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Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis

Andrew M. Moon, MD MPH[1], **Amit G. Singal, MD MS**[2], **Elliot B. Tapper, MD**[3,4]

[1]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC

[2]Division of Digestive and Liver Diseases, UT Southwestern Medical Center, Dallas, TX

[3]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI

[4]Gastroenterology Section, VA Ann Arbor Healthcare System, Ann Arbor, MI

Abstract

Background: Accurate estimates for the contemporary burden of chronic liver disease (CLD) are vital for setting clinical, research, and policy priorities. We aimed to review the incidence, prevalence, and mortality of CLD and its resulting complications, including cirrhosis and hepatocellular carcinoma (HCC).

Findings: The epidemiology of CLD is shifting, reflecting implementation of large-scale hepatitis B vaccination and hepatitis C treatment programs, the rising prevalence of the metabolic syndrome, and increasing alcohol misuse. In this setting, data from the Centers for Disease Control and the Global Burden of Disease Study demonstrate the incidence and clinical impact of CLD and its complications continue to rise worldwide. We conclude by discussing limitations of available data and outline steps on improving data infrastructure.

Conclusion: The global burden of CLD and cirrhosis is substantial. Although vaccination, screening, and anti-viral treatment campaigns for hepatitis B and C have reduced CLD burden in some parts of the world, concomitant increases in injection drug use, alcohol misuse and metabolic syndrome threaten these trends. Ongoing efforts to address CLD-related morbidity and mortality require accurate contemporary estimates of epidemiology and outcomes.

Corresponding Author: Elliot Tapper MD, 3912 Taubman, SPC 5362, 1500 E Medical Center Dr, Ann Arbor, MI 48109, T: (734) 647-9252, F:(734) 936-7392, etapper@umich.edu.

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Singal: Study design, critical revision of manuscript

Tapper: Study design, drafting of manuscript, critical revision of manuscript

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Keywords

Alcoholic liver disease; Hepatitis B; Liver cancer; Hepatitis C; Nonalcoholic fatty liver disease

Introduction

Chronic liver disease (CLD) and cirrhosis account for 44,000 deaths in the United States and 2 million deaths worldwide each year, in addition to a high burden of disability and increased healthcare utilization.[1, 2] However, mortality estimates for CLD are likely conservative and underestimate its true burden.[3] The most common etiologies of CLD and cirrhosis are chronic hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-related liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). Multiple recent developments are reshaping the epidemiology of CLD and cirrhosis including neonatal HBV vaccination campaigns, improved HCV treatment access and effectiveness, the opioid crisis, the obesity epidemic, and increasing rates of alcohol misuse.

Accurate estimates of the contemporary burden of cirrhosis is vital for setting clinical, research, and policy priorities. In light of the ever-changing nature of CLD epidemiology, we aimed to review the global incidence, prevalence, and mortality of CLD and its resulting complications including cirrhosis and hepatocellular carcinoma (HCC).

Incidence, Prevalence and Mortality of CLD

Global Burden of CLD

Globally, 1.5 billion persons had CLD in 2017, most commonly due to NAFLD (60%), HBV (29%), HCV (9%), and ALD (2%).[4] In European countries, the median cirrhosis prevalence was 833/100,000 (range 447-1100) but data on cirrhosis prevalence in other areas, particularly resource-limited settings, are sparse.[5, 6] Similarly, accurate accounting of cirrhosis and CLD incidence is difficult in most areas due to a paucity of high-quality, prospective data.[6] Based on data from the Global Burden of Disease study, the age-standardized incidence rate of cirrhosis and CLD was 20.7/100,000 in 2015, a 13% increase from 2000 (Tables 1-2).[7] The estimated incidence of cirrhosis in Europe is 26.0/100,000, and the incidence in Asia ranges from 16.5/100,000 in East Asia to 23.6/100,000 in Southeast Asia.[7]

There have been small increases in cirrhosis incidence in Europe, high-income Asia-Pacific, East Asia, Southeast Asia, and South Asia from 2000-2015.[7] Although HBV vaccination and viral hepatitis treatment programs have curbed the incidence of cirrhosis in many countries, including Japan and Taiwan, the rising burden of obesity, metabolic syndrome, and alcohol misuse threatens these trends.[7-9]

The major complications of CLD – cirrhosis (1.2 million deaths) and liver cancer (790,000 deaths) – account for 3.5% of all deaths worldwide.[10] In Figure 1 we detail the global age-adjusted mortality per 100,000 persons across regions. Cirrhosis-related mortality decreased from 20.0/100,000 person-years in 1980 to 15.8/100,000 person-years in 2010.[1] Although decrease mortality rates were pronounced in East Asia, North Africa/Middle East, and high-

income Asia Pacific, increases in mortality were observed in many other parts of the world including South Asia, Central Asia, and Eastern Europe. These disparate trends are likely related to differences in the distribution of underlying CLD etiologies and strategies to curb CLD burden. Deaths from cirrhosis increased two-fold in sub-Saharan Africa between 1980 and 2010, primarily due to viral hepatitis and ALD.[1] Although viral hepatitis remains the driving force behind cirrhosis-related mortality in Asia, deaths are declining due to increased HBV vaccination and treatment of viral hepatitis.[1, 11, 12] ALD is currently responsible for most cirrhosis-related deaths in Europe but trends vary between countries with mortality decreasing in some (Austria, Denmark, France, Germany, Hungry) and increasing in others (Finland, Ireland, UK).[9] Beyond mortality, disability is another metric of morbidity. We therefore detail in Figure 2 the years lost to disability attributed to cirrhosis.

Burden of CLD in North America

Estimates detailing the epidemiology of CLD in North America are also limited by the paucity of longitudinal, population-based data. Baby boomers (born 1945-1965) comprise half of cirrhosis cases in North America with a relatively higher prevalence among blacks, Hispanics, and those with lower levels of education.[13-15] The estimated prevalence of cirrhosis ranges from 300-1,000/100,000 conditional on the variable risk of CLD across populations (Table 2).[13-15] For example, the estimated incidence of cirrhosis is 167/100,000 person-years within the US Veterans Affairs (VA) system compared to 90/100,000 person-years in a population from Ontario, Canada.[13, 14] These discrepant estimates may be explained by ascertainment bias or differences in the patient populations including the VA's predominantly male population with a higher burden of viral hepatitis, alcohol misuse, and metabolic syndrome.[16, 17]

The prevalence of cirrhosis has increased 1.5-2 fold over the past two decades.[13-15] While most prevalent cirrhosis cases are in the baby boomer cohort, incident cirrhosis diagnoses are highest and rising disproportionately in younger Americans.[13, 14] As reflected in a Canadian population-based cohort where risk-factors such as metabolic syndrome and alcohol misuse are rising among young people, age-specific cirrhosis incidence increased 22% from 1997-2016.[13]

After several decades of stability from the 1970-2008, CLD-related mortality has since steadily risen with disproportionate relative increases among young people, women, non-Hispanics, whites, and Native Americans.[2, 3] Following a National Center for Health Statistics (NCHS) study that demonstrated a 65% increase in cirrhosis mortality from 2009-2016, we present updated statistics through 2017 (Table 3).[2] Age-adjusted mortality rates from CLD and cirrhosis continued to rise, with estimates of 14.2 (95% CI 14.0-14.3) and 9.2 (95% CI 9.1-9.3) per 100,000, respectively in 2017 (Figure 3).

