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

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Alcoholic cirrhosis (AC) is a major cause of liver-related morbidity and mortality in the United States. Rising rates of alcohol use disorders in the United States will likely result in more alcoholic liver disease. Our aim was to determine the prevalence, health care use, and costs of AC among privately insured persons in the United States. We collected data from persons aged 18-64 with AC (identified by codes from the *International Classification of Diseases*, Ninth and Tenth Revisions) 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 AC and costs as well as admissions and readmissions. In 2015, 294,215 people had cirrhosis and 105,871 (36%) had AC. Mean age at AC diagnosis was 53.5 years, and 32% were women. Over the 7 years queried, estimated national cirrhosis prevalence rose from 0.19% to 0.27% ($P < 0.001$) and for AC from 0.07% to 0.10% ($P < 0.001$). 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 versus 23,319). *Conclusion:* In a nationally representative cohort of privately insured persons, AC enrollees were disproportionately sicker at presentation, were admitted and readmitted more often, and incurred nearly double the per-person health care costs compared to those with non-AC. (HEPATOLOGY 2018;68:872-882).

Alcoholic liver disease (ALD) resulting from chronic heavy alcohol consumption is a large and growing problem in the United States, 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 United States. 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

Abbreviations: AC, alcoholic cirrhosis; ALD, alcoholic liver disease; AUD, alcohol use disorder; ESI, employer-sponsored insurance; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD-9/10, International Classification of Diseases, Ninth and Tenth Revisions*; MEPS, Medical Expenditure Panel Survey; VA, Veterans Affairs.*

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specialty addiction care use in the United States 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 data set analyses have focused on noncirrhotic ALD, with estimated prevalence ranging from 2% to 2.5%.[14] Another analysis from a large national data set, inclusive of all insurance types, assessed the prevalence of all-cause cirrhosis to be 0.27%.[15] In the Department of Veterans Affairs (VA) system, the prevalence of all-cause cirrhosis is high at 1.0%, but these data cannot be generalized to the US population owing to low female representation and differences in socioeconomic status and comorbidities.[16] These studies, however, did not provide direct estimates of AC in the privately insured US population. While many European databases include comprehensive population data from birth to death, US health insurance data are 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 health care burden is essential to create sensible policy initiatives, design effective treatment protocols, and appropriately allocate resources. Because half of Americans are privately insured (employer-based insurance 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 United States. 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.

Materials and Methods

DATABASE

This study was reviewed by the institutional review board of the University of Michigan and was exempted from institutional review board review. We queried the 2009-2015 MarketScan Commercial Claims and Encounters 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 data sets that is widely used in health care delivery, epidemiology, and economic burden research.[17-21] Drawing on all regions of the United States, 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 that 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 and 64.

COHORT SELECTION

Study enrollees from MarketScan data (2009-2015) were between the ages of 18 and 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[22] (see Supporting Table S1). All study data were restricted to the continuous enrollment period containing the cirrhosis diagnosis. Cirrhosis diagnosis was determined by *International Classification of Diseases*, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), cirrhosis codes identified

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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, hepatorenal syndrome, varices with or without bleeding, hepatic encephalopathy) or cirrhosis was observed (see Supporting Table S1). Single ICD-9 codes for cirrhosis and its complications have been validated in administrative data with positive predictive values of 80% or greater.[22,23]

Using published criteria,[16] 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 Supporting Table S1 for list of codes used). Enrollees who met criteria for comorbid AC and hepatitis C virus (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 Supporting Table S1), and Elixhauser scores were calculated excluding the liver and alcohol categories.[24] Decompensated cirrhosis was defined by a cirrhosis code and a portal hypertensive complication (ascites, hepatic encephalopathy, or variceal bleeding).

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 the 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).[25] MarketScan provides weights based on five factors: age (<45 or ≥ 45), sex, census region, employee status, and metropolitan statistical area, a standard unit of geographic analysis. However, in 2015, Truven Analytics changed the weighting criteria, removing metropolitan statistical area. 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 (policyholder versus covered dependent). The ESI population was then stratified into 32 strata based on these factors, and for each year from 2009 to 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 Supporting Information Appendix B for further details.

