Real-World Trends and Future Projections of the Prevalence of Cirrhosis and Hepatic Encephalopathy Among Commercially and Medicare-Insured Adults in the United States

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INTRODUCTION: **Describing cirrhosis and hepatic encephalopathy (HE) burden over time can inform clinical management and resource allocation. Using healthcare claims data, this observational study examined recent trends in the prevalence of cirrhosis and HE and associated healthcare resource utilization among commercially and Medicare-insured adults in the United States.**

METHODS: **Data from the MarketScan Commercial Claims and Encounters Database and 100% Medicare Research Identifiable Files were analyzed (2007–2020). Annual prevalence of cirrhosis, HE, overt HE (OHE) hospitalizations, and rifaximin ± lactulose use, and costs per hospitalization per year were calculated. Average year-over-year changes in prevalence of cirrhosis, and HE were estimated. Trends were extrapolated to 2030 using ordinary least-squares regression.**

RESULTS: **From 2007 to 2020, the prevalence of cirrhosis increased by an average of 4.6% year-over-year in the Commercial population and 8.1% in the Medicare population; the prevalence of HE increased by 4.3% and 2.5%, respectively. Rates of OHE hospitalizations decreased from 27.5% to 5.5% (Commercial) and from 26.2% to 9.5% (Medicare), and rates of liver transplantation increased. Average payer costs (Commercial) and provider charges (Medicare) per OHE hospitalization increased (from $40,881 to $77,699 and from $45,913 to $74,894, respectively). Use of rifaximin ± lactulose showed an increasing trend during the observation period, whereas lactulose use declined steadily.**

DISCUSSION: **The healthcare burden of cirrhosis and HE in the United States is increasing. Trends are projected to continue unless action is taken, such as improving medication access and developing policies addressing the contributing factors.**

KEYWORDS: costs; healthcare resource utilization; hospitalizations; lactulose; rifaximin

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B274

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INTRODUCTION

Cirrhosis and cirrhosis-related complications remain a leading cause of morbidity and mortality worldwide. Similar trends have been observed in the United States, and the changing epidemiology of cirrhosis among US adults reflects the shift from viral hepatitis-related chronic liver disease to the emergence of steatotic liver disease—both alcohol-associated and metabolic-related—as leading causes of chronic liver disease and cirrhosis. In fact, alcohol-associated liver disease and metabolic dysfunction-associated steatotic liver disease (MASLD) are now the leading etiologies of liver disease among adults awaiting liver transplantation in the United States (1).

During the compensated phase of cirrhosis, there may be no apparent clinical manifestations, but progressive liver

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dysfunction and/or portosystemic shunting can lead to decompensated cirrhosis characterized by variceal bleeding, ascites, and ascitic fluid infections including spontaneous bacterial peritonitis (2), and hepatic encephalopathy (HE) (3–9). HE can significantly impair cognitive, emotional, and social functioning, leading to decreased overall quality of life and increased rates of morbidity and mortality, especially with deterioration of minimal (covert) HE to overt HE (OHE) (10,11), a decompensation event that presents as a spectrum of neurologic abnormalities, including motor deficits, behavioral changes, and coma (12). The reported prevalence of covert HE among patients with cirrhosis is variable but has been found to be between 20% and 80%, depending on the cirrhosis stage, diagnosis strategy, and world region (8,13–15), whereas OHE is reported to be experienced by up to 40% of patients with cirrhosis (16–18). In a retrospective US study assessing the 1-year prevalence of HE, an estimated 38% of patients with cirrhosis had HE in 2018 (19). Disease etiology is a key factor affecting HE prevalence (14). Prospective studies have shown that OHE is more common among patients with alcohol-associated cirrhosis than cirrhosis of other causes and that OHE is one of the most common decompensation events among patients with MASLD (20,21); thus, trends in HE epidemiology will likely continue to be influenced by the evolving epidemiology of the etiologies of liver disease in the United States (1,14). Preventing the clinical manifestations of HE is crucial, as each episode of OHE increases the risk of subsequent episodes and worsens cognitive decline and prognosis (3,6,9), with a median survival associated with HE of just 1 year (7,8). Therefore, early detection and management of HE has the potential to improve patient outcomes.

The recurrent nature of OHE and associated deterioration of liver function constitute a clinical challenge and imposes a large economic burden on the healthcare system (22). Medical costs related to hospitalizations for recurrent episodes of OHE can be substantial, particularly for severe cases requiring intensive care or liver transplantation (23,24). Despite the burden associated with cirrhosis and its complications, there are limited treatment options available besides managing symptoms or preventing progression of cirrhosis to a decompensated state. Further deterioration of liver function can be minimized and the need for liver transplantation potentially averted by treating complications of cirrhosis such as HE (5,25). Lactulose is the standard of care for the treatment of acute OHE and is used prophylactically to maintain remission. Rifaximin therapy added on to lactulose is guideline recommended for prevention of recurrence of OHE events and OHE hospitalizations (8,26). Despite the clinical benefits of rifaximin, prior research has shown evidence of barriers to access and a high unmet therapeutic need among patients with HE (27,28).

Characterizing the evolving epidemiology and healthcare burden associated with cirrhosis and HE can help to identify gaps in care and opportunities for preventing OHE recurrence by improving management practices. These data also provide important updated information on the clinical and healthcare economic burden of cirrhosis as well as HE, an important predictor of mortality and poor health outcomes in patients with cirrhosis (29), which are critical data to guide healthcare resource planning and public health policies. In this context, the aim of this study was to examine changes in the prevalence of cirrhosis, decompensated cirrhosis, and HE in the United States from 2007 to 2020 in populations of adults covered by Commercial or Medicare insurance. Trends in rifaximin and lactulose use were also assessed to identify potential gaps in OHE management. In addition, trends in the prevalence of cirrhosis and HE over the next decade were modeled to estimate the prevalence in 2030 under the assumption that the observed trends persist, to highlight the future burden, inform policy planning, and guide patient management.

METHODS

Data source

This study used data from the MarketScan Commercial Claims and Encounters Database (2007–2020) and 100% Medicare Research Identifiable Files (RIF) database (2007–2020).

The Commercial Claims database contains medical and pharmacy claims of employer-sponsored private health insurance beneficiaries in the United States, including hospitalizations and outpatient services and prescription drug claims. The Medicare RIF database contains healthcare encounters of Medicare beneficiaries, including institutional claims (Part A; e.g., hospital services), noninstitutional claims (Part B), and prescription drug claims (Part D). Data on Medicare Advantage beneficiaries (Part C) were not analyzed in this study. Both databases include information on enrollment, diagnoses/procedures, and costs of treatments and medical services.

