Trends in Chronic Liver Disease-Related Hospitalizations: A Population-Based Study

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OBJECTIVES: **In a population-based study, we examined time trends in chronic liver disease (CLD)-related hospitalizations in a large and diverse metroplex.**

METHODS: **We examined all CLD-related inpatient encounters (2000–2015) in Dallas–Fort Worth (DFW) using data from the DFW council collaborative that captures claims data from 97% of all hospitalizations in DFW (10.7 million regional patients).**

RESULTS: **There were 83,539 CLD-related hospitalizations in 48,580 unique patients across 84 hospitals. The age and gender standardized annual rate of CLD-related hospitalization increased from 48.9 per 100,000 in 2000 to 125.7 per 100,000 in 2014. Mean age at hospitalization increased from 54.0 (14.1) to 58.5 (13.5) years; the proportion of CLD patients above 65 years increased from 24.2% to 33.1%. HCV-related hospitalizations plateaued, whereas an increase was seen in hospitalizations related to alcohol (9.1 to 22.7 per 100,000) or fatty liver (1.4 per 100,000 to 19.5 per 100,000). The prevalence of medical comorbidities increased for CLD patients: coronary artery disease (4.8% to 14.3%), obesity (2.8% to 14.6%), chronic kidney disease (2.8% to 18.2%), and diabetes (18.0% to 33.2%). Overall hospitalizations with traditional complications of portal hypertension (ascites, varices, and peritonitis) remained stable over time. However, hospitalization with complications related to infection increased from 54.7% to 66.4%, and renal failure increased by sevenfold (2.7% to 19.5%).**

CONCLUSION: **CLD-related hospitalizations have increased twofold over the last decade. Hospitalized CLD patients are older and sicker with multiple chronic conditions. Traditional complications of portal hypertension have been superseded by infection and renal failure, warranting a need to redefine what it means to have decompensated CLD.**

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INTRODUCTION

Chronic liver disease (CLD)-related hospitalizations are traditionally defined by complications of portal hypertension such as ascites and variceal bleeding and often not considered a disease of the elderly [1]. However, several salient features may signal a change in epidemiology of CLD. First, non-portal hypertension-related complications such as infection and renal failure are increasingly encountered among patients with CLD and associated with a fourfold and a sevenfold increase in the risk of mortality, respectively; however, these complications are not routinely identified as discrete stages in the progression of liver disease [2, 3]. Second, an anticipated shift from hepatitis C to non-alcoholic fatty liver disease may signal an evolving population with multiple chronic conditions with an unknown impact on the natural history and clinical course of CLD [4–6]. Finally, patients with decompensated cirrhosis being evaluated at liver transplant centers in the US are now older with more comorbidities compared with patients evaluated in the previous decade, further suggestive of a changing population [7].

Population-based studies cataloging the clinical course of CLD in the US are sparse. Current data on CLD-related burden are based on trends in selected patient populations with access to healthcare (including studies form US Veterans), specific diagnoses, or those seen in specialized tertiary care settings—all factors limiting the

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generalizability of these findings [5, 8–11]. Further, available data are often limited to studying complications of portal hypertension rather than other well-known manifestations (e.g., infection) of liver disease. It is unclear whether there has been a change in the patient demographic and clinical presentation of CLD over time (e.g., less variceal bleeding but more infection).

In a population-based study, we examined time trends in CLD-related hospitalizations in a large and diverse metroplex. We show that the burden of CLD has increased over time with a shift toward sicker and older patients with multiple chronic conditions. Further, traditional complications of portal hypertension (e.g., variceal bleeding) have been supplanted by infection and renal failure.

METHODS

Setting

The Dallas–Fort Worth–Arlington (DFW) metroplex is the largest metropolitan area in Texas and the fourth largest metropolitan area (out of 382) in the US. In 2010, the demographics of the metroplex were similar to the overall US population in regard to gender (50.7% women vs. 50.8% women), race (65.3% vs. 74.8% white, 15.1% vs. 13.6% black), age (9% vs. 13.0% age > 65 years), but with a higher percentage of Hispanic ethnicity (27.4% vs. 16.3%) than the general population [12]. Almost all hospitalization data in the DFW metroplex are captured by the Dallas–Fort Worth Hospital Council Foundation (DHWHC), a collaborative data warehouse containing hospital-related information on 10.7 million patients with more than 51 million encounters since 1999. This warehouse collects data from 95% of the hospitals in North Texas that serves 97% of DFW metroplex and surrounding communities in rural, urban, and community settings (84 hospitals, 17 counties, and over 5.5. million hospital visits per year). A unique ID is assigned to all patients across the various hospital systems to track any patient over time and access any of the hospitals [13]. Death data are further linked to the Social Security Death Index and the Death Master Index to allow complete ascertainment.

