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Research Paper

Increasing Hospitalization Rates for Cirrhosis: Overrepresentation of Disadvantaged Australians

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ABSTRACT

Background: Limited information is available about hospitalization rates for cirrhosis in Australia.
Methods: Using information on all hospital episodes of care for patients admitted to Queensland hospitals during 2008–2016, we report age-standardized hospitalization rates/10,000 person-years, in-hospital case-fatality rate among these admissions (n = 30,327), and examine the factors associated with hospital deaths using logistic regression analyses.
Findings: Hospitalization rates increased from 8.50/10,000 (95% confidence interval (CI) 8.18–8.82) to 11.21/10,000 (95%CI 10.87–11.54) between 2008 and 2016, and peaked in men aged 55–59 years (34.03/10,000) and in Indigenous Australians (32.79/10,000). The number of admissions increased by 61.7% from 2701 admissions in 2008 to 4367 in 2016. During the same period, the percentage increase varied by socioeconomic disadvantage (3.2%/year in the most affluent vs. 9.4%/year in the most disadvantaged quintile; $p < 0.001$). Alcohol misuse was a contributing factor for cirrhosis in 55.1% of admissions, and socioeconomic disadvantage in 26.8%. The overall in-hospital case-fatality rate was 9.7% for males and 9.3% for females, and decreased in males ($p < 0.001$). Predictors of in-hospital mortality included hepatorenal syndrome (adjusted odds ratio (AOR) = 7.24, 95%CI 5.99–8.75), HCC (AOR = 2.53, 95%CI 2.20–2.91), hepatic encephalopathy (AOR = 1.94, 95%CI 1.61–2.34), acute peritonitis (AOR = 1.93, 95%CI 1.61–2.33), jaundice (AOR = 1.82, 95%CI 1.20–2.75), age ≥ 70 years (AOR = 1.63, 95%CI 1.38–1.92), a higher comorbidity index ($p = 0.021$), and residence outside of a "major city" ($p < 0.001$).
Interpretation: The increasing healthcare use by Australians with cirrhosis has resource and economic implications. Our data highlight the disproportionate impact of cirrhosis on Indigenous Australians and people from the most socioeconomically disadvantaged areas.
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Abbreviations: Adjusted odds ratios, AOR; Charlson Comorbidity Index, CCI; Chronic liver diseases, CLDs; Confidence interval, CI; Hepatic encephalopathy, HE; Hepatitis B virus, HBV; Hepatitis C virus, HCV; Hepatocellular carcinoma, HCC; Interquartile range, IQR; International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian, ICD-10-AM; Least Absolute Shrinkage and Selection Operators, LASSO; Length of stay, LOS; Non-alcoholic fatty liver disease, NAFLD; Odds ratios, OR; Radio-frequency ablation, RFA; Transarterial chemoembolization, TACE.

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Research in context

Evidence before this study

We searched PubMed for key articles describing population-based hospitalization rates for cirrhosis. The search terms 'liver', 'cirrhosis' and 'hospitalization rate' ('hospitalization rate' or 'hospital admission rate') were used to select manuscripts of interest. While there have been a few studies reporting hospitalization rates for chronic liver disease (CLD), the burden of CLD is underestimated, and there is a dearth of data on hospital admissions for cirrhosis. The few reports on hospital admissions for cirrhosis in the literature included selected subgroups of patients (e.g. hepatitis B and/or C and cirrhosis, alcoholic liver cirrhosis).

Added value of this study

Hospitalization rates for cirrhosis increased 1.3-fold during 2008–2016. The absolute number of cirrhosis admissions in Queensland, the third most populous Australian state, increased 1.6-fold during this period. Moreover, the percentage increase was significantly higher in the most disadvantaged quintile of the population. Alcohol misuse was a cause or contributing factor for cirrhosis in over half of these admissions. Our findings from a geographically vast country with a universal healthcare system that does not provide uniform care across rural, regional and metropolitan areas provide an important contribution to the global perspective on the impact of CLD, and more specifically cirrhosis.

Implications of all the available evidence

The increasing hospitalization rate for cirrhosis has resource and economic implications. The disproportionate impact of cirrhosis on disadvantaged Australians and Indigenous Australians highlights the need for specific plans for prevention (e.g. public health policies discouraging harmful alcohol consumption) and diagnosis of cirrhosis in these groups.

1. Introduction

Chronic liver diseases (CLDs) are a major global public health problem [1,2], due largely to obesity-related non-alcoholic fatty liver disease (NAFLD), hazardous alcohol consumption and chronic viral hepatitis B (HBV) and C (HCV). Regardless of etiology, most of the morbidity and mortality from CLDs occur among people with cirrhosis, who are at risk of developing hepatocellular cancer (HCC) and decompensation events including ascites, hepatic encephalopathy (HE) and variceal hemorrhage.

CLD has a long latency period, during which affected individuals remain asymptomatic despite progressive hepatic fibrosis and development of cirrhosis. The occurrence of ascites is usually the first sign that cirrhosis has progressed to a decompensated phase. Optimal care of decompensated cirrhosis is complex and associated with very high use of hospital services due to frequent admissions that are often unplanned [3]. Patients often have comorbidities that increase the burden of illness and use of healthcare resources [4]. Despite the fact that much of the burden of clinical care occurs in patients with cirrhosis, there is a paucity of literature describing hospitalization rates for cirrhosis.