Institutional review board approval was not required for this study as all patient data were deidentified and complied with Health Insurance Portability and Accountability Act requirements. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Study design and sample selection

A retrospective observational cohort study design was used to identify adults with evidence of cirrhosis and HE based on the presence of diagnosis codes in the MarketScan Commercial Claims and Encounters Database and the 100% Medicare RIF database from 2007 to 2020. The diagnosis codes used to identify cirrhosis and HE were based on *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* codes described in prior work (19,30). Criteria for inclusion in this study for each calendar year from 2007 to 2020 were as follows: (i) patients were required to have continuous health plan enrollment for the entire calendar year (i.e., patients were excluded as of the year of their death) and (ii) were aged 18 years or older as of January 1 and younger than 65 years as of December 31 (for Commercial) or aged 65 years or older as of January 1 (for Medicare). Patients with evidence of a secondary malignant neoplasm of the liver in any year and those with evidence of liver transplantation in a prior year were excluded (i.e., patients were censored at the year following a liver transplant). Diagnosis and procedure codes used in this study are presented in Supplementary Tables S1 and S2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/B274). As an annual prevalence-based approach was used, a sample selection diagram is not reported.

Measures and outcomes

The primary outcomes were prevalence estimates for cirrhosis, decompensation (defined as ascites, variceal bleeding, spontaneous bacterial peritonitis, HE, and hepatorenal syndrome), HE, and OHE hospitalizations. In this study, HE was considered as an ongoing decompensation of cirrhosis, and OHE was considered as acute worsening events marked by hospitalizations experienced by some patients with HE. Secondary outcomes included the assessment of use of rifaximin ± lactulose and use of lactulose

without rifaximin in patients with cirrhosis and HE, and costs per OHE hospitalization and rates of liver transplantation in patients with HE. All prevalence estimates were calculated for each year, separately for Commercial and Medicare populations. All eligible adults in each population constituted the denominator for prevalence estimates of cirrhosis, whereas prevalence estimates of decompensation, HE, rifaximin use, and lactulose use were calculated among adults with cirrhosis, and prevalence estimates of OHE hospitalizations (defined as ≥1 hospitalization with a primary diagnosis for HE) and liver transplantation were calculated among adults with HE. Because of the chronic nature of cirrhosis, adults identified with cirrhosis, decompensation, or HE were carried forward in the numerator of each subsequent year, provided they met inclusion criteria for the denominator in that year.

Cirrhosis and HE prevalence estimates were stratified by sex and age groups (Commercial: 18–44, 45–64 years; Medicare: 65–74, ≥75 years). The 2020 prevalence estimates of cirrhosis, HE, and rifaximin use stratified by US state were graphically depicted as heatmaps, and cirrhosis and HE prevalence estimates were applied to the US population counts by insurance type from the US Census Bureau to derive estimated population counts in 2020. Rifaximin use was defined as ≥1 claim for rifaximin 550 mg twice daily with ≥30 days of supply and was evaluated from 2010 (year of US Food and Drug Administration [FDA] approval for HE) to 2020. Average payer costs per OHE hospitalization were calculated and reported in 2020 US dollars; for Medicare, provider charges per OHE hospitalization were also analyzed (31,32). Outcomes were identified using diagnosis, procedure, and medication codes (see Supplementary Tables S1–S3, Supplementary Digital Content 1, http://links.lww.com/CTG/B274).

Statistical analyses

Observed trends in the prevalence of cirrhosis and HE among adults with cirrhosis from 2007 to 2020 were extrapolated to 2030 using ordinary least-squares (OLS) regression models, reported as projected 2030 prevalence estimates with 95% prediction intervals and *P* values. To assess the robustness of the OLS regression-based simulation, a sensitivity analysis was conducted using autoregressive integrated moving average models, which account for moving trends in nonstationary data (i.e., time trends). Projected population counts of adults with cirrhosis and HE in 2030 were estimated based on US Census Bureau projections by age group (33). Average year-over-year (YOY) changes in prevalence estimates were calculated from log-transformed OLS regression models for 2007–2020 and 2020–2030 (separately for each period) and were reported with 95% confidence intervals (CIs) and prediction intervals, respectively, and *P* values. Statistical significance was determined at $P < 0.05$. All statistical analyses were conducted using SAS Enterprise Guide Version 7.1 (SAS Institute, Cary, NC) and Stata Version 16.1 (StataCorp LLC, College Station, TX).

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (see Supplementary Table S4, Supplementary Digital Content 1, http://links.lww.com/CTG/B274) (34).

RESULTS

Trends in the prevalence of cirrhosis

Between 2007 and 2020, the prevalence of cirrhosis increased by an average of 4.6% YOY (95% CI 4.4%–4.9%; $P < 0.01$) from 0.23% to 0.45% in the Commercial population, representative of 617,870 commercially insured adults with cirrhosis in the United States in 2020, and by 8.1% YOY (95% CI 7.3%–8.9%; $P < 0.01$) from 0.41% to 1.20% in the Medicare population, representative of 628,515 Medicare-insured adults with cirrhosis in the United States in 2020 (Figure 1a). The prevalence of decompensation among adults with cirrhosis increased by an average of 1.6% YOY (95% CI 1.3%–2.0%; $P < 0.01$) from 36.9% to 45.2% in the Commercial population and by 0.7% YOY (95% CI 0.5%–0.8%; $P < 0.01$) from 39.0% to 42.7% in the Medicare population. The share of the prevalence of decompensation accounted for by HE (i.e., prevalence of HE divided by prevalence of decompensation) increased over time, from 35.4% in 2007 to 47.4% in 2020 in the Commercial population and from 38.8% in 2007 to 49.0% in 2020 in the Medicare population (see Supplementary Figure S1, Supplementary Digital Content 1, http://links.lww.com/CTG/B274).

Subgroup analyses stratified by sex and age group in the Commercial population revealed a consistently higher prevalence of cirrhosis among men and older adults (aged 45–64 vs 18–44 years) (Figure 2a, b). In the Medicare population, the prevalence of cirrhosis was higher among men but also in the younger age group (65–74 years vs ≥75 years) (Figure 2c, d).

