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Current and Future Burden of Chronic Nonmalignant Liver Disease

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Abstract

Disease burden is an important indicator of the state of health of a population. It can be measured as the frequency (e.g. incidence and prevalence) of a condition or its effects including: fatal and non-fatal health loss from disease (e.g. disability-adjusted life years (DALYs)) as well as the financial costs (e.g. direct health care costs and indirect health care expenditures related to lost income due to premature death). Accurate disease burden information is essential for policy-making such as prioritization of health interventions and allocation of resources.

Chronic Liver Disease (CLD) causes substantial health and economic burden in the US, where nearly two million deaths annually are attributable to CLD. In the recent past, overall mortality rate of CLD has been increasing. Viral hepatitis and alcoholic liver disease are thought to be the most common etiologies of chronic liver diseases. More recently, the prevalence of non-alcoholic steatohepatitis (NAFLD) is rapidly increasing and non-alcoholic steatohepatitis (NASH) has become a leading indication for liver transplantation. In this work, we assemble available data on the burden of CLD in the United States, focusing on non-malignant complications, whereas the impact on mortality and healthcare expenses of hepatocellular carcinoma (HCC), an important consequence of CLD is discussed elsewhere.

Globally, chronic liver disease (CLD) is an important source of health and economic burden. According to the Global Burden of Disease Study of 2010, 1.75 million deaths were attributable to CLD. There is a large degree of geographic variation in the burden of CLD, depending on the prevalence of causative factors such as viral hepatitis infection, including hepatitis B virus (HBV) and hepatitis C virus (HCV), alcohol consumption, diabetes and metabolic syndrome. In general, HBV infection tends to have a large burden in resource-limited countries and nonalcoholic fatty liver disease (NAFLD) in more established economies, whereas HCV infection and alcohol use are prevalent throughout. Since CLD has a long latent period between initial occurrence of liver disease and diagnosis of CLD, it is difficult to determine the accurate incidence of CLD. Instead, most available epidemiological data estimate prevalence of CLD and its later consequences.

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With regard to CLD in the US, recent data indicate that there has been a substantial increase in the burden of CLD. Although, the exact prevalence of cirrhosis worldwide remains unknown¹, the prevalence of cirrhosis in the US was estimated to be approximately 0.27%, corresponding to 633,323 adults.² The National Center for Health Statistics reports that CLD and cirrhosis represent the 12th leading cause of death in the United States in 2013, accounting for 36,427 (1.4%) of the 2,596,993 deaths (mortality rate, 11.5/100,000). This mortality rate increased over time, from 9.4 in 1999 to 11.5 in 2013 (www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf).³

More impressively, the global burden of disease investigators calculated a metric that addresses premature mortality, namely years of life lost (YLL), cirrhosis was one of the conditions that had the most rapid increase in the burden between 1990 and 2010. In 1990, cirrhosis was ranked as the 14th highest YLL in the US with an estimated 917,300 years of life lost. By 2010, cirrhosis rose to 8th with 1,232,700 years lost, which places cirrhosis between diabetes (7th) and Alzheimer's disease (9th), higher than colorectal cancer (10th), breast cancer (13th) or chronic kidney disease (16th). In terms of number of deaths, cirrhosis claimed 33,700 lives in 1990, which increased to 49,500 lives in 2010.⁴ Globally, cirrhosis-related deaths increased approximately 46% from 838,000 lives in 1990 to 1,221,100 lives in 2013.⁵

Figure 1 depicts mortality rates from liver disease (ICD-10: K70-76) in the US by gender and Hispanic ethnicity for years 1999–2013 from Deaths: Final Data for 2013 collected by Centers for Diseases Control and Prevention (CDC).⁶ In general, men have higher mortality from liver disease than in women, whereas Hispanic ethnicity did not affect mortality. Over time, there was an increase in mortality from liver disease. In women, mortality from liver disease rose from 11.8 deaths per 100,000 in 1999 to 15.2 per 100,000 in 2013. In men, it increased from 22.2 deaths per 100,000 to 26.7 per 100,000 during the same period. Figure 2 analyzes the same data by age groups. Overall, mortality from liver disease increased with age. The increase in mortality over time was most pronounced in people of 55–64 years in age, followed by those of 45–54 years. An increase is also seen in the 65–74 year old group in the last few years. These increasing trends in mortality are likely related to the aging of the HCV birth cohort (please see below). Finally, Figure 3 displays racial differences in liver disease mortality. Mortality is highest among Native Americans and Alaskan natives, followed by Caucasians, Africans, and Asian-Pacific Islanders. In all racial groups, men have higher mortality from liver disease than women. An increase in liver mortality over time was mainly seen among Caucasian Americans, both men and women, as well as among Native American or Alaskan native women. Again, at least part of this trend may be attributed to HCV. While several reasons may be postulated to underlie the racial disparity in CLD mortality, these data could help guide appropriate resource allocation for prevention and treatment as well as to improve access to healthcare for the underprivileged.⁷