In the United Kingdom, the poorest and most vulnerable members of society have the highest incidence of liver disease [5]. In the United States, patients with CLD have higher rates of hospitalization than other chronic diseases [2]. In Australia, availability of health services generally decreases with increase in remoteness [6]. For many chronic diseases, higher rates of disease burden are experienced by populations in regional and remote areas or in the most socioeconomically disadvantaged areas, compared to people living in major cities and areas of least socioeconomic disadvantage [7]. Health inequalities are also seen for the Indigenous population who have a chronic disease burden rate 2.3 times the non-Indigenous rate [8]. The impact of these sociodemographic factors on cirrhosis health outcomes in Australia remains unknown.

We report population-based hospitalization rates for cirrhosis in the large state of Queensland, Australia and examine the sociodemographic and clinical factors associated with hospital deaths.

2. Methods

2.1. Setting

Queensland is a large state in the north-east of Australia with a population of 4.9 million and an area approximately equivalent to Western Europe. The primary data for this study includes information on all hospital episodes of care for patients admitted to Queensland hospitals during 2008–2016.

2.2. Case Ascertainment

We identified all hospital admissions for cirrhosis for patients who were aged 20 years or older. The study cohort was identified via a comprehensive list of diagnosis (based on ICD-10 AM codes) and procedure codes provided to the Statistical Analysis Linkage Unit (see online **supplementary material** for further details). We excluded hospital admissions where the patient's age was less than 20 years or residential location at time of admission was unknown as well as people whose primary residence was interstate or overseas.

An admission for cirrhosis was defined by hospitalization in any given year from 1 January 2008 to 31 December 2016 with any one of the following as the *primary* diagnosis: alcoholic fibrosis and sclerosis of liver, alcoholic cirrhosis of liver, alcoholic hepatic failure, chronic hepatic failure, fibrosis and cirrhosis of liver, primary biliary cirrhosis/cholangitis, secondary biliary cirrhosis, biliary cirrhosis, unspecified, other and unspecified cirrhosis of liver, portal hypertension, hepatorenal syndrome, gastroesophageal varices with/without bleeding, and hepatocellular carcinoma (HCC) (referred to here as 'classic diagnosis').

To minimize the potential of missing cases, we extended the definition to include hospitalization with any of the abovementioned codes as "*other*" diagnosis and: (i) any of the following ICD-codes as *primary* diagnosis: alcoholic hepatitis, alcoholic liver disease unspecified, toxic liver disease with fibrosis and cirrhosis of liver, hepatic failure unspecified, hepatic sclerosis, hepatic fibrosis with hepatic sclerosis, acute peritonitis, alcoholic encephalopathy, encephalopathy unspecified, ascites, unspecified jaundice, and hyponatremia; or (ii) a procedure code for cirrhosis, namely: abdominal paracentesis, endoscopic banding of esophageal varices, endoscopic banding of gastric varices, or transjugular intrahepatic portosystemic shunt.

We also considered an admission for cirrhosis as any hospitalization with: (iii) a procedure code for HCC (radio-frequency ablation (RFA), trans-arterial chemoembolization (TACE), or liver resection) and a diagnosis of HCC; (iv) a primary diagnosis of alcoholic hepatitis or alcoholic liver disease unspecified and ascites, varices or HCC as other diagnosis; (v) a primary diagnosis of gastrointestinal hemorrhage and gastroesophageal varices with bleeding; (vi) a primary diagnosis of gastrointestinal hemorrhage and rectal varices with portal hypertension.

2.3. Measures

Sociodemographic, clinical data and health service identity (data not provided for private hospitals) were obtained from Queensland

Hospital Admitted Patient Data Collection (referred to here as hospital admissions database). Health sector was categorized as public hospital or private hospital. Place of residence was mapped according to the level of remoteness [9] and socioeconomic advantage and disadvantage [10]. Indigenous status for an individual may vary across records for the same individual as it is based on self-identification. Patients were coded as Indigenous if identified in at least one of their records within the study period. As medical records were not reviewed, the specific etiology of liver disease was determined based on recorded primary or other diagnosis. Comorbidity at the time of hospital admission was measured using the Charlson Comorbidity Index (CCI) [11]. All diseases listed in the CCI as primary or other diagnosis were analyzed (excluding liver disease). Although hepatocellular carcinoma is included in the Charlson comorbidity index as a cancer, it largely occurs as a *complication* of cirrhosis, rather than as a comorbidity. For this reason, we conducted a sensitivity analysis by excluding HCC. The CCI score was categorized as score '0' meaning 'no known comorbidity' with higher scores indicating higher comorbidity burden.

The hospital admissions database covers all admitted patient separations from public hospitals, private hospitals and day surgery units in the state of Queensland. A separation can be a formal separation (e.g. discharge, transfer or death) or a statistical separation (episode type changes e.g. when patients are transferred from the emergency department to a ward). Every day the patient was an admitted patient is known as a 'patient day'. When patients were transferred within the same hospital (e.g. from the emergency department to a ward) or to another hospital, we considered these three episodes of care as one hospital stay. Length of stay (LOS), defined as the time from admission to discharge in days, was calculated by adding all 'patient days' accrued during one hospital stay. LOS was capped at 30 days. Patients were categorized as 'live discharge' if status at separation of patient was 'discharge' or 'transfer', and as 'in-hospital death' if status at separation was 'death'.

