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Liver (J Bajaj, Section Editor)

Contemporary Epidemiology of Cirrhosis

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Abstract

Purpose of Review We sought to review the contemporary epidemiology of cirrhosis, focusing on the relative burden of the most common chronic liver diseases.
Recent Findings The key findings in the review highlight the increasing prevalence and impact of alcohol-related liver disease, particularly among young people, and the epidemic of nonalcoholic fatty liver commensurate with rising rates of obesity. We also contrast recent advances in the care of persons with hepatitis C with the lamentable rise in new infections associated with intravenous drug use. Finally, we highlight the impact of both conventional complications of cirrhosis (namely hepatic encephalopathy) but also the host of patient-reported outcomes adversely impacted by the symptoms of cirrhosis.
Summary Cirrhosis is associated with an expanding footprint in contemporary public health. In order to improve global outcomes, we must not only focus on the identifying and treating persons with viral hepatitis but also preventing the rise of alcohol-related liver disease and nonalcoholic fatty liver disease while attending to the urgent patient-centered needs posed by the symptoms of cirrhosis.

Introduction

Cirrhosis is end-stage liver disease characterized by the extensive fibrosis caused by any chronic liver disease (CLD). The prevalence of CLD is rising and cirrhosis with it. Although the personal and financial burden of CLD is substantial, it is disproportionately related to the impact attributable to the minority with cirrhosis [1–5]. Most patients with cirrhosis are asymptomatic and compensated but are at risk of decompensation (5–7% per

year or 58% over 10 years [6]) at a rate commensurate with the nature and activity of the underlying CLD [5]. In turn, the impact of cirrhosis is related to its stage. Whereas patients with compensated cirrhosis are at low (< 5%) annual risk of death [5], however, after developing complications such as ascites or variceal hemorrhage, the annual risk of death climbs to 20% and 57%, respectively [5]. In tandem with these classic complications are several symptoms related to the perturbed physiology of CLD including fatigue, sexual dysfunction, pruritus, muscle cramps, and falls; all of which can devastate quality of life (QOL) [2]. Herein, we review recent data regarding the epidemiological trends and impact of contemporary cirrhosis.

Public Health Burden of Cirrhosis

Cirrhosis has an increasingly large footprint in American public health. The true national prevalence of cirrhosis is difficult to determine since asymptomatic, well-compensated patients can go undiagnosed for years. However, recent data from Mellinger et al. suggests that in 2015, at least 294,215 or 0.27% of American adults with private health insurance through an employer had cirrhosis [7••]. These results are consistent with those of Scaglione et al. who reported that based on noninvasive indices of fibrosis (AST to Platelet Ratio Index (APRI) > 2), 633,323 or 0.27% of all American adults evaluated from 1999 to 2010 in a nationally representative sample had cirrhosis [8]. In the Veteran's Affairs system, where the prevalence of CLD—particularly hepatitis C—is greater than in the general population, Beste et al. found that the prevalence of cirrhosis rose to 1.1%, a 59% increase from 2001 to 2013 [9]. These trends are likely generalizable. Cirrhosis is becoming more common, including among young people. In a population-based age-period-cohort analysis from Ontario, Canada, Flemming et al. found that compared with people born in 1951, the risk of developing cirrhosis was 1.31 times greater for those born in 1966, 1.55 times greater for those born in 1980, and 2.16 times greater for those born in 1990, with higher risk observed among women in each birth cohort [10••]. These trends translate into worsening outcomes. Indeed, Beste reported that cirrhosis mortality rose by 52% from 2001 to 2013 [9]. Tapper et al. recently reported that since 1999, during a period when deaths due to cardiovascular disease, cancer, and infections have declined, the number of deaths due to cirrhosis has risen by 65% in the USA, with as many as 51,127 patients dying from cirrhosis in 2016 alone [11••]. Notably, deaths due to cirrhosis are rising by 10.5% each year and have climbed by more than 200% from 2009 to 2016 [11••].