Case ascertainment

We examined all CLD-related encounters from January 2000 to September 2015 among adult patients (>18 years) hospitalized at any of the 84 hospitals. In order to minimize ascertainment bias, we classified a hospitalization as CLD related if it was associated with (a) a primary discharge diagnosis of CLD (e.g., alcoholic cirrhosis or acute alcoholic hepatitis) or (b) a primary discharge diagnosis of CLD-related complications (e.g., sepsis) in combination with secondary diagnosis of CLD. (**Supplemental Table**) [14] Hospitalizations that were related to organ transplantation, observations for planned procedures or less than 24 h were excluded. Given that patients may be admitted more than once, we used the first hospitalization during a given year as the index hospitalization for that year.

Statistical analysis

We calculated standardized annual CLD-related hospitalization rates by dividing number of unique patients hospitalized with CLD in a specific year by the age- and gender-stratified population of DFW–Arlington metroplex during that year using US Census data, considering the entire population at risk. Direct standardization was used to adjust for age and gender using 2000 US census population as the reference population [15]. We further examined trends in standardized rates by (i) underlying liver disease (hepatitis C, alcoholic liver disease, fatty liver disease, and other) and (ii) deciles of age.

We also examined time trends in the clinical presentation of CLD. For this analysis, the numerator was a CLD complication-related hospitalization with denominator being all CLD-related hospitalizations in a given year. Given that patients may present with more than one CLD complication, we examined both primary and secondary reasons for hospitalization to define CLD complications. We also used the primary reason for hospitalization in a sensitivity analysis to examine the robustness of our results. We calculated trends in the hospitalizations related to complications of CLD that were portal hypertension related (variceal and gastrointestinal hemorrhage, hyponatremia, ascites, hepatic encephalopathy), renal dysfunction related (acute renal failure, hepatorenal syndrome, and volume overload or volume depletion), and infection-related complications (sepsis, bacteremia, cellulitis, peritonitis, unspecified infection, cholangitis, clostridium difficile, pneumonia, and urinary tract infection) (**Supplemental Table**).

Among patients with CLD-related hospitalizations, we also examined trends in the severity of illness (SOI) using the validated APR-DRG SOI categories (minor, moderate, major, or extreme risk; http://solutions.3m.com/wps/portal/3M/en_US/Health-Information-Systems/HIS/) and trends in relevant medical comorbidities over time (chronic kidney disease, diabetes, hypertension, coronary artery disease, obesity, and dyslipidemia). Finally, we examined age and gender standardized inpatient mortality rates over time in unique patients with CLD.

Data were expressed as numerical values and percentages of total hospitalizations for categorical variables, and as mean ± standard deviation (SD) or median (interquartile range; IQR) for continuous variables. The Cochran–Armitage test for trend was used to determine the significance of trends over time. A P-value < 0.05 was considered statistically significant. Statistical analyses utilized the SAS Enterprise Guide statistical package (version 5.1; SAS Institute Inc., Cary, NC, USA). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the appropriate institutional review committee.

RESULTS

Patient and hospitalization characteristics

Between January 2000 and September 2015, there were 83,539 CLD-related hospitalizations in 48,580 unique patients across 84 hospitals (Table 1). The mean age was 56.8 (SD 13.9) years: 69% were Caucasian, 17% African-American, 16% Hispanic, and 43% were women. Infection (23.0%) was the most common primary discharge diagnosis associated with CLD hospitalization, followed by hepatic encephalopathy (8.3%), and GI bleeding (7.9%). The overall median length of stay was 5.0 days (IQR 3.0–8.0)

and the overall readmission rate was 25.3%; 43.4% of hospitalizations had associated ICU stays. In total, 10.1% of patients had two hospitalizations and 15.2% patients had three or more hospitalizations within 1 year of index hospitalization. When limited to patients with cirrhosis diagnosis, 14.9% of patients had two hospitalizations and 26.6% patients had three or more hospitalizations within 1 year of index hospitalization.