2.4. Data Analysis

Analyses were conducted using Stata/SE (Version 15; Stata Corporation, College Station, TX) and JMP Pro 14.1.0 (SAS Institute, Cary, NC). The unit of analysis was a hospital admission. Categorical variables were presented as numbers and percentages and compared using the Chi-square test (Fisher exact test was used for sparse tables). Continuous variables were presented as medians (interquartile range (IQR)). Statistical significance was set at alpha = 0.05, and all p values were 2-sided.

Hospital admissions were categorized by gender, age group, and Indigenous status. Corresponding population data were available from the Australian Bureau of Statistics. Age-specific hospitalization rates per 10,000 person-years were computed and stratified by gender. As the Indigenous Australian population has a relatively young age structure [12], we age-standardized the rates, taking into account differences in the age structures of the groups. Age-standardized hospitalization rates per 10,000 person-years were similarly estimated using the Australian standard population. To examine temporal patterns, age-adjusted hospitalization rates were also computed by gender, for each calendar year.

Case-fatality rate (hospital deaths divided by hospital admissions) was calculated per calendar year and overall (2008–2016). A logistic regression model was used to examine factors that were independent predictors of in-hospital mortality. The primary outcome was in-hospital mortality and results are presented as odds ratios (OR) with 95% confidence interval (CI). First, unadjusted ORs from simple logistic regressions are presented. Secondly, the Least Absolute Shrinkage and Selection Operators (LASSO) procedure was used with logistic regression to identify a parsimonious model of in-hospital mortality [13]. Due to the high number of predictors [27] selected on a clinical basis, a review of the literature (variables identified to be strongly associated with cirrhosis deaths), availability of data for our cohort, and potentially complex patterns of collinearity among predictor variables, the Lasso procedure was chosen. The Lasso procedure is a shrinkage method that shrinks coefficient estimates of predictors with little or no predictive value to zero (an odds ratio of 1) thus eliminating them from the model. The amount of shrinkage is controlled by the penalty parameter λ. This value was optimized using 10-fold cross validation. The selected parameters were then fit again using ordinary maximum likelihood logistic regression, and odds ratios with 95% confidence intervals were estimated using the Wald method. A sensitivity analysis was conducted by repeating the analysis excluding HCC from the Charlson Index.

The study was approved by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute (P2209) and Metro South Hospital and Health Services (HREC/17/QPAH/23).

3. Results

3.1. Patient Population and Admission Rates

During 2008–2016, there were 30,327 hospital admissions from 10,254 unique individuals, in Queensland, Australia that were identified as an admission for cirrhosis, with 77% occurring in the public sector and 23% in the private sector. The majority (97.4%) of cirrhosis admissions had at least one diagnosis (primary or other) from the 'classic diagnosis' list. The remaining admissions were included based on the extended definitions (iii) to (vi) (see **online supplementary material** for further details). Of the 30,327 admissions, 29,820 (98.3%) had at least one ICD-10 code for cirrhosis or its complications (varices, ascites, HE and HCC) listed in a recent cirrhosis code validation study [14]; 78.2% had at least two ICD-10 codes and 507 (1.2%) had none of these ICD-10 codes.

Overall, the age-adjusted hospitalization rate for cirrhosis was 9.54 (95%CI 9.43–9.65) per 10,000 person-years. However, admission rates were substantially different based on gender and age (Fig. 1), with 2.5-fold higher admission rates in men that peaked at 34.03 per 10,000 person years in the 55–59 year age group. There was a striking increase in the number of cirrhosis admissions per year for both men and women over the study period, and this temporal pattern was also seen when age-adjusted hospitalization rates were computed for each calendar year ranging from 8.50 (95%CI 8.18–8.82) per 10,000 person-years in 2008 to 11.21 (95%CI 10.87–11.54) per 10,000 person-years in 2016 (Fig. 2).

The number of cirrhosis admissions increased by 61.7% from 2701 admissions in 2008 to 4367 in 2016. The percentage increase in the number of cases varied by socioeconomic disadvantage (Fig. 3); for the same period there was a 3.2% (95%CI 1.2%-5.2%) increase in the number of cases per year in the most affluent quintile compared to 9.4% (95%CI 7.3%-11.6%) in the most disadvantaged quintile (comparison of slopes in regression, $p < 0.001$). The number of admissions classified as "Indigenous" increased from 201 in 2008 to 341 in 2016, an increase of 8.8% (95%CI 6.7%-11.0%) vs. 5.9% (95%CI 3.8%-8.0%) per year for non-Indigenous (comparison of slopes in regression, $p = 0.058$).

Table 1 summarizes the clinical and demographic characteristics of the cirrhosis admissions; 7.4% of admissions were classified as "Indigenous", and the age-standardized admission rate was 3-fold higher for Indigenous Australians (32.79 (95%CI 31.28–34.31) per 10,000 person-years) than the overall rate. Over one-quarter of cirrhosis admissions (26.8%) were from patients residing in most socioeconomically disadvantaged areas. Co-morbid conditions were present in 40% of admissions, with 12.7% having a Charlson comorbidity index ≥3 (reflecting a greater number and severity of comorbidities). While the presence of type 2 diabetes was recorded in 20.5% of admissions, obesity was not consistently documented (recorded for only 3.1% of admissions).