The expanding impact of CLD and cirrhosis can be measured in many other ways. Peery et al. reported that in the USA in 2014, there were over 1 million ambulatory visits associated with a diagnosis of CLD [12•]. They also reported that CLD accounted for 251,790 hospital admissions in 2014, an increase of 25% from 2005, with the estimated total charges in excess of $13.6 billion [12•]. In fact, cirrhosis is outpacing the impact of other common chronic diseases. Asrani et al. reported that from 2000 to 2014, after adjusting for age and sex, the rates of hospitalization throughout Texas that were associated with CLD and cirrhosis increased by about 257% and 342%, respectively [13••]. Further, the rate of hospitalization for CLD increased by 92%, dwarfing increases in hospitalization rates for CHF and COPD, respectively 6.7% and 48.8% [14].

The healthcare needs of patients with CLD are not evenly distributed. According to a nationally representative study, as many as 1 in 4 patients admitted with cirrhosis are readmitted within 30 days [15, 16], driven by the presence of cirrhotic complications such as hepatic encephalopathy. These admissions are complex and costly, with a median charge per readmission of $30,607 (2015 USD) [12•]. Nguyen et al. reported that so-called "high-need, high-cost (HNHC)" [17] patients with CLD accounted for a disproportionate consumption of the total healthcare resources. They found that among patients hospitalized for CLD in the first half of 2013, the lowest decile of healthcare utilizers spent a median of 0.13 days/month hospitalized at a median cost of $480 per month compared with the highest decile of utilizers who spent a median of 4.14 days/month hospitalized at a median cost of $8925 per month [17]. Higher needs and costs were strongly associated with poorer patients and patients whose CLD was complicated by infection and cardiovascular comorbidities [17].

Burden of Complications

In general, the personal and healthcare burdens of cirrhosis are proportional to the degree of cirrhotic decompensations [5], the worst of which being hepatic encephalopathy (HE). In a cohort of 1979 VA patients with cirrhosis and portal hypertension and/or APRI > 2.0, Tapper et al. reported a 22.6% probability of developing overt HE after 1 year which increases to a 43.6% probability after 5 years [18], suggesting that a significant proportion of patients with cirrhosis experience HE at some point in their disease course. While HE itself presents as a spectrum, even the earliest stage (termed covert hepatic encephalopathy [CHE]) is strongly associated with adverse events. The association between HE and very poor quality of life has been well characterized. Patidar et al. also showed that even presence of CHE is associated with a 2.5 times greater risk of hospitalization and a 4.9 times greater risk of death [19]. Further, Bajaj et al. reported that this association between HE and increased mortality remains consistent even among the sickest patients with cirrhosis, those with acute-on-chronic liver failure [20]. Adjusting for disease severity and MELD, these investigators found that having HE of grade 3 or greater was associated with a 3-fold greater risk of death in the hospital and a 4.6-fold greater risk of death after 30 days [20]. Additionally, the financial impact of HE due to frequent admission and readmission is of great significance. Peery et al. reported that in 2015, 19,563 index admissions (with a median cost of $27,816 per admission) for HE were followed by 2847 associated readmissions (with a median cost of $30,250 per readmission) after 30 days [12•].

The most common hepatic decompensation, however, is ascites [3, 5, 6]. Ascites develops at annual rates of 4.4% and 6.6% in patients with compensated cirrhosis without and with varices [5]. Gomez et al. reported 21% and 45% 6-year risks of developing ascites in patients with compensated HCV cirrhosis without and with varices. [3] Similar to HE, ascites has a direct and measurable financial impact due to hospitalization. Peery et al. reported that in 2015, for the 6142 hospitalizations with a primary diagnosis of ascites, the median cost per admission was $28,058 [12•]. Ascites is also associated with significantly depressed quality of life [2], commensurate with the severity of volume of overload and its interference with physical functioning [21] as well as the serum sodium [22].