Specific Chronic Liver Diseases

The relative contribution of viral hepatitis, NAFLD, and ALD to the global burden of CLD is rapidly shifting.[4, 7, 8, 18, 19] Globally, HBV incidence and its complications have been reduced by widespread vaccination and anti-viral treatment programs. In contrast, although many patients with chronic HCV infection are being successfully treated with direct acting

antiviral (DAA) therapy, reducing future risk of developing cirrhosis or HCC[20], the opioid epidemic and intravenous drug use patterns have resulted in an increased number of acute HCV infections.[21] In parallel, NAFLD is becoming an increasingly important cause of CLD worldwide concurrent with a rising burden of obesity and metabolic syndrome. Similarly, alcohol consumption is responsible for an estimated 27% of liver-related deaths worldwide, highest in Europe, and has been increasing in many countries globally.[22]

HCV Infection

Approximately 71 million people worldwide (1.0%) have chronic HCV with a prevalence of 1.0% in the US, 1.5-1.8% in Europe, 1.0% in Africa, and 0.5-0.7% in Asia.[23-26] Most HCV infections are caused by genotypes 1 and 3, which are estimated to account for 44% and 25% of infections, respectively.[26] There are an estimated 1.8 million new HCV infections per year (incidence rate 23.7/100,000) with the highest rates in the Eastern Mediterranean (62.5 per 100,000) and Europe (61.8/100,000).[24] In the US, an estimated 41,200 new HCV infections occurred in 2016 (incidence rate 13.9/100,000).[27] In contrast to other infectious diseases, including human immunodeficiency virus, malaria and tuberculosis, deaths from viral hepatitis have been increasing over the last 15 years.[28] HCV has been a leading cause of cirrhosis and hepatocellular carcinoma (HCC), accounting for an estimated 400,000 liver-related deaths worldwide in 2015.[24]

Highly-effective DAAs were introduced in 2014 and have increased treatment eligibility and success dramatically. The US VA system, Egypt, Republic of Georgia, and Iceland are prime examples of success for large-scale screening, anti-viral treatment and micro-elimination efforts. [17, 29-33] However, in other areas, the potential benefit of DAAs has been blunted by incomplete HCV screening and linkage to care, particularly in rural and socioeconomically disadvantaged areas.[34] Despite recommendations for HCV screening in at-risk individuals in many countries, an estimated 80% of chronic HCV infections remain undiagnosed worldwide, ranging from 94% in Africa to 68% in the Americas.[35] Even among those who undergo HCV screening, there are suboptimal rates of confirmatory HCV RNA testing and linkage to care.[36] Finally, HCV treatment is often not covered by insurance or withheld for high-risk groups such as those who inject drugs, potentially as a result of abstinence requirements from some payers, despite professional society guidance statements recommending otherwise.[37-39]

Worldwide the number of newly infected individuals (1.75 million) exceeds the sum of patients dying from HCV (399,000) and those being successfully treated and cured (843,000).[24, 35] Injection drug use accounts for increasing numbers of HCV infections in the US, particularly among those who reside in rural areas, aged 20-29 years, and are non-Hispanic white. [27, 40-42] HCV seroprevalence is now higher among young adults than baby boomers in several areas of the US.[43] Unfortunately, the rapidly changing policy landscape and shifting trends describe above render data inadequate even after one year, limiting our understanding of true contemporary HCV prevalence.[44]

Chronic HBV Infection

Worldwide, 257 million (3.5%) people had chronic HBV infection in 2015.[5, 24, 45] Western Pacific nations (6.2%) and Africa (6.1%) had the highest prevalence of HBV and accounted for more than two-thirds of all cases.[24] A recent survey from NHANES estimated the US prevalence of chronic HBV as 840,000 (0.35%) overall in 2011-2016, varying from 3.85% among Asian immigrants and 0.79% among American-born Asians.[46]

Encouraging trends in HBV incidence have resulted from large-scale neonatal vaccination efforts in many countries.[5, 47] Vaccination is particularly important for the estimated 65 million women of childbearing age with chronic HBV.[24] Worldwide, HBV prevalence among children <5 years (a surrogate of HBV incidence) has decreased from 4.7% in the pre-HBV vaccination era (1980s-2000s) to 1.3% in 2015. Improvements in vaccination coverage and subsequent decreases in childhood HBV infection have been specifically seen in South East Asia, Western Pacific, and the Eastern Mediterranean region. [7, 24, 48] However, HBV vaccination coverage remains low in some regions, particularly in Africa, and coverage with the initial birth vaccination dose continues to lag (<40%).[24] Beyond vaccination programs, efforts to curb HBV mortality are limited by inadequate diagnosis and treatment of chronically infected patients, partly due to the lack of uniform HBV treatment guidelines, poor awareness of active infection (15.2% in one US study), and limited access to risk-assessment tools such as non-invasive tests for fibrosis.[35, 46, 49] Overall, among the estimated 250 million individuals with chronic HBV, 10% are aware of their diagnosis and 2% are currently on treatment.[50]

NAFLD

NAFLD encompasses a spectrum including hepatic steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis. While accurate estimates of NAFLD are difficult to obtain, it is likely a major driver of the increasing cirrhosis incidence, concordant with trends in obesity and metabolic syndrome.[16, 51, 52] The pitfalls of NAFLD epidemiology are partly specific to fibrosis assessment. Hepatic steatosis in the absence of other causes (e.g. significant alcohol use) can be estimated among cohorts receiving abdominal imaging or liver enzyme testing; NASH, a histological diagnosis, can only be estimated from cohorts including histology data or self-reported diagnoses[53]; cirrhosis can be estimated from cohorts with adequate laboratory, histology or imaging data.

