Why Are Liver Disease Mortality Trends Shifting?

Better treatments for hepatitis B and C and a lack of such advances for fatty liver or alcoholic liver disease are driving outcomes.

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Thanks to improved treatments for both hepatitis B and C viruses (HBV and HCV), the causes of death of people with these viruses have shifted considerably. In short, liver disease–related deaths have declined while, alarmingly, rates have risen for deaths not directly related to liver disease, also known as extrahepatic causes.

This shift requires a reordering of the approach to monitoring and caring for those with viral hepatitis, according to the authors of a new paper published in Gastroenterology regarding mortality trends among those with chronic liver disease.

Lacking the treatment advances seen in the viral hepatitis field, non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) have driven particularly concerning mortality rates. Although cardiovascular disease (CVD) is the most frequent cause of death for those with fatty liver, liver-related mortality for this group has increased swiftly, following a trend similar to that seen among those with ALD.

Seeking clarity regarding such trends, a team of researchers led by Donghee Kim, MD, PhD, of the division of gastroenterology and hepatology at Stanford University School of Medicine, conducted an analysis of data from the U.S. Census and the National Center for Health Statistics mortality records, covering the 11-year period from 2007 through 2017.

Previous research has found that people with HCV are at a higher risk for extrahepatic health conditions connected to dysregulation of the immune system, including lymphoma and cryoglobulinemia (abnormal proteins in the blood), as well as metabolic dysfunction including CVD and type 2 diabetes. Additionally, the virus has been linked to extrahepatic cancers, including non–Hodgkin lymphoma and pancreatic, kidney and throat cancers. HBV has likewise been linked to cancers outside the liver.

People with HCV have benefited greatly from the introduction of highly effective direct-acting antivirals (DAAs), starting with the launch of Gilead Sciences' Sovaldi (sofosbuvir) in late 2013. Today, almost everyone with hep C can be cured in two or three months. Although there is not yet

a cure for hep B, the arrival of increasingly potent antiviral treatments in the 1990s improved the landscape for those living with HBV as well. Consequently, death rates for those with each condition have declined in recent years, although the hep B trend got a head start.

But ALD mortality has seen no such improvements. Consequently, death rates for those with the condition have only increased—form 7.8 to 10.5 deaths per 100,000 people between 2007 and 2016. Between 2016 and 2017, the study authors noted, there was a widening gap between the ALD and HCV death rates, thanks to improved treatment for the latter condition and a lack of such benefits for the former disease.

All told, the new study's authors combed over the records of nearly 30 million deaths of U.S. residents 20 years old and older and standardized mortality rates for age.

They found that deaths from any cause among those with hep C plateaued in 2013, followed by a considerable decline between 2014 and 2014. As for deaths directly related to HCV, they increased by an average of 2.2% per year from 2007 to 2014 and then declined by 6.5% per year from 2014 to 2017.

Between 2014 and 2017, age-standardized mortality resulting from hep C–related liver disease fell 9.8% per year while deaths from CVD and diabetes increased by 1.9% and 3.3% per year, respectively. Extrahepatic cancer–related mortality among those with HCV increased by 4.6% annually from 2007 to 2014 and then plateaued going forward.

People with HBV saw a 2.4% annual decline in liver-related death during the study period, but extrahepatic cancer–related mortality rose 2.0% per year.

As for those with ALD and NAFLD, age-standardized mortality followed an accelerated increase between 2007 and 2017. For ALD, this meant an increase in the rates of both all-cause and liver-related deaths while death rates from CVD were stable between 2007 and 2009 and then increased by 3.5% annually through 2017.

For those with NAFLD, throughout the study period, the CVD-related death rate increased by 2.0% per year; overall, 20% of deaths among individuals with fatty liver were a result of CVD. During the same period, liver-related mortality for those with fatty liver increased much faster, following a 12.6% annual increase.

The study authors divided their analysis of cancer trends by solid tumors and blood cancers, or hematologic malignancies. Among those with hep B and C, deaths from hematologic cancers held steady during the study period while mortality rose from extrahepatic solid cancers. In contrast, deaths from hematologic and solid cancer increased among those with ALD or NAFLD.

"With the expected decline in liver-related complications during the era of antiviral agents," the study authors concluded, "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).”

Speaking to the lack of effective treatments for ALD, the investigators wrote: “[T]he quest for newer therapies must remain the cornerstone in our efforts to improve the care of individuals with ALD.”

And as a final conclusion, they wrote: “If our findings are reproduced, then surveillance programs and forecasting models will need reevaluations 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 following treatment with DAA agents.”

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