It's also important to emphasize that morbidity due to cirrhosis is not limited to traditional decompensations such as ascites and HE. Many under-recognized symptoms play equally if not more important roles in determining quality of life. Falls are common, occurring in up to 4 in 10 patients with cirrhosis (namely those with covert HE) [23]. Further, Ezaz et al. found that patients with cirrhosis were at 2.2-fold increased risk of severe injury after a fall [24]. Itching is common, present in up to 40% of patients with cirrhosis [25]. Liver insufficiency also has a significant impact on sexual function and satisfaction. Paternostro et al. reported that most (63.8%) male patients with cirrhosis suffered from some degree of erectile dysfunction [26]. Among 71 women with cirrhosis who had not undergone liver transplantation, Sorrell and Brown found that 42.3% experienced decreased interest in sexual activity post-diagnosis [27]. Muscle cramps can be disabling. Chatrath et al. reported that among 150 patients with cirrhosis, 67% suffered from cramps, which were independently associated with depressed quality of life [28].

Etiologies of Cirrhosis

The most common etiologies of cirrhosis include hepatitis C virus (HCV) infection, alcoholic liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD). Rarer diseases such as autoimmune hepatitis (prevalence < 10/100,000) [29], primary biliary cirrhosis (< 30/100,000) [30], primary sclerosing cholangitis (< 8/100,000) [31], and hemochromatosis-associated cirrhosis (< 6/100,000) [32] play smaller roles in the overall burden of cirrhosis. As detailed below, even within the most common causes of CLD, shifting demographic trends are changing the contemporary face of cirrhosis. We show that while the prevalence of HCV cirrhosis is declining, the incidence of HCV may be rising associated with the opiate epidemic. Meanwhile, steady increases in the incidence of ALD and NAFLD are met by a rising prevalence of cirrhosis due to these conditions.

Hepatitis C Virus

Recent innovations in treatment of HCV infection using direct-acting antiviral agents (DAAs) have resulted in much higher rates of sustained virologic response (SVR). With DAAs, there was a marked increase in the rate of SVR among patients with cirrhosis between 1999 and 2015, from 11.0% to 87.0%, respectively [33]. This will transform the epidemiology of cirrhosis. For patients with HCV-cirrhosis, the result will be improved outcomes. Patients with cirrhosis who achieve SVR have much lower rates of mortality (1.01 vs 2.93 per 100 person-years), and development of HCC (0.55 vs 2.63 per 100 person-years) [34]. Additionally, for patients with HCV, the result of DAA therapy will be lower rates of cirrhosis. Whereas Beste found that HCV was associated with 48% of cirrhosis [9] among VA patients in 2013, this proportion is certain to fall. Indeed, even now, HCV is no longer the biggest indication for liver transplant, giving way to ALD [35]. Second, the prognosis of the vast majority of contemporary patients with HCV-related cirrhosis who have experienced SVR remains unclear. The expected natural history of HCV-related cirrhosis in the pre-DAA era

cannot be extrapolated to contemporary patients. More research is necessary to fully ascertain the extent of these changes.

Two emerging factors related to HCV play potentially important yet unclear roles in the future of CLD epidemiology. First, for many, it is a dispiriting postscript to the transformational changes of the DAA era that the incidence of HCV is rising. Commensurate with rising rates of intravenous drug use (IVDU) among young persons, there has been a doubling in the incidence of acute hepatitis C (0.3 to 0.7 cases/100,000) [36]. Among active users of intravenous drugs followed at one center in New York, the rate of HCV infection is 13 per 100 person-years [37]. Second, there remain millions of individuals with active, untreated HCV who may be unaware of their serostatus. Recent survey data from 2013 to 2016 showed that 38.5% of evaluated baby boomers with HCV were unaware of their infection, including > 60% with elevated noninvasive indices for fibrosis [38].