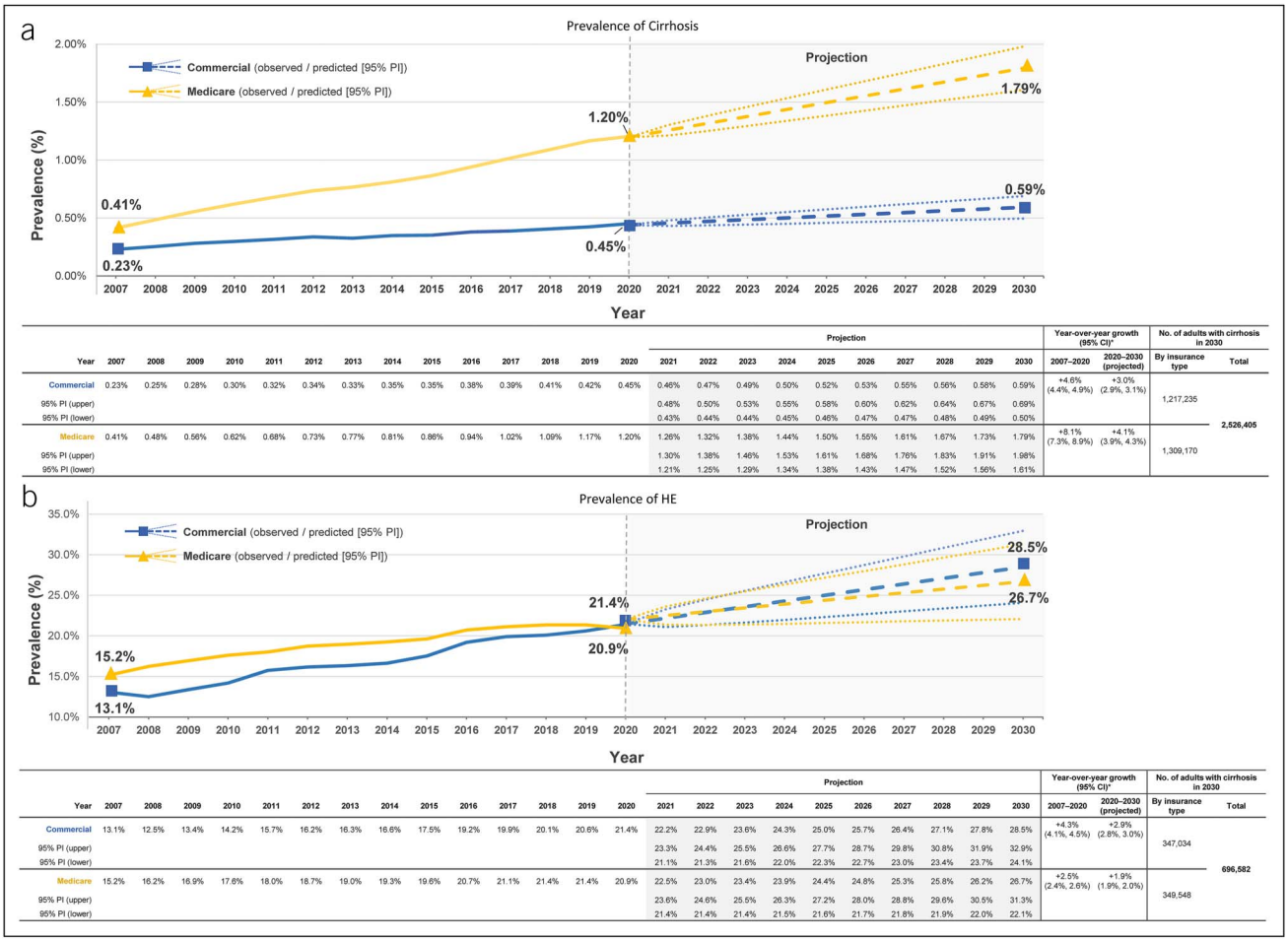
Heatmaps depicting the regional variation across the United States in the prevalence of cirrhosis in 2020 for the Commercial and Medicare populations are shown in Figure 3a. In the Commercial population, the prevalence was lowest in Rhode Island (0.21%) and highest in New Mexico (0.74%). In the Medicare population, the prevalence was lowest in Nebraska (0.64%) and highest in District of Columbia (1.61%).

When extrapolating observed linear trends, the prevalence of cirrhosis was projected to increase by 3.0% YOY (95% CI 2.9%–3.1%; $P < 0.01$) from 2020 to 0.59% (95% CI 0.50%–0.69%; $P < 0.01$) in 2030 in the Commercial population and by 4.1% YOY (95% CI 3.9%–4.3%; $P < 0.01$) to 1.79% (95% CI 1.61%–1.98%; $P < 0.01$) in 2030 in the Medicare population (Figure 1a). In 2030, the projected prevalence of cirrhosis corresponds to an estimated 2.53 million adults with cirrhosis regardless of insurance type (1.22 million adults aged 18–64 years; 1.31 million adults aged ≥65 years).

Trends in the prevalence of HE

Between 2007 and 2020, the prevalence of HE among adults with cirrhosis increased by an average of 4.3% YOY (95% CI 4.1%–4.5%; $P < 0.01$) from 13.1% to 21.4% in the Commercial population, representative of 130,087 commercially insured adults with HE in the United States in 2020, and 2.5% YOY (95% CI 2.4%–2.6%; $P < 0.01$) from 15.2% to 20.9% in the Medicare population, representative of 132,706 Medicare-insured adults with HE in the United States in 2020 (Figure 1b). Subgroup analyses by sex revealed a consistently higher prevalence among men in both populations (Figure 4b, d). Subgroup analyses by age revealed a consistently higher prevalence among adults aged 65–74 years in the Medicare population; however, in the Commercial population, prevalence among adults aged 18–44 years surpassed that of the 45–64-year age group from 2015 onward (Figure 4a, c).

The prevalence of HE among adults with cirrhosis showed regional variation across the United States in 2020. In the Commercial population, the prevalence was lowest in Illinois (17.3%) and highest in New Mexico (29.0%). In the Medicare population, the prevalence was lowest in Vermont (14.0%) and highest in Utah (28.9%) (Figure 3b).



Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2007–2020	2020–2030 (projected)	By insurance type	Total
Commercial	0.23%	0.25%	0.28%	0.30%	0.32%	0.34%	0.33%	0.35%	0.35%	0.38%	0.39%	0.41%	0.42%	0.45%	0.46%	0.47%	0.49%	0.50%	0.52%	0.53%	0.55%	0.56%	0.58%	0.59%	+4.6% (4.4%, 4.9%)	+3.0% (2.9%, 3.1%)	1,217,235	2,526,405
95% PI (upper)															0.48%	0.50%	0.53%	0.55%	0.58%	0.60%	0.62%	0.64%	0.67%	0.69%				
95% PI (lower)															0.43%	0.44%	0.44%	0.45%	0.46%	0.47%	0.47%	0.48%	0.49%	0.50%				
Medicare	0.41%	0.48%	0.56%	0.62%	0.68%	0.73%	0.77%	0.81%	0.86%	0.94%	1.02%	1.09%	1.17%	1.20%	1.26%	1.32%	1.38%	1.44%	1.50%	1.55%	1.61%	1.67%	1.73%	1.79%	+8.1% (7.3%, 8.9%)	+4.1% (3.9%, 4.3%)	1,309,170	
95% PI (upper)															1.30%	1.38%	1.46%	1.53%	1.61%	1.68%	1.76%	1.83%	1.91%	1.98%				
95% PI (lower)															1.21%	1.25%	1.29%	1.34%	1.38%	1.43%	1.47%	1.52%	1.56%	1.61%				