The global prevalence of NAFLD is estimated at approximately 24% with considerable variability from Africa (13.5%) to South America (30.5%), the Middle East (31.8%), and Asia (33.9%).[54, 55] Approximately one in three US residents has hepatic steatosis and it is more commonly seen in Hispanics followed by whites and blacks.[56, 57] Based on the prevalence of biopsy-proven NASH in patients with NAFLD (6.7-29.9%), it is estimated that approximately 1.5-6.5% of the general US population have NASH.[54] A study from 5 European countries estimated the prevalence of NASH as 0.29% using self-reported diagnoses.[53] An estimated 178 of 100,000 Americans have NASH cirrhosis based on data from NHANES and its prevalence has increased 2.5-fold from 1999-2002 to 2009-2012.[51]

Population-based, longitudinal data to track NAFLD incidence are lacking in many places. In studies with varying case definitions and populations, the reported incidence of hepatic steatosis per 100,000 person-years has ranged from 1,850 in Italy, 2,714 in Israel, 3,400 in Hong Kong, 5,090 in Asia, and 9,100 in China.[55, 58-62] A population-based study in Minnesota reported that the age- and sex-adjusted NAFLD incidence, defined by diagnostic codes, was 317/100,000 person-years. This is considerably lower than the estimated NAFLD incidence of 2,500/100,000 person-years reported in the US VA system, in which cases were defined by elevated liver enzymes without viral hepatitis or significant alcohol use.[16, 52]

The increasing burden of obesity in children is particularly concerning given its association with future development of NAFLD, cirrhosis, and HCC.[63-65] It is estimated that the pooled mean prevalence of NAFLD in children is 7.6% overall and 34.2% in obese children, with a higher in prevalence in males compared to females.[66] Computer simulations based on the current estimates of NAFLD, obesity and diabetes, project that, from 2015-2030, the respective NAFLD and NASH prevalence will rise by 21% and 63%.[67] In addition, the prevalence of NAFLD-related decompensated cirrhosis, HCC, and deaths will increase by 168%, 137%, and 178%, respectively.

ALD

ALD encompasses alcoholic hepatitis, steatosis, steatohepatitis and fibrosis/cirrhosis. A lack of accurate reporting and referral bias limit the ability to estimate ALD incidence and prevalence globally but alcohol misuse is responsible for an estimated 27% percent of deaths from liver disease and 30% of liver cancer deaths worldwide.[68-70] In the US, the prevalence of ALD is estimated to be 4.7% and alcohol is estimated to account for approximately 20% (NHANES) to 36% (private-insurance claims data) of cirrhosis cases.[15, 71-73] Hispanics have a higher prevalence of ALD cirrhosis (16.9/100,000) compared to whites (11.1/100,000) or blacks (9.9/100,000).[74]

The relationship between alcohol use and liver disease is well established, with prospective cohorts demonstrating that cirrhosis incidence is strongly related to amount of alcohol consumed.[75, 76] The estimated burden of ALD can therefore be indirectly estimated by alcohol consumption patterns. An estimated 2.3 billion people drink alcohol worldwide and alcohol is consumed by more than half the population in the Americas, Europe and the Western Pacific.[72] The highest per-capita alcohol consumption levels are observed in Eastern Europe (8.1L/woman, 24.9L/man) and lowest in North Africa/Middle East (0.2L/woman, 1.7L/man).[68] Existing data suggest ALD prevalence is increasing. In China, the proportion of all hospitalizations for liver disease attributable to alcohol more than doubled from 2002-2013.[77] Population-based data from Denmark demonstrated that the incidence of hospitalizations for alcoholic hepatitis increased from 1999-2008.[78] Similarly, the prevalence of alcohol-related cirrhosis in the North America is increasing, particularly among young persons.[14, 71, 79, 80] The global burden of ALD may continue to escalate given increases in alcohol consumption worldwide (per capita consumption from 5.5L in 2005 to 6.4L in 2016).[81, 82]

Other CLD Etiologies

Primary biliary cholangitis (PBC) occurs primarily in women and has a reported annual prevalence and incidence of 1.9-40.2 and 0.3-5.8 per 100,000, respectively.[83-85] In a systematic review of PBC, all longitudinal studies identified reported increases in the PBC prevalence over time.[85] Similarly, data from a multicenter PBC consortium within the US demonstrates a stable incidence (4.2-4.3/100,000 person-years) and rising prevalence (21.7-39.2/100,000 population) from 2006-2014.[86] PBC is diagnosed at earlier stages over time suggesting additional data are needed to understand longitudinal differences in its prevalence in the context of widespread antimitochondrial antibody test utilization.[87]

Similar to PBC, most studies on the epidemiology of primary sclerosing cholangitis (PSC) come from North America and Europe. The reported prevalence of PSC ranges from 0-16.2/100,000 person-years and its incidence ranges from 0-1.3/100,000.[85] Prevalence estimates vary from zero cases among Alaskan Natives[84] to higher estimates from the UK (12.7/100,000), general US population (13.6/100,000), and Sweden (16.2/100,000).[88-90] The incidence of PSC is slowly increasing in populations in both North America and Europe.[85]

Epidemiologic data on autoimmune hepatitis (AIH) are scant and there are no population-based data from the US. It occurs primarily in women and its prevalence has been reported to be 4/100,000 in Singapore and 16-24 per 100,000 in Europe.[91-95] The annual incidence of AIH has been reported to be 0.7/100,000 in Israel and 2.0/100,000 in New Zealand.[94, 95] In Denmark, the incidence of AIH has nearly doubled from 1994-2012.[91]

While hereditary hemochromatosis mutations are relatively common, particularly in Northern Europeans, C282Y homozygosity is weakly penetrant, rarely developing clinical manifestations (<1%), making it a rare cause of CLD.[96-99] Wilson Disease also occurs infrequently (worldwide prevalence 3/100,000), although a recent study from the UK reported a higher prevalence of individuals carrying two mutant pathogenic ATP7B alleles (14/100,000).[100] This apparent discrepancy may be due to incomplete penetrance of ATP7B mutations or under-diagnosis. The prevalence of Wilson Disease among persons with undergoing evaluation for elevated liver enzymes at a referral center is estimated to be 160/100,000.[101]

Liver Cancer

Hepatocellular Carcinoma (HCC)

Patients with cirrhosis from any etiology are at high risk for HCC, with annual incidence ranging from 1-4%.[102] In 2015, there were an estimated 854,000 incident liver cancer cases (75% increase from 1990) and 810,000 cancer-related deaths worldwide.[103] The most significant increases in liver cancer-related mortality were in North America, Europe, and Australia. Many countries, including China, have experienced a decrease in liver cancer burden due to improved HBV vaccination and decreased aflatoxin exposure.[104]