Nonalcoholic Fatty Liver Disease

The fatty infiltration of the liver associated with NAFLD can lead to nonalcoholic steatohepatitis (NASH), a major source of hepatocellular damage which can lead to cirrhosis. Estimates vary, though it is now estimated that more than 25% of the adult population in the USA has some form of NAFLD, a product of sharp increases in obesity and diabetes, both in youth and adults [39•]. It is predicted that the prevalence of NAFLD will continue to rise and play an increasingly important role as an indication for liver transplant [40], with a projected 21% and 63% increase in the prevalence of NAFLD and NASH [41], respectively, from 2015 to 2030. In the same time period, the prevalence of NAFLD-related decompensated cirrhosis and HCC are expected to increase by 180% and 146%, respectively [41]. Patients with NAFLD-related cirrhosis pose unique challenges since we lack a cure for NAFLD as offered by DAAs for HCV. However, what differentiates NAFLD from traditional CLD and makes it particularly dangerous is its prevalence among young people [10••]. Although it is unclear whether NAFLD poses most risk for cardiovascular-morbidity or liver-related morbidity, NAFLD is associated with higher rates of all-cause mortality after 10 years [42••]. Obesity can affect children in their very first years and follow them for the rest of their lives, allowing the effects of NAFLD to begin so early in life that, even by early adulthood, the adverse effects of metabolic syndrome and cirrhosis begin to take their toll [43].

Alcoholic Liver Disease

Perhaps the most surprising shift in the epidemiology of cirrhosis is the sharp increase in the prevalence of ALD. Mellinger et al. reported that among Americans with private insurance through an employer in 2015, the prevalence of alcohol-related cirrhosis (AC) was 0.10% and rising, a stunning increase of 43% from 2009 [7••]. AC has traditionally been observed in older patients. For unclear reasons, potentially related to the pattern of drinking (more binge consumption) [44], alcohol-related injuries are increasingly common among young people. Many young adults are

now presenting to clinics with decompensated cirrhosis due to ALD. We reported that, in 2016, rates of death due to cirrhosis for persons aged 25–34 had climbed by more than 200% since 2009, almost entirely due to ALD [11••]. As above, similar trends were later observed by Flemming in Ontario where young people born as late as 1990 have the highest incidence-rate ratio for the development of cirrhosis [10••]. Compared with other forms of CLD, patients with ALD tend to present a later stage with a higher prevalence of cirrhotic decompensations [45], require more intense healthcare resource utilization [7••], and have a higher mortality [46, 47].

Given these increases in the prevalence of ALD and AC, it's important to note that AC poses unique challenges when compared with non-AC. In the same study from Mellinger et al., patients with AC had higher rates of decompensated cirrhosis and more comorbidities than patients with non-AC [7••]. It is therefore not surprising that they report that 1 year after diagnosis, the average cost caring for an AC patient ($44,835) was almost double the average cost of a non-AC patient ($23,319) [7••]. The net result is that alcohol abuse in youth is fueling a deadly surge in ALD among young adults which has already shown to have a tremendously negative impact on public health.

Understanding Recent Data

Changing epidemiological data must be interpreted in the context of study design and secular trends. We believe there are a few key forces pertinent to CLD epidemiology, which we graphically summarize in Fig. 1. First, increasingly, we must recognize that any given person with CLD may have multiple discrete etiologies of CLD. Given the rising prevalence of alcohol abuse and obesity/diabetes, the result will be that most other forms of CLD will share an overlap with ALD or NAFLD. Second, the ubiquitous use of imaging in patients with CLD is one of the principal ways in which patients with CLD and cirrhosis come to the attention of their clinicians. By shifting the diagnosis of cirrhosis from the symptomatic decompensated stages to the pre-symptomatic compensated stages and expanding the pool of diagnosed patients, data regarding the natural history of cirrhosis may change in important ways. However, even despite the currently expanding use of imaging, we are likely still systematically underestimating the true impact of cirrhosis [48]. Third, the trajectory of any given liver disease is related to the therapeutic interventions available. As described by D'Amico et al., the prognosis and natural history of cirrhosis follows a nonlinear progression beginning from the stable, low-cost, to low-need compensated state [5]. The cardinal event that governs risk of decompensation is the development of portal hypertension and varices, after which the development of ascites, hemorrhage, and encephalopathy become more commonplace [4]. Gomez et al. studied patients with compensated cirrhosis due to HCV and found that individuals with non-bleeding esophageal varices at baseline experienced a higher rate of decompensation, death, liver transplant, and even development of HCC when compared with those without varices [3]. Further, sustained virologic response is associated with reduced risk of decompensation and mortality [3, 49, 50]. Similar observations have been made across hepatology with respect