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2007–2020	2020–2030 (projected)	By insurance type	Total
Commercial	13.1%	12.5%	13.4%	14.2%	15.7%	16.2%	16.3%	16.6%	17.5%	19.2%	19.9%	20.1%	20.6%	21.4%	22.2%	22.9%	23.6%	24.3%	25.0%	25.7%	26.4%	27.1%	27.8%	28.5%	+4.3% (4.1%, 4.5%)	+2.9% (2.8%, 3.0%)	347,034	696,582
95% PI (upper)															23.3%	24.4%	25.5%	26.6%	27.7%	28.7%	29.8%	30.8%	31.9%	32.9%				
95% PI (lower)															21.1%	21.3%	21.6%	22.0%	22.3%	22.7%	23.0%	23.4%	23.7%	24.1%				
Medicare	15.2%	16.2%	16.9%	17.6%	18.0%	18.7%	19.0%	19.3%	19.6%	20.7%	21.1%	21.4%	21.4%	20.9%	22.5%	23.0%	23.4%	23.9%	24.4%	24.8%	25.3%	25.8%	26.2%	26.7%	+2.5% (2.4%, 2.6%)	+1.9% (1.9%, 2.0%)	349,548	
95% PI (upper)															23.6%	24.6%	25.5%	26.3%	27.2%	28.0%	28.8%	29.6%	30.5%	31.3%				
95% PI (lower)															21.4%	21.4%	21.4%	21.5%	21.6%	21.7%	21.8%	21.9%	22.0%	22.1%				

Figure 1. Prevalence of cirrhosis and HE from 2007 to 2020 and projected prevalence from 2021 to 2030 in the Commercial and Medicare populations. (**a**) Prevalence of cirrhosis. (**b**) Prevalence of HE. *$P < 0.01$. CI, confidence interval; HE, hepatic encephalopathy; PI, prediction interval.

The prevalence of HE among adults with cirrhosis was projected to increase by 2.9% YOY (95% CI 2.8%–3.0%; $P < 0.01$) in 2020 to 28.5% (95% CI 24.1%–32.9%; $P < 0.01$) in 2030 in the Commercial population, and by 1.9% YOY (95% CI 1.9%–2.0%; $P < 0.01$) to 26.7% (95% CI 22.1%–31.3%; $P < 0.01$) in 2030 in the Medicare population (Figure 1b). In 2030, the projected prevalence of HE corresponds to an estimated 697,000 adults with HE regardless of insurance type (347,000 adults aged 18–64 years; 350,000 adults aged ≥65 years). The sensitivity analysis of the projected prevalence of cirrhosis and HE using autoregressive integrated moving average models yielded similar results (see Supplementary Figure S2, Supplementary Digital Content 1, http://links.lww.com/CTG/B274).

Trends in the burden and management of OHE

Between 2007 and 2020, the rate of OHE hospitalizations among adults with HE decreased from 27.5% to 5.5% in the Commercial population and from 26.2% to 9.5% in the Medicare population (Figure 5a). Between 2007 and 2020, the inflation-adjusted average payer costs per OHE hospitalization increased from $40,881 to $77,699 in the Commercial population (Figure 5b). Over the same period in the Medicare population, average payer costs per OHE hospitalization remained relatively stable, increasing from $14,384 to $16,368; however, associated provider charges increased from $45,913 to $74,894. Rates of liver transplantation among adults with HE increased from 1.7% to 3.4% in the Commercial population and from <0.1% to 0.6% in the Medicare population (see Supplementary Figure S3, Supplementary Digital Content 1, http://links.lww.com/CTG/B274).

The prevalence of rifaximin use ± lactulose among adults with cirrhosis increased from 2.2% in 2010 to 6.3% in 2020 in the Commercial population (Figure 5c). In the Medicare population, the prevalence of rifaximin use ± lactulose among adults with cirrhosis increased from 1.2% in 2010 to 4.1% in 2014 and then decreased to 3.1% in 2020 (Figure 5d). Between 2010 and 2020, the prevalence of lactulose use without rifaximin among patients with cirrhosis decreased from 4.5% to 3.3% in the Commercial population and decreased from 9.5% to 8.4% in the Medicare population. Regional variation in the prevalence of rifaximin use among adults with cirrhosis was also apparent, ranging from 4.5% in Michigan to 10.6% in Kansas in the Commercial population and from 2.2% in Arizona to 5.6% in North Dakota in the Medicare population (see Supplementary Figure S4, Supplementary Digital Content 1, http://links.lww.com/CTG/B274). The prevalence of rifaximin use ± lactulose and use of lactulose only were also calculated among adults with HE, which revealed a higher use of rifaximin ± lactulose in 2020 in the Commercial population with HE (29.6%) relative to the Medicare population