HCC incidence in the US has been rising in recent years but the rate of rise has slowed.[105] Based on data from the US Cancer Statistics registry, the age-adjusted incidence of HCC increased from 4.4/100,000 in 2000 to 6.7/100,000 in 2012.[106] However the annual increase

of 4.5% between 2000-2009 slowed to 0.7% per year from 2010-2012, suggesting a possible impending plateau of new HCC cases. HCC incidence stratified by age categories demonstrated that increases in HCC incidence were most pronounced in those in the peak-HCV cohort (born 1945-1965) and is decreasing among younger individuals and Asian-Americans.[106, 107] However, observed improvements in HCC incidence related to implementation of HBV vaccination and therapy or HCV treatment programs may be mitigated or even overshadowed in the future by increasing childhood obesity and early-onset NASH, and increasing ALD among younger individuals. Finally, HCV therapy is likely to improve survival with cirrhosis, however these patients remain at persistent risk of HCC.[108]

There are also several notable trends in HCC incidence by race/ethnicity. Age-adjusted incidence rates are higher among Hispanics (6.3/100,000) and blacks (5.0/100,000) compared to non-Hispanic whites (2.4/100,000).[109] HCC incidence is also increasing disproportionately in Hispanics (4.7%/year since 2000) compared to other racial/ethnic groups.[109, 110] Furthermore, blacks and Hispanics diagnosed with HCC are less likely to have it detected at an early stage.[111]

There were approximately 150,000 HCC-related deaths (age-adjusted 2.3/100,000) in the US from 1999-2017 (Table 4). Mortality rates in 2017 were highest among males, Asian/Pacific Islanders, and those age 75-84 years. HCC mortality has increased overall (Figure 1) and in nearly every group with the exception of Asian/Pacific Islanders.[2] Racial disparities in HCC mortality persist and studies suggest that this may in part be related to treatment process failures, with lower rates of early detection and lower odds of curative treatment, including liver transplantation, among racial/ethnic minorities compared to non-Hispanic whites.[111]

Complications of CLD and Cirrhosis

Hepatic Decompensation

As CLD progresses, patients develop complications of hepatocellular dysfunction and portal hypertension that contribute to liver-related morbidity and mortality.[112] Approximately 4-12% patients with cirrhosis develop at least one decompensating event annually and the most common decompensating events are ascites, variceal hemorrhage, and hepatic encephalopathy (HE). [71, 113, 116] As many as 40% of patients with cirrhosis will develop HE within 5 years of observation.[117] The presence of these complications are important prognostic indicators with significantly increased mortality in decompensated compared to compensated cirrhosis.[118] Decompensation events also require significant healthcare utilization – hepatic encephalopathy and ascites/spontaneous bacterial peritonitis (SBP) each accounted for 59,000 emergency department visits in 2014.[119]

Infection

Patients with cirrhosis have a significantly increased risk of sepsis and infection-related mortality, likely as a result of immune dysfunction, changes in gut microbiota and bacterial translocation.[120] Among hospitalized patients, the prevalence of bacterial infections ranges

from 25-50%, with wide regional variability in the type and microbiology of infections.[121] There is a high prevalence of multidrug resistant bacteria in infected cirrhosis patients (34%) with the highest prevalence in India (73%).[121]

Acute Kidney Injury (AKI)

AKI is common in patients with cirrhosis, particularly those with ascites.[112, 122] The physiology of portal hypertension increases the risk of AKI due to splanchnic vasodilation and decreased intravascular blood volume with resulting renal vasoconstriction. Hepatorenal syndrome (HRS), the abrupt and severe form of AKI that occurs in the absence of nephrotoxic medications and shock and despite a trial of volume explanation, portends the worst prognosis.[122] Among patients with ascites followed prospectively, AKI will ultimately develop in half, with a 1-year probability of 24%.[123] AKI has been reported in approximately 20% of all hospitalized patients with cirrhosis and is more common in those with ascites, SBP and gastrointestinal bleeding.[124, 125] The burden of HRS has changed somewhat as definitions have evolved; its annual incidence ranges from 8-18% and 13-27% of patients with AKI qualify as HRS.[123, 126, 127]

Frailty

Physical frailty is common in cirrhosis due to muscle wasting and poor nutrition. Frailty in those with liver disease is a strong predictor of mortality independent of traditional prognostic tools like the Child Pugh score and Model for End-Stage Liver Disease.[128] Frailty can be assessed in a number of ways including grip strength, chair stands per second, gait speed, balance time and activities of daily living.[129, 130] Cirrhosis-related frailty, especially in combination with cognitive dysfunction or psychoactive medications, increases the risk of falls and decreased health-related quality of life.[131-134] Estimates of its burden are highly variable due to heterogeneity in case definitions, but the reported prevalence of frailty among patients on the liver transplant waitlist ranges from 17-43%, and is more common among older patients and those with NAFLD.[130, 135]

Acute on Chronic Liver Failure (ACLF)

ACLF, defined as deterioration of liver function and extrahepatic organ failure, is an increasingly recognized entity associated with considerable morbidity and mortality.[136, 137] Definitions for ACLF are heterogeneous, with some based on physiologic markers of end-organ dysfunction and others based purely on clinical assessments of organ failure (coma, hemodialysis, mechanical ventilation).[138] Algorithms for use in administrative data have been used but have never been validated. The prevalence of ACLF is reported to range from 24-40% among hospitalized patients with cirrhosis.[136, 139, 140] In a large cohort of US veterans with ACLF, deaths occurred in 26% and 40% of patients at one and three months, respectively.[140] In a multicenter European cohort defining and grading ACLF based on the sequential organ failure assessment (SOFA), 28-day mortality was approximately 30% and ranged from 22-77% depending on the number of organs affected.[136, 141]

Health Care Utilization, Direct Costs and Disability for CLD and Cirrhosis in the US

Health Care Utilization

In the US in 2014, CLD accounted for over 1,000,000 outpatient and 325,000 emergency department (ED) visits (40% increase in ED visits since 2006).[119] Cirrhosis-related hospitalizations have increased every year between 2001-2011, with these increases outpacing both congestive heart failure and chronic obstructive pulmonary disease.[142, 143] Inpatient care, which comprises approximately 40% of all costs, accounts for the majority of expenditures in CLD.[144] Annual inpatient costs for cirrhosis patients increased from $4.8 billion ($13,079/hospitalization) to $9.8 billion ($15,193/hospitalization) from 2001-2011.[142] Readmissions are common (25.8% at 30-days),[145]conditional on the severity of liver disease,[146] and are particularly related to HE and alcohol-use disorder. There are several ongoing efforts to reduce readmissions in the future, although few have proven successful to date.[147] In addition to inpatient costs, overall annual health care costs from CLD were $29.9 billion overall, with 3.5-fold higher per-patient costs among patients with ACLF.[142, 144]