Two issues with limited time windows in administrative data sets can result in an overestimate of prevalence trends. First, because patients with cirrhosis enrolled over several years may go a year or longer between cirrhosis codes, prevalence estimates calculated by simply counting the number of cases of cirrhosis 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 health care system in 2010, and reappear in the data set in 2011 after receiving some type of health care. Because 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 data set 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 Supporting Information, Appendix B.

EVENT RATES ANALYSIS

The primary event rates analysis used competing risks methodology to assess the time from diagnosis to the onset of various cirrhosis complications, treating death as a competing event to complications and censoring at loss of coverage.[26] 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 because each complication competes with death. Determining the burden of portal hypertensive events after the index cirrhosis diagnosis requires adjusting for enrollees lost from the data set 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 nonindependent 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.[24] Event rates were then estimated using stratified competing risks methodology, with strata defined by individual risk for coverage loss.[26] We performed an additional sensitivity analysis of event rates among enrollees with AC but without hepatitis C, using the same methodology.

OVERALL DIRECT HEALTH CARE COSTS

Direct health care 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. Copayments, coinsurance, and coordination of benefits fees were excluded. Enrollees had to have coverage and be alive for at least 1 month postdiagnosis 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 among these variables). Fitted costs were calculated at 1 year postdiagnosis for enrollees who did not die within 1 year and 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

Admissions were analyzed using similar statistical methods as discussed above for costs except that 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 Supporting Table S1). 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). The 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 (Fig. 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 aged <45 had a more pronounced 300% increase from 0.01% to 0.03% ($P <$

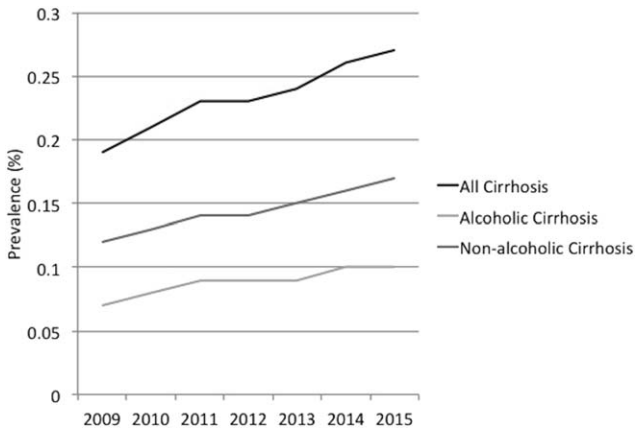

FIG. 1. Prevalence trends for all-cause and alcoholic cirrhosis, 2009-2015.

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%) (Fig. 2).

CHARACTERISTICS OF MARKETSCAN ENROLLEES WITH AC AND NON-AC AT DIAGNOSIS

At some time during the period 2009-2015, 169,531 MarketScan enrollees had a cirrhosis diagnosis; 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% versus 10%, $P < 0.001$) (Table 1). The proportion with hepatocellular carcinoma (HCC) between the two groups was similar at baseline (2% versus 2%). AC enrollees had more comorbidities at diagnosis (2.63 versus 2.30, $P < 0.001$) compared to those with non-AC.

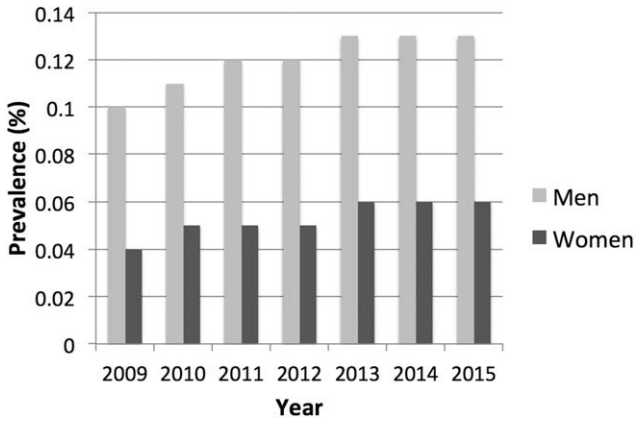

FIG. 2. Prevalence trends for alcoholic cirrhosis by gender, 2009-2015.