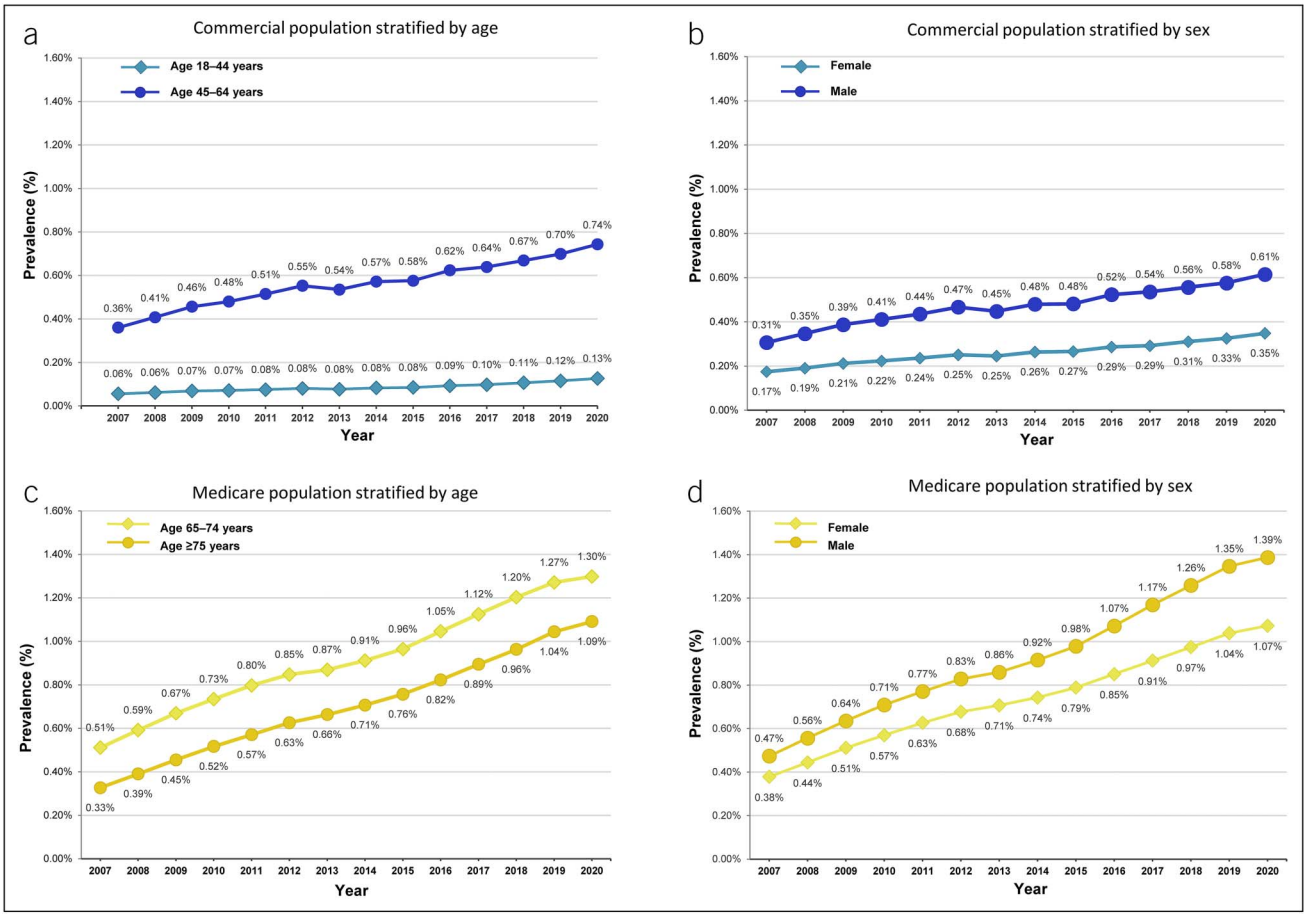


Figure 2. Prevalence of diagnosed cirrhosis from 2007 to 2020 in the Commercial and Medicare populations—stratification by sex and age. (**a**, **b**) Commercial population stratified by sex (**a**) and age (**b**). (**c**, **d**) Medicare population stratified by sex (**c**) and age (**d**).

(14.8%), and conversely, a higher proportion of adults with HE using lactulose only in the Medicare population (40.2%) relative to the Commercial population (15.5%) (see Supplementary Table S5, Supplementary Digital Content 1, http://links.lww.com/CTG/B274).

DISCUSSION

In this study using 2 large insurance claims-based healthcare databases in the United States, the projected prevalence of cirrhosis in 2030 was an estimated 2.53 million adults (1.22 million adults aged 18–64 years; 1.31 million adults aged ≥65 years). Similarly, the projected prevalence of HE in 2030 was an estimated 697,000 adults (347,000 adults aged 18–64 years; 350,000 adults aged ≥65 years). The observed rise in cirrhosis and HE prevalence over time may be partly attributable to growing disease awareness and improved coding practices. Prior research has identified gaps in providers' knowledge and inadequate management in cirrhosis care (35,36), which may have contributed to delayed identification and general undercoding and miscoding of the disease. Research focusing on improving cirrhosis care (e.g., by increasing the quality of process measures and using a centralized web-based patient registry (37,38)) may contribute to ongoing improvements in the identification of disease in claims data. In addition, as of October 2022 (after the completion of this study), a specific diagnosis code for HE was released (K76.82), which will help to ensure the proper documentation of disease and reduce concerns around misdiagnosis/miscoding in the future (39). Nonetheless, findings of this study align with previous research reporting global increases in the prevalence of cirrhosis and its complications, most notably the tripling of decompensated cirrhosis prevalence in the United States between 1990 and 2017 (40) and the high prevalence of HE among patients with cirrhosis (8,13–15,19), highlighting the need to improve cirrhosis and HE detection and management.

In the present work, a greater increase in cirrhosis prevalence from 2007 to 2020 was observed in the Medicare population than in the Commercial population, with the prevalence being nearly 3 times higher in Medicare-insured adults in 2020, underscoring the positive association between age and risk of liver diseases (41). It is well established that the management of chronic liver disease among older patients is complex (42), and hospitalization outcomes are poor compared with younger adults (43). These findings highlight the need for patient-specific approaches to care for older adults with cirrhosis, including considering factors such as comorbidities that could increase the risk of decompensation events and improved medication management. In addition, proactive measures to prevent further liver deterioration and complications of cirrhosis are crucial in this population to improve clinical outcomes and quality of life.

The prevalence of cirrhosis was higher among older age groups than that in younger age groups in this study, and there were therefore more older adults with HE in absolute terms; however, younger adults with cirrhosis had a similar and

