The High Burden of Alcoholic Cirrhosis in Privately Insured Persons in the United States

Short title: Alcoholic cirrhosis burden in the US

Jessica L. Mellinger MD MSc[1], Kerby Shedden PhD[2], Gerald Scott Winder MD MSc[3], Elliot Tapper MD[1], Megan Adams MD MSc[1,4], Robert J Fontana MD[1], Michael L. Volk, MD MSc[5], Frederic C. Blow, PhD[3,4], and Anna SF Lok, MD.[1]

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI [2]Department of Statistics, University of Michigan, Ann Arbor, MI, [3]Department of Psychiatry [4]VA Center for Clinical Management Research (CCMR), Ann Arbor, MI, [5]Transplantation Institute, Loma Linda University Health, Loma Linda CA.

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Corresponding Author:
Jessica L. Mellinger MD MSc
1500 E. Medical Center Dr.
3912 Taubman Center, SPC 5362
Ann Arbor, MI 48109
Email: jmelling@med.umich.edu
Phone: 734-936-8745

Abbreviations:
AC: alcoholic cirrhosis
AKI: acute kidney injury
ALD: alcoholic liver disease
AUD: alcohol use disorder
CMS: Center for Medicare and Medicaid
ESI: employer-sponsored insurance
HCC: hepatocellular carcinoma
HCV: hepatitis C
HRS: hepatorenal syndrome
ICD: International Classification of Disease (9th and 10th Editions)
MEPS: Medical Expenditure Panel Survey
SBP: spontaneous bacterial peritonitis

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Background and Aims: Alcoholic cirrhosis (AC) is a major cause of liver-related morbidity and mortality in the United States (US). Rising rates of alcohol use disorders in the US will likely result in more alcoholic liver disease. Our aim was to determine the prevalence, healthcare utilization, and costs of AC among privately insured persons in the US. **Methods:** We collected data from persons aged 18-64 with AC (identified by ICD-9/ICD-10 codes) enrolled in the Truven MarketScan Commercial Claims and Encounters database (2009-2015). We determined yearly prevalence, weighted to the national employer-sponsored, privately insured population. Using competing risk analysis, we estimated event rates for portal hypertensive complications and estimated the association between alcoholic cirrhosis and costs as well as admissions and readmissions. **Results:** 294,215 people had cirrhosis in 2015 and 105,871 (36%) had AC. Mean age at AC diagnosis was 53.5 years. 32% were women. Over the 7 years queried, estimated national cirrhosis prevalence rose from 0.19% to 0.27% ($p<0.001$) and from 0.07% to 0.10% ($p<0.001$) for AC. Compared to non-AC, AC enrollees were significantly more likely to have portal hypertensive complications at diagnosis, and higher yearly cirrhosis and alcohol-related admissions (25 excess cirrhosis admissions and 6.3 excess alcohol-related admissions per 100 enrollees) as well as all-cause readmissions. Per-person costs in the first year after diagnosis nearly doubled for AC versus non-AC persons (US$ 44,835 vs 23,319). **Conclusion:** In a nationally representative cohort of privately insured persons, AC enrollees were disproportionately sicker at presentation, admitted and readmitted more often, and incurred nearly double the per-person healthcare costs compared to those with non-AC.

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Alcoholic liver disease (ALD) resulting from chronic heavy alcohol consumption is a large and growing problem in the United States (US), making it the second leading indication for liver transplantation(1-3). Worldwide, ALD is thought to be responsible for nearly half of the liver-related mortality(4,5). ALD is a spectrum of liver disease, ranging from mild fatty liver to more severe forms, such as alcoholic cirrhosis (AC) and alcoholic hepatitis. Chronic heavy alcohol consumption results in AC and portal hypertension, causing high rates of variceal bleeding, ascites, hepatic encephalopathy, and death(6-8). Alcohol abstinence frequently improves liver function, portal hypertensive complications, and mortality, even in advanced stages of AC or alcoholic hepatitis(9,10).

Unfortunately, alcohol consumption is increasing in the US. From 2001 to 2012, the prevalence of alcohol use disorder (AUD) increased by 50% in the US general population (from 8.5% to 13%), affecting nearly 1 in 6 Americans(11). This increase disproportionately affected women, older adults, and persons of lower socioeconomic status(11). The annual rates of specialty addiction care use in the US are approximately 8% and are subject to variable degrees of coverage by insurance payors(12). The impact of these trends is compounded by the increasing rates of cirrhosis-related death already affecting several segments of the US population(13). Given these increased rates of AUD, the overall incidence of AC will likely increase, magnifying the importance of accurate data on AC prevalence, costs, hospitalizations, and complications.

Prior large US dataset analyses have focused on *non-cirrhotic* ALD, with estimated prevalence ranging from 2-2.5%(14). Another analysis from a large national dataset, inclusive of all insurance types, assessed the prevalence of all-cause cirrhosis to be 0.27%(15). In the Veteran's Administration (VA) system, the prevalence of all-cause cirrhosis is high at 1.0%, but this data cannot be generalized to the US population owing to low female representation and differences in socio-economic status and comorbidities(18). These studies, however, did *not* provide direct estimates of AC in the privately

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insured US population. While many European databases include comprehensive population data from birth to death, US health insurance data is fragmented between private insurance, Medicare and Medicaid, the VA, and the uninsured, making national estimates of AC burden more challenging.

A correct assessment of AC's healthcare burden is essential to create sensible policy initiatives, design effective treatment protocols, and appropriately allocate resources. Since half of the US is privately insured (employer-based being by far the most common), large databases representative of this population are useful in efforts to estimate AC's broader impact and burden in the US. Our aim was to query a large, nationally representative cohort of employer-sponsored insurance claims to determine the impact of AC on the privately insured US population.

Methods

Database

This study was reviewed by the Institutional Review Board of the University of Michigan and was exempted from IRB review. We queried the 2009-2015 MarketScan Commercial Claims and Encounters (CCAE) database, a large administrative claims database maintained by Truven Analytics. The database's structure permits a researcher to follow a single enrollee through multiple years of enrollment across inpatient and outpatient settings. MarketScan is one of the largest and most comprehensive private insurance administrative datasets that is widely used in healthcare delivery, epidemiology, and economic burden research(19-23). Drawing on all regions of the US, it contains private, employer-based insurance claims from more than 100 insurers, catalogs nearly 500 million claims from over 100 million enrollees and their dependents, and calculates population-level weights so research findings can be generalized to the approximately 150 million privately insured US adults. MarketScan nearly approximates the entire population with employer-sponsored insurance (ESI), which, in 2012, numbered 115,510,639 persons between the ages of 18-64.