Regarding etiology of liver disease, an admission may have had more than 1 liver disease diagnosis (e.g. HCV infection and alcohol misuse). Table 2 summarizes the overall prevalence of specific liver diseases

that were coded for during the admissions. Alcohol-related liver disease was diagnosed in 55.1% of admissions followed by chronic HCV in 23.8%, NAFLD/NASH in 4.9% and chronic HBV in 4.3%.

Ascites was the most frequent complication of cirrhosis (42.3% of admissions), followed by gastrointestinal bleeding (34.5%), HCC (14.6%) and hepatic encephalopathy (4.3%) (Table 2). This is reflected in the procedures performed, with abdominal paracentesis performed in 36.6% of admissions, endoscopic banding in 10.5% and TACE in 3.5%.

In 40% of admissions (Table 1), the length of stay was one day. Moreover, the proportion of 1-day admissions did not change over time; there was an average 41.2% of 1-day admissions in 2008–2010 and 40.5% in 2014–2016 (Ztest for differences in proportions, p = 0.311). The primary diagnoses reported for these one day admissions were ascites in 25.1%, varices in 24.4%, unspecified cirrhosis of liver in 14.7%, alcoholic cirrhosis in 11.3%, and HCC in 8.3%. In the remaining admissions, length of stay varied widely from 2 to 4 days in 21.4%, 5 to 9 days in 18.6%, 10 to 19 days in 11.4% and ≥20 days in 8.6%.

3.2. Case-fatality Rate

The overall in-hospital case-fatality rate among male admissions during the study period was 9.69% (95%CI 9.30–10.10), and decreased over time from a peak of 11.69 in 2009 (95%CI 10.35–13.14) to 8.32 in 2016 (95%CI 7.37–9.35; Z test for differences in proportions, p < 0.001). The in-hospital case-fatality rate among female admissions during the study period was 9.26% (95%CI 8.66–9.89), and did not change progressively over time (Z test for differences in proportions, p = 0.987 for 2008–2016; Fig. 4).

3.3. Predictors of In-hospital Mortality

Characteristics of the cirrhosis-related admissions by discharge status (live discharge vs. hospital death) are summarized in Table 1. A higher proportion of hospital deaths occurred in the older age groups (≥60 years) and in admissions with a longer length of stay (≥5 days). The presence of comorbidities was also important, with a higher proportion of hospital deaths in admissions with a Charlson comorbidity index ≥2. Socioeconomic disadvantage and a marital status of "no partner" were also associated with a greater risk of in-hospital mortality. Discharge status differed according to rurality of residence and hospital sector: greater risk of in-hospital mortality was observed in hospitals outside of "major city" and in the "public" hospital sector.

Of the sociodemographic data obtained at point of entry to care, and the clinical factors obtained during admission, ten independent risk factors were identified (Table 3). The highest adjusted odds ratios (AOR) were for hepatorenal syndrome (AOR = 7.24, 95%CI 5.99–8.75), followed by HCC (AOR = 2.53, 95%CI 2.20–2.91), hepatic encephalopathy (AOR = 1.94, 95%CI 1.61–2.34), acute peritonitis (AOR = 1.93, 95% CI 1.61–2.33), jaundice (AOR = 1.82, 95%CI 1.20–2.75) and age ≥ 70 years (AOR = 1.63, 95%CI 1.38–1.92). For every 1 unit increase in the Charlson index, the likelihood of in-hospital mortality increased by 1.13 times (95%CI 1.09–1.17). Longer LOS was significantly associated with in-hospital mortality; patients who were in hospital for 30 + days were 5.61 times as likely to die in hospital (95%CI 4.85–6.50) and patients admitted for one day were less likely to die in hospital (AOR = 0.32, 95%CI 0.27–0.37) compared to patients admitted for 2–4 days. Having a cirrhosis- or HCC-related procedure was negatively associated with in-hospital mortality.

While 1-day admissions are hospital admissions strictly speaking, their clinical significance is likely different from that of longer admissions (e.g. diagnostic or therapeutic procedures versus management of disease complications). We have therefore also analyzed the data excluding 1-day admissions. The results were very similar to the main analysis, the direction of the associations was unchanged and, with the exception of length of stay, AORs changed by 15% or less.

3.4. Sensitivity Analysis

With the exclusion of HCC from the Charlson index, comorbidities were present in 9618 (31.8%) admissions, and the CCI score was strongly associated with in-hospital mortality. For every 1 unit increase in the Charlson index, the likelihood of in-hospital mortality increased by 1.10 times (95%CI 1.05–1.15; see further details in Supplementary Table 2).