Epidemiological data other than mortality related to liver disease tend to be difficult to obtain on a population level in the US. Commonly, epidemiologic data have been derived from academic, tertiary referral practices, which likely may not represent the true epidemiological burden of CLD in the whole US population.^{8,9} An example may be trends in liver transplant waiting list (Figure 4). At the end of 2002, the year in which the current

MELD score-based allocation system was implemented, there were 15,507 patients awaiting an organ, of whom 400 had a diagnosis of a liver malignancy and 15,107 did not. Ten years later, at the end of 2012, 15,290 patients were waiting, of whom 13,944 did not have a diagnosis of malignancy. The decrease in liver transplant waitlist registrants likely reflects changes in listing practices rather than a true reduction in the burden of end stage liver disease in the US. Over time, as organ scarcity worsened, fewer patients with low MELD score have been listed.¹⁰

Figures 5A and 5B show the breakdown of underlying liver disease diagnosis in patients awaiting and undergoing liver transplantation in 2012 respectively. The single most common etiology represented in liver transplant candidates is chronic HCV infection, which accounted for nearly 1/3. The other major diagnoses included ALD and other/unknown etiologies - most of these latter patients are presumed to have NAFLD. A similar pattern is seen with patients undergoing liver transplantation with HCV and alcohol being the most common etiologies at the time of LT.

Chronic Hepatitis C Virus infection

An estimated 2–3% of the world's population or 130–170 million people are living with chronic HCV infection. The epidemiology of HCV infection varies throughout the world, with its prevalence ranging from <1% to >10%.¹¹ Egypt is known to have the highest prevalence of HCV infection, which has been attributed to healthcare-related viral transmission.¹² While there is no effective vaccine against HCV, prevention of transmission and widespread application of effective antiviral agents may potentially reduce the burden of HCV infection over time. To date, however, lack of screening and limited access to appropriate diagnosis and treatment remain barriers to substantially reducing the global burden of HCV and morbidity and mortality from cirrhosis and liver cancer complicating chronic HCV infection continue to increase.

In the US, HCV infection is known as the most common chronic blood-borne infection. The National Health and Nutrition Examination Survey (NHANES) data have been used to estimate its prevalence. There have been three publications addressing the HCV prevalence in the NHANES samples. These reported the prevalence of HCV infection (i.e., detectable serum HCV RNA) at 1.3% for surveys from 1988–94, at 1.3% for 1999–2002 and at 1.0% for 2003–2010, corresponding to 2.7 (95% confidence interval [CI]: 2.4–3.0) million, 3.2 (95%CI: 2.7–3.9) million and 2.7 (95%CI: 2.2–3.2) million American adults with HCV viremia, respectively. It is likely that these data underestimate the true prevalence of HCV, as NHANES does not include parts of the population that are expected to have high prevalence of HCV infection, including the homeless and the incarcerated.

Chronic HCV infection may result in cirrhosis, end-stage liver diseases (ESLD), and HCC. In a study that utilized 2007 death certificate data, HCV infection was listed as the underlying cause of 6,605 deaths and as the underlying or contributing cause of 15,106 deaths with the age-adjusted mortality rate of 4.58 deaths per 100,000 persons per year (95%CI: 4.50–4.67).¹³ In comparison, HIV infection was listed as the underlying cause of 11,332 deaths and as the underlying or contributing cause of 12,734 deaths (age-adjusted

mortality rate of 4.16 deaths per 100,000 persons per year (95%CI: 4.09–4.24). Thus, as of 2007, HCV infection resulted in more deaths than HIV infection in the US.¹⁴

A peculiar aspect of HCV infection in the US is that the infection is concentrated in a certain age group, namely individuals born between 1945–1965, the so-called baby-boomer generation. This is thought to reflect high-risk behaviors (e.g., injection drug use while sharing needles) as well as transfusion of contaminated blood prior to the development of diagnostic tests for HCV. More recently, however, resurgence of acute HCV infection has been reported as a result of increased use of heroin among young adults. As HCV infection remains asymptomatic prior to development of complications of advanced liver disease, many of these individuals remain to be diagnosed. In an estimate based on the NHANES sample, nearly 50% of American adults with HCV infection were unaware of their infection. Even among those who were diagnosed, only 38% accessed healthcare for further diagnosis and treatment.