Trends in CLD-related hospitalization

The age and gender standardized annual rate of CLD-related hospitalization increased from 48.9 per 100,000 in 2000 to 125.7 per 100,000 in 2014 (Fig. 1). The age and gender standardized annual rate of hospitalization for cirrhosis (limited only to codes specific to cirrhosis) increased from 14.7 per 100,000 in 2000 to 50.2 per 100,000 in 2014. Figure 2 describes age-specific (and gender-adjusted) trends in CLD-related hospitalization by deciles of age. Age-specific rates increased from 17.6 to 31/100,000 (ages 18–44), 82.3 to 154.0/100,000 (45–54 years), 77.4 to 295.3/100,000 (55–64 years), and 93.7 to 281.1/100,000 (age > 65 years).

Figure 3 describes trends in underlying etiology of CLD. A large proportion (35–40%) did not have descriptors of underlying etiology. However, among those with documented etiology, adjusted rates for HCV-related hospitalizations increased from 22.4 to 44.8 per 100,000, but plateaued in recent years. In the same time, an increase was seen in hospitalizations related to alcohol (9.1 to 22.7 per 100,000) and fatty liver (1.4 per 100,000 to 19.5 per 100,000).

Trends in patient characteristics among patients with CLD-related hospitalizations

Of the patients with CLD-related hospitalizations, the mean age increased from 54.0 (SD 14.1) in 2000 to 58.5 (SD 13.5) years in 2015. The proportion of women increased from 39.8% to 43.2%. There were no changes in the race or ethnicity distribution of patients hospitalized for CLD. Medicare increased as a primary payer from 26.5% to 32.0%, whereby the proportion of uninsured patients decreased from 26.1% to 21.2%.

Trends in CLD-related complications among patients with CLD-related hospitalizations

In our primary analysis, traditional complications of portal hypertension (i.e., ascites, varices, and hepatic encephalopathy) remained stable over time. Infection increased (54.7% to 67.5%) ($P < 0.0001$) and renal failure increased nearly sevenfold (2.7% to 19.5%) ($P < 0.0001$) from 2000 to 2014 (Fig. 4). Hospitalizations related to hepatic encephalopathy remained stable from 14.1% in 2000 to 15.4% in 2014 ($P = 0.52$). Hospitalizations with DVT or PVT increased from 2.6% to 6.7% ($P < 0.0001$). Infection-related hospitalizations were driven by an increase in sepsis diagnosis (from 12.9% in 2000 to 33.1% in 2014, $P < 0.0001$) (Fig. 5). Pneumonia, urinary tract infection, and cellulitis were the main causes of infection. There was also an increase in *C. difficile* (1.0% to 4.1%, $P < 0.0001$) and other unspecified bacterial infections (6.9% to 11.3%, $P = 0.001$) over time. These trends did not change in the sensitivity analysis limited to primary discharge diagnoses.

Comorbidities. There was an increase in the SOI over time (Fig. 6). The percentage of CLD hospitalizations with major or extreme SOI increased from 53.3% (2000) to 75.9% (2015) ($P < 0.0001$). SOI did not vary by race or ethnicity. Figure 7 describes the trends in the associated medical comorbidities. As compared with 2000, the proportion of patients with comorbidities increased from 4.8% to 13.0% (CAD) ($P < 0.01$), 2.7% to 14.9% (obesity) ($P < 0.01$), 1.0% to 22.6% (dyslipidemia) ($P < 0.01$), 2.4% to 20.8% (chronic kidney disease) ($P < 0.01$), and