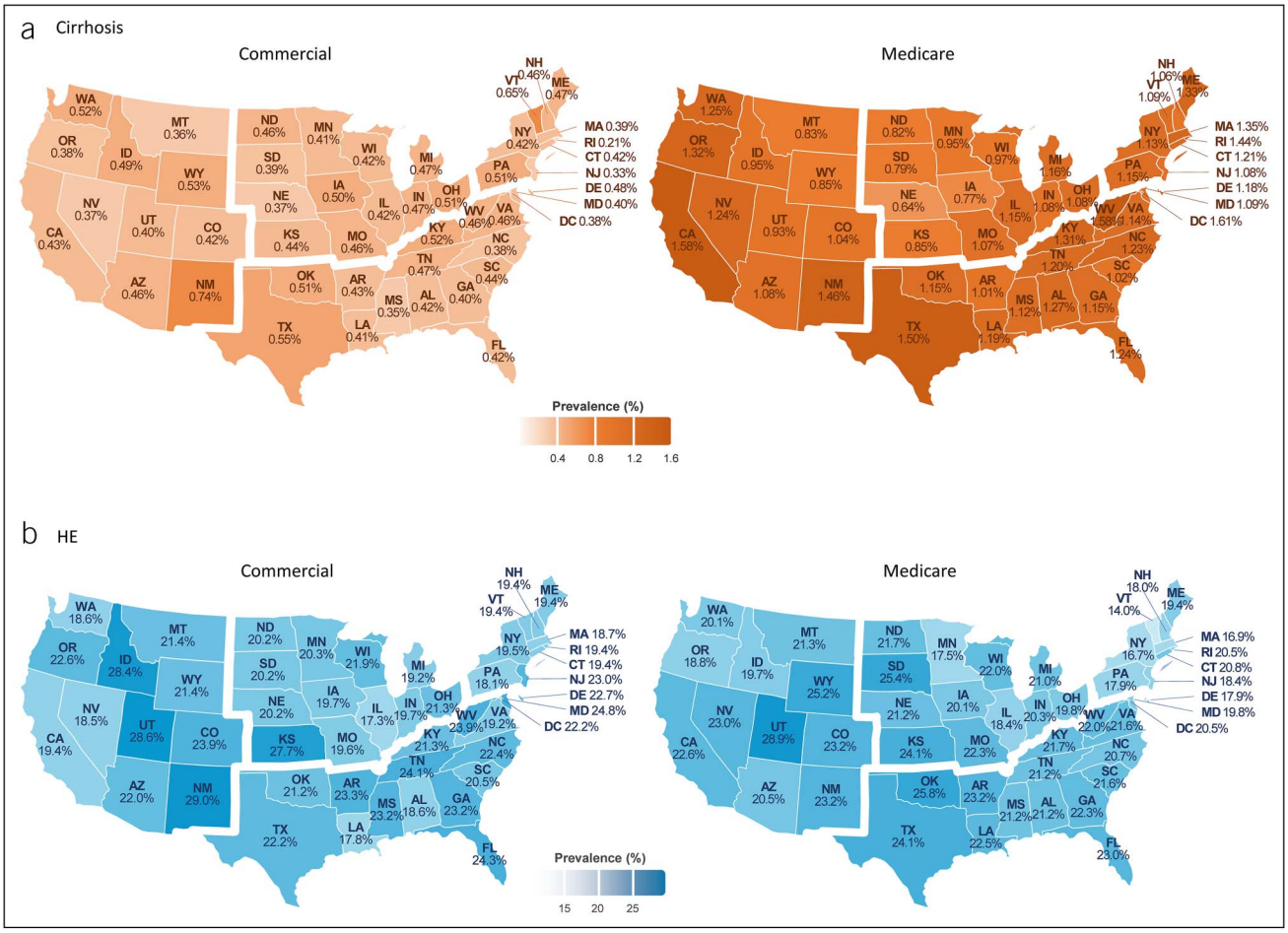


Figure 3. Regional variations across the United States in cirrhosis and HE prevalence in the Commercial and Medicare populations (2020). (**a**) Cirrhosis prevalence in the Commercial and Medicare populations. (**b**) HE prevalence in the Commercial and Medicare populations. AL, Alabama; AK, Alaska; AZ, Arizona; AR, Arkansas; CA, California; CO, Colorado; CT, Connecticut; DE, Delaware; FL, Florida; GA, Georgia; HE, hepatic encephalopathy; HI, Hawaii; ID, Idaho; IL, Illinois; IN, Indiana; IA, Iowa; KS, Kansas; KY, Kentucky; LA, Louisiana; ME, Maine; MD, Maryland; MA, Massachusetts; MI, Michigan; MN, Minnesota; MS, Mississippi; MO, Missouri; MT, Montana; NE, Nebraska; NV, Nevada; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NY, New York; NC, North Carolina; ND, North Dakota; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VT, Vermont; VA, Virginia; WA, Washington; WV, West Virginia; WI, Wisconsin; WY, Wyoming.

sometimes higher prevalence of HE once cirrhosis developed. Specifically, adults with cirrhosis aged 18–44 years in the Commercial population had the highest prevalence of HE in 2020 among all studied subgroups of adults with cirrhosis. This unexpected result may be partly driven by societal and behavioral shifts occurring in the United States, with increasing rates of obesity, type 2 diabetes, and high-risk drinking and deaths due to alcohol-related liver disease, which may have disproportionately affected younger adults (44–46). For instance, a US study using data from the National Health and Nutrition Examination Survey found increasing trends in the prevalence of obesity among young adults in the past 2 decades (47), which coincided with a period of increasing prevalence of MASLD among young adults aged 20–39 years in North America (48), and such increase was not observed in other age groups (49). Meanwhile, alcohol consumption increased during the COVID-19 pandemic, particularly among young adults (50). Altogether, these trends highlight the increasing vulnerability of younger adults to liver disease given behavioral changes within this population. Of note, several global epidemiology studies have found declining rates of liver cirrhosis attributed to viral hepatitis (51–53), and changes in the predominant etiologies of cirrhosis over the last 2 decades—with most newly diagnosed cases of cirrhosis now being due to MASLD and alcohol-associated liver disease (40,54)—may have had a greater impact in younger adults compared with older adults, leading to larger shifts in HE trends.

The increasing prevalence of cirrhosis and HE may lead to increases in recurrent and costly hospitalizations associated with OHE (14,22), which place a substantial burden on the US healthcare system (4,55). This study found that the rate of OHE hospitalizations among patients with HE declined over the study period, suggesting improved management of cirrhosis complications over time or earlier identification of HE that resulted in fewer recurrent hospitalizations. The reduction in hospitalizations could also be influenced by increased physician awareness of the high costs associated with such hospital stays and the consequent decision to treat OHE on an outpatient basis when possible. Thus, only the more severe cases of OHE would be associated with hospitalizations, resulting in a reduction in the rate of OHE hospitalizations and an increase in the average costs