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 diagnosis of cirrhosis (Table 1). At 2 years postdiagnosis, a significantly higher proportion of AC enrollees had portal hypertensive complications than those with non-AC, though the rates of increase in the two 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-increases 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% versus 14%) and HCC (2% versus <1%) at baseline (see Supporting Table S2).

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 postdiagnosis (see Table 2). HCC, however, occurred with greater frequency at baseline (1.7% versus 0.08%, $P < 0.001$) and at 2 years postdiagnosis (8% versus 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 postdiagnosis (3% versus 2%, $P < 0.001$, data not shown).

TABLE 1. Demographic Characteristics and Prevalence of Portal Hypertensive Complications

Characteristic	Baseline* (n = 169,531) AC (n = 66,053) n (%)	Baseline* (n = 169,531) Non-AC (n = 103,478) n (%)	1 year* AC (%)	1 year* Non-AC (%)	2 years* AC (%)	2 years* 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%

*$P < 0.05$ 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.
AKI, acute kidney injury; GI, gastrointestinal; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

ADMISSIONS AND READMISSIONS 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. The mean per-person all-cause admissions in the first year after diagnosis was 1.1 for AC compared to 0.5 for non-AC. Those with 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 ($P < 0.01$). The 30-day readmissions were also higher for AC (30 excess all-cause readmissions per 100 enrollees per year).

TABLE 2. Portal Hypertensive Event Rate Analysis at Index Diagnosis, 1 and 2 Years Postdiagnosis Comparing AC Enrollees With and Without Comorbid HCV

Event	Baseline (n = 66,053 AC patients) With HCV (n = 18,817) n (%)	Baseline (n = 66,053 AC patients) Without HCV (n = 47,236) n (%)	1 year With HCV (%)	1 year Without HCV (%)	2 year With HCV (%)	2 year 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%
HCC	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 one occurrence of ascites, hepatic encephalopathy, or variceal bleeding.

DIRECT HEALTH CARE COSTS FOR AC AND NON-AC IN NATIONALLY WEIGHTED ESI POPULATION

Overall direct health care 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$), even though these enrollees only comprised 36% of the total cirrhosis population (see Fig. 3). Per-person health care costs for AC were markedly higher than for non-AC, with a mean of 44,835 US$ 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 health care costs in the first year after index cirrhosis diagnosis were higher for those with decompensated cirrhosis (68,982 US$ versus 12,316 US$) compared to those 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).

TABLE 3. Mean Estimated Per-Person Costs in US Dollars Over 1 Year Postdiagnosis in Enrollees With and Without AC

Condition	Present	Absent
AC*	$44,835	$23,319
AC without comorbid HCV	$39,299	$23,319
Ascites†	$77,545	$13,791
Variceal bleed†	$80,745	$25,271
Hepatic encephalopathy†	$108,838	$19,534
HCC†	$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 AC (inclusive of those with comorbid HCV) versus nonalcoholic cirrhosis regardless of presence or absence of portal hypertensive complications, HCV, HCC, and liver transplant.
†Cost of portal hypertensive complications, HCC, and liver transplant regardless of etiology of cirrhosis: alcohol versus nonalcohol.

Discussion

In this large cohort of private, ESI-covered persons with cirrhosis, AC patients made up just over one third of the total cirrhosis burden in the nationally weighted ESI population in the United States, consumed just over half the overall direct health care expenditures among persons with cirrhosis, and had health care 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.