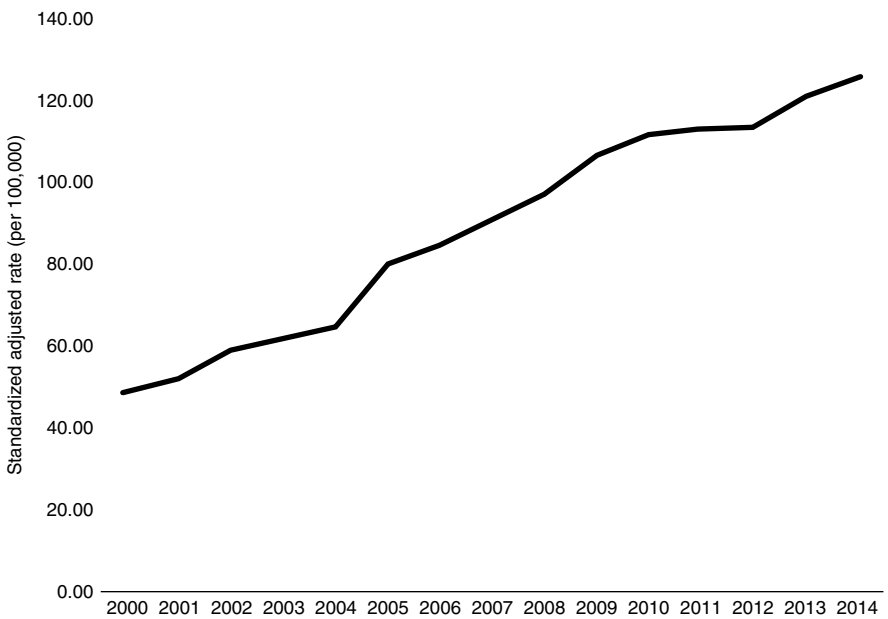

Fig. 1 Standardized chronic liver disease-related hospitalization rates, 2000–2014

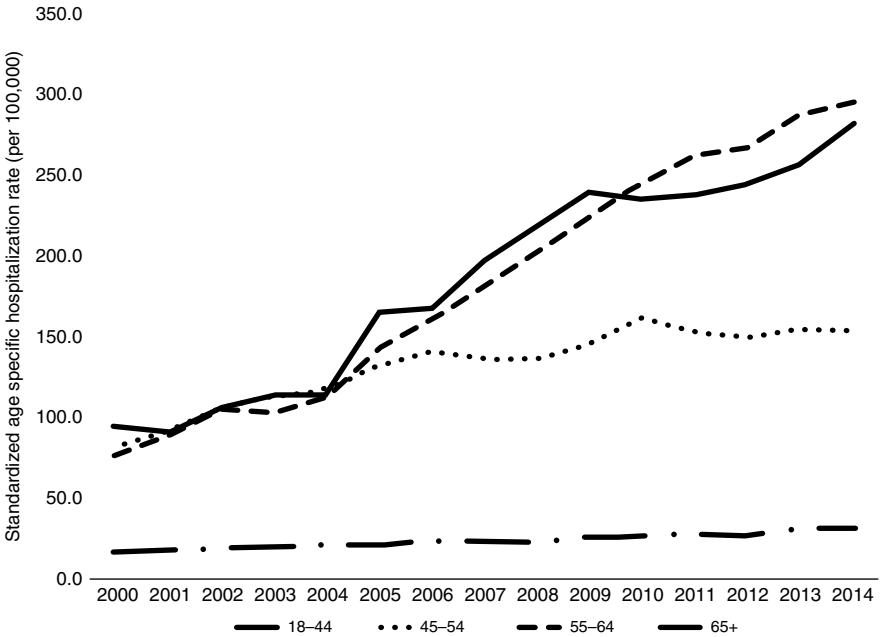

Fig. 2 Time trends in age at presentation, 2000–2014

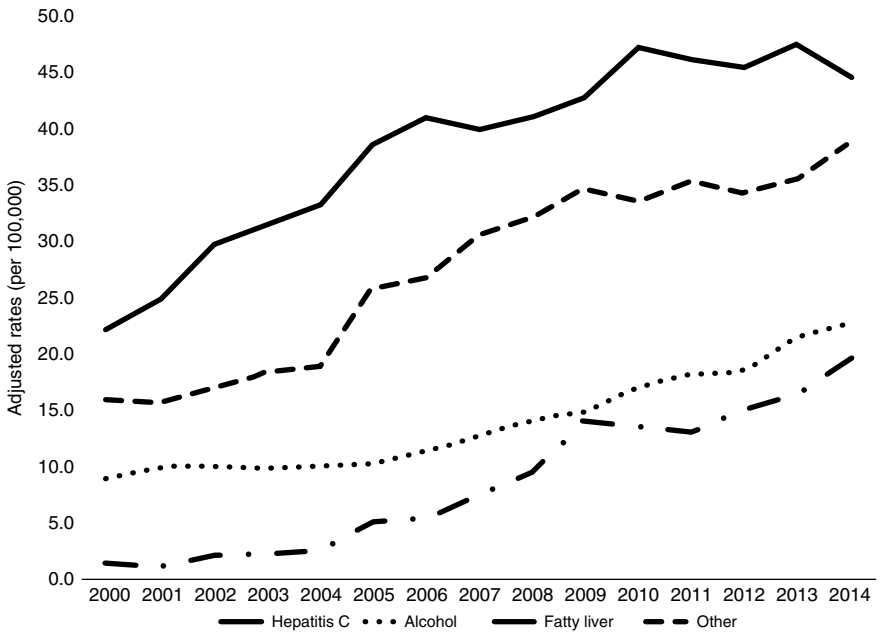

Fig. 3 Time trends in etiology of chronic liver disease, 2000–2014

18.7% to 36.2% (diabetes) ($P < 0.01$). The number of patients with 1, 2, and ≥3 comorbidities increased from 24.1% to 30.1%, 7.8% to 27.1%, and from 1.5% to 21.0% over time ($P < 0.01$).