Projection studies have estimated that while the incidence of new HCV infection in the US decreased over time, the number of individuals living with advanced fibrosis and cirrhosis will rise as the birth cohort of baby boomers with HCV infection grows older and their duration of infection reaches long enough time for their liver fibrosis to have progressed to cirrhosis. However, systematic data to assess the prevalence and burden of advanced liver disease as a result of chronic HCV infection have been sparse. Kanwal et al utilized data from the Veterans Administration data to assess time trends in the prevalence of cirrhosis and its related complications. Among veterans with HCV infection, the proportion diagnosed with cirrhosis increased from 9% in 1996 to 18.5% in 2006 and that with decompensated cirrhosis from 5% in 1996 to 11% in 2006.¹⁵

These increases in morbidity and mortality associated HCV infection have a substantial impact on healthcare costs. Several studies have utilized health insurance payer databases to estimate all-cause and HCV-related healthcare costs. Gordon et al divided their 53,796 patients with HCV infection into noncirrhotic liver disease (NCD, n=41,858, 78%), compensated cirrhosis (CC, n=3,718, 7%), and end stage liver disease (n=8,220, 15%). When the per-patient-per-month (PPPM) healthcare costs were calculated, the mean all-cause PPPM costs were 32% and 247% higher for patients with CC and ESLD compared to those with NCD (\$1,870 and \$4,931 versus \$1,420; $P < 0.001$). The top three cost components included pharmacy, ambulatory care, and hospital inpatient, which altogether accounted for 90% of NCD costs and 93% of CC and ESLD costs. The largest cost components were inpatient costs for those with ESLD (56%) and ambulatory costs for those with CC and NCD (37% and 36%, respectively). More than half (56%) of the healthcare costs were attributable to HCV and this proportion increased with severity (46%, 57%, and 71% for patients with NCD, CC, and ESLD, respectively). El Khoury et al. studied the components of the costs involved in the management of patients with ESLD. They estimated the cost of a liver transplant at \$201,110 (\$178,760–\$223,460), variceal hemorrhage at \$25,595, refractory ascites at \$24,755, and hepatic encephalopathy at \$16,430, compared to the cost of compensated cirrhosis of \$585–\$1,110.¹⁶ Putting available data together, Razavi et al estimated that the total healthcare costs associated with HCV infection may be as high as \$6.5 billion annually.¹⁴

While these data on the current burden of HCV infection is already substantial, projection studies have forecasted that the future burden will be even higher, because the prevalence of advanced liver disease is expected to continue to rise. Davis et al. projected that from the year 2000 to 2020, the prevalence of compensated cirrhosis and HCC will increase by over 80%, decompensated cirrhosis by over 100% and liver-related deaths by 181%.¹⁷ Razavi et al projected that the prevalence of compensated cirrhosis would peak in 2015 at 626,500 cases, while that of decompensated cirrhosis would reach 107,400 in 2019.¹⁴ As a result, the total healthcare costs for HCV would increase to a peak in 2024 at \$9.1 billion. The costs associated with compensated cirrhosis are expected to peak in 2022 at \$1.9 billion and those for decompensated cirrhosis in 2025 at \$4.2 billion. According to the study from Hatzakis et al., the prevalence of HCV viremia in most countries has already peaked. Yet, the prevalence of ESLD and liver-related deaths will continuously increase until 2030.¹⁸ Hopefully, widespread application of antiviral agents will dampen these future impacts.

HCV therapy has been revolutionized by the approval of the direct-acting antiviral agents (DAAs) and availability of new regimens for chronic HCV infection. These innovations afford shorter treatment durations, lower pill burden, fewer side effects, and higher rates of sustained virological response compared with the conventional therapies. With the implementation of birth-cohort screening and the availability of highly effective new therapies, Kabiri et al projected that HCV infection would become a rare disease in the US by 2036.¹⁹

At the same time, the new DAA regimens present challenges to public health as well. While DAAs are expected to reduce the number of patients with ESLD and liver transplantation, the high cost of DAAs places a substantial burden on the healthcare system. Economic constraints and limited access to healthcare may further exacerbate disparities that are already present among HCV patients. Moreover, potential consequences of emergence of resistance-associated variant viruses and the emerging concerns for cross-resistance need to be recognized.²⁰ For HCV patients in resource-limited regions, barriers to HCV care not only includes high cost of antiviral therapies, but also the lack of medical infrastructure and laboratories, as well as shortage of healthcare workers and diagnostic tools.^{21, 22}

In summary, the prevalence of chronic HCV infection has the geographic variation ranging from <1% to >10% throughout the world. HCV infection is the most common indication for liver transplantation in the US. Though the incidence of HCV infection decreases, the mortality rate continuously increases and leads to substantial healthcare and economic burden. The promising outcomes of HCV treatment with the DAAs suggest that the novel, highly effective therapies may help reduce the long term burden. However, obstacles remain in the HCV treatment, especially in the resource-limited settings. These challenges call for collaboration among policy makers, pharmaceutical companies, health-care providers and researchers.