Disability and Health-related Quality of Life (HRQOL)

CLD is also associated with disability and significant decreases in HRQOL.[53, 148] Compared to age-matched controls, CLD patients have higher levels of unemployment (65.3% vs 31.4%), inability to work due to disability (30.5% vs 6.6%), and reported days of disability per year (10.2 vs 3.4).[144] Among individuals ≥65 years with cirrhosis, approximately one in four report their health as “poor” and 40% have at least one impaired activity of daily living (ADL).[133] Decrements in HRQOL can be seen in CLD even without cirrhosis; however, HRQOL is lowest in those with cirrhosis complications including hepatic decompensation.[149]

Directions for Future Research

Complicating our knowledge of the present burden of disease is the lack of prospective, national registries and our reliance on variable definitions of CLD in administrative data. Existing data sources for identifying burden and trends in CLD each have unique strengths and limitations and there is ample opportunity for improvement (Table 4). Prospective population-based patient registries, such as the Danish National Patient Registry (DNPR), serve as benchmarks for epidemiologic data sources.[150] While resource-intensive, these can yield invaluable findings on the incidence, prevalence, natural history, and real-world treatment of CLD.[91, 151, 152]

In the US, while comprehensive national registries are lacking, there have been efforts to prospectively track specific liver diseases and complications of cirrhosis. For instance, a multisite Cirrhosis Quality Collaborative (CQC), funded by the American Association for the Study of Liver Diseases (AASLD), has set out to track patient-reported outcomes (PROs) in cirrhosis and define standard processes of care and quality metrics.[153] There are several

specific areas in need of higher quality data such as ALD; its burden is likely underestimated due to late referral of patients with liver disease and underreporting of alcohol use.[79]

Finally, the paucity of reliable data on CLD in many developing nations cripples efforts to improve care.[6] This could be addressed by building infrastructure to define, track and manage cirrhosis through global partnerships. The WHO, for instance, has announced plans to establish centers of excellence to improve data collection on CLD and HCC throughout the world.[154] In addition, global surveillance of CLD could be improved by emulating existing models in cancer, where international registries have been immensely important for research on epidemiology, interventions and outcomes.[155]

Conclusion

Recent data demonstrate that the burden of CLD, cirrhosis, and its complications remains substantial. Improvements in the prevalence and outcomes of viral hepatitis contrast with adverse trends in the prevalence and complications of alcohol-related and nonalcoholic fatty liver diseases. Investment and innovation are vital to maintain adequate surveillance of CLD and develop strategies to reduce its burden. Liver disease, liver cancer, viral hepatitis, organ transplantation, obesity, and alcohol use are all projected to have decreases in NIH funding, which may hamper these efforts.[119] Continued attempts to track the burden of liver disease will help identify priorities for clinical care improvements, research investment, and health policy initiatives.

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Abbreviations:

ACLF	acute on chronic liver failure
ADL	activities of daily living
ALD	alcohol-related liver disease
APRI	aspartate aminotransferase to platelet ratio index
CCA	cholangiocarcinoma
CDC	Centers for Disease Control and Prevention
CLD	chronic liver disease
CQC	Cirrhosis Quality Collaborative
DAAs	direct acting antivirals
DNPR	Danish National Patient Registry

ED	emergency department
FIB-4	fibrosis-4
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCUP	Healthcare Cost and Utilization Project
HCV	hepatitis C virus
HRQOL	health-related quality of life
ICD	International Classification of Diseases
MELD	model for end-stage liver disease
MEPS	Medical Expenditure Panel Survey
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCHS	National Center for Health Statistics
NEDS	National Emergency Department Sample
NHANES	National Health and Nutrition Examination Survey
NRD	National Readmission Database
PEth	phosphatidylethanol
PROs	patient-reported outcomes
SBP	spontaneous bacterial peritonitis
SOFA	Sequential Organ Failure Assessment
UNOS	United Network for Organ Sharing
USPSTF	United States Preventive Services Task Force
VA	Veterans Affairs
WHO	World Health Organization
YLD	years lived with disability

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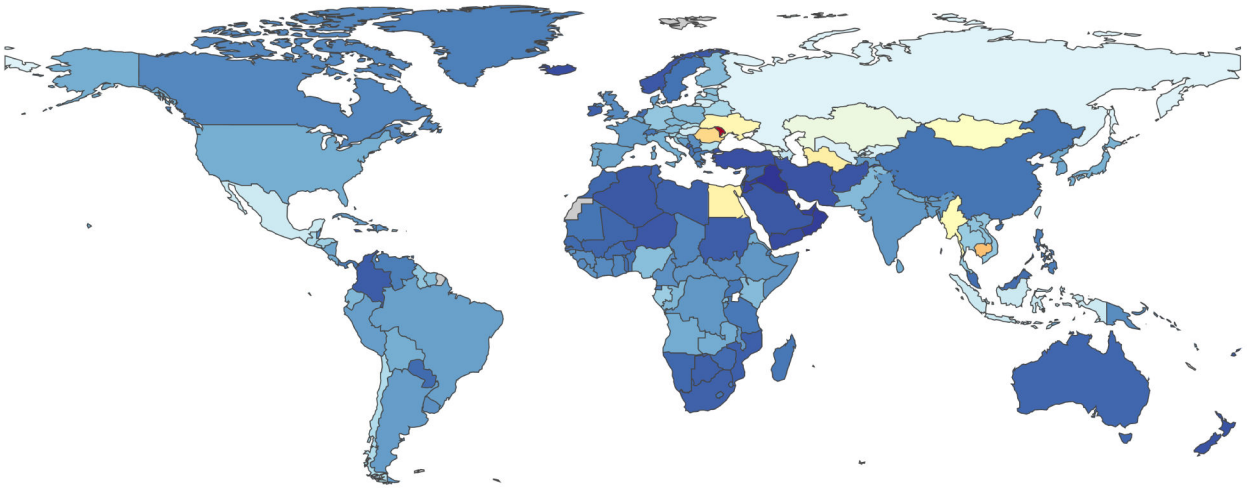

Figure 1: Global Burden of Cirrhosis Mortality

In this figure, abstracted from the Global Burden of Disease Study (https://vizhub.healthdata.org/gbd-compare/. accessed 4/2/19), we detail the age-adjusted risk of mortality (per 100,000 persons) attributed to cirrhosis. Legend (mortality per 100,000 persons): Dark to light blue (0-40). Yellow (40-50), Yellow-Orange (50-60), Orange-Red (60-70), Red (>70)