Inpatient mortality. Reliable mortality data were available from 2005 to 2014. Annual adjusted age and sex standardized inpatient mortality rates changed from 72.1 per 1000 in 2005 to 61.4 per 1000 CLD patients in 2014 ($P = 0.02$ for trend over time). There was a non-significant increase in discharge to hospice over the same time period from 35.1 per 1000 CLD patients in 2005 to 40.7 per 1000 CLD patients in 2014 ($P = 0.4$).

DISCUSSION

In a population-based study of one of the largest and diverse metroplexes in the US, we found that CLD-related hospitalizations increased twofold over the last 15 years, Table 1. Several salient features of the study bear a comment. First, in the current era,

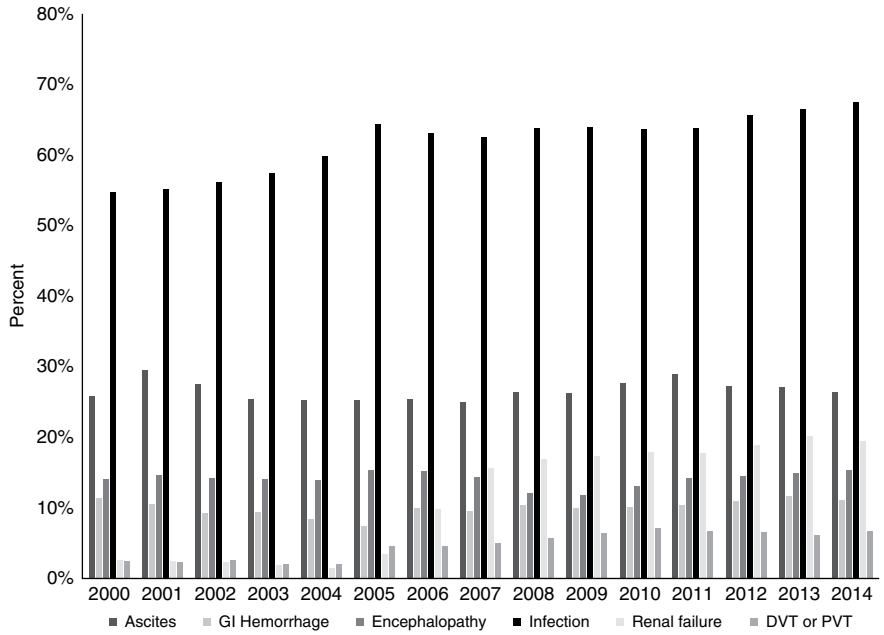

Fig. 4 Patient trends in chronic liver disease-related complications or reasons for hospitalizations, 2000–2014

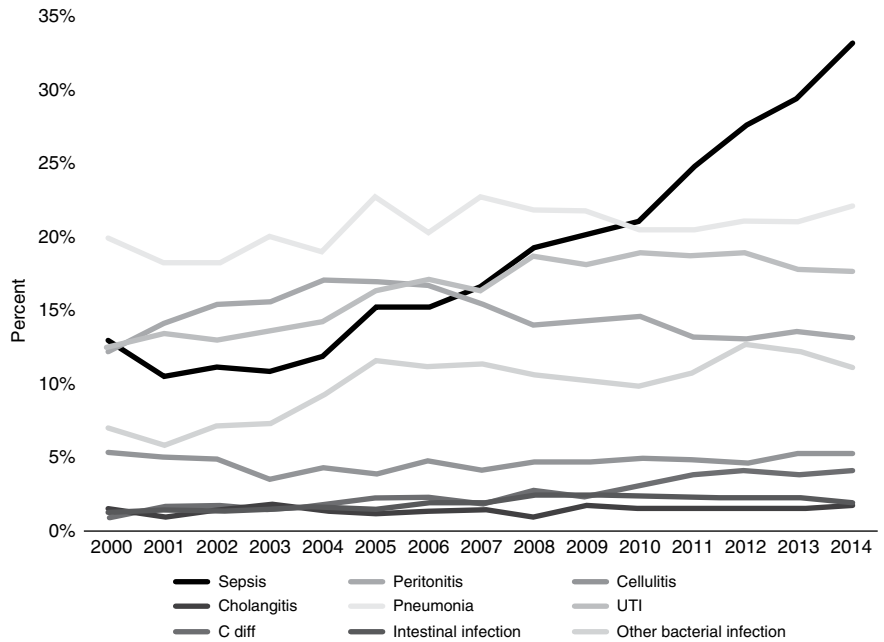

Fig. 5 Trends in specific infection diagnoses in chronic liver disease hospitalizations related to infection, 2000–2014