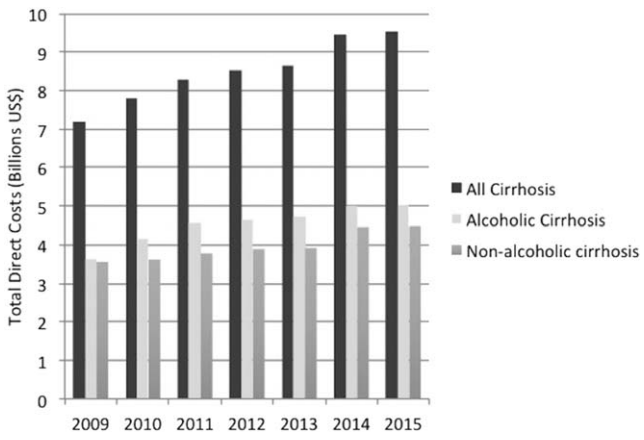

FIG. 3. Total direct health care costs for the first year after index cirrhosis diagnosis, 2009-2015.

Our overall cirrhosis prevalence of 0.27% is consistent with the findings of the US National Health and Nutrition Examination Survey,[15] but our data highlight the burden of AC, which was not directly assessed in that study. We found that AC accounted for 37% of all cirrhosis cases, giving a national ESI AC prevalence of 0.10%, or approximately 100 people with AC per 100,000 people with ESI. Studies in the 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.[16] 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 underestimates the attributable burden of ALD and masks its importance as a driver of progressive liver disease.[27] 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.

Our data add to and extend 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 data set of administrative claims, the Truven MarketScan database. This large-scale national database of private ESI-covered US adults has been widely used to estimate disease prevalence, outcomes, and costs for a number of disease conditions, including gastroenterological diseases.[17-20] With nearly half the US population obtaining insurance through an employer, the scope of MarketScan enrollment, which includes >100 million individually 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, because 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 understate the overall burden of ALD among the entire US population and represent the best-case scenario for AC in the United States.[28,29] The true prevalence of AC in the United States 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 had previously eliminated all substance use disorder claims from their available data sets, thus limiting analysis of substance-related medical disease like ALD in persons covered by Medicare or Medicaid.[30] 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.[31] 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 underestimated by 2-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 was excluded from this analysis except for cases with a cirrhosis code, thus underestimating the burden of advanced ALD.[32]

The burden of cirrhosis in the United States 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 use. 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 (21,000-90,000 US$ in commercially insured persons).[34] Our estimates of yearly costs of managing decompensated cirrhosis, hepatorenal syndrome, and HCC are similar to 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 burden exceeded that of other alcohol-related malignancies.[38] The global burden of AC is likewise high, estimated at 12.8% of total health care costs and 2.5% of total gross domestic product 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 among enrollees <45 years old as well as a greater rate of increase among 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 noncirrhotic ALD prevalence. One study showed an increase in prevalence of noncirrhotic 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.[14,28] Increases in prevalence and mortality had also been reported for non-AC patients.[13,28] 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 healthcare costs and use in subsequent years should these young persons survive. The higher rate of increase in AC among women (50% versus 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 health care costs for cirrhosis while representing only 36% of all cirrhosis cases. Further, the per-person costs were nearly double those 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 published data from AC patients in Europe and the United States, though our cost findings are unique 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 AUDs 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 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 data set 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 by 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 data set 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 prediagnosis and postdiagnosis follow-up, and changing representation of the ESI population in MarketScan data. Second, the movement toward capitated claims could result in underestimation of costs as capitated services are poorly represented in fee-for-service claims data. Third, MarketScan data do not include race or ethnicity information, precluding an analysis of racial disparities in AC burden. Fourth, ALD codes have not been validated in administrative data sets. 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 used in large-scale estimates of cirrhosis burden.[16,22] 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.[22,40] 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. 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 among women. Persons with AC are sicker at presentation, admitted and readmitted more frequently for liver-related and alcohol-related reasons, and incur twice the health care 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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