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Cohort Selection

Study enrollees from MarketScan data (2009-2015) were between the ages of 18-64 and had at least one diagnosis code for cirrhosis (571.2 or 571.5) with at least 1 year of continuous enrollment, inclusive of the index cirrhosis diagnosis(24) (see Appendix A). All study data were restricted to the continuous enrollment period containing the cirrhosis diagnosis. Cirrhosis diagnosis was determined by International Classification of Diseases 9th revision (ICD-9) or 10th revision (ICD-10) cirrhosis codes identified during the study period. Because cirrhosis complications, such as variceal bleeding or ascites, could be coded prior to a code for cirrhosis, the index cirrhosis diagnosis date was defined as the earliest date on which a diagnosis code for a portal hypertensive complication (portal hypertension, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, varices with or without bleeding, hepatic encephalopathy) *or* cirrhosis was observed (see Appendix A). Single ICD-9 codes for cirrhosis and its complications have been validated in administrative data with positive predictive values of 80% or greater (24,25).

Using published criteria(18), an AC diagnosis was defined in our study as a discrete AC diagnosis code or a general, non-alcohol-related cirrhosis code *plus* either an alcohol use code or a code for an alcohol-related comorbidity (see Appendix A for list of codes used). Enrollees who met criteria for comorbid AC and hepatitis C (HCV) or other liver disease were included in the AC cohort. Non-AC was defined as the presence of a non-alcohol-related cirrhosis code, regardless of etiology, *without* any alcohol-related comorbidity diagnoses. Comorbidities were ascertained using ICD-9 and ICD-10 codes (see Appendix A) and Elixhauser scores were calculated excluding the liver and alcohol categories(26). Decompensated cirrhosis was defined by a cirrhosis code *and* a portal hypertensive complication (ascites, hepatic encephalopathy, or variceal bleeding).

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Prevalence

Yearly prevalence was defined as the number of eligible ESI covered persons with cirrhosis in a given year who were covered throughout that year *and* whose index cirrhosis diagnosis date fell between January 1, 2009 and the last day of the year of interest (for example, prevalence for 2010 would include all cirrhosis diagnoses for 2009 as well as those occurring on or before December 31, 2010). Prevalence of cirrhosis in ESI US population by year was estimated by projecting the estimated number of MarketScan enrollees with cirrhosis to the national ESI population using weights derived from the Medical Expenditure Panel Survey (MEPS)(27). MarketScan provides weights based on 5 factors: age (<45 or ≥45), sex, census region, employee status, and Metropolitan Statistical Area (MSA), a standard unit of geographic analysis. However, in 2015, Truven Analytics changed the weighting criteria, removing MSA. In order to derive uniform weights across all years, we calculated weights for each year (2009-2015) using the four remaining MEPS factors: age (<45 or ≥45), sex, census region, and employee status (policy-holder versus covered dependent). The ESI population was then stratified into 32 strata based on these factors and, for each year from 2009-2015, the ESI population size for each stratum was calculated using data from MEPS. For each stratum, we determined the proportion of MarketScan subjects with a cirrhosis or AC code in a given year, and then multiplied these values by the corresponding ESI stratum size to obtain preliminary totals. Please see Supplemental Methods for further details.

Two issues with limited time windows in administrative datasets can result in an overestimate of prevalence trends. First, because cirrhosis patients enrolled over several years may go a year or longer between cirrhosis codes, prevalence estimates calculated by simply counting the number of cirrhosis cases based on encounters in a given year would be falsely low. For example, an enrollee with continuous enrollment over several years may receive a diagnosis of cirrhosis without any other complications in 2009, not interact with the healthcare system in 2010, and reappear in the dataset in

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2011 after receiving some type of healthcare. Since cirrhosis does not go away, we would want to count this individual in our prevalence estimates for 2010. Second, given that patients may be diagnosed with cirrhosis in the years before our data window (for example, 2007 or 2008), the early years of the data may be falsely low in prevalence, thus overestimating the slope of the overall trend. To account for these downward biases which underestimate yearly prevalence in the early years of the dataset and overestimate the time trend, we used standard methods for undercount adjustment in which we first estimated prevalence by determining the number of people with cirrhosis-related encounters in each year, then adjusted these numbers by a stratum-specific estimate of the undercounting due to missing people who had cirrhosis but had no claim in the given year. For detailed statistical methods, please see Supplementary Methods: Appendix B.

Event rates analysis

The primary event rates analysis used competing risks methodology to assess the time from diagnosis to onset of various cirrhosis complications, treating death as a competing event to complications, and censoring at loss of coverage(28). Because portal hypertensive complications can co-occur and be present at the same time (as when a patient has both hepatic encephalopathy and a variceal bleed), the complications do not compete with each other and we estimate their rates separately. Competing risks is used for analysis of deaths since each complication competes with death. Determining the burden of portal hypertensive events after the index cirrhosis diagnosis requires adjusting for enrollees lost from the dataset due to loss of insurance coverage, change in employment, or transition to disability due to progressive illness. Competing risk analysis alone is sufficient when time to loss of coverage is independent of time to each event ("independent censoring"). To accommodate any bias due to non-independent censoring, we performed an additional sensitivity analysis in which we fit a proportional hazards regression model using loss of coverage as the outcome with age and Elixhauser comorbidity scores as predictors(26). Event rates

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were then estimated using stratified competing risks methodology with strata defined by individual risk for coverage loss(28). We performed an additional sensitivity analysis of event rates among enrollees with AC but without hepatitis C, utilizing the same methodology.

Overall Direct Healthcare Costs

Direct healthcare costs result from tangible, billable services such as clinic visits, medications and hospitalizations. Indirect costs represent missed days of work or impaired quality of life, as examples. Cumulative direct costs for each person from index diagnosis date up to 12 months from cirrhosis diagnosis were calculated by summing the net payments to a provider across all claims. Co-payments, co-insurance, and coordination of benefits fees were excluded. Enrollees had to have coverage and be alive for at least one month post-diagnosis to be included in the cost analysis. Per-person costs were capped at 1 million US$ in the first year after diagnosis to exclude outliers resulting from inaccurate data entry. Values were log transformed and regressed against a variety of risk factors (portal hypertensive complications, Elixhauser, age, gender, census region, year of diagnosis as well as interactions amongst these variables). Fitted costs were calculated at 1-year post-diagnosis for enrollees who did not die within one year, and were calculated at the date of death otherwise. The resulting fitted costs were then projected to the 2012 ESI population with national weights in the same method as described above. In determining which specific factors contributed to rising costs, we distinguished costs attributed to AC directly as well as costs associated with specific portal hypertensive complications using multivariable regression analysis, which allowed us to disaggregate the influences on costs of multiple cirrhosis-related complications, even when these complications co-occurred in a given enrollee.