CLD patients were older and sicker with multiple chronic medical conditions compared with CLD patients hospitalized in the earlier years. CLD patients are living longer, partly driven by improvement in the management of CLD [10, 16–20]. The natural history of liver disease in the HCV birth cohort may contribute to a higher number of hospitalizations at an older age being seen in the current era [21–23]. As the CLD population gets older with more comorbidities, medicare may be expected to increasingly absorb charges related to CLD-related care over time [21, 24]. We recently compared inpatient hospitalizations for CLD versus other chronic diseases, congestive heart failure (CHF), and chronic obstructive pulmonary disease (COPD) [25]. The median age at the time of hospitalization as well as coverage by medicare increased for CLD, but not for the other chronic diseases. Similarly, in the current study we found that Medicare was responsible for 32.2% of hospitalizations in 2015 compared with 26.6% in 2000.

Second, traditional complications of portal hypertension (e.g., variceal bleeding) remained stable. Instead, there was an increase

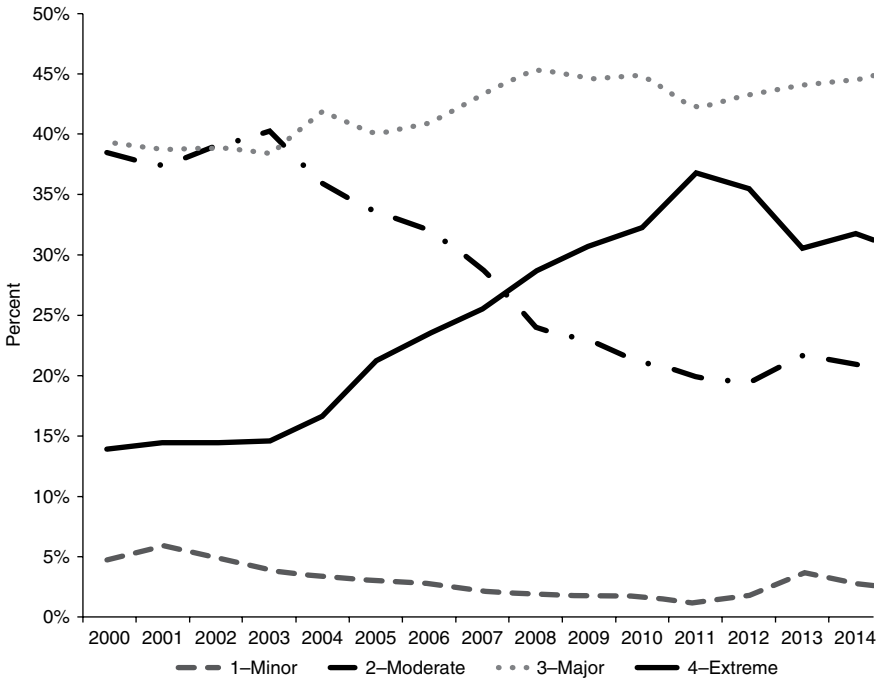

Fig. 6 Time trends in severity of illness as classified by APR-DRG severity of illness (SOI) categories: minor, moderate, major, or extreme risk