Alcoholic Liver Disease (ALD)

Ethanol, widely consumed in most parts of the world, is a well-known cause of chronic liver disease. ALD ranges from reversible alcoholic fatty liver, to alcoholic hepatitis, and to

cirrhosis and ESLD. Alcohol, in addition, may accelerate the progression of coexisting liver diseases, for example HCV infection.²³ Clearly, not all drinkers develop ALD – in addition to the duration and amount of drinking, other factors such as gender and genetic predisposition may determine the incidence and severity of ALD.²⁴

ALD is an important global public health problem. In 2010, alcoholic cirrhosis was responsible for 493,300 deaths (death rate = 7.2 deaths per 100,000) and for loss of 14,544,000 disability adjusted life years (DALYs). ALD accounts for 47.9% of all cirrhosis deaths and 46.9% of all cirrhosis DALYs. Central Europe had the highest percentages of cirrhosis deaths and DALYs attributable to alcohol consumption, with 72.3% of all cirrhosis deaths and 74.6% of all cirrhosis DALYs.²⁵ The World Health Organization has a goal to reduce ALD mortality to below 3.2 per 100,000 by year 2020.

It is estimated that as of 2013, 16.6 million American (7%) adults (≥ 18 years) had an alcohol use disorder, consisting of 10.8 million men and 5.8 million women.²⁶ Up to 30–45% of patients with chronic alcohol use disorder may develop alcoholic hepatitis sometime during their lifetime. ALD remains a major cause of cirrhosis and constitutes the second most common indication for liver transplantation in the US. Because only a fraction of patients with ALD qualify for liver transplantation candidacy, liver transplantation waiting list database is not a representative sample for epidemiological studies of ALD in the population. Further, since many ALD patients lack optimal access to healthcare, analyses based on healthcare administrative databases likely underestimate the true burden of ALD on the population level.

Paula et al conducted a longitudinal assessment of ALD mortality using death certificate data from the National Vital Statistics System for 1980 – 2003.²⁷ A total of 287,365 records were identified as potential ALD deaths over the 24-year period. The age- and sex- adjusted incidence rate of ALD-related deaths was 6.9/100,000 persons in 1980 and 4.4/100,000 persons in 2003. During the study period, ALD mortality (per 100,000 persons) decreased from 6.3 to 4.5 among Caucasians, 11.6 to 4.1 among African Americans, and 8.0 to 3.7 among other race group. When the mortality rate trend for ALD was assessed in conjunction with that for HCV, the reduction in ALD mortality was reciprocally matched by an increase in mortality from HCV, which reached 2.9/100,000 persons by 2003. These data suggest that there were HCV deaths misclassified as ALD deaths prior to recognition of HCV and that ALD mortality may not have decreased over time. Age-specific mortality related to ALD was highest in decedents of 45 – 64 years in age. More recent data confirm that alcohol-related mortality affects mainly on young and middle-age individuals and estimate that approximately 18,000 Americans died from ALD in 2013.²⁸

The cost of excessive alcohol consumption in the US is estimated to have reached \$223.5 billion in 2006, predominantly resulting from workplace productivity losses (72% of the total cost), healthcare expenses (11% of total), criminal justice expenses related to excessive alcohol consumption (9% of total), and motor vehicle accident costs (6% of the total).²⁹ These financial and human costs of alcohol use disorders including ALD are clearly enormous yet potentially preventable. Although some alcoholic hepatitis may be

pharmaceutically treated, the most effective means to reduce the burden of ALD remains to prevent, recognize and intervene with the underlying alcohol use disorders.³⁰

In summary, ALD ranges from reversible alcoholic fatty liver, to alcoholic hepatitis, and to cirrhosis and ESLD. It accounts for nearly half of all cirrhosis and remains a leading indication for liver transplantation in the US. While ALD only accounts for a fraction of alcohol use disorders, it incurs enormous financial and human costs. The most effective means to reduce the burden of ALD is to prevent, recognize and intervene with the underlying alcohol use disorders.