Overall admissions

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Admissions were analyzed using similar statistical methods as discussed above for costs except negative binomial regression was used as appropriate for count data. Admissions were subdivided into three main types based on primary diagnosis at admission: all-cause, cirrhosis-related, and alcohol-related. Cirrhosis-related admissions were defined as hospitalizations in which the primary diagnosis was for either cirrhosis or a portal hypertensive complication, and for alcohol-related admissions, an alcohol-related diagnosis code (see Appendix A). The cumulative number of admissions from time of cirrhosis diagnosis through the first year after diagnosis was calculated for each enrollee. Associations between risk factors of interest and admissions/readmissions were estimated using identical methods as above for costs. Results are reported as differences in the number of admissions per 100 enrollees per year, contrasting two groups of interest (for example, comparing the number of admissions in the first year after diagnosis for 100 persons with AC to 100 persons with non-AC). 30-day readmission rates following any admission type were calculated in a similar manner as for admissions.

Results

Prevalence of cirrhosis and AC in the privately insured (nationally adjusted ESI) US population

Prevalence of all-cause cirrhosis in the privately insured US population based on the projected national ESI population increased by 42%, from 0.19% (236,349) in 2009 to 0.27% (294,215) ($p<0.001$) by 2015 (Figure 1). During the same period, prevalence of AC increased by 43%, from 0.07% to 0.10% ($p<0.001$). In a sensitivity analysis, the prevalence of AC without HCV increased by 44% (0.05% to 0.072%). Persons age <45 had a more pronounced 300% increase from 0.01% to 0.03% ($p<0.001$), compared to a 46% increase in those ≥45 years old (0.13% to 0.19%). Women had a greater increase in prevalence of AC of 50% (0.04% to 0.06%) over 2009 to 2015, while men had a less pronounced increase of 30% (0.10% to 0.13%) (Figure 2).

Characteristics of MarketScan enrollees with AC and non-AC at diagnosis

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169,531 MarketScan enrollees had a cirrhosis diagnosis at some time during the period 2009-2015; of these, 66,053 (39%) had AC (see Table 1). The median age at AC diagnosis was 53.5 years versus 53.0 years for non-AC. Notably, approximately one-third (32%) of those with AC and 49% of those with non-AC were women. At diagnosis, 19% of AC enrollees and 28% of non-AC enrollees had an HCV diagnosis. A higher proportion of enrollees with AC were decompensated compared to those with non-AC (28% vs 10%, p<0.001) (Table 1). The proportion with HCC between the two groups was similar at baseline (2% vs 2%). AC enrollees had more comorbidities at diagnosis (2.63 vs 2.30, p<0.001) compared to those with non-AC.

Events in MarketScan enrollees with AC and those with non-AC

The median duration of coverage was 688 days for enrollees with AC and 655 days for those with non-AC (p<0.001). The proportion with HCV diagnosis code increased in both groups, from 19% to 29% in those with AC and from 28% to 35% in those with non-AC at 2 years after index cirrhosis diagnosis (Table 1). At 2 years post diagnosis, a significantly higher proportion of AC enrollees had portal hypertensive complications than those with non-AC though the rates of increase in both groups were similar. For example, ascites was diagnosed in 45% of AC enrollees and in 18% of those with non-AC (p<0.001) by 2 years' post-cirrhosis diagnosis but the fold-increase were 2.0 and 2.4, respectively (Table 1). Results were similar for sensitivity analyses accounting for dependent censoring (data not shown). In an analysis comparing men with AC versus women with AC, women had slightly higher rates of decompensation at baseline (23% versus 21%) while men had higher rates of comorbid HCV (21% vs 14%) and HCC (2% vs <1%) at baseline (see Supplemental Table 1).

In a sensitivity analysis comparing AC enrollees with and without comorbid HCV, those with cirrhosis attributed to alcohol alone had slightly higher rates of decompensation at baseline, but overall decompensation rates were similar at 2-years post-diagnosis (see Table 2). HCC, however, occurred

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with greater frequency at baseline (1.7% vs 0.08%, p<0.001) and at 2-years post-diagnosis (8% vs 4%, p<0.001) in those with versus those without comorbid HCV. AC enrollees with comorbid HCV were also more likely to be transplanted at 2-years post-diagnosis (3% vs 2%, p<0.001, data not shown).

Admissions and re-admissions in the MarketScan enrollees

The projected annual all-cause admissions for the MarketScan enrolled cohort in 2015 for cirrhosis were 216,203, of which 107,501 (50%) were for those with AC. AC enrollees had higher rates of all-cause, cirrhosis-related, as well as alcohol-related admissions compared to those with non-AC. Mean per-person all-cause admissions in the first-year after diagnosis was 1.1 for AC compared to 0.5 for non-AC. AC had 58.5 excess all-cause admissions, 25 excess cirrhosis-related admissions, and 6.3 excess alcohol-related admissions per 100 enrollees per year compared to non-AC. In regression models controlling for all demographic and baseline complications, AC contributed to 37% higher all-cause admissions (p<0.01) and 99% higher cirrhosis-specific admissions (p<0.01). 30-day readmissions were also higher for AC (30 excess all-cause readmissions per 100 enrollees per year).

Direct healthcare costs for AC and non-AC in nationally weighted ESI population

Overall direct healthcare costs in the nationally weighted ESI population for all cirrhosis was 9.5 billion US$ in 2015 alone, with 53% of costs accrued by those with AC (5.04 billion US$) even though these enrollees only comprised 36% of the total cirrhosis population (see Figure 3). Per-person healthcare costs for AC were markedly higher than for non-AC, with a mean of 44,835 US$ per person in the first year after index diagnosis compared to 23,319 US$ for non-AC. In a sensitivity analysis of AC without HCV, mean per-person costs were slightly attenuated at 39,299 US$ for AC without HCV. Mean per-person healthcare costs in the first year after index cirrhosis diagnosis were higher for those with decompensated cirrhosis (68,982 US$ vs 12,316 US$) compared to those

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without decompensation. Decompensating events, admissions and readmissions were significantly more common in persons with AC contributing to the higher per-person costs (see Table 3).

