (1.2 to 3.1)[a]	2007–2013	–1.2 (–2.5 to –0.0)[a]	2013–2017	7.4 (4.9 to 10.0)[a]
Cancer	7.0	9.8	2.9 (2.3 to 3.6)[a]				
Diabetes	1.7	2.4	3.4 (2.2 to 4.7)[a]				

NOTE. HIV infection was defined by using ICD-10 codes B20 to B24.
[a]$P < .05$.

Supplementary Table 5. Age-Standardized Mortality Due to Chronic HBV Infection Without Coinfection With HIV, Cause-Specific Mortality Among Individuals With HBV Infection, and APC Among US Adults ≥20 Years, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
All-cause mortality							
	0.576	0.499	–1.3 (–2.1 to –0.6)[a]				
Cause-specific death among individuals with HBV							
Age-standardized mortality rate							
Liver disease	0.39	0.301	–2.4 (–3.2 to –1.5)[a]				
Cardiovascular disease	0.04	0.036	–0.0 (–1.9 to 1.9)				
Cancer	0.056	0.063	1.6 (–0.8 to 3.9)				
Diabetes	0.009	0.012	0.8 (–2.7 to 4.4)				
Proportion, %							
Liver disease	67.9	59.7	–1.2 (–1.4 to –0.9)[a]				
Cardiovascular disease	6.8	7.4	1.6 (–0.1 to 3.2)				
Cancer	9.6	13.0	3.3 (1.6 to 5.0)[a]				
Diabetes	1.6	2.5	2.8 (–0.8 to 6.5)				

NOTE. HIV infection was defined by using ICD-10 codes B20 to B24.
[a]$P < .05$.

Supplementary Table 6. Age-Standardized Mortality Due to Chronic HCV Infection, and Cause-Specific Mortality Among Individuals With HCV Infection, and APC According to the Presence or Absence of Cirrhosis

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
Cause-specific death in HCV-related cirrhosis							
Age-standardized mortality rate							
All-cause mortality	3.232	3.327	0.4 (–0.2 to 1.0)	2007–2014	3.7 (3.1 to 4.3)[a]	2014–2017	–6.9 (–8.8 to –5.0)[a]
Liver disease	2.632	2.505	–0.3 (–0.8 to 0.1)	2007–2014	3.2 (2.8 to 3.6)[a]	2014–2017	–8.2 (–9.6 to –6.7)[a]
Cardiovascular disease	0.122	0.170	3.4 (2.1 to 4.8)[a]				
Cancer	0.097	0.168	5.2 (2.1 to 8.4)[a]	2007–2011	10.7 (2.9 to 19.1)[a]	2011–2017	1.6 (–2.2 to 5.7)
Diabetes	0.025	0.033	3.2 (1.5 to 4.9)[a]				
Proportion, %							
Liver disease	81.5	75.2	–0.7 (–1.0 to –0.5)[a]	2007–2013	–0.4 (–0.8 to –0.1)[a]	2013–2017	–1.2 (–1.9 to –0.6)[a]
Cardiovascular disease	3.8	5.2	2.7 (1.4 to 4.0)[a]	2007–2013	–0.1 (–1.7 to 1.5)	2013–2017	7.0 (3.8 to 10.3)[a]
Cancer	3.0	5.2	4.0 (2.5 to 5.5)[a]				
Diabetes	0.8	1.0	1.7 (–2.0 to 5.4)	2007–2010	–5.2 (–16.6 to 7.8)	2010–2017	4.8 (1.2 to 8.4)[a]
Cause-specific death in HCV without cirrhosis							
Age-standardized mortality rate							
All-cause mortality	3.678	3.256	–1.1 (–1.8 to –0.5)[a]	2007–2013	1.3 (0.5 to 2.2)[a]	2013–2017	–4.7 (–6.1 to –3.2)[a]
Liver disease	1.874	1.198	–4.4 (–5.4 to –3.4)[a]	2007–2013	–0.1 (–1.4 to 1.3)	2013–2017	–10.6 (–12.9 to –8.3)[a]
Cardiovascular disease	0.467	0.509	1.0 (–0.3 to 2.2)	2007–2009	–3.2 (–9.9 to 3.9)	2009–2017	2.1 (1.3 to 2.9)[a]
Cancer	0.381	0.461	2.0 (0.3 to 3.8)[a]	2007–2014	3.9 (2.2 to 5.6)[a]	2014–2017	–2.3 (–8.0 to 3.8)
Diabetes	0.090	0.120	3.4 (1.0 to 5.9)[a]	2007–2012	6.6 (2.3 to 11.1)[a]	2012–2017	0.3 (–3.8 to 4.5)
Proportion, %							
Liver disease	50.9	36.9	–3.1 (–3.9 to –2.4)[a]	2007–2012	–0.7 (–2.1 to 0.6)	2012–2017	–5.4 (–6.7 to –4.1)[a]
Cardiovascular disease	12.7	15.6	2.3 (1.2 to 3.4)[a]	2007–2012	–1.5 (–3.4 to 0.4)	2012–2017	6.3 (4.2 to 8.3)[a]
Cancer	10.3	14.5	3.7 (3.0 to 4.4)[a]				
Diabetes	2.5	3.7	4.4 (3.1 to 5.6)[a]				