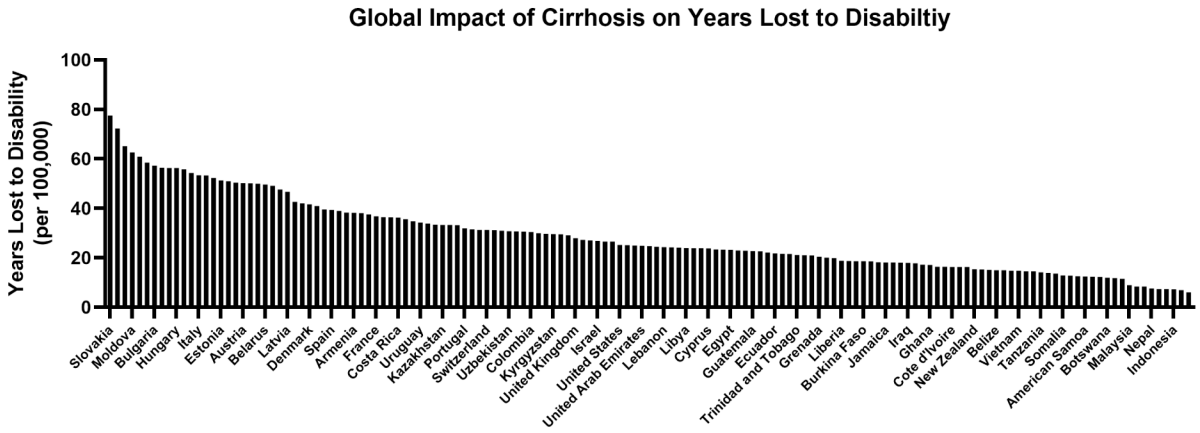

Figure 2: Global Burden of Years Lost to Disability Due to Cirrhosis

In this this figure, we detail the years lost to disability (YLD) due to cirrhosis. YLD is a function of the disease incidence, the disability weight (on functioning) and the average duration of illness. Data abstracted from the Global Burden of Disease Study (https://vizhub.healthdata.org/gbd-compare/, accessed 4/2/19).

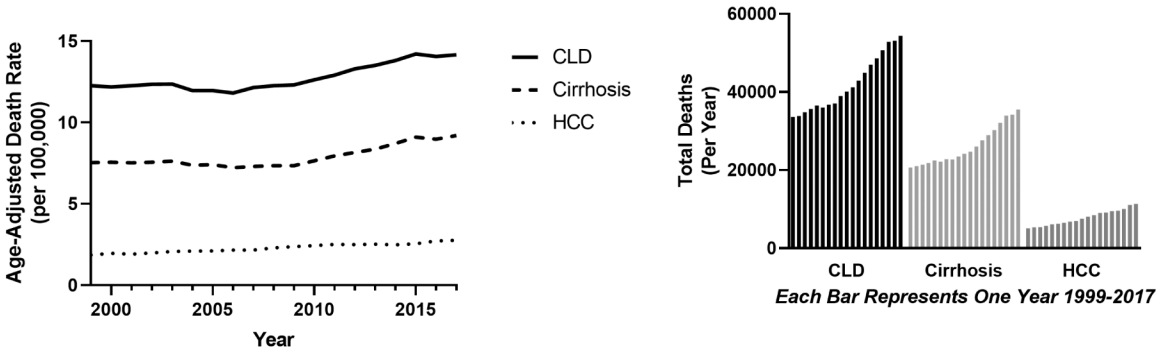

Figure 3: Mortality Due to Chronic Liver Disease (CLD), Cirrhosis and Hepatocellular Carcinoma (HCC) in the US (1999-2017)

In the left panel we show how the age-adjusted mortality for CLD, cirrhosis, and HCC has changed over time. While HCC-related mortality has slowly climbed from 1999, mortality due to CLD and cirrhosis began rising after 2008, continuously through 2017

In the right panel we show the raw numbers of deaths attributed primarily to CLD, cirrhosis, and HCC for each year from 1999-2017

Table 1.

Prevalence, Incidence, Mortality and Costs of CLD and Cirrhosis Globally

	Author (year)	Country/Region	Prevalence (per 100,000 pop.)*	Incidence (per 100,000 person-years)*	Mortality (per 100,000 person-years)*	Costs
Cirrhosis						
	Global Burden of Disease (2018)[4]	All	Cirrhosis and CLD: 1.5 billion (2017) *	Cirrhosis and CLD: 5.2 million (2017) *	-	Cirrhosis and CLD YLDs 1.8 million (2017)
	Mokdad (2014)[1]	All	-	-	15.7 (2010)	-
	Mokdad (2014)[1]	Asia	-	-	8.2-33.7 (2010)	-
	Mokdad (2014)[1]	Europe	-	-	10.2-20.0 (2010)	-
	Mokdad (2014)[1]	Latin America	-	-	15.8-27.5 (2010)	-
	Mokdad (2014)[1]	North Africa/MiddleEast	-	-	20.2 (2010)	-
	Mokdad (2014)[1]	Oceania	-	-	41.5 (2010)	-
	Mokdad (2014)[1]	Sub-Saharan Africa	-	-	12.9-24.2 (2010)	
	Ratib (2017)[156]	United Kingdom	-	35.9 (2009)	5.9 (2009)	
HCV						
	WHO (2017)[24]	All	1,000 (2015)	23.7 (2015)	402,000 (2015) *	-
	WHO (2017)[24]	Africa	1,000 (2015)	31.0 (2015)	-	-
	WHO (2017)[24]	Eastern Mediterranean	2,300 (2015)	62.5 (2015)	-	-
	WHO (2017)[24]	Europe	1,500 (2015)	61.8 (2015)	-	-
	WHO (2017)[24]	Americas	700 (2015)	6.4 (2015)	-	-
	WHO (2017)[24]	South-East Asia	500 (2015)	14.8 (2015)	-	-
	WHO (2017)[24]	Western Pacific	700 (2015)	6.0 (2015)	-	-
HBV						
	WHO (2017)[24]	All	3,500 (2015)	1,300 (age <5 years) (2015)	884,000 (2015) *	-
	WHO (2017)[24]	Africa	6,100 (2015)	3,000 (age <5 years)(2015)	-	-
	WHO (2017)[24]	Eastern Mediterranean	3,300 (2015)	1,600 (age <5 years) (2015)	-	-