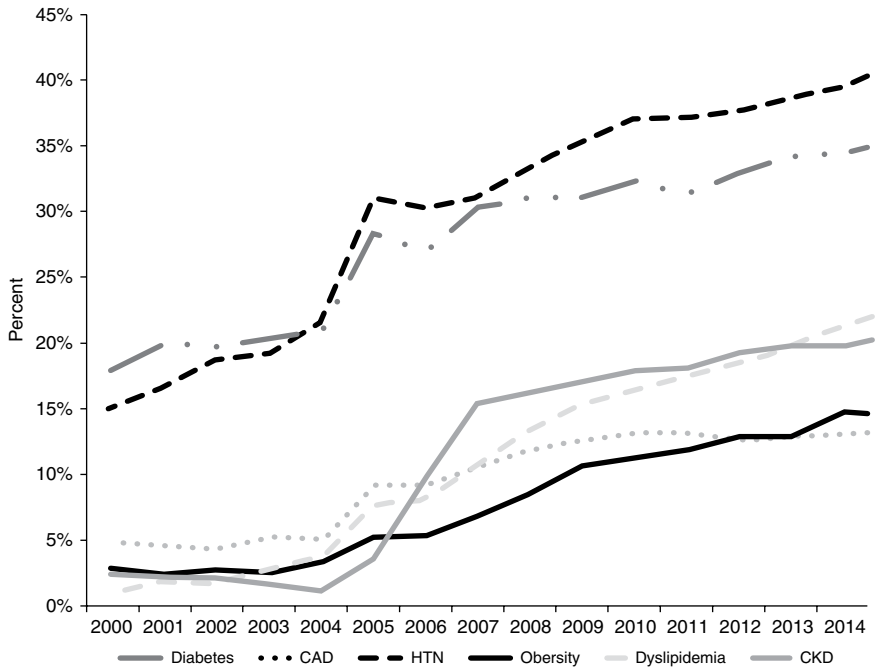

Fig. 7 Patient trends in comorbid conditions among patients hospitalized for chronic liver disease-related hospitalizations, 2000–2014

in infection and renal failure-related complications, the importance of which is increasingly recognized across a spectrum of studies [3, 16, 26–32]. These are common causes of morbidity in patients with cirrhosis that are often not considered in ascertainment of cirrhosis-related inpatient or outpatient burden, yet quite reflective of the natural progression of liver disease [1, 5, 8, 10, 26, 33–35]. Arvaniti et al. have also suggested that infection should be considered the fifth stage of cirrhosis, subsequent to development of complications of portal hypertension [3, 36]. Patients with non-alcoholic fatty liver disease often have comorbidities such as diabetes, coronary artery disease, and obesity, all of which may be independent risk factors for infection and renal failure [37–41]. In addition, infection

Table 1 Baseline demographics

	Overall (*n*=48,580)
Race/ethnicity	
White	33,372 (68.7%)
Black	8102 (16.7%)
Asian	1092 (2.2%)
Other	6014 (12.4%)
Hispanic ethnicity	7567 (15.6%)
Age (Med, IQR)	55.8 (47.7, 65.4)
≤24	384 (0.8%)
25–34	1924 (4.0%)
35 –44	5742 (11.8%)
45–54	13,458 (27.7%)
55–64	13,530 (27.9%)
65–74	7552 (15.6%)
75+	5990 (12.2%)
Gender	
Male	27,922 (57.5%)
Female	20,658 (42.5%)
Insurance	
Insured	15,999 (32.9%)
Medicaid	5310 (10.9%)
Medicare	14,885 (30.6%)
Uninsured	12,386 (25.6%)
Etiology	
Hepatitis C	17,552 (36.2%)
Alcohol	9141 (18.8%)
Fatty liver	5985 (12.3%)
Other	15,902 (32.7%)

and renal failure are common in other chronic diseases such as CHF and COPD, suggesting a shared propensity for development of complications in chronic conditions. There was a disproportionate increase in sepsis-related hospitalizations and pneumonia, urinary tract infection and cellulitis were the main causes of infection. There was also an increase in C Difficile and other unspecified bacterial infections. Though sepsis might have been over diagnosed, our results are concordant with other national trends [36].

Overall inpatient mortality rates improved. This has been seen in other populations [8, 10]. Significant utilization of hospice services at discharge was also observed in this diverse population-based setting and mirrors observations from other studies using the nationwide inpatient sample [14, 25]. Consideration of disposition to hospice likely tempers improvements observed in inpatient mortality rates.

Our study has several implications at the patient level and system level. Collectively, our results suggest that the burden of CLD encountered in the inpatient setting has changed from that related to the management of acute complications of CLD to management of chronic conditions. Further, our study corroborates trends seen at the national level regarding the increasing burden of liver disease, presence of NAFLD, aging CLD population, a decline in inpatient mortality, and the impact on infection and renal failure, supporting external generalizability [8, 10, 16, 42–44]. The spectrum shift in manifestation, comorbidities, and age suggest a burgeoning CLD population with a palpable impact on existing healthcare infrastructure.