Nonalcoholic Fatty Liver Diseases (NAFLD)

NAFLD is defined as the presence of hepatic steatosis after the exclusion of other causes of hepatic fat accumulation, including significant alcohol consumption; other causes of liver disease; and other medical conditions. NAFLD includes a spectrum of histologic abnormalities ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), cirrhosis and eventually hepatocellular carcinoma. Although NAFLD is seen in all ethnic groups, it has a lower prevalence in African-Americans compared with Hispanic and Caucasian Americans, even after adjustment for obesity and insulin resistance, which may be related to ethnic differences in lipid homeostasis.^{31, 32} According to the Dallas Heart Study, a population-based cohort study performed in an ethnically diverse community in the US, the prevalence of NAFLD was approximately 34%.³³

Prevalence estimates for NAFLD has varied among studies in part because of differences in the sensitivity of the test modality used to determine steatosis of the liver. In the Framingham Heart Study, the prevalence of NAFLD was 17%, when assessed by computed tomography.³⁴ A study utilizing the NHANES data revealed that ultrasound-diagnosed steatosis was as common as 34%.³⁵ In a study based on a largely middle-aged Americans, NAFLD and histologically confirmed NASH was found in 46% and 12.2%, respectively.³⁶ Finally, a recent meta-analysis estimated the prevalence of NAFLD and NASH to be 6–35% (median 20%) and 3–5%, respectively.³⁷

NAFLD is pathogenetically associated with obesity, hyperinsulinemia and insulin resistance and the increasing prevalence of obesity, type II diabetes, and metabolic syndrome in the general population has led a rapid rise in the prevalence of NAFLD.^{38–40} A study based on NHANES data estimated that the prevalence of NAFLD increased from 18% in 1988–1991 to 29% in 1999–2000 to 31% in 2011–2012.⁴¹

Several cohort studies have reported the progression of NAFLD to cirrhosis. However, the rate of progression is variable – it is higher in patients with NASH compared to those with NAFL. Adams et al. reported incident cirrhosis in 3.1% of cases during 7.6 years of follow-up in Olmsted County.⁴² In this NAFLD cohort, cirrhosis did not develop in patients with NAFL. In subjects diagnosed with NASH, the progression rate to end stage liver disease was reportedly as high as 10% during 13.7 years of followup.⁴³ Another study reported that histological fibrosis, rather than steatosis grade or presence of NASH, was associated with liver-related events.^{44, 45} When hepatic fibrosis was evaluated by noninvasive NAFLD

fibrosis score, liver-related events were more frequent in the intermediate (HR 7.7, 95% CI 1.4–42.7) and high-risk groups (HR 34.2, 95% CI 6.5–180.1) than in the low-risk group.⁴⁴

Studies evaluating long-term survival have shown that NAFLD was associated with increased overall mortality, with standardized mortality ratios of 1.3–2.6.^{42, 43, 46–49} Some of these studies are confounded because in analyzing survival of NAFLD patients, they failed to account for obesity and related metabolic traits. Ekstedt et al. demonstrated that NAFLD patients have increased risk of death, attributable to cardiovascular disease and liver-related disease during a mean follow-up of 26.4 years.⁵⁰ Patients with NAFL may be more likely to die from cardiovascular causes rather than advanced liver disease.⁵¹ Moreover, fibrosis stage predicted both overall and disease-specific mortality.^{44, 50} Soderberg et al. studied liver biopsy-diagnosed NAFLD and showed that mortality was increased in the NASH group but not in those with simple NAFL.⁴⁹ A population-based study using NHANES III evaluated the association between noninvasive fibrosis markers and mortality and demonstrated that patients with advanced fibrosis had an increased risk of overall mortality compared with patients without advanced fibrosis. The increase in mortality was almost entirely from cardiovascular causes.³⁵ Other investigators have shown that NASH-related cirrhosis is associated with mortality comparable to HCV-related cirrhosis.^{52–54} NAFLD is thought to contribute to fibrosis, mortality and disease burden when it coexists with other CLD. In summary, most studies have consistently shown that NASH with advanced fibrosis is associated with increased mortality whereas NAFL without fibrosis has a benign long-term outcome.

NASH is quickly becoming a major etiology in liver transplantation in the US and it may soon become the most common indication.^{55, 56} According to data from the Scientific Registry of Transplant Recipients (SRTR), the proportion of recipients receiving a liver transplant for NASH increased from 1.2% in 2001 to 9.7% in 2009.⁵⁵ Between 2004 and 2013, new waitlist registrants with NASH increased by 170%, compared to 45% for ALD and 14% for HCV.⁵⁷

While it is likely that NAFLD has a substantial economic impact, representative data are scarce. A German population cohort study reported that subjects with ultrasonographic fatty liver disease with increased liver enzyme had 26% higher overall healthcare costs over 5 years of follow-up, controlling for comorbid conditions.⁵⁸ According to data from national outpatient claims of Medicare beneficiaries (2005 to 2010), the number of outpatient visits because of NAFLD rose between 2005 and 2010 - the mean annual charge and payment increased significantly from \$2,624 and \$561 in 2005 to \$3,608 and \$629 ($p<0.05$), respectively.⁵⁹

In summary, the increasing prevalence of obesity and type II diabetes and the metabolic syndrome is leading to an increased prevalence of NAFLD in the US. It has become a leading cause of liver transplantation in the US. The mortality and financial burden related to NAFLD is not limited to liver related events but includes the increased risk in cardiovascular morbidity and mortality.