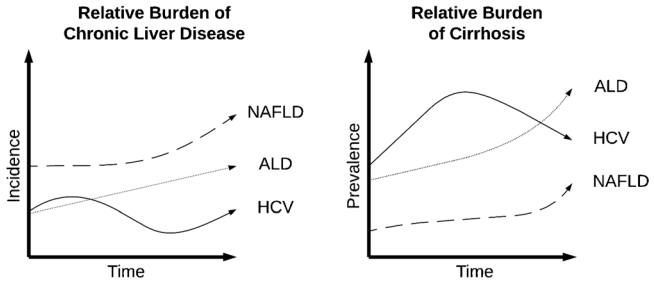

Fig. 1. The relative burden of chronic liver disease and cirrhosis by etiology over time. In this stylized figure, we depict how the incidences of the most common forms of chronic liver disease are changing over time. These trends reflect the relatively greater severity of disease inherent to ALD (alcohol-related liver disease) and the recent resurgence of incident HCV (hepatitis C virus). NAFLD, nonalcoholic fatty liver disease.

to intensity of alcohol consumption, control of hepatitis B, and cholestatic liver disease [51–54]. Finally, in order to curb projected increases in the prevalence of cirrhosis, public health interventions to forestall the spread of HCV by addressing the opiate crisis are essential. Identification of and linkage to care for persons with HCV are critical to ensure our optimistic predictions for the future of HCV.

Conclusion

The use of DAAs to cure HCV on a wide scale, the modern obesity epidemic, and the recent increase in alcohol abuse and alcoholic liver disease all contribute to a clinically significant shift in the face of the typical cirrhosis patient to young individuals with lifestyle-dependent disease. A proper understanding of these changes is necessary to properly approach contemporary cirrhosis from both clinical and public health standpoints. As alcohol and obesity become the two most important causes of cirrhosis, we are beginning to see younger and younger patients with lifestyle-dependent disease which cannot be cured by pharmacologic means. The design and implementation of nonpharmacologic and policy-based interventions in the treatment of contemporary cirrhosis and CLD are therefore more necessary now than ever before (Fig. 1).

Compliance with Ethical Standards

Conflict of Interest
Jad Baki reports no potential conflicts of interest.
Elliot Tapper reports grants from Valeant and Gilead and personal fees from Novartis and Salix.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577–86.
2. Tapper E, Kanwal F, Asrani S, et al. Patient reported outcomes in cirrhosis: a scoping review of the literature. Hepatology (Baltimore, Md). 2017.
3. Gomez EV, Rodriguez YS, Bertot LC, Gonzalez AT, Perez YM, Soler EA, et al. The natural history of compensated HCV-related cirrhosis: a prospective long-term study. J Hepatol. 2013;58(3):434–44.
4. D'amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther. 2014;39(10):1180–93.
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44(1):217–31.
6. Ginés P, Quintero E, Arroyo V, et al. Compensated cirrhosis: Natural history and prognostic factors. Hepatology. 1987;7(1):122–8.
7. •• Mellinger JL, Shedden K, Winder GS, et al. The high burden of alcoholic cirrhosis in privately insured persons in the United States. Hepatology. 2018;68(3):872–82

These data from a commercial claim database highlight the rising incidence of cirrhosis and the disproportionate economic burden associated with alcohol-related liver disease.

8. Scaglione S, Kliethermes S, Cao G, et al. The epidemiology of cirrhosis in the United States: a population-based study. J Clin Gastroenterol. 2015;49(8):690–6.
9. Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001–2013. Gastroenterology. 2015;149(6):1471–1482.e5.
10. •• Flemming JA, Dewit Y, Mah JM, Saperia J, Groome PA, Booth CM. Incidence of cirrhosis in young birth cohorts in Canada from 1997 to 2016: a retrospective population-based study. Lancet Gastroenterol Hepatol. 2018.

This population-based study from Ontario demonstrates a rising incidence for cirrhosis, particularly among young people.

11. •• Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. BMJ. 2018;362.

This study evaluates trends in mortality due to liver disease in the USA and demonstrates substantial increases following 2008, particularly among young persons aged 25-34.

12. • Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology. 2019;156(1):254–272.e1.

This annual survey updates the outcomes of and healthcare costs associated with multiple gastrointerstinal illnesses.

13. •• Asrani SK, Hall L, Hagan M, et al. Trends in chronic liver disease-related hospitalizations: a population-based study. Am J Gastroenterol. 2018.

This population-based study from Texas demonstrates that persons with chronic liver disease are at higher risk of hospitalization compared with other organ failure states such as COPD and CHF.

14. Asrani SK, Kouznetsova M, Ogola G, et al. Increasing health care burden of chronic liver disease compared with other chronic diseases, 2004–2013. Gastroenterology. 2018;155(3):719–729.e4.
15. Tapper EB, Halbert B, Mellinger J. Rates of and reasons for hospital readmissions in patients with cirrhosis: a multistate population-based cohort study. Clin Gastroenterol Hepatol. 2016;14:1181–1188.e2.
16. Tapper EB. Building effective quality improvement programs for liver disease: a systematic review of quality improvement initiatives. Clin Gastroenterol Hepatol. 2016;14(9):1256–1265.e3.
17. Nguyen NH, Khera R, Ohno-Machado L, Sandborn WJ, Singh S. Annual burden and costs of hospitalization for high-need, high-cost patients with chronic gastrointestinal and liver diseases. Clin Gastroenterol Hepatol. 2018;16(8):1284–1292.e30.
18. Tapper EB, Parikh ND, Sengupta N, et al. A risk score to predict the development of hepatic encephalopathy in a population-based cohort of patients with cirrhosis. Hepatology. 2018;68(4):1498–507.
19. Patidar KR, Thacker LR, Wade JB, Sterling RK, Sanyal AJ, Siddiqui MS, et al. Covert hepatic encephalopathy is independently associated with poor survival and increased risk of hospitalization. Am J Gastroenterol. 2014;109:1757–63.
20. Bajaj JS, O'Leary JG, Tandon P, et al. Hepatic encephalopathy is associated with mortality in patients with cirrhosis independent of other extrahepatic organ failures. Clin Gastroenterol Hepatol. 2017;15(4):565–574.e4.
21. Onishi Y, Wakita T, Fukuhara S, Noguchi Y, Okada M, Sakaida I, et al. Development and validation of a symptom scale specific for ascites accompanied with cirrhosis: the ASI-7. Clin Transl Gastroenterol. 2014;5(2):e48.
22. Solà E, Watson H, Graupera I, Turón F, Barreto R, Rodríguez E, et al. Factors related to quality of life in

