Editorial

Liver-related mortality in the United States: hepatitis C declines, non-alcoholic fatty liver and alcohol rise

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With the advent of highly effective and accessible direct-acting antiviral (DAA) therapy for patients with hepatitis C virus (HCV), the landscape of chronic liver disease is rapidly changing. In the study by Kim *et al.* (1) using data from the U.S. Census and National Center for Health Statistics, a striking reduction in HCV-related mortality rates was observed from 8.14 per 100,000 persons in 2013 to 7.15 per 100,000 persons in 2016, coinciding with the approval of second generation DAAs. While inferential, as DAA use was not directly measured, these data align with other recent studies showing the association of DAAs with reversal of hepatic decompensation, reduced likelihood of liver transplant (LT) listing, and improved survival among patients with HCV-related cirrhosis (2,3). Collectively, evidence of population-level benefits of HCV treatment on liver and non-liver outcomes continues to be amassed, providing strong support of HCV elimination efforts in the U.S. and globally.

More concerning was the observed rise in all-cause and liver-related mortality rates for non-alcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD) (1). Kim *et al.* (1) show that the liver-related mortality rates for ALD have consistently increased over the past decade, and that the increase is accelerating with the annual percentage change in age-standardized mortality rates for ALD being +2.3% from 2007–2013 and +5.3% from 2013–2016. In contrast, the annual percentage changes for HCV during the similar time periods were –0.4% and –13.7%, respectively. These data suggest that ALD, despite long recognized as a principal cause of chronic liver disease and mortality, may be increasing. Similar, and equally striking trends were evident for NAFLD, with the annual percentage change in age-standardized liver-related mortality rates increasing from +10.5% from 2007–2013 and +16.0% from 2013–2016, though cardiovascular deaths still outnumbered deaths due to liver disease. The reasons for this increase in ALD and NAFLD-related mortality are likely multifactorial, but these chronic liver diseases share some commonalities that might explain the increase: (I) changing epidemiology with true increase in disease burden; (II) lack of highly effective liver therapies; and (III) limited access to LT.

Alcohol is actively consumed by 2.4 billion people worldwide, and is the seventh leading cause of premature death and disability, accounting for 2.8 million or 6% of global deaths in 2016 (4). In the U.S., ALD accounts for 48% of liver-related deaths, and has recently emerged as most common indication for LT. U.S. drinking patterns are changing. In a recent study of the National Epidemiology Survey on Alcohol and Related Conditions between 2001–2002 and 2012–2013, which were nationally representative surveys of U.S. adults, alcohol use, and particularly high-risk drinking, has increased significantly across the U.S. (5). The prevalence of alcohol use disorder by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria increased from 8.5% in 2001–2002 to 12.7% in 2012–2013; increases were most significant among women, racial/ethnic minorities, and the socioeconomically disadvantaged (5). In another recent study using U.S. Census data between 2009–2016, people aged 25–34 years

experienced the highest average annual increase in cirrhosis-related mortality, which was attributed entirely to ALD (6). From a public health standpoint, where years of potential life lost are an important metric, these mortality trends in young adults are particularly concerning. Indeed, on a population level, the volume of alcohol consumption has been found to be strongly correlated with death rates from cirrhosis (7,8). Although there are limited U.S. legislative examples, in Europe and Canada, government interventions to reduce population-wide alcohol consumption (e.g., marketing regulation, setting minimum prices for alcohol) have been associated with declines in liver-related mortality (8,9). On a patient-physician level, interventions such as Screening, Brief Intervention, and Referral to Treatment (SBIRT), are recommended, but consistent data showing efficacy and feasibility are lacking (10-12). Clearly, further study and effective implementation of measures to identify and reduce harmful patterns of alcohol use are needed.

Effective medical therapies for ALD are lacking. Beyond abstinence from alcohol, there exist no targeted therapies to specifically treat and reverse chronic liver disease from ALD. In alcoholic hepatitis (AH), the most acute and severe hepatic presentation of heavy chronic alcohol use and accounting for 10% of deaths in ALD, corticosteroids improve short-term survival, but no pharmacotherapies have shown long-term survival benefits (13). LT for ALD is increasing and is the most common indication for LT in the U.S. and Europe currently. While waitlist and post-LT outcomes for ALD are comparable or higher than non-ALD conditions (14), actual referral and listing of patients with ALD can be complex. In a veterans affairs (VA) cohort examining LT referral patterns among patients satisfying American Association for the Study of Liver Diseases (AASLD) referral guidelines for LT, presence of ALD was the strongest negative determinant for referral (15). Although the results have been cited as possible evidence for implicit transplant provider bias due to stigma associated with ALD (15,16), one must note that ALD is a complex disease with psychosocial and medical co-morbidities which may preclude LT—indeed, in the VA study, active alcohol use was the most common inferred reason for lack of LT referral (15).