	Author (year)	Country/Region	Prevalence (per 100,000 pop.)*	Incidence (per 100,000 person-years)*	Mortality (per 100,000 person-years)*	Costs
	WHO (2017)[24]	Europe	1,600 (2015)	400 (age <5 years) (2015)	-	-
	WHO (2017)[24]	Americas	700 (2015)	200 (age <5 years) (2015)	-	-
	WHO (2017)[24]	South-East Asia	2,000 (2015)	700 (age <5 years) (2015)	-	-
	WHO (2017)[24]	Western Pacific	6,200 (2015)	900 (age <5 years) (2015)	-	-
NAFLD						
	Global Burden of Disease (2018)[4]	All	NASH cirrhosis 11,061 (2017)	-	-	-
	Younossi (2015)[54]	All	25,000	-	-	-
	Younossi (2015)[54]	Africa	13,500	-	-	-
	Li (2019)[55]	Asia	33,900(2012-2017)	5,090 (1999-2019)		
	Wong (2015)[60]	Hong Kong	-	3,400 (2008-2013)	-	-
	Zhou (2011)[59]	China	-	9,100 (2009)	-	-
	Chang (2016)[62]	South Korea		2,970 (2002-2013)		
	Younossi (2015)[54]	Europe	23,710	-	-	-
	Younossi (2016)[157]	Germany, France, Italy, United Kingdom				€35 billion direct costs (€354-1163 per patient)
	Kanerva (2014)[158]	Finland	41,150	-	-	-
	Zelber-Sagi (2014)[61]	Israel	-	2,714 (2003-2010)	-	-
	Younossi (2015)[54]	Middle East	31,790	-	-	-
	Younossi (2015)[54]	South America	30,450	-	-	-
	Riquelme (2009)[159]	Chile	23,400	-	-	-
ALD						
	Global Burden of Disease (2018)[4]	All	26 million (2017) *	903,700 annually (2017) *		YLDs 400,100
	Rehm (2013)[68]	All	-	-	7.2 (2010)	-
HCC						
	Global Burden of Disease (2017/2018)[4,103]	All	803,400 (2017) *	953,100 annually (2017) *	12.1 (2015)	YLDs 229,500 (2017)

YLD: years lived with disability

* Where total population unavailable, the total number of cases are presented

Table 2.

Prevalence, Incidence, Mortality and Costs of CLD and Cirrhosis in North America

	Author (year)	Data Source	Prevalence (per 100,000 pop.)	Incidence (per 100,000 person-years)	Mortality (per 100,000 person-years)	Costs
Cirrhosis						
	Beste (2015)[14]	US VA system	1,058 (2013)	167 (2012)	126 (2013)	-
	Flemming (2018)[13]	Routinely collected health data from Ontario, Canada	840 (2016)	90 (2016)	-	-
	Scaglione (2015)[15]	NHANES	302 (2010)	-	2-year mean proportion of deaths 26.4% (1999-2006)	-
	Mellinger (2018)[71]	Truven Marketscan Commercial Claims and Encounters Database	270 (2015)	-	-	-
	Tapper (2018)[2]	CDC	-	-	12.2 (1999-2016)	-
HCV						
	CDC (2018)[27]	National notifiable diseases surveillance system	-	1.0 (2016)	4.5 (2016)	-
	Hofmeister (2019)[21]	NHANES	900 (2013-2016)			
	Beste (2015)[14]	US VA system	HCV cirrhosis:503 (2013)	HCV cirrhosis: 77.9 (2012)	-	-
HBV						
	CDC (2018)[27]	National notifiable diseases surveillance system	-	1.0 (2016)	0.5 (2016)	
	Roberts (2016)[160]	NHANES	300 (2012)	-	-	-
	Beste (2015)[14]	US VA system	HBV cirrhosis:503 (2013)	HBV cirrhosis: 3.3 (2012)		
NAFLD						
	Browning (2004)[57]	Dallas Heart Study	34,000			
	Kanwal (2016)[16]	US VA system	17,610 (2011)	2,500 (2011)	-	-
	Allen (2018)[52]	Olmsted County, Minnesota	-	329 (2014)	-	-
	Younossi (2016)[157]	Markov model	-	-	-	$103 billion direct costs ($1613 per patient)
	Beste (2015)[14]	US VA system	NASH cirrhosis: 161 (2013)	NASH cirrhosis: 30.3 (2012)	-	-

	Author (year)	Data Source	Prevalence (per 100,000 pop.)	Incidence (per 100,000 person-years)	Mortality (per 100,000 person-years)	Costs
	Kabbany (2017)[51]	NHANES	NASH cirrhosis: 178 (2009-2012)			
ALD						
	Mellinger (2018)[71]	Truven Marketscan Commercial Claims and Encounters Database	Alcoholic cirrhosis: 100 (2015)	-	-	$44,835 per-person (alcoholic cirrhosis) vs. $23,319 per-person (non-alcoholic cirrhosis)
	Beste (2015)[14]	US VA system	Alcoholic cirrhosis: 327 (2013)	Alcoholic cirrhosis: 47.8 (2012)	-	-
HCC						
	White (2017)[106]	US Cancer Statistics registry	-	6.7 (2012)	-	-
	Altekruse (2014)[105]	SEER/CDC	-	5.9 (2006-2010)	4.3 (2006-2010)	-
	Tapper (2018)[2]	CDC	-	-	3.6 (1999-2016)	-

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Table 3.

Mortality from CLD, cirrhosis and HCC in the US, overall and among various subgroups from 1999-2017