Discussion

In this large cohort of private, employer-sponsored insured cirrhosis persons, AC made up just over one-third of the total cirrhosis burden in the nationally weighted ESI population in the US, consumed just over half the overall direct healthcare expenditures among persons with cirrhosis, and had healthcare costs nearly double their non-AC counterparts. AC enrollees presented with more portal hypertensive complications and had similar rates of disease progression during the follow-up period. They were also more frequently admitted and readmitted even after covariate adjustment.

Our overall cirrhosis prevalence of 0.27% is consistent with the findings of the US National Health And Nutrition Examination Survey (NHANES)(15), but our data highlight the burden of AC which was not directly assessed in the NHANES study. We found that AC accounted for 37% of all cirrhosis giving a national ESI AC prevalence of 0.10%, or approximately 100 people with AC per 100,000 people with ESI. Studies in the Department of Veteran's Affairs (VA) health care system in 2013 demonstrated a higher cirrhosis prevalence of 1.03%, with AC making up 30%. In that study, however, 61% of those with HCV had comorbid AC and these patients were coded as HCV cirrhosis and not AC, resulting in an underestimate of the attributable burden of AC in the VA population(18). A recently published study showed decreasing prevalence of AC, despite rising rates of liver transplantations done for ALD(1). Similar to the VA study, this study classified all AC with HCV as HCV cirrhosis and *not* AC. Excluding AC with comorbid HCV or nonalcoholic fatty liver disease (NAFLD) underestimates the attributable burden of ALD and masks its importance as a driver of progressive liver disease(29). To obtain accurate estimates of ALD burden, future studies should report overall liver disease burden related to alcohol use and the contributions of comorbid HCV.

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Our data adds to and extends the literature on cirrhosis prevalence by focusing specifically on AC prevalence, as well as determining cirrhosis and AC prevalence in the national ESI population drawn from a well-characterized dataset of administrative claims, the Truven MarketScan database. This large-scale national database of private employer-sponsored insured US adults has been widely used to estimate disease prevalence, outcomes, and costs for a number of disease conditions, including gastroenterological diseases.(19-22) With nearly half the US population obtaining insurance via their employer, the scope of MarketScan enrollment, which includes >100 million individual covered lives with half a billion claims over multiple years, allows for such large-scale estimates and greater generalizability to a broader subset of the US population. Importantly, since AC has been shown to represent more than half of all US inpatient cirrhosis-related admissions while only 23% of cirrhosis discharges had private insurance, our data likely *understates* the overall burden of ALD amongst the entire US population and represents the *best case scenario* for AC in the US(30,31). The true prevalence of AC in the US may be much higher when accounting for Medicare and Medicaid patients, particularly given that many patients with cirrhosis are 65 or older and were excluded from our study. Though recently reversed, the Center for Medicare and Medicaid (CMS) had previously eliminated all substance use disorder claims from their available datasets, thus limiting analysis of substance-related medical disease like ALD in persons covered by Medicare or Medicaid(16). Many AC patients are Medicaid-insured due to low income and socioeconomic status, and as many as 50% of them will lose eligibility yearly due to income fluctuations, making large-scale national analyses of this population over time challenging(17). Even within our well-characterized cohort, AC prevalence may be underestimated due to failure to recognize an alcohol etiology, which has been shown to occur in other studies where mortality from ALD was under-estimated by two-fold due to patient concealment and stigma(5). In addition, alcoholic hepatitis, which is also associated with high costs, readmissions, and mortality, is poorly ascertained using diagnostic coding and were excluded from this analysis except for those with a cirrhosis code, thus underestimating the burden of advanced

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ALD(32).

The burden of cirrhosis in the US has not been given the same priority as other high-cost diseases, such as cancer, because of lower prevalence. However, burden of disease should be compared on the basis of similar mortality risks and resource utilization. The prevalence of AC and non-AC is comparable to or surpasses that of lung and colorectal cancers (0.13% and 0.33%, respectively)(33). One-year mortality rates for decompensated AC patients are 29-64%, compared to 11-12% for colorectal cancer patients and 50% for lung cancer patients aged 18-64(33). The costs of AC and non-AC also approximate the range of per-person yearly costs of cancer patients regardless of treatment (21,000 US$ to 90,000 US$ in commercially insured persons)(34). Our estimates of yearly costs of managing decompensated cirrhosis, hepatorenal syndrome and HCC are similar to previously published cost estimates supporting the robustness of our cost estimates(35-37). In studies of the global burden of AC, its disability-adjusted life year (DALY) burden exceeded that of other alcohol-related malignancies(38). The global burden of AC is likewise high, estimated at 12.8% of total healthcare costs and 2.5% of total Gross Domestic Product (GDP) in high-income countries and 5.6% and 2.1%, respectively in middle-income countries(38).

Our study showed an increase in AC prevalence in all age groups during the study period 2009-2015, with a more pronounced increase amongst enrollees <45 years old as well as a greater rate of increase amongst women. Although some of the increase may be related to diagnostic coding limitations (i.e. the diagnosis might be present but not entered until after the subject had been followed for a time), we adjusted prevalence results to mitigate this bias. Other studies have shown an increase in non-cirrhotic ALD prevalence. One study showed an increase in prevalence of non-cirrhotic ALD from 1.38% to 2.05% from 1988 to 2008 with projected AC soon comprising the largest portion of the cirrhosis and liver transplant burden(14,30). Increases in prevalence and mortality had

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also been reported for non-AC patients(13,30). The rise in AC for younger persons has implications for indirect costs as well, including early mortality and decreased work productivity, as well as continued higher direct health-care costs and utilization in subsequent years should these young persons survive. The higher rate of increase in AC amongst women (50% vs 30% for men over 2009-2015) mirrors the rise in AUDs recently reported in the US population, where women experienced an 80% increase in rates of AUDs compared to 30% for men(11). This is particularly concerning given that the hepatotoxic dose of alcohol for women is lower than that for men(11). These rising rates of AUDs in women will likely worsen existing rising trends in cirrhosis and substance abuse-related mortality for middle-aged women, rates which are already at historically high levels (13). With these rising rates, increased attention to early diagnosis of ALD and AC in women will be needed. In particular, attention to developing AUD treatment options tailored for women's preferences and helping both women and men connect to alcohol use treatment will be critical in improving outcomes for this population.