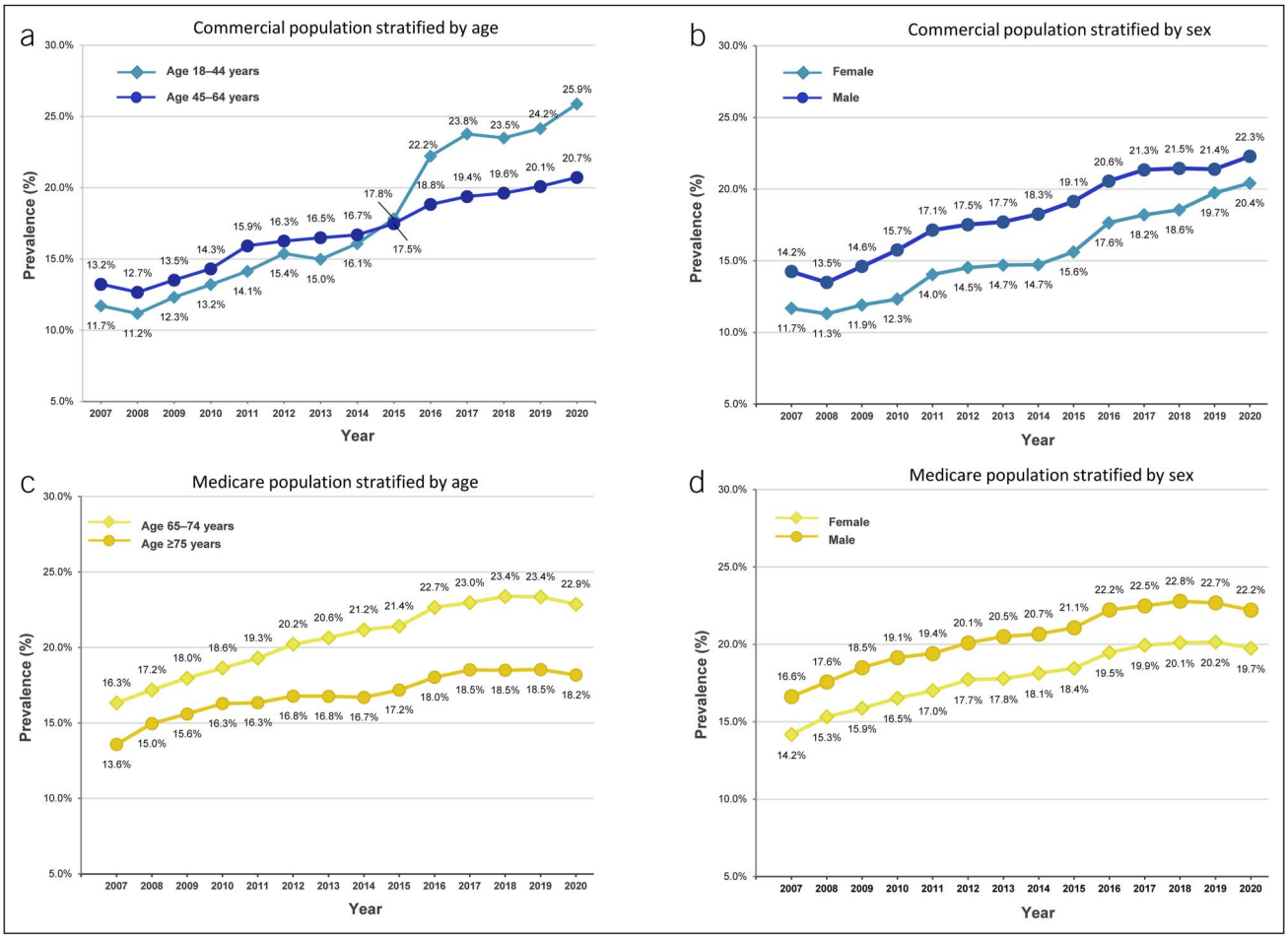


Figure 4. Prevalence of hepatic encephalopathy from 2007 to 2020 in the Commercial and Medicare populations—stratification by sex and age. (**a**, **b**) Commercial population stratified by sex (**a**) and age (**b**). (**c**, **d**) Medicare population stratified by sex (**c**) and age (**d**).

of an OHE hospitalization over time as outpatient care becomes more common. However, other studies have found that between 2010 and 2014, the prevalence of OHE hospitalizations per 100,000 hospitalizations in the United States increased by 24% (56). This could indicate that although a smaller proportion of patients with HE require hospitalization in a given year, because of the increasing prevalence of HE, a larger proportion of hospitalizations in the United States can be attributed to OHE.

Although the rate of OHE hospitalizations among patients with HE may be decreasing, the results of this study suggest that the economic burden of HE may be increasing. Among OHE hospitalizations, payer costs increased by over $40,000 per hospitalization among commercially insured adults from 2007 to 2020. Although payer costs were stable in the Medicare population, provider charges increased similarly to payer costs in the Commercial population, which may indicate an increasing resource burden to providers. The observed trend of hospitalization costs likely encompass the general increase in the cost of health care in the United States (57) and the greater complexity of care being provided, as evidenced by the increasing rate of liver transplantations (1,58). It should be noted that by design, this study did not include patients in outcome estimates for the year of their death, given the requirement for continuous health plan enrollment for the entire calendar year. Therefore, the most severe OHE hospitalizations were likely censored, and in-hospital death was not included, resulting in an underestimation of the rate and cost of OHE hospitalizations (56).

At least 1 of 5 hospital readmissions within 30 days of discharge for patients with decompensated cirrhosis are thought to be avoidable (25), yet management strategies vary. Some studies have shown that the use of rifaximin reduced the number of all-cause and OHE hospitalizations, length of hospital stay, and readmissions compared with lactulose, placebo, or no medication/treatment (28,59,60). Nonetheless, rifaximin may be underused in the management of HE, as evidenced by the discrepancy between HE prevalence and rifaximin use among adults with cirrhosis in both the Commercial and Medicare populations. The potential underuse of rifaximin may be in part due to the limited providers' knowledge of cirrhosis complications and inadequate HE management practices in hospitals (35,36,61); racial disparities in rifaximin access have also been reported (62). Furthermore, the rate of rifaximin use was lower in the Medicare population than in commercially insured adults, despite a higher prevalence of cirrhosis and similar prevalence of HE among adults with cirrhosis, suggesting the complexity of managing older patients or treatment cost concerns may have resulted in lower rifaximin use (63,64). There were also state-level disparities in both HE prevalence and prevalence of rifaximin use among