patients with cirrhosis and ascites: relevance of serum sodium concentration and leg edema. J Hepatol. 2012;57(6):1199–206.
23. Soriano G, Román E, Córdoba J, Torrens M, Poca M, Torras X, et al. Cognitive dysfunction in cirrhosis is associated with falls: a prospective study. Hepatology. 2012;55(6):1922–30.
24. Ezaz G, Murphy SL, Mellinger J, Tapper EB. Increased morbidity and mortality associated with falls among patients with cirrhosis. Am J Med. 2018;131(6):645–650.e2.
25. Oeda S, Takahashi H, Yoshida H, et al. Prevalence of pruritus in patients with chronic liver disease: a multicenter study. Hepatol Res. 2018;48(3):E252–62.
26. Paternostro R, Heinisch BB, Reiberger T, et al. Erectile dysfunction in cirrhosis is impacted by liver dysfunction, portal hypertension, diabetes and arterial hypertension. Liver Int. 2018;38(8):1427–36.
27. Sorrell JH, Brown JR. Sexual functioning in patients with end-stage liver disease before and after transplantation. Liver Transpl. 2006;12(10):1473–7.
28. Chatrath H, Liangpunsakul S, Ghabril M, Otte J, Chalasani N, Vuppalanchi R. Prevalence and morbidity associated with muscle cramps in patients with cirrhosis. Am J Med. 2012;125(10):1019–25.
29. Kim BH, Choi HY, Ki M, Kim K-A, Jang ES, Jeong S-H. Population-based prevalence, incidence, and disease burden of autoimmune hepatitis in South Korea. PLoS One. 2017;12(8):e0182391.
30. Lu M, Zhou Y, Haller IV, et al. Increasing prevalence of primary biliary cholangitis and reduced mortality with treatment. Clin Gastroenterol Hepatol. 2018;16(8):1342–1350. e1.
31. Liang H, Manne S, Shick J, Lissoos T, Dolin P. Incidence, prevalence, and natural history of primary sclerosing cholangitis in the United Kingdom. Medicine. 2017;96(24).
32. Åsberg A, Hveem K, Thorstensen K, et al. Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons. Scand J Gastroenterol. 2001;36(10):1108–15.
33. Moon AM, Green PK, Berry K, Ioannou GN. Transformation of hepatitis C antiviral treatment in a national healthcare system following the introduction of direct antiviral agents. Aliment Pharmacol Ther. 2017;45(9):1201–12.
34. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis c and advanced hepatic fibrosis. JAMA. 2012;308(24):2584–93.
35. Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. Clin Gastroenterol Hepatol. 2018;16(8):1356–8.
36. Zibbell JE, Asher AK, Patel RC, Kupronis B, Iqbal K, Ward JW, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. Am J Public Health. 2018;108(2):175–81.
37. Des Jarlais DC, Arasteh K, Feelemyer J, McKnight C, Barnes DM, Perlman DC, et al. Hepatitis C virus prevalence and estimated incidence among new injectors during the opioid epidemic in New York City, 2000–2017: protective effects of non-injecting drug use. Drug Alcohol Depend. 2018;192:74–9.
38. Kim H-s, Yang JD, El-Serag HB, Kanwal F. Awareness of chronic viral hepatitis in the United States: an update from National Health and Nutrition Examination Survey. J Viral Hepat. 201
39.• Parikh ND, Marrero WJ, Wang J, et al. Projected increase in obesity and non-alcoholic-steatohepatitis–related liver transplantation waitlist additions in the United States. Hepatology. 2017.
This modeling study combines multiple data sources to demonstrate how rising rates of obesity are driving an increasing burden of NAFLD and NAFLD-related cirrhosis and liver failure.
40. Parikh ND, Marrero WJ, Wang J, et al. Projected increase in obesity and non-alcoholic-steatohepatitis–related liver transplantation waitlist additions in the United States. Hepatology. 0(0).
41. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123–33.
42.•• Allen AM, Therneau TM, Larson JJ, Coward A, Somers VK, Kamath PS. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. Hepatology. 2018;67(5):1726–36
This population-based study from Olmstead county demonstrates a rising incidene of NAFLD including among young persons.
43. Ezaz G, Tapper EB. Driving in the dark: cirrhosis in young adults. Lancet Gastroenterol Hepatol. 2018.
44. Yang JC, Roman-Urrestarazu A, Brayne C. Binge alcohol and substance use across birth cohorts and the global financial crisis in the United States. PLoS One. 2018;13(6):e0199741.
45. Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology. 2010;51(5):1675–82.
46. Nilsson E, Anderson H, Sargenti K, Lindgren S, Prytz H. Incidence, clinical presentation and mortality of liver cirrhosis in Southern Sweden: a 10-year population-based study. Aliment Pharmacol Ther. 2016;43(12):1330–9.
47. Jepsen P, Lash TL, Vilstrup H. The clinical course of alcoholic cirrhosis: development of comorbid diseases. A Danish nationwide cohort study. Liver Int. 2016;36(11):1696–703.
48. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. Gastroenterology. 2013;145(2):375–382.e2.

49. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584–93.
50. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147(10):677–84.
51. Teli MR, Day CP, James O, Burt A, Bennett M. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. Lancet. 1995;346(8981):987–90.
52. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130(3):678–86.
53. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology. 1998;28(3):805–9.
54. Poupon RE, Poupon R, Balkau B. Group U-Ps. Ursodiol for the long-term treatment of primary biliary cirrhosis. N Engl J Med. 1994;330(19):1342–7.

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