4. Discussion

Although chronic liver disease is often a "silent" condition, the impact of decompensated cirrhosis and its associated complications is not, with 4367 cirrhosis-related hospital admissions in 2016, in the single state of Queensland, Australia alone. Our longitudinal, population-based state-wide study has shown that the number of cirrhosis admissions has increased 1.6-fold over the last eight years, and alcohol misuse was a cause or contributing factor for cirrhosis in over half of these admissions. Indigenous Australians and patients residing in most socioeconomically disadvantaged areas were overrepresented among patients admitted. While overall the hospitalization rates in Australia vary by socioeconomic disadvantage (e.g. in 2015–16, 21.7% of hospitalizations were from patients residing in the most socioeconomically disadvantaged quintile vs. 18.6% for the most affluent quintile) [15], in our

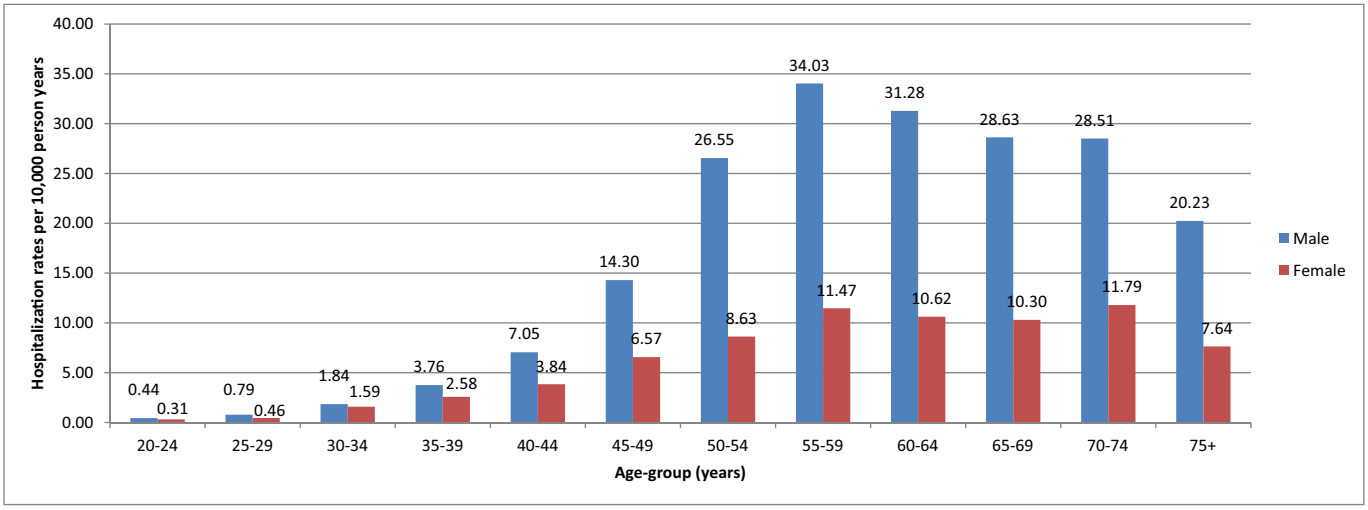

Fig. 1. Average annual age-specific hospitalization rate per 10,000 person years for liver cirrhosis by gender in Queensland, Australia, during 2008 to 2016.

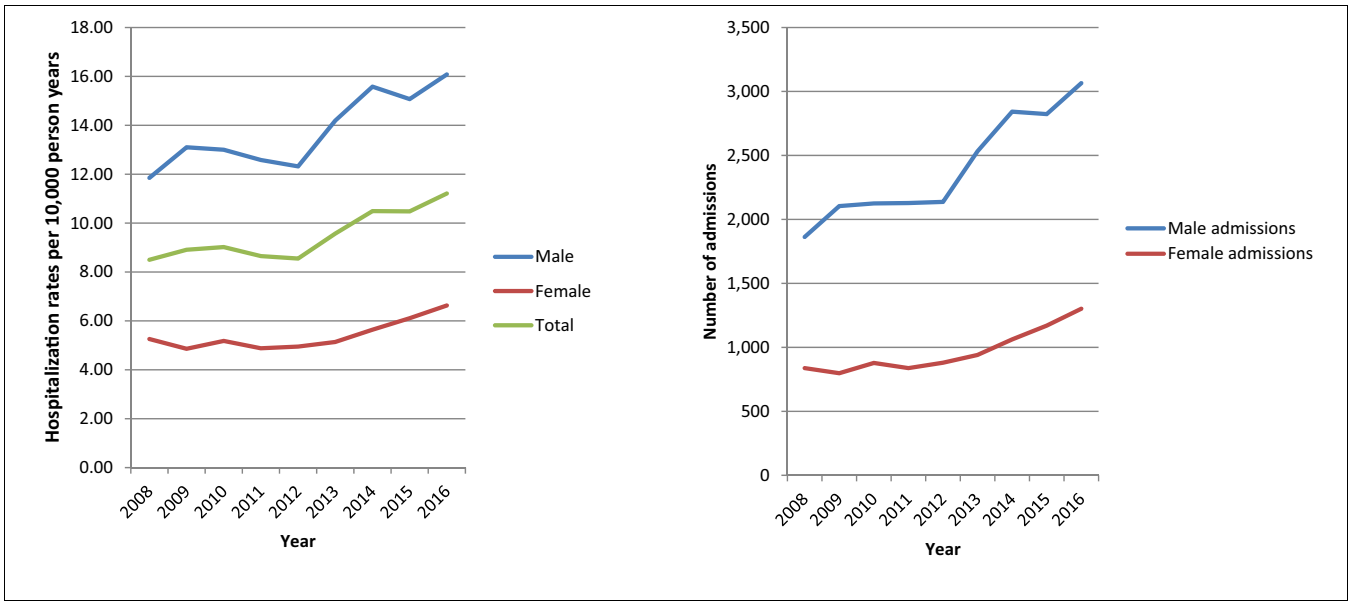

Fig. 2. Number of hospital admissions and age-adjusted hospitalization rate per 10,000 person years for liver cirrhosis by year and gender in Queensland, Australia during 2008 to 2016.

cohort of cirrhosis admissions, there was a greater discrepancy between areas most disadvantaged (26.8% of admissions) and most affluent (15.5%).