The changing landscape of CLD may additionally warrant a need to redefine what it means to have decompensated liver disease. Our models of care for CLD are often limited to domains of management of portal hypertension (e.g., varices screening) and monitoring for hepatocellular carcinoma. A multidisciplinary approach may be needed that takes all relative comorbidities into account. Our data also underscore the importance of adapting lessons learnt from successful management of other chronic diseases, such as CHF to mitigate the increasing CLD-related burden [45, 46].

The strength of the paper lies in its population-based study design, ability to capture almost all hospitalizations and to examine patients across hospitals and competing healthcare systems. As recently shown, a quarter of hospitalizations for liver CLD are at hospitals other than the index hospital; inability to capture these data may underestimate the true disease burden [43]. Inclusion of several centers with variation in center practice further strengthened the findings. In addition, we had an almost complete enumeration of the population at risk, which is often missing from large studies. We were able to describe a broad definition of CLD-related hospitalization to overcome underestimation of true disease burden [14, 25]. We examined this by consideration of a primary versus all discharge diagnoses as is often the case in decompensated liver disease.

Our study also has limitations. Misclassification bias may be present, whereby a purported increase may partially be explained by a change in coding practices, whereby aggressive and judicious coding of all encounter related diagnoses may manifest as an artificial increase in comorbidities and complications [9]. Indeed, this may have resulted a marked increase in fatty liver as an underlying cause or inclusion of renal failure as a primary reason for hospitalization. However, our inclusion of a mix of hospitals across different settings (urban vs. rural) as well as discrete healthcare systems (university or non-university) with both conservative and liberal coding practices likely reduces the misclassification due to coding alone. Regardless, analysis of VA populations, where financial incentives have remained stable over the last decade, and national transplant registries also confirm the trends observed in our study [4, 21, 47]. Regional referral patterns and changes in population may have affected our results. However, a wide variety of urban, rural, teaching, and private systems were represented, rendering this possibility less likely. Migration patterns might be a confounding factor. However, racial and ethnic distribution remained stable. We were only able to examine inpatient burden rather than outpatient burden and practices in the immediate post-hospitalization

period [18, 44, 46]. However, inpatient burden is a common and relevant metric in other conditions such as CHF and COPD, and [48] similar to other chronic diseases, a large proportion of CLD-related morbidity is reflected in inpatient healthcare utilization. In addition, hospitalizations often reflect penultimate expressions of decompensation in chronic disease states and have linkage to early mortality [45, 46].

The impact of relevant conditions, such as obesity, was incompletely ascertained, given the inability to link to data on actual body weight across systems. The increase of non-alcoholic fatty liver disease seen in our study is congruent with other reports in the non-transplant and transplant population [6]. There was a large percentage of patients without an identified underlying etiology. Though some hospitalizations in the "other" category were attributed to other chronic diseases (e.g., autoimmune hepatitis or cholestatic liver disease), most hospitalizations in this category were assigned non-specific descriptors of liver disease (e.g., cirrhosis liver unspecified).

In summary, we found that CLD-related hospitalizations have increased twofold over the last decade. CLD patients are older and sicker with multiple chronic medical conditions. Traditional complications of portal hypertension have been augmented by hospitalizations for infection and renal failure, warranting a need to redefine what it means to have decompensated CLD.

CONFLICT OF INTEREST

Guarantor of the article: Sumeet K Asrani

Specific author contributions: Study concept and design: S.A., S.S., J.T., J.T., and F.K. Acquisition of data: S.A., L.H., and M.H. Analysis and interpretation of data: S.A., S.S., L.H., S.Y., J.T., J.T., and F.K. Drafting of the manuscript: S.A., M.H., F.K., and S.S. Critical revision of the manuscript for important intellectual content: S.A., L.H., S.Y., J.T., J.T., F.K., S.S., and M.H. Statistical analysis: L.H. and S.Y.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The burden of chronic liver disease (CLD) is increasing. Liver-related mortality remains high.

WHAT IS NEW HERE

- ✓ In a population-based study between 2000 and 2015, there was a marked increase in liver-related hospitalizations.
- ✓ HCV-related hospitalizations plateaued, whereas hospitalizations related to alcohol (9.1 to 22.7 per 100,000) or fatty liver (1.4 per 100,000 to 19.5 per 100,000) increased between 2000 and 2015.
- ✓ Over time, CLD patients were sicker, older, and had more comorbidities.
- ✓ Hospitalizations with traditional complications of liver disease (e.g., ascites) remained stable over time. However, hospitalization with complications related to infection increased and those related to renal failure increased by sevenfold.

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