		Combined liver-related mortality rate/100,00 (95% CI)	CLD mortality rate/100,000 (95% CI)	Cirrhosis mortality rate/100,000 (95% CI)	HCC mortality rate/100,000 (95% CI)
Overall		15.20 (15.16-15.23)	12.86 (12.84-12.89)	7.96 (7.94-7.98)	2.34 (2.33-2.35)
Sex	Female	10.04 (10.00-10.07)	9.06 (9.03-9.09)	5.27 (5.25-5.30)	0.97 (0.96-0.98)
	Male	21.04 (20.99-21.09)	17.10 (17.05-17.15)	10.96 (10.93-11.00)	3.92 (3.90-3.95)
Age	25-34	1.81 (1.78-1.84)	1.71 (1.69-1.74)	0.73 (0.71-0.75)	0.10 (0.09-0.11)
	35-44	8.53 (8.47-8.60)	8.18 (8.11-8.24)	4.62 (4.57-4.67)	0.36 (0.35-0.37)
	45-54	26.15 (26.04-26.27)	23.56 (23.46-23.67)	14.68 (14.59-14.76)	2.59 (2.56-2.63)
	55-64	42.33 (42.17-42.49)	34.95 (34.81-35.10)	22.28 (22.16-22.39)	7.37 (7.30-7.44)
	65-74	47.73 (47.52-47.94)	38.53 (38.34-38.72)	24.79 (24.64-24.94)	9.21 (9.11-9.30)
	75-84	53.68 (53.39-53.96)	42.15 (41.89-42.40)	27.16 (26.96-27.37)	11.53 (11.40-11.66)
	85+	46.30 (45.88-46.72)	37.32 (36.94-37.70)	21.17 (20.88-21.45)	8.98 (8.80-9.17)
Race	Native American	33.00 (32.51-33.49)	29.89 (29.42-30.35)	16.93 (16.59-17.28)	3.12 (2.96-3.29)
	Asian/Pacific Islander	9.70 (9.57-9.82)	4.96 (4.87-5.05)	2.90 (2.83-2.97)	4.76 (4.67-4.84)
	Black	14.40 (14.31-14.49)	10.99 (10.91-11.07)	6.29 (6.23-6.35)	3.43 (3.38-3.47)
	White	15.20 (15.16-15.23)	13.31 (13.28-13.34)	8.33 (8.31-8.36)	2.06 (2.05-2.07)
Ethnicity	Hispanic	22.08 (21.95-22.21)	18.33 (18.21-18.45)	12.49 (12.39-12.59)	3.74 (3.69-3.80)
	Non-Hispanic	14.56 (14.53-14.59)	12.33 (12.30-12.36)	7.52 (7.50-7.54)	2.22 (2.20-2.23)
Geographic region	Northeast	12.97 (12.91-13.04)	10.71 (10.65-10.77)	6.38 (6.33-6.43)	2.28 (2.25-2.30)
	Midwest	13.71 (13.65-13.77)	11.69 (11.63-11.75)	7.08 (7.03-7.12)	2.00 (1.98-2.03)
	South	16.16 (16.11-16.21)	13.82 (13.78-13.87)	8.85 (8.81-8.89)	2.31 (2.29-2.33)
	West	15.20 (15.16-15.23)	14.24 (14.18-14.30)	8.71 (8.66-8.76)	2.79 (2.76-2.82)

Data source: Centers for Disease Control and Prevention National Center for Health Statistics

Age-adjusted rate listed for all categories with exception of age strata

Combined liver-related definition: C22.0, K70, K71, K72, K73, K74, K75, K76

Cirrhosis mortality definition: K74.6, K74.5, K70.3

CLD mortality definition: K70, K71, K72, K73, K74, K75, K76

HCC mortality definition: C22.0

Table 4.

Potential Data Sources for Liver Disease Epidemiologic Research

Data source	Country/ Region	Strengths	Weaknesses
National Health and Nutrition Examination Survey (NHANES)	United States	• Nationally representative sample of non-institutionalized individuals • Cirrhosis definition based on interview, examination, laboratory data • Provides estimates of undiagnosed cirrhosis	• Cross-sectional design • Small sample size (~5,000) • Potential for selection bias • Potential misclassification of mild liver disease
Veterans Affairs (VA)	United States	• Large sample size • Includes clinical notes, laboratory data, and imaging • Well-validated ICD coding strategies for liver disease and its associated complications	• Predominantly male population • VA enrollees may differ from general population regarding access or delivery of care • Limited information on care received outside VA system
Medicare	United States	• Large sample size • Nationally representative of population age ≥65 years • Patients followed until death	• No laboratory data available • Relies on diagnosis and procedure codes alone and is subject to misclassification
Medicaid	United States	• Large sample size • Includes sample of patients with low socioeconomic status	• No laboratory data available • Relies on diagnosis and procedure codes alone and is subject to misclassification
Private-insurance claims data	United States	• Large sample size • Nationally representative of privately insured population	• Unable to ascertain death • Enrollment relies on ongoing insurance coverage • No laboratory data available • Relies on diagnosis and procedure codes alone and is subject to misclassification
National Inpatient Sample (NIS)	United States	• Large sample size • Nationally-representative sample of inpatient population • Includes all payers	• No laboratory data available • Relies on diagnosis and procedure codes alone and is subject to misclassification • Inability to link hospitalizations to individual patients limits longitudinal follow-up post-discharge
National Readmissions Database (NRD)	United States	• Large sample size • Accurate assessment of patient readmission	• No laboratory data available • Unable to account for events that may preclude readmission (e.g. death)

Data source	Country/ Region	Strengths	Weaknesses
			• Relies on diagnosis and procedure codes alone and is subject to misclassification
Medical Expenditure Panel Survey (MEPS)	United States	• Nationally-representative of non-institutionalized individuals • Includes health care expenditures from all payers	• Potential for recall bias • Subgroup analyses among certain groups (e.g. race/ethnicity minorities) may not be possible
Surveillance Epidemiology, and End Results (SEER) program	United States	• Includes information on clinical information, tumor stage at diagnosis, first treatment and survival • Allows linkage to Medicare	• Unable to determine etiology or severity of liver disease • May not be entirely representative of US given that it only covers selected subset of population • Generalizability for Medicare-linked data limited by age of enrollees (≥65 years old)
US Cancer Statistics registry	United States	• Nationally-representative data source on HCC incidence from all 50 states (~97% of population)	• Unable to determine etiology of liver disease due to lack of laboratory data • Unable to determine HCC stage at diagnosis
Organ Procurement and Transplant Network (OPTN)	United States	• Granular data on waitlisted individuals, liver transplantation, and post-liver transplant outcomes • Linked by UNOS to social security death index	• Potential for selection bias by transplant centers
National patient registries	Denmark, Finland, Iceland, Norway, Sweden	• Longitudinal, nationwide clinical data with individual-level linkage • Includes detailed information on clinical characteristics, laboratory data, imaging, procedures and outcomes	• Resource-intensive
Clinical Practice Research Datalink (CPRD)	United Kingdom	• Nationally-representative data • Granular data on diagnoses and prescriptions of patients seen by participating providers	• Covers only a subset of the population • Longitudinal follow-up depends on ongoing treatment by a participating practice • Limited data on liver-specific information
European Liver Transplant Registry (ELTR)	Europe	• Large sample size (155 centers from 28 countries) • Standardized questionnaire used • Detailed information on liver transplant indications, transplant types and complications	• Potential for misclassification due to inaccurate completion of questionnaire • No information on patient ethnicity or socioeconomic information
NORDCAN database	Denmark, Finland, Faroe Islands,	• Population-based incidence, prevalence and mortality data for HCC	• Inclusion of only Nordic countries limits generalizability, particularly to racial/ethnic minorities

Data source	Country/ Region	Strengths	Weaknesses
	Greenland, Iceland, Norway, Sweden	• Longitudinal data allows for examination of HCC trends	
Global Burden of Disease (GBD) project	Worldwide	• Captures data from a wide range of sources to estimate incidence, prevalence and mortality from liver disease and HCC	• Data quality highly variable, particularly in resource-limited areas • In many areas, relies on verbal autopsy (post-mortem interview with relatives and/or witnesses of death)