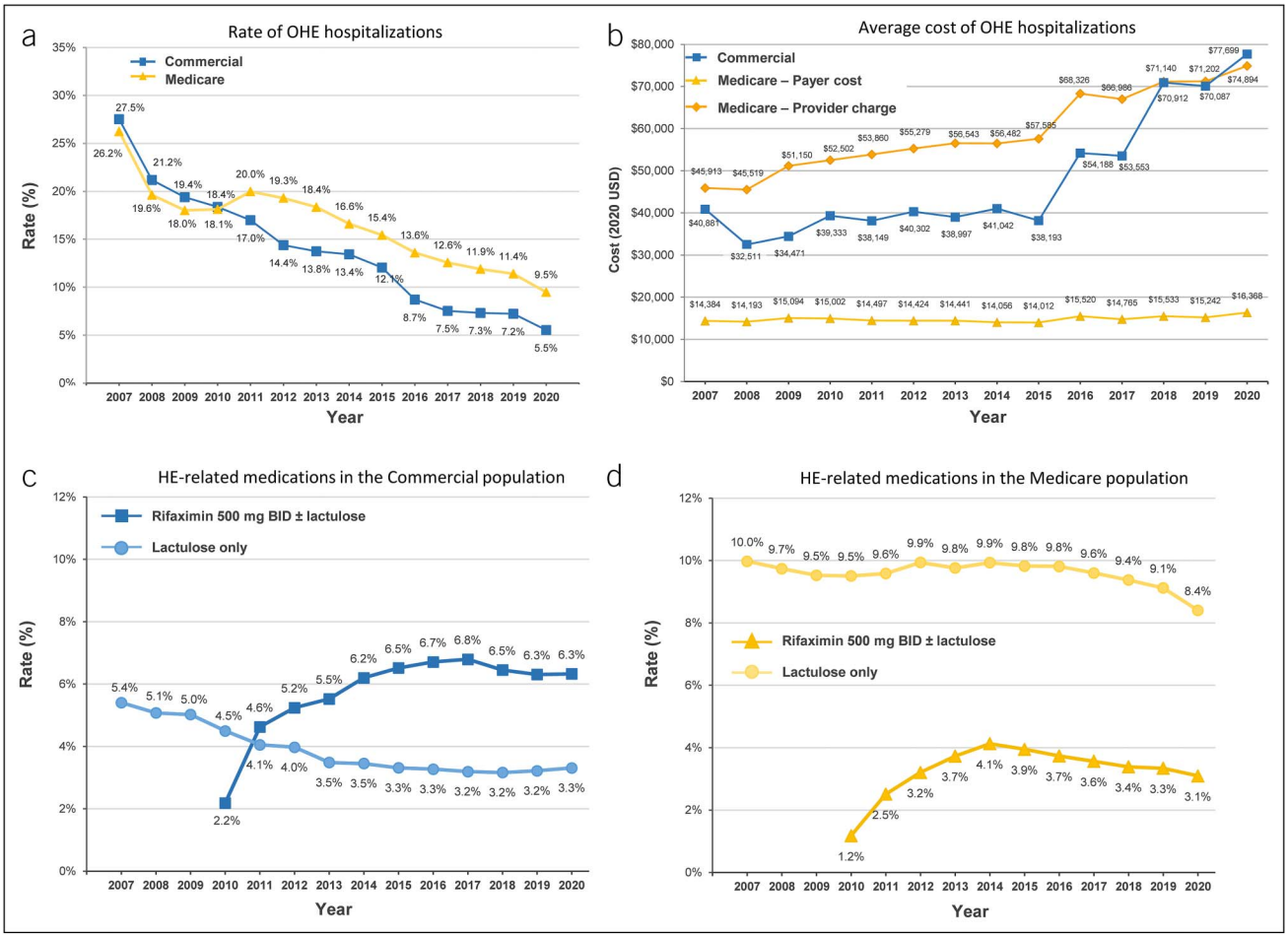


Figure 5. Rate of OHE hospitalizations and associated costs among adults with HE and rate of HE-related medication use among adults with cirrhosis in the Commercial and Medicare populations (2007–2020). (**a**) Rate of OHE hospitalizations. (**b**) Average cost of OHE hospitalizations. (**c**) Rate of HE-related medications in the Commercial population. (**d**) Rate of HE-related medications in the Medicare population. For the Commercial Claims database, payer costs per hospitalization were defined as total net payment plus coordination of benefits amounts listed on claims associated with each hospitalization. For the Medicare Research Identifiable Files database, payer costs were defined as the Medicare claim payment plus the sum of claim pass-through per diem amounts as applicable for each hospitalization. Provider charge per hospitalization was defined as the claim total charge amount for each hospitalization (i.e., total charges for all services included on the institutional claim prior to adjustments). BID, twice daily; HE, hepatic encephalopathy; OHE, overt HE; USD, United States dollars.

patients with cirrhosis. Taken together, these findings suggest variations in care practices across the United States and suboptimal management—especially of older patients—including delays in treatment and barriers to access. Strategies to ensure access to care are thus critical for optimizing patient management including the potential for the US government to negotiate prescription drug prices for Medicare beneficiaries.

The prevalence projections in this study indicate that the burden of cirrhosis of HE will continue to grow with cirrhosis and HE projected to affect approximately 2.5 million and 700,000 adults in the United States, respectively, in 2030. Without concerted efforts to alter this epidemiologic trajectory—such as policy changes or interventions that address excessive alcohol consumption and obesity and related disorders (51,65,66)—the prevalence of cirrhosis and HE will continue increasing over time. The study findings shed light on this growing public health challenge and underscore the importance of improving strategies for managing cirrhosis, including the critical need for novel therapies to address the underlying liver disease etiologies, especially for MASLD and alcohol-associated liver disease (51), proactive measures to identify patients at high risk of decompensation, and early detection and prevention of HE (18,67). Furthermore, the current US healthcare system is close to capacity and occupancy demand can sometimes surpass capacity (68). To this end, in addition to improving cirrhosis and HE identification and management strategies, future healthcare planning should also consider reducing barriers and inequities to access for cirrhosis-related medications, improving administrative efficiency, and ensuring comprehensive care, which are essential to address the concerning epidemiologic trends of cirrhosis and HE and to ensure the healthcare system has the capability to alleviate the associated burden (27,68).

This study was limited to commercially and Medicare-insured adults and did not examine cirrhosis epidemiology in populations with Medicaid insurance, which covers low-income individuals, or no insurance. As the prevalence of chronic liver disease and cirrhosis is higher among adults with low socioeconomic status

(69), applying the prevalence estimates from commercially and Medicare-insured individuals to those with Medicaid insurance and the uninsured may underestimate the actual prevalence of cirrhosis and HE in the United States. In addition, when estimating prevalence, prevalent cases of cirrhosis and HE were carried forward under the assumption that both conditions are chronic in nature; however, this does not account for potential recompensation of cirrhosis.

Trend projections through 2030 were based on data from 2007 to 2020 and did not account for future shifts in etiologies, advances in liver disease and cirrhosis treatment, or new policy initiatives. This limitation is of particular interest, given changes in factors that could affect cirrhosis and HE prevalence that have occurred since 2021 including increased rates of alcohol-associated liver disease during and after the COVID-19 pandemic (70) and the FDA approval of the first pharmacologic treatment for metabolic dysfunction-associated steatohepatitis (71). The cumulative impact of such factors on the prevalence of cirrhosis and HE should be further analyzed in future research. This study was also subject to limitations inherent to healthcare claims analyses such as lack of access to clinical confirmation of the diagnoses and possible misclassification of cirrhosis or HE due to erroneous or missing data.

In summary, the prevalence of cirrhosis and HE is increasing in the United States and is projected to continue to increase if current trends persist. Our data estimate that in 2030, the projected prevalence of cirrhosis will be 2.53 million adults, and the projected prevalence of HE will be 697,000 adults.

These trends may be influenced by multiple factors including changes in clinical practice and guidelines, shifting etiologies of cirrhosis, growing awareness of disease complications, and the aging population. Overall, the results of this study highlight the need to improve management of cirrhosis and HE, reduce barriers to accessing medications, and consider policy actions to alleviate the burden of disease for patients with chronic liver disease.

CONFLICTS OF INTEREST

Guarantor of the article: Jessica Maitland, MScPH.

Specific author contributions: R.J.W.: conceptualization, formal analysis, methodology, writing—review and editing. P.G.-S.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing—original draft, writing—review and editing. Z.H.: conceptualization, formal analysis, methodology, writing—review and editing. J.M.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing—original draft, writing—review and editing. R.B.: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing—original draft, writing—review and editing. A.G.: conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing—original draft, writing—review and editing. A.S.: conceptualization, formal analysis, methodology, project administration, writing—review and editing. O.O.: conceptualization, formal analysis, methodology, project administration, writing—review and editing. B.B.: conceptualization, formal analysis, methodology, project administration, resources, supervision, writing—review and editing.

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Study Highlights

WHAT IS KNOWN

- ✓ Cirrhosis and hepatic encephalopathy (HE) are a leading cause of morbidity and mortality.
- ✓ Updated epidemiologic trends of cirrhosis and HE in the United States are lacking.

WHAT IS NEW HERE

- ✓ Prevalence of cirrhosis and HE in the United States had been increasing from 2007 to 2020.
- ✓ In 2030, cirrhosis and HE may affect approximately 2.5 million and 700,000 US adults, respectively.
- ✓ Improved management strategies and policies are needed to alleviate the burden of chronic liver disease.

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