Limited information is available in the literature to compare the hospitalization rates observed in this study with those from other Australian states or data sources. In a report commissioned by the Gastroenterological Society of Australia, the total number of Australian hospital separations for diseases of the liver in 2009–10 was 13,555 [16]. This statistic was based only on the principal diagnosis chiefly responsible for the patient's episode of care in hospital. These statistics likely substantially underrepresent cirrhosis-related hospital admissions as they only used the principal diagnostic code, and may not have captured admissions due to decompensation events, complications or procedures such as abdominal paracentesis for cirrhosis-related ascites. Comparable to our data, a study in the US found the age-adjusted incidence rate for admission for complications of cirrhosis was 10.01 (95%CI 9.03, 10.98) per 10,000 population [17].

The reason for hospitalization in patients with cirrhosis is usually due to consequences of portal hypertension and decompensation events [18]. In our study, the most frequently reported cirrhosis complications during admission were ascites (in 42.3% of admissions) and gastroesophageal bleeding (34.5%), requiring abdominal paracentesis (36.6%) and endoscopic variceal ligation (10.5%). However, HCC was the third most common indication, accounting for 14.6% of admissions, with cancer-related procedures (TACE, RFA, liver resection) performed in 4.9%. Liver cancer is reported to be the fastest growing cause of cancer death in Australia and has a very poor prognosis (5-year survival of 16%) [7,19]. This is particularly troubling since the majority of HCC is potentially preventable if the cause of chronic liver disease is identified and interventions are undertaken (e.g. treatment of viral hepatitis, interventions for alcohol misuse and dependence, and optimization of metabolic risk factors such as obesity and diabetes).

Our data highlight the key role of alcohol as a significant causative factor, since it was recorded in 55% of cirrhosis-related hospital

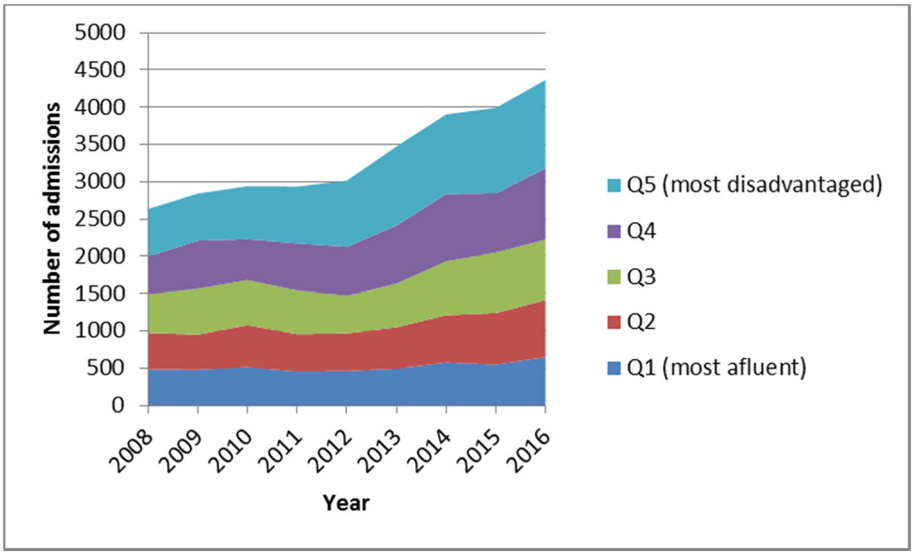

Fig. 3. Number of hospital admissions by socioeconomic status.

Table 1
Characteristics of cirrhosis-related hospital admissions in Queensland during 2008–2016 by discharge status.