Chronic Hepatitis B Virus infection

Globally, HBV remains an important cause of acute and CLD. At least 240 million individuals have chronic HBV infection – HBV may account for up to 30% of cirrhosis and 45% of HCC. The prevalence of HBV infection varies by geography, with the highest (>8%) prevalence in sub-Saharan Africa and Asia. In contrast, HBV prevalence is lowest (<2%) in regions such as North America, Western Europe and Australia.⁶⁰ With increasing uptake of universal infant immunization, the global prevalence of HBV infection is expected to decrease.

In the US, 700,000 to 1.4 million are estimated to have chronic HBV infection. Chronic HBV infection is most commonly a result of transmission in infancy or childhood which occurs in HBV endemic populations, whereas most incident HBV infections in the US are in adults and rarely become chronic.⁶¹ Thus, the bulk of chronic HBV infection in the US is borne by immigrants or their children who have come from HBV-endemic areas of the world. Kowdley et al. estimated that 3.5% or 1.23–1.42 million of all foreign-born persons in the US have chronic hepatitis B, which is more than 10-fold higher than the prevalence of HBV in the general US population.⁶² In the recent few decades, more than 60% of new immigrants to the US come from countries of high HBV endemicity.⁶³ However, there are few empirical data to accurately measure the prevalence of HBV infection. For example, data based on NHANES samples indicate that the age-adjusted prevalence of HBsAg seropositivity decreased from 0.38% in 1988–1994 to 0.27% in 1999–2006. These are, however, likely underestimates, as NHANES samples do not include sufficient number of individuals from population subgroups with high HBV prevalence.

In the analysis of 2007 mortality data by Ly et al.¹³, HBV infection was listed as the underlying cause of death in 724 decedents and as the underlying or contributing cause of death in 1,815. The age-adjusted mortality rate was 0.56 death per 100,000 persons per year (95% CI, 0.54 to 0.59), which is approximately 1/8 of that for HCV. The lower death rate for HBV is not only attributable to the lower prevalence of HBV than HCV in the general population, but also consequent to widespread institution of effective antiviral therapy. In an analysis of liver transplant waiting list, the incidence of waitlist registration for ESLD from HBV cirrhosis decreased significantly coincident with the introduction of effective oral antiviral agents, whereas the effect of those agents on the need for liver transplantation for HCC was less certain.

Today, oral antivirals are the mainstay of chronic HBV therapy. The cost depends on the regimens and the duration of treatment. Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are potent nucleoside and nucleotide analogues, respectively, recommended as first-line agents for chronic hepatitis B. The approximate annual cost of for ETV and TDF has been reported to be \$5100–5,800 and \$3,400–3,900 respectively.^{64, 65}

There are limited data about the impact of HBV on healthcare resource utilization. According to a report on the burden of digestive diseases, outpatient visits for a HBV-related diagnosis occurred at a rate of <100 visits per 100,000 in 1996, which increased to >400 visits per 100,000 by 2004. Similarly, the rate of hospitalization for a HBV-related illness

was 5 per 100,000 in 1996, which increased to >20 per 100,000 in 2002. The total charges for HBV hospitalizations increased from \$357 million in 1990 to \$1.5 billion in 2003. As of 2006, hospitalization charges did not increase further, which may also reflect the impact of antiviral therapy.⁹

In summary, while HBV does not have as large a burden as HCV does in the US as a whole, it affects certain groups of Americans, namely recent immigrants from endemic countries. Recent data suggest that effective antiviral therapy has contributed to a substantial decrease in morbidity and healthcare services related to ESLD (e.g., liver transplantation). However, continued emphasis on screening, early diagnosis and treatment is needed to continue the trend.