A striking finding of our study was the disproportional cost burden of AC comprising just over half of the total direct healthcare costs for cirrhosis while representing only 36% of all cirrhosis. Further, the per-person costs were nearly double that of non-AC. Much of this cost burden was attributable to significantly higher rates of portal hypertensive complications, as well as admissions and readmissions in AC enrollees, findings which support previously published data from AC patients in Europe and the US, though our cost findings are novel with respect to privately insured US AC and non-AC populations(2). While reasons for the higher prevalence of portal hypertensive complications at diagnosis in AC enrollees are not fully clear from our data, delayed diagnosis of ALD prior to cirrhosis, delays by patients with alcohol use disorders in seeking medical care, and ongoing alcohol use despite the presence of liver disease may be contributory as the higher prevalence of portal hypertensive complications at index diagnosis persisted in sensitivity analyses controlling for comorbid HCV. Our data suggest that the costs of AC will continue to increase unless measures are

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implemented to find and treat AC patients earlier by facilitating alcohol abstinence, the most effective intervention to halt liver disease progression(4). Admissions and readmissions for AC were likewise higher than for non-AC, contributing to the cost burden. Our findings confirm data from the Healthcare Utilization Project, a large well-characterized dataset of nationally-representative hospital discharges, which similarly showed that AC patients make up the majority of cirrhosis-related discharges(39). Higher admission rates among AC enrollees in our study were driven not only by liver-related admissions but also alcohol-related admissions, highlighting the unique importance of alcohol use interventions and treatment.

Our study has several limitations. First, the nature of private insurance administrative claims data means that patients can be lost from the dataset due to change in or loss of employment. However, our robust statistical methodology included multiple techniques to account for complicating factors such as dependent censoring, unequal duration of pre- and post-diagnosis follow-up, and changing representation of the ESI population in MarketScan data. Second, the movement towards capitated claims could result in underestimation of costs, as capitated services are poorly represented in fee-for-service claims data. Third, MarketScan data does not include race or ethnicity information, precluding an analysis of racial disparities in AC burden. Fourth, ALD codes have not been validated in administrative datasets. Our cirrhosis and portal hypertension codes, however, are well-validated with positive predictive values >80% and alcohol use ascertainment codes in our study have been previously used in large-scale estimates of cirrhosis burden(18,24). Several validation studies for cirrhosis in non-VA administrative data have concluded that to maximize both sensitivity and specificity, codes for both cirrhosis as well as portal hypertensive complications must be included in the coding algorithm (24,40). Such coding algorithms, while highly specific for decompensated cirrhosis, exclude compensated cirrhosis. Furthermore, this coding strategy would miss enrollees with alcoholic hepatitis, who do not have a cirrhosis code. As such, our coding strategy favored specificity and positive predictive value to ensure that the accuracy of cirrhosis in the cohort was high.

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We acknowledge that this strategy may miss some persons with as yet undiagnosed compensated cirrhosis and some persons with alcoholic hepatitis and underestimate the overall burden of cirrhosis and ALD.

In conclusion, our study shows a high burden of AC in the private ESI US population, which increased further in recent years with a more pronounced increase amongst women. Persons with AC are sicker at presentation, admitted and re-admitted more frequently for liver- and alcohol-related reasons, and incur twice the healthcare costs as their non-AC counterparts. Our results highlight the urgent need to more effectively detect and prevent ALD and, even more importantly to aid ALD patients in achieving and maintaining alcohol abstinence given its key role in improving morbidity and mortality in ALD.

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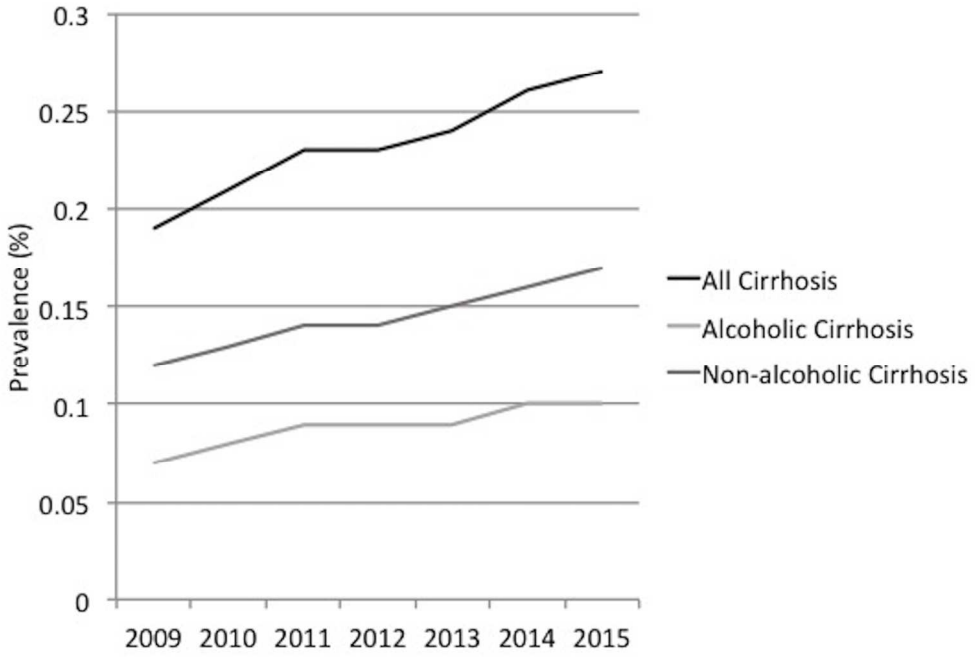