[a] $P < .05$.

Supplementary Table 7. Age-Standardized Mortality Due to Alcoholic Liver Disease, Cause-Specific Mortality Among Individuals With ALD, and APC According to the Presence or Absence of Cirrhosis

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
Cause-specific death in ALD-related cirrhosis							
Age-standardized mortality rate							
All-cause mortality	5.209	8.091	4.8 (4.0 to 5.5)[a]	2007–2012	3.2 (1.9 to 4.4)[a]	2012–2017	6.4 (5.1 to 7.6)[a]
Liver disease	4.450	6.792	4.6 (3.8 to 5.5)[a]	2007–2012	3.1 (1.6 to 4.6)[a]	2012–2017	6.2 (4.7 to 7.7)[a]
Cardiovascular disease	0.242	0.350	3.6 (1.3 to 5.9)[a]	2007–2009	–3.2 (–14.8 to 9.8)	2009–2017	5.3 (3.9 to 6.8)[a]
Cancer	0.093	0.165	5.6 (4.0 to 7.2)[a]				
Diabetes	0.023	0.036	5.0 (1.7 to 8.3)[a]				
Proportion, %							
Liver disease	85.5	83.7	–0.2 (–0.2 to –0.1)[a]				
Cardiovascular disease	4.6	4.4	–0.2 (–1.0 to 0.6)				
Cancer	1.7	2.2	1.7 (0.2 to 3.1)[a]				
Diabetes	0.4	0.5	0.6 (–2.8 to 4.0)				
Cause-specific death in ALD without cirrhosis							
Age-standardized mortality rate							
All-cause mortality	2.547	2.547	–0.0 (–0.3 to 0.0)				
Liver disease	1.994	1.932	–0.3 (–0.5 to –0.0)[a]				
Cardiovascular disease	0.186	0.169	0.1 (–0.8 to 1.0)				
Cancer	0.045	0.037	–2.4 (–4.7 to –0.0)[a]				
Diabetes	0.02	0.011	–3.0 (–7.8 to 2.0)				
Proportion, %							
Liver disease	78.4	75.6	–0.3 (–0.4 to –0.1)[a]				
Cardiovascular disease	7.3	6.8	0.5 (–0.4 to 1.5)				
Cancer	1.7	1.6	–1.3 (–3.6 to 1.1)				
Diabetes	0.8	0.4	–2.9 (–7.7 to 2.2)				

[a] $P < .05$.

Supplementary Table 8. Age-Standardized Mortality Due to HBV Infection, Cause-Specific Mortality Among Individuals With HBV Infection, and APC According to the Presence or Absence of Cirrhosis

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
Cause-specific death in HBV-related cirrhosis							
Age-standardized mortality rate							
All-cause mortality	0.213	0.211	0.1 (–0.7 to 1.0)				
Liver disease	0.176	0.156	–0.7 (–1.6 to 0.1)				
Cardiovascular disease	0.007	0.010	2.7 (–0.9 to 6.3)				
Cancer	0.008	0.014	3.0 (–0.3 to 6.6)				
Diabetes	0.002	0.002	5.6 (–2.2 to 14.0)				
Proportion, %							
Liver disease	82.8	73.4	–0.9 (–1.2 to –0.7)[a]				
Cardiovascular disease	3.2	5.0	3.0 (–0.8 to 7.0)				
Cancer	3.8	6.7	2.7 (–0.7 to 6.3)				
Diabetes	0.9	0.9	8.5 (–2.2 to 20.3)				
Cause-specific death in HBV without cirrhosis							
Age-standardized mortality rate							
All-cause mortality	0.393	0.319	–2.0 (–2.9 to –1.0)[a]				
Liver disease	0.216	0.147	–3.9 (–5.1 to –2.7)[a]				
Cardiovascular disease	0.034	0.027	–2.7 (–0.6 to 2.7)				
Cancer	0.049	0.053	1.8 (–0.3 to 4.0)				
Diabetes	0.007	0.011	0.3 (–4.5 to 5.3)				
Proportion, %							
Liver disease	54.9	45.5	–2.0 (–2.7 to –1.4)[a]				
Cardiovascular disease	8.4	8.7	1.8 (–0.3 to 3.9)				
Cancer	12.3	16.9	4.3 (2.5 to 6.0)[a]				
Diabetes	1.8	3.3	2.2 (–2.4 to 7.0)				

[a] $P < .05$.