Pre-LT abstinence policies, where patients traditionally require six months of abstinence prior to LT eligibility, are controversial and a potential barrier to accessing LT (17,18). Recent alcohol use is a common reason for acute-on-chronic liver failure for any chronic liver disease; furthermore, AH, the most acute and severe presentation of ALD, implies by definition recent alcohol use, contributing to a subset of very ill ALD patients which are made ineligible for LT due to pre-LT abstinence rules (19,20). However, with recent U.S. have shown that on LT for severe AH without a specific requirement of pre-LT abstinence in carefully selected patients (i.e., first alcohol-associated liver decompensation, strong social support, thorough psychosocial evaluation for alcohol relapse risk factors) is feasible (21-23), with acceptable post-LT survival and alcohol use rates, and provider attitudes across the United States appear to be changing (20). Indeed, the most recent American College of Gastroenterologists guidelines (10) on the management of ALD state that LT may be considered for highly selected patients with severe AH. Whether other national guidelines will follow suit, and the impact of these shifting attitudes on overall national LT trends and mortality for ALD remain to be seen.

In exploring the reasons for increases in mortality related to NAFLD over the past decade, these same three themes (i.e., U.S. epidemiologic trends, limitations of current medical therapies, and access to LT) appear relevant. First, in the U.S. and globally, rates of obesity and diabetes have markedly increased, fueling an epidemic of NAFLD and nonalcoholic steatohepatitis (NASH) prevalence, recently estimated to affect 30% and 5%, respectively, of the U.S. population (24). This staggering disease burden has led to predictions that NASH cirrhosis will become the most frequent indication for LT in the near future. Importantly, non-liver causes of deaths are more common among persons with NAFLD; in the Kim *et al.* (1) study, only 51% of the 4,672 NAFLD deaths in 2016 were liver-related, whereas 86% of the 25,306 ALD deaths were liver-related in this same time period. Cardiovascular disease and non-liver malignancies are important non-liver causes of mortality in patients with NAFLD and these comorbidities may also present potential barriers to LT.

Therapies for NASH are limited, particularly for patients with established cirrhosis. Parallel to abstinence in ALD, the mainstay of treatment in NAFLD is lifestyle intervention to achieve weight loss and optimize metabolic comorbidities, which can be difficult to achieve. Pharmacotherapies to prevent progression of NAFLD are desired, as fibrosis stage is the strongest independent risk factor among NAFLD patients for both overall and liver-specific mortality. Although there is currently no Food and Drug Administration (FDA)-approved medication for NASH, this is an active area of drug development, with several phase 3

studies underway and with results expected in 2019–2020. Though many drugs appear promising, it must be admitted that no therapy directed to NASH can achieve the efficacy seen with DAAs for HCV-associated liver disease. Thus, the rates of liver-related deaths due to NASH may be expected to increase in the foreseeable future. Finally, as with ALD, there are barriers to LT access for NAFLD as well. While LT is an effective therapy for end-stage liver disease attributed to NASH, with patient and graft survival similar to other indications, co-morbidities common in NAFLD (e.g., cardiovascular disease, extreme obesity) can preclude LT. However, unlike ALD, the proportion of total LTs performed for NASH is not disproportionate to its disease burden as measured by its contribution to total U.S. liver-related deaths—LT for NASH has risen rapidly, and in 2016, NASH was the 2nd most common etiology for LT, accounting for 19% of total U.S. LT recipients.

Epidemiologic studies like those by Kim *et al.* (1) highlight the powerful population-wide impact of a highly effective therapy; DAAs being one of the more remarkable accomplishments of modern medicine. However, such comparative studies underscore the looming burden of chronic liver diseases related to alcohol and metabolic fatty liver, for which no FDA-approved therapies exist. A recent study found that despite accounting for 50% of the liver disease burden, ALD received the least amount of research attention among the most common etiologies of liver disease (ALD, NAFLD, HCV, and hepatitis B) and allocated only 3% of liver-related National Institutes of Health (NIH) funding opportunities between 2010–2014; NAFLD fared somewhat better receiving 20% of liver-related NIH funding (25). Given that this same study found that 48% of liver-related NIH funding opportunities were allocated to HCV between 2010–2014, (25) this provides evidence of the tangible improvements in disease-specific mortality (i.e., for HCV) with focused research funding. A more equitable distribution of resources to those liver diseases with high disease burden and increasing mortality (i.e., ALD and NAFLD) is essential. Only with enhanced disease surveillance and determination of the factors contributing to the increasing mortality, coupled with innovative pharmacotherapies and expanded access to LT, will the rising mortality rates related to ALD and NAFLD be averted.

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Footnote

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