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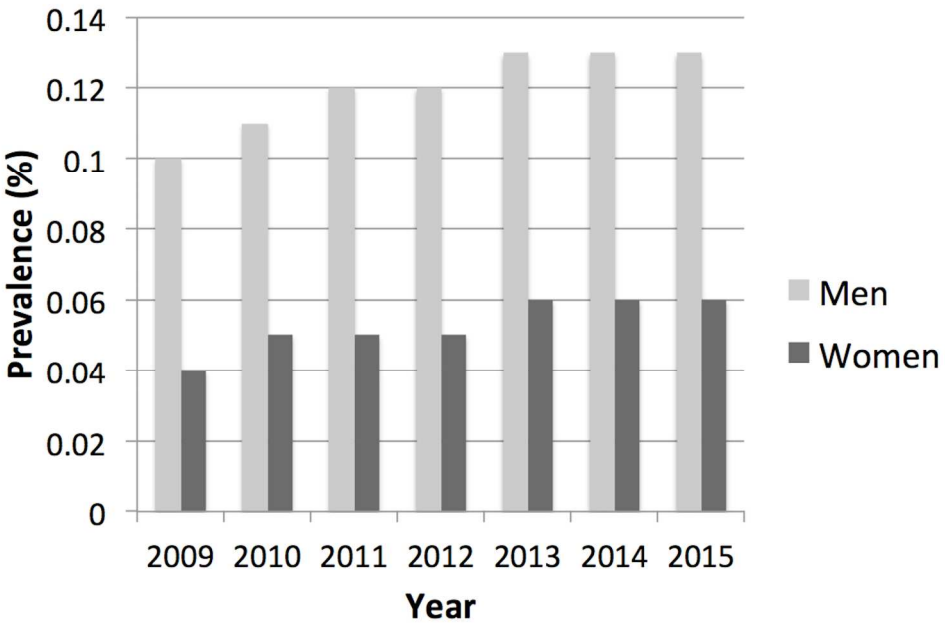

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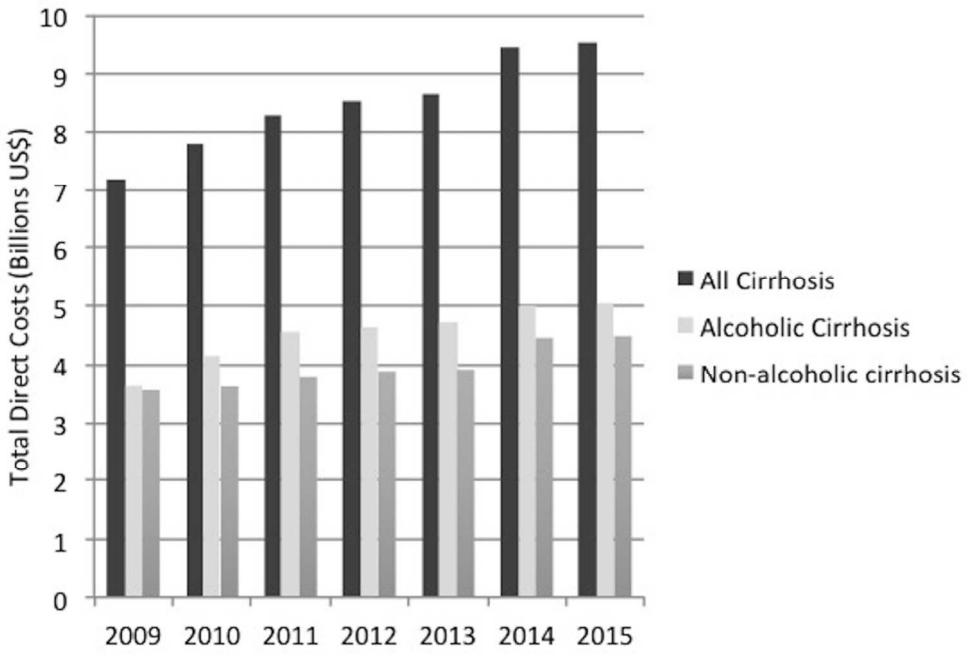

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Table 1. Demographic characteristics and prevalence of portal hypertensive complications.

	Baseline* N=169,531		1-year*		2-year*	
Characteristic	**AC** N=66,053 **N (%)**	**Non-AC** N=103,478 **N (%)**	**AC (%)**	**Non-AC (%)**	**AC (%)**	**Non-AC (%)**
Median age at diagnosis (years) (Range 19-64)	53.5	53.0				
Female	21,442 (32%)	50,196 (49%)				
Mean Coverage Duration (days)	688	655				
Elixhauser	2.63	2.30				
HCV	12,550 (19%)	28,973 (28%)	27%	33%	29%	35%
Ascites	14,531 (22%)	8,278 (8%)	38%	14%	45%	18%
Hepatic Encephalopathy	3,963 (6%)	1,035 (1%)	19%	5%	26%	7%
Variceal bleeding	2,642 (4%)	1,035 (1%)	10%	4%	13%	5%
GI Bleeding	10,568 (16%)	8,278 (8%)	29%	14%	35%	18%
HCC	1,321 (2%)	2,069 (2%)	5%	5%	8%	6%
SBP	396 (<1%)	103 (<1%)	4%	1%	5%	1%
HRS	528 (<1%)	103 (<1%)	4%	1%	6%	2%
AKI	5,284 (8%)	4,139 (4%)	19%	9%	26%	12%
Decompensation[@]	18,495 (28%)	10,348 (10%)	47%	18%	54%	22%
GI Outpatient Visit[§]	19,155 (29%)	43,460 (42%)	56%	60%	62%	64%
Liver transplant	13 (<1%)	36 (<1%)	1%	1%	3%	1%

AC: alcoholic cirrhosis; HCV: Hepatitis C virus; HCC: hepatocellular carcinoma; SBP: spontaneous bacterial peritonitis; HRS: hepatorenal syndrome; AKI: acute kidney injury *P<0.05 for all between-group comparisons (AC versus non-AC). [§]Gastroenterology outpatient visits were defined as a single code for an outpatient visit with a GI specialist. [@]Decompensation defined as at least 1 occurrence of ascites, hepatic encephalopathy, or variceal bleeding.

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Table 2. Portal hypertensive event rate analysis at index diagnosis, 1- and 2-years post-diagnosis comparing alcoholic cirrhosis (AC) enrollees with and without comorbid hepatitis C (HCV).