Supplementary Table 9. Age-Standardized Mortality Due to NAFLD, Cause-Specific Mortality Among Individuals With NAFLD, and APC According to the Presence or Absence of Cirrhosis

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
Cause-specific death in NAFLD-related cirrhosis							
Age-standardized mortality rate							
All-cause mortality	0.209	0.908	15.7 (14.8 to 16.6)[a]				
Liver disease	0.150	0.703	16.5 (15.7 to 17.3)[a]				
Cardiovascular disease	0.013	0.05	12.6 (10.1 to 15.2)[a]				
Cancer	0.004	0.025	18.6 (12.1 to 25.3)[a]				
Diabetes	0.014	0.033	9.7 (5.3 to 14.2)[a]				
Proportion, %							
Liver disease	71.4	77.6	0.8 (0.3 to 1.2)[a]				
Cardiovascular disease	6.5	5.3	–3.2 (–5.6 to –0.7)[a]				
Cancer	1.8	2.8	3.2 (–1.5 to 8.2)				
Diabetes	6.7	3.7	–5.0 (–8.2 to –1.8)[a]				
Cause-specific death in NAFLD without cirrhosis							
Age-standardized mortality rate							
All-cause mortality	0.683	1.054	4.3 (3.0 to 5.7)[a]	2007–2014	2.7 (1.5 to 4.0)[a]	2014–2017	8.1 (3.4 to 13.1)[a]
Liver disease	0.191	0.423	8.3 (7.4 to 9.2)[a]				
Cardiovascular disease	0.239	0.287	1.0 (–0.5 to 2.5)				
Cancer	0.009	0.034	13.2 (9.9 to 16.6)[a]				
Diabetes	0.017	0.044	10.1 (7.5 to 12.8)[a]				
Proportion, %							
Liver disease	27.6	41.9	4.6 (3.8 to 5.5)[a]				
Cardiovascular disease	35.0	26.0	–3.3 (–4.3 to –2.3)[a]				
Cancer	1.3	3.4	9.6 (7.0 to 12.2)[a]				
Diabetes	2.5	4.2	5.9 (3.5 to 8.4)[a]				

[a] $P < .05$.

Supplementary Table 10. Age-Standardized Cancer-Related Mortality and APC Among US Adults With Chronic Liver Disease, 2007–2017

	Age-standardized rate		Average APC (95% CI)	Trend segment 1		Trend segment 2	
	2007	2017	2007–2017	Year	APC (95% CI)	Year	APC (95% CI)
HCV							
Cancer (total)	0.478	0.630	2.6 (1.0 to 4.1)[a]	2007–2014	4.6 (3.2 to 6.1)[a]	2014–2017	–2.1 (–7.1 to 3.2)
Solid cancer	0.409	0.564	3.0 (1.5 to 4.5)[a]	2007–2014	5.2 (3.7 to 6.6)[a]	2014–2017	–1.9 (–6.8 to 3.3)
Hematologic cancer	0.069	0.065	–0.5 (–2.0 to 0.9)				
ALD							
Cancer (total)	0.138	0.203	3.6 (1.9 to 5.4)[a]				
Solid cancer	0.132	0.191	3.5 (1.6 to 5.4)[a]				
Hematologic cancer	0.006	0.011	4.6 (0.7 to 8.7)[a]				
HBV							
Cancer (total)	0.057	0.066	2.0 (–0.1 to 4.2)				
Solid cancer	0.041	0.046	2.9 (0.5 to 5.3)[a]				
Hematologic cancer	0.015	0.020	0.1 (–3.9 to 4.3)				
NAFLD							
Cancer (total)	0.013	0.059	15.1 (13.0 to 17.2)[a]				
Solid cancer	0.011	0.049	14.8 (11.6 to 18.0)[a]				
Hematologic cancer	0.002	0.011	16.0 (7.7 to 24.9)[a]				

[a] $P < .05$.