		All admissions	Live discharges	In-hospital deaths	
		N = 30,327	N = 27,425	N = 2902	p-value*
Age group (years)	20–29	296 (1.0%)	285 (1.0%)	11 (0.4%)	<0.001
	30–39	1380 (4.6%)	1296 (4.7%)	84 (2.9%)	
	40–49	4493 (14.8%)	4153 (15.1%)	340 (11.7%)	
	50–59	10,246 (33.8%)	9392 (34.2%)	854 (29.4%)	
	60–69	8189 (27.0%)	7361 (26.8%)	828 (28.5%)	
	70 and over	5723 (18.9%)	4938 (18.0%)	785 (27.1%)	
Gender	Male	21,620 (71.3%)	19,524 (71.2%)	2096 (72.2%)	0.240
	Female	8707 (28.7%)	7901 (28.8%)	806 (27.8%)	
Indigenous status[a]	Indigenous	2249 (7.4%)	2036 (7.4%)	213 (7.4%)	0.920
	Non-Indigenous	28,040 (92.6%)	25,366 (92.6%)	2674 (92.6%)	
Marital status[b]	Married or De Facto	15,495 (52.0%)	14,112 (52.3%)	1383 (49.0%)	<0.001
	No partner	14,318 (48.0%)	12,879 (47.7%)	1439 (51.0%)	
Country of birth[c]	Australia	22,320 (77.5%)	20,181 (77.5%)	2139 (77.9%)	0.630
	Overseas	6469 (22.5%)	5862 (22.5%)	607 (22.1%)	
Rurality of residence	Major city	18,726 (61.7%)	17,090 (62.3%)	1636 (56.4%)	<0.001
	Inner regional	6595 (21.7%)	5917 (21.6%)	678 (23.4%)	
	Outer regional	4360 (14.4%)	3848 (14.0%)	512 (17.6%)	
	Remote	457 (1.5%)	407 (1.5%)	50 (1.7%)	
	Very remote	189 (0.6%)	163 (0.6%)	26 (0.9%)	
Socioeconomic advantage and disadvantage[d]	Q1 most affluent	4680 (15.5%)	4314 (15.8%)	366 (12.7%)	<0.001
	Q2	5171 (17.2%)	4706 (17.3%)	465 (16.1%)	
	Q3	5762 (19.1%)	5196 (19.1%)	566 (19.6%)	
	Q4	6419 (21.3%)	5784 (21.2%)	635 (22.0%)	
	Q5 most disadvantaged	8081 (26.8%)	7225 (26.5%)	856 (29.6%)	
Hospital sector[e]	Public	23,345 (77.0%)	21,033 (76.7%)	2312 (79.7%)	<0.001
	Private	6982 (23.0%)	6392 (23.3%)	590 (20.3%)	
Charlson comorbidity index (median; interquartile range)		1 (0–2)	1 (0–2)	2 (1–5)	<0.001
Charlson comorbidity group	CCI = 0	18,187 (60.0%)	17,162 (62.6%)	1025 (35.3%)	<0.001
	CCI = 1	2900 (9.6%)	2623 (9.6%)	277 (9.5%)	
	CCI = 2	5395 (17.8%)	4706 (17.2%)	689 (23.7%)	
	CCI ≥ 3	3845 (12.7%)	2934 (10.7%)	911 (31.4%)	
Length of stay (days)	1	12,149 (40.1%)	11,853 (43.2%)	296 (10.2%)	<0.001
	2–4	6483 (21.4%)	6007 (21.9%)	476 (16.4%)	
	5–9	5631 (18.6%)	4994 (18.2%)	637 (22.0%)	
	10–19	3456 (11.4%)	2748 (10.0%)	708 (24.4%)	
	20–29	1189 (3.9%)	841 (3.1%)	348 (12.0%)	
	≥30	1419 (4.7%)	982 (3.6%)	437 (15.1%)	

Data are presented as number (%) unless specified.
* p-value by Chi square testing for comparisons between live discharges vs. in hospital deaths.
[a] Indigenous status missing for 38 admissions.
[b] Marital status missing for 514 admissions.
[c] Country of birth not stated for 1538 admissions.
[d] Socioeconomic advantage and disadvantage missing for 214 admissions.
[e] Includes 582 admissions that were a mix of private and public.

admissions. Despite policies and regulations to reduce alcohol-related harm, alcohol misuse remains a major health and social problem in Australia [20]. Chronic HCV was also an important etiological factor (19.2% of admissions). It will be important to repeat this analysis in the next few years to assess the impact of newly available direct-acting antiviral therapies, which became widely accessible in Australia in 2016. Although NAFLD was reported in 4.9% of admissions, this is highly likely to be an underrepresentation, as type 2 diabetes (a key risk factor for NAFLD and advanced fibrosis) was recorded in 20.5% of admissions, and obesity was recorded in only 3.1% of admissions. NAFLD may also be the etiological factor for many of the cases of cryptogenic or unspecified cirrhosis of liver or where no etiology was recorded (27.8% and 15.4% of admissions respectively). A recent large primary care study from the UK and Europe found that recorded rates of NAFLD were a great deal lower than expected, implying wide-spread under-diagnosis and under-recording [21].

Of concern, in this study both absolute numbers and age-adjusted hospitalization rates for cirrhosis were found to be increasing over time. This trend contrasts with the slower growth or decrease in hospitalization rates for some other common chronic conditions [2,22–25], where there has been a shift in health care utilization from inpatient to ambulatory care. Our data on in-hospital case-fatality rate of cirrhosis-related admissions is comparable to studies from Europe and the US where the mortality rate of patients admitted for cirrhosis complications varied from 12% to 7.4% [4,26,27] and has declined over the last decade [4,27,28]. This has been attributed to improved liver-specific interventions such as variceal bleeding management, early diagnostic paracentesis and use of albumin for spontaneous bacterial peritonitis, along with the publication and implementation of evidence-based practice guidelines. No curative treatments are available; however, for patients with decompensated cirrhosis (if ineligible for liver transplantation) and reduced mortality is likely to lead to more admissions. Not unexpectedly, there was a greater likelihood of in-hospital mortality in older patients (≥70 years), a higher Charlson index, a greater length of hospitalization, and admissions associated with HCC and hepatorenal syndrome.