Event	Baseline N= 66,053 AC patients		1 year		2 year	
	With HCV N=18,817 N (%)	**Without HCV** N=47,236 N (%)	**With HCV** (%)	**Without HCV** (%)	**With HCV** (%)	**Without HCV** (%)
Ascites	3,951 (21%)	10,864 (23%)	38%	39%	45%	44%
Hepatic Encephalopathy	1,053 (5.6%)	2,928 (6.2%)	19%	19%	26%	25%
Hepatorenal syndrome	188 (1%)	377 (0.08%)	4.3%	4.4%	6.3%	6.0%
Variceal Bleed	677 (3.6%)	1,700 (3.6%)	9.8%	9.2%	13%	12%
Hepatocellular carcinoma	319 (1.7%)	377 (0.08%)	5.5%	2.6%	8%	4%
GI bleeding	2,822 (15%)	8,030 (17%)	29%	29%	35%	35%
Spontaneous Bacterial Peritonitis	112 (0.06%)	283 (0.06%)	3.6%	3.3%	5.4%	4.7%
Decompensation[@]	5,268 (28%)	14,170 (30%)	47%	47%	54%	53%

[@]Decompensation defined as at least 1 occurrence of ascites, hepatic encephalopathy, or variceal bleeding.
AC: alcoholic cirrhosis; HCV: hepatitis C

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Table 3. Mean estimated per-person costs in US dollars over 1 year post-diagnosis in enrollees with and without alcoholic cirrhosis.

Condition	Present	Absent
Alcoholic cirrhosis*	$44,835	$23,319
Alcoholic cirrhosis without comorbid HCV	$39,299	$25,652
Ascites#	$77,545	$13,791
Variceal bleed#	$80,745	$25,271
Hepatic encephalopathy#	$108,838	$19,534
Hepatocellular carcinoma#	$101,718	$25,656
Hepatorenal syndrome or Acute kidney injury#	$131,937	$18,127
Spontaneous bacterial peritonitis#	$177,183	$25,650
Liver transplant#	$436,813	$24,840

*Cost of alcoholic cirrhosis (inclusive of those with comorbid HCV) vs non-alcoholic cirrhosis regardless of presence or absence of portal hypertensive complications, HCV, hepatocellular carcinoma and liver transplant

#Cost of portal hypertensive complications, hepatocellular carcinoma and liver transplant regardless of etiology of cirrhosis: alcohol vs non-alcohol

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Supplementary Appendix A. ICD-9 and ICD-10 codes used for cohort selection and comorbidities

Disease	ICD-10 Code (started 10/1/2015)	ICD-9 Code
Cirrhosis	K74.6x	571.5
Alcohol use	F10.x, T51.x, K86.0, I42.6, K29.20, K29.21, G62.1	790.3, 425.5, 535.30, 535.51, 577, 357.5, 291.x, 303.x, 305.0x, V113.0, E860.01-.03, 980.x
Alcoholic liver disease Alcoholic cirrhosis	K70.x K70.3x	571.1, 571.2, 571.3 571.2
Upper GI bleed	K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, I85.01, I85.11, K22.11, K26.0, K26.2, K26.4, K26.6	456.0, 456.2, 530.82, 530.00, 530.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.20, 534.21, 534.40, 534.41, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 578.0, 578.1, 578.9,
Hepatitis C	B18.2	070.41, 070.44, 070.51, 070.54, 070.70, 070.71
Ascites	R18.8, K71.51	789.59, 789.50
Varices without bleed	I85.00, I85.10	456.1, 456.21
Variceal bleed	I85.01, I85.11	456.0, 456.2
Portal hypertension	K76.6	572.3
Hepatic encephalopathy	K72.91	572.2
Hepatorenal syndrome	K76.7	572.4
Hepatocellular carcinoma	C22.0	155.0
Diabetes	E08.xx, E10.xx, E11.xx, E13.xx	250.x

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Acute kidney injury	N17.xx	584.5, 584.6, 584.7, 584.8, 584.9
Spontaneous bacterial peritonitis	K65.2	567.23

More specific alcohol use codes and definitions:

ICD-9 Codes	**Definitions**
790.30	Excessive blood alcohol level
425.5	Alcoholic cardiomyopathy
535.30, 535.31	Alcoholic gastritis, with and without bleeding
577	Alcoholic pancreatitis
357.5	Alcoholic polyneuropathy
291.x	Alcohol-induced mental disorders
303.x	Alcohol dependence syndromes
980.x	Toxic effect of alcohol
305.0x	Nondependent alcohol abuse
E860.0, E860.1	Accidental poisoning by alcohol
V113	Personal history of alcoholism

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Supplementary Table 1. Event rate analysis at index diagnosis, 1- and 2-years post-diagnosis comparing alcoholic cirrhosis enrollees with and without comorbid hepatitis C.

Event	Baseline		1 year		2 year	
	With HCV	Without HCV	With HCV	Without HCV	With HCV	Without HCV
Ascites	22%	23%	38%	39%	45%	44%
Hepatic Encephalopathy	6%	6%	19%	19%	26%	25%
Hepatorenal syndrome	1%	1%	4%	4%	6%	6%
Variceal Bleed	4%	4%	10%	9%	13%	12%
Hepatocellular carcinoma	2%	1%	6%	3%	8%	4%
GI bleeding	16%	17%	29%	29%	35%	35%
Spontaneous Bacterial Peritonitis	<1%	<1%	4%	3%	5%	5%
Decompensation@	28%	30%	47%	47%	54%	53%
Liver transplant	<1%	<1%	1%	1%	3%	2%

@Decompensation defined as at least 1 occurrence of ascites, hepatic encephalopathy, or variceal bleeding.

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Appendix B: Supplementary Methods

Prevalence estimation

For prevalence estimation, the ESI population was stratified into 32 strata based on the following four factors: age (18-45 or 45-64), sex, census region (4 categories), and employee status (policy holder versus covered dependent). For each of these strata, and for each year from 2009-2015, the total ESI population size was calculated from the Medical Expenditure Panel Survey(1). For each stratum, we estimated the cirrhosis or ALD/cirrhosis prevalence in Marketscan as discussed below, and then multiplied this prevalence estimate by the corresponding ESI stratum size to determine a per-stratum population count. These counts were then summed to produce an overall estimated prevalence count per year. This prevalence count was then divided by the ESI population size to produce a prevalence rate.

Estimation of the per-stratum Marketscan ESI prevalence is complicated by the need to reduce bias resulting from differing lengths of observation among the subjects. If we consider a person's cirrhosis status on a particular date to be determined by having had a cirrhosis code on or prior to that date in our data, the prevalence estimates for the earlier years will be biased downward, due to shorter lengths of preceding data. This leads to two potential areas of bias in the data: 1) under-reported prevalence and 2) an artificially steep estimate of trend increase. The first bias, of under-reported prevalence, is due to subjects being diagnosed with cirrhosis in one year, remaining enrolled in the dataset but not interacting with the healthcare system in subsequent years, and then re-appearing in the dataset once a claim is entered (for example, a patient is diagnosed with cirrhosis in 2009, remains enrolled but does not interact with the healthcare system in 2010, and then does so in 2011 when a claim appears in the dataset). Because cirrhosis is a chronic condition that does not wax and wane but, once present remains present, failure to account for these "skipped" years would produce artifically low prevalence estimates. The second bias results from underestimation of cirrhosis prevalence in the early years of the cohort because we are unable to include patients with diagnoses in 2008 or earlier, which is outside our dataset window. This produces an artificially steep estimate of the rate of increase in cirrhosis prevalence, since the later years in our data record will be less biased than the earlier years.