Metabolic Liver Diseases

Hereditary Hemochromatosis (HH) is known as the most common genetic disease in North America, although it still represents a relatively uncommon etiology of CLD. HH is most commonly characterized by defects in the HFE gene, although more recently, mutations in other genes coding for iron regulatory proteins have been discovered to be responsible for the inherited iron overload syndrome (i.e. hepcidin (HAMP), hemojuvelin (HJV), transferrin receptor 2 (TfR2) and ferroportin (SLC40A1)). The HFE gene codes for a membrane protein involved in dietary iron absorption.⁶⁶ Up to 90% of typical HH patients carry a C282Y mutation of the gene. Conversely, however, the penetrance of disease among subjects with the mutation is relatively low, suggesting contribution of non-genetic factors in the disease progression.⁶⁷ The highest allelic prevalence of HFE gene mutation is seen in people of Northern European ancestry (6%).⁶⁸ The prevalence was only 0.11, 0.027, 0.014, 0.012 and 0.000039 % in Native American, Hispanic, African American, Pacific Islander and Asian populations, respectively.⁶⁹

HH is an uncommon indication for liver transplantation, in part due to the higher morbidity and mortality from cardiac, infectious and malignant complications in liver transplantation for HH-related conditions. A single center UK study by Faisal et al. reported that HH accounted for 1% of the liver transplants performed over a period of 12 years. They revealed that postoperative infectious and cardiac complications are common.⁷⁰

Wilson Disease (WD) is an autosomal recessive disorder of copper metabolism. The most common genetic abnormality associated with WD is absence of decrease in function of ATP7B protein, which leads to decreased copper excretion into bile, resulting in copper accumulation and injury. To date, more than 500 distinct mutations have been described, 380 of which have a confirmed role in the pathogenesis of the disease.⁷¹ The average prevalence of WD worldwide is about 3 per 100,000. Liver involvement in WD is more common among children and younger adults, while neurological symptoms may be seen more often in older patients.⁷² Untreated patients may present with acute liver failure, which is associated with nearly 95% mortality unless liver transplantation is performed.⁷³

WD is the primary indication for liver transplantation in 0.5% and 1.5 % of adults and children respectively.⁷⁴ In children, metabolic liver diseases are the second most common indication for liver transplantation after biliary atresia. Fifteen percent of children enrolled in

the studies in the pediatric liver transplantation (SPLIT) registry underwent liver transplantation for metabolic diseases and 7.6% of them represented WD.⁷⁵

Alpha-1 antitrypsin deficiency (A1ATD) is known as a common genetic liver disease in infant and children. It is an autosomal co-dominant genetic disease affecting 1 per 3,000–5,000 individuals^{76–78} and has been described in all races. However, it is most common in Whites (14.0 per 1,000), as the most prevalent deficiency alleles, Z and S are strongly associated with Northern European ancestry (Z and S alleles), and some Southern European ancestry (S allele). It is less common in Hispanics (9.1 per 1,000) and African American (2.6 per 1,000) and extremely rare in Asian and Mexican Americans.⁷⁹ It is estimated that 25 million people carry at least one defective A1AT gene.⁷⁹ While 2–3% of A1ATD children progress to advanced fibrosis and cirrhosis requiring liver transplantation, about one-third of genetically susceptible adults with the most severe phenotype (i.e., PiZZ) develop clinically significant liver injury.⁸⁰ The association between heterozygosity of alpha 1-antitrypsin deficiency alleles and risk of developing CLD is controversial.⁸¹

According to Kemmer et al. study, A1ATD was the indication for liver transplantation in 1.1% of adults and 3.5% in children. The transplantation rate remained stable in adults, but the pediatric age groups had a downward trend, although the reason for the decline in the latter group remained unclear.^{82, 83}

In summary, three genetic diseases that commonly affect the liver are hereditary hemochromatosis (HH), Wilson disease (WD), and alpha-1 antitrypsin deficiency (A1ATD). National statistics for their morbidity, mortality or economic burden are sparse, since these diseases tend to be rare. Based on data in liver transplantation, HH, WD and A1ATD each may account for approximately 1% of liver transplantation.

Autoimmune and Cholestatic Liver Diseases

The natural history of autoimmune and cholestatic liver diseases is a chronically progressive course. Since these diseases are relatively rare and dependent on special laboratory or histological diagnosis, it is difficult to obtain population-based epidemiological data.⁸ This is particularly true with *autoimmune hepatitis (AIH)* for which high quality population-based epidemiological data are unavailable. The incidence and prevalence of AIH was estimated to be 0.1–0.4 per 100,000 children per year and 2.3–3.0 per 100,000 children, respectively.⁸⁴ Adult estimates vary, with the incidence and prevalence ranging from 1.7 to 1.9 per 100,000 per year and from 16.9 to 42.9 per 100,000, respectively.^{85–87}

Primary Biliary Cirrhosis (PBC) is the most common form of autoimmune liver disease, although there is significant geographic variability. In a Canadian population-based study by Myers et al. the incidence and prevalence of PBC was 3.6 and 22.7 per 100,000, respectively.⁸⁸ A US study in Olmsted County reported incidence of 2.7 per 100,000 and prevalence of 40.2 per 100,000.⁸⁹ In contrast, the prevalence is much lower in other parts of the world, with 2.7 per 100,000 in Japan⁹⁰ and 1.9 per 100,000 in Australia.⁹¹ Over past two decades, the number of PBC patients undergoing liver transplantation decreases.⁹² This may be partially explained by early diagnosis and treatment with ursodeoxycholic acid.⁹³

Primary sclerosing cholangitis (PSC) is less common than PBC. A meta-analysis by Molodecky et al. estimated the overall incidence of PSC to be approximately 1 per 100,000⁹⁴ and the prevalence according to the study by Toy et al was 4.15 per 100,000.⁹⁵ Recently, the incidence of PSC appears to be increasing, which may be a result of an increase in inflammatory bowel disease incidence worldwide. However, effective medical therapy to stop the disease progression remains to be discovered.⁹⁶

In summary, autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) are relatively rare, which altogether account for a quarter of the indications for liver transplantation. To date, the comprehensive data related to the economic burden of autoimmune and cholestatic liver diseases are lacking. Furthermore, indirect costs from the pronounced symptoms of these diseases such as fatigue, pruritus may be substantial, but remains difficult to quantify.

Conclusion

The overall burden, including mortality, associated with CLD has increased in the US. Based on available epidemiological data, viral hepatitis, ALD, and NAFLD are the most common etiology for CLD. Over the foreseeable future, the burden of viral hepatitis is expected to decrease and that for NAFLD to increase, where no significant change in ALD is anticipated. While population level epidemiological trends have a large impact on these predictions, ground-breaking therapeutic innovations may also hasten or reverse these trends. Available data, or lack thereof, suggest that population-based data addressing CLD with a possible exception of viral hepatitis, are limited in the US and judicious societal investment in data infrastructure to detect and monitor the impact of CLD longitudinally is called for to guide public health policy and health care resources allocation decisions.

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Figure 1.

Annual trends in mortality from liver disease by Hispanic ethnicity and gender in the US (deaths per 100,000 per year, adults >25 years of age)

Abbreviations: Non-Hispanic (NH), Hispanic (H), Male (M), Female (F)

Figure 2.

Annual trends in mortality from liver disease by age group (deaths per 100,000 per year, adults >25 years of age)

Figure 3.

Annual trends in mortality from liver disease by race and gender in the US (deaths per 100,000 per year, adults >25 years of age)

Abbreviations: Native American and Alaskan Native (NA), Caucasian (CA), African (AA), Asian-Pacific Islander (AP), Male (M), Female (F)

Figure 4. Annual trends in the number of waitlist registrants for liver transplantation (number on December 31 of each year)

■ Hepatocellular carcinoma indication Non- ■ HCC indication

Fig 5A

Figure 5.
Indication for liver transplantation
5(A): Indication at the time of waitlist registration
5(B): Indication at the time of transplantation

Table

Summary table outlining the estimates of disease prevalence and diseases specific mortality rate

Chronic liver diseases	Prevalence (per 100,000 individuals)	Mortality rate (deaths per 100,000 per year)
Chronic Hepatitis C	2,000–3,000 ¹¹	4.6 ¹³
Alcoholic Liver Disease	2,000–3,000 ^{*26}	7.2 ²⁵
Nonalcoholic Fatty Liver Diseases	6,000–35,000 ³⁷	1.3–2.6 ^{42, 43, 46–49}
Chronic Hepatitis B	2,000–8,000 ⁶⁰	0.6 ¹³
Hereditary Hemochromatosis	3.9–6000 ^{*,68, 69}	1% of all liver transplantation ^{#, 70}
Wilson Disease	3 ⁷²	1.5% of all liver transplantation ^{#, 74}
Alpha-1 antitrypsin deficiency	20–33.3 ^{76–78}	1% of all liver transplantation ^{#, 82,83}
Primary Biliary Cirrhosis	22.7–40.2 ^{88, 89}	12% of all liver transplantation ^{#, 92}
Primary Sclerosing Cholangitis	4.15 ⁹⁵	8% of all liver transplantation ^{#, 92}
Autoimmune Hepatitis	16.9–42.9 ^{85–87}	4% of all liver transplantation ^{#, 92}

* These numbers were estimated from the reference no.23.

** The prevalence of hereditary hemochromatosis varied by ethnicity (lowest in Asians, highest in Northern European)

The population-based data for the mortality rates of these diseases are not available. Hence, we used the proportions of patients who were undergone liver transplantation for each disease as a surrogate marker of the mortality rate.