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To mitigate these two biases, we adjusted results as follows: To estimate yearly cirrhosis prevalence, for each year from 2009-2015 we selected the people who were enrolled for the entire year, and directly calculated the proportion of these people who had a cirrhosis code during that year in each stratum. These rates underestimate the true prevalences since people with cirrhosis can go a year or longer without receiving a cirrhosis code, as discussed above, even while they remain covered. Therefore, we used the 2015 data to estimate the downward bias in this rate so that we can correct for it. We considered everyone who was covered for all of 2015 (the year for which we have the greatest length of historical data) and then calculated two rates: one based on subjects having a cirrhosis code in 2015, and one based on subjects having a cirrhosis code in any year from 2009-2015. The ratio of these rates (approximately 1.7) reflects the undercount when considering only people who have cirrhosis codes in a particular year. To produce our final prevalence estimates, we adjusted the per-stratum Marketscan counts by this factor prior to projecting them to the ESI population.

Cost analysis

Raw per-person costs were calculated by summing the “netpay” values in the Marketscan O, S, and D tables. Costs were summed over the first year following diagnosis, capping the total cost at 1 million dollars. A “time” value was calculated as the duration of coverage from diagnosis up to 1 year. Subjects who lost coverage or who died during the first year were coded with time equal to their coverage/survival duration, all other subjects had time=1. We then fit linear regression models to model the costs as a function of numerous controls. Forward variable selection was used to select main effects and interactions from the following variables: year of diagnosis, time (as described above), female, age at diagnosis, Elixhauser score, ascites, variceal bleed, hepatic encephalopathy, alcoholic liver disease, gastrointestinal bleeding, liver cancer, hepatitis C, HRS or AKI, portal hypertension, liver transplant, SBP, and census region. All time-varying covariates were coded based on their value at the end of the cost-summation period (1 year for most subjects). The final model had 32 terms in all. We then used the fitted values from this model to produce a modeled cost for each Marketscan person. When forming these fitted values, the time variable was reset to 1 for everyone who did not die (thereby accounting for censoring), but remained at the survival duration for people who died.

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These predicted log costs were then averaged within subgroups of interest using 2012 weights (derived as in the prevalence analysis) to account for discrepancies between the Marketscan and ESI populations. Subgroups of interest included, for example, subjects who do and who do not have ascites during their first year post-diagnosis. This allowed us to compare average per-person costs for these subgroups in a way that reflects the ESI population, and is minimally biased due to differing follow-up times. These cost estimates do not attempt to isolate a given risk factor from other factors that correlate with it. For example, the difference in mean costs between people with and without ALD is inflated by costs of ALD-associated comorbidities, such as ascites or variceal bleeding.

We also calculated regression effects for factors of interest, expressing the results as the percent change in cost associated with each risk factor. Since the regression analysis considers cost on the log-scale, associations between individual factors, such as ascites, and costs can be calculated directly from the regression slopes, and presented as percent changes, e.g. the percentage difference in total costs associated with having, versus not having ascites.

Admissions and readmissions analysis

The admissions and readmissions analyses used a similar model-based strategy as the cost analyses. Negative binomial regression models were used for admission counts in place of the linear model used in the cost analysis. Regression effects, controlling for all other modeled factors were estimated as in the cost analysis. In addition, comparisons between risk groups of interest were conducted in two ways. First, as in the cost analysis, the weighted mean modeled admissions counts in two subgroups were computed, e.g. for comparing people who do and who do not have ascites within the first year after cirrhosis diagnosis. The results are presented as excess events per 100 subjects, meaning the difference between the number of admissions for 100 subjects with ascites and for 100 subjects without ascites. These differences are referred to as the “excess admissions per 100 cases”. Note that these comparisons are influenced by the factor of interest (e.g. ascites) and by other risk factors correlated with it.

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Supplementary Table 1. Gender and portal hypertensive complication event rates.

	Baseline N=169,531				1-year				2-year			
Characteristic	**AC Men** N=44,611	**AC Women** N=21,442	**Non-AC Men** N=53,282	**Non-AC Women** N=50,196	**AC Men**	**AC Women**	**Non-AC Men**	**Non-AC Women**	**AC Men**	**AC Women**	**Non-AC Men**	**Non-AC Women**
HCV	21%	14%	35%	20%	30%	21%	42%	24%	32%	23%	43%	25%
Ascites	21%	23%	8%	7%	38%	40%	15%	14%	45%	46%	18%	17%
Hepatic Encephalopathy	5.3%	6.2%	1.2%	1.3%	19%	20%	5%	5%	26%	26%	7%	7%
Variceal bleeding	4,2%	2.3%	1,3%	1.0%	11%	7.6%	4%	3.1%	15%	11%	5%	4.5%
GI Bleeding	16%	14%	8%	7%	29%	27%	14%	13%	36%	33%	18%	17%
HCC	2%	<1%	3%	1.3%	7%	3%	7%	3%	9.4%	4%	9%	4%
SBP	<1%	<1%	<1%	<1%	4%	4%	1%	1%	6%	5%	2%	1%
HRS	<1%	1%	<1%	<1%	4%	4%	1%	1%	6%	6%	2%	1%
AKI	8%	8%	5%	3%	20%	18%	10%	8%	27%	24%	13%	10%
Decompensation@	27%	29%	10%	9%	47%	47%	19%	17%	55%	53%	23%	21%

AC: alcoholic cirrhosis; HCV: Hepatitis C virus; HCC: hepatocellular carcinoma; SBP: spontaneous bacterial peritonitis; HRS: hepatorenal syndrome; AKI: acute kidney injury
*P<0.05 for all between-group comparisons (AC versus non-AC). §Gastroenterology outpatient visits were defined as a single code for an outpatient visit with a GI specialist.
@Decompensation defined as at least 1 occurrence of ascites, hepatic encephalopathy, or variceal bleeding.

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