Our data show that residence outside of a major city was associated with an increase in hospital deaths. Australians in rural and remote areas commonly have less access to health services, with shortages in health professions and health-related infrastructure [6]. In addition, hepatology services are largely limited to tertiary and large regional hospitals and the care of cirrhosis patients is usually complex, requiring a multidisciplinary approach [29]. In other settings such as the US, cirrhosis mortality has been shown to differ greatly between hospitals [30]. Higher hospital resource intensity and high cirrhosis volume were factors associated with lower cirrhosis mortality, prompting the

Table 2
Diagnosis, complications and selected procedures of cirrhosis-related hospital admissions in Queensland during 2008–2016 by discharge status.

	All admissions	Live discharges	In-hospital deaths	
	N = 30,327	N = 27,425	N = 2902	p-Value*
Presumed etiology[a]				
Alcohol	16,721 (55.1%)	14,903 (54.3%)	1818 (62.6%)	<0.001
Cryptogenic or unspecified cirrhosis of liver	8440 (27.8%)	7780 (28.4%)	660 (22.7%)	<0.001
Chronic HBV	1308 (4.3%)	1175 (4.3%)	133 (4.6%)	0.450
Chronic HCV	7210 (23.8%)	6581 (24.0%)	629 (21.7%)	0.005
NAFLD/NASH	1471 (4.9%)	1345 (4.9%)	126 (4.3%)	0.180
Haemochromatosis	287 (0.9%)	238 (0.9%)	49 (1.7%)	<0.001
Wilson's disease	11 (0.0%)	10 (0.0%)	1 (0.0%)	1.000[b]
Alpha-1 antitrypsin deficiency	3 (0.0%)	2 (0.0%)	1 (0.0%)	0.260[b]
Primary biliary cholangitis	442 (1.5%)	416 (1.5%)	26 (0.9%)	0.008
Primary sclerosing cholangitis	145 (0.5%)	122 (0.4%)	23 (0.8%)	0.010
Autoimmune hepatitis	140 (0.5%)	126 (0.5%)	14 (0.5%)	0.860
Budd-Chiari syndrome	66 (0.2%)	63 (0.2%)	3 (0.1%)	0.210[b]
Inflammatory liver disease unspecified	258 (0.9%)	223 (0.8%)	35 (1.2%)	0.028
No etiology recorded[c]	4683 (15.4%)	4273 (15.6%)	410 (14.1%)	0.039
Complications of cirrhosis				
Ascites	12,822 (42.3%)	11,376 (41.5%)	1446 (49.8%)	<0.001
Gastrointestinal bleeding	10,475 (34.5%)	9687 (35.3%)	788 (27.2%)	<0.001
Hepatic encephalopathy	1318 (4.3%)	943 (3.4%)	375 (12.9%)	<0.001
Jaundice	153 (0.5%)	111 (0.4%)	42 (1.4%)	<0.001
Hepatorenal syndrome	926 (3.1%)	445 (1.6%)	481 (16.6%)	<0.001
Hepatocellular carcinoma	4422 (14.6%)	3606 (13.1%)	816 (28.1%)	<0.001
Procedures				
Abdominal paracentesis	11,090 (36.6%)	9965 (36.3%)	1125 (38.8%)	0.010
Endoscopic banding	3197 (10.5%)	3022 (11.0%)	175 (6.0%)	<0.001
Transjugular intrahepatic portosystemic shunt	81 (0.3%)	74 (0.3%)	7 (0.2%)	1.000
Trans-arterial chemoembolization	1049 (3.5%)	1025 (3.7%)	24 (0.8%)	<0.001
Liver resection	211 (0.7%)	201 (0.7%)	10 (0.3%)	0.017
Radiofrequency ablation	213 (0.7%)	213 (0.8%)	0 (0.0%)	<0.001[b]
Liver transplant	348 (1.1%)	337 (1.2%)	11 (0.4%)	<0.001

Data are presented as number (%).
* p-Value by Chi square testing for comparisons between live discharges vs. in hospital deaths.
[a] Patient may have more than one diagnosis.
[b] p-Value by Fisher's exact test for comparisons between live discharges vs. in hospital deaths.
[c] None of the etiologies listed here were identified.

authors to speculate that development of "care networks" between resource-intensive and resource-poor institutions may improve the quality of cirrhosis care [30]. While greater socioeconomic disadvantage and hospitalization in the public sector were also associated with an increase in hospital deaths in the univariable analysis, these factors were not independently associated with in-hospital mortality.

Conducting this study in Queensland (the second largest and third most populous Australian state, with a greater proportion of its population in regional areas than the states of New South Wales and Victoria, and the second largest population of Indigenous Australians) allowed the inclusion of relatively large numbers of patients from regional areas and Indigenous Australians [12]. The study includes near complete population-based data for hospital admissions for cirrhosis and a reliable source of clinical and sociodemographic data. While the hospital admissions database provides valuable information about a patient's diagnosis and use of hospital services, data are collected for administrative purposes rather than to address research questions. Our study relied on the accuracy and completeness of hospital coded data. Whereas hospital services follow strict guidelines for the collection of demographic and clinical data, and for monitoring accuracy through validation audits, data quality is reliant on the accuracy of coding and the clinical information recorded in patients' medical notes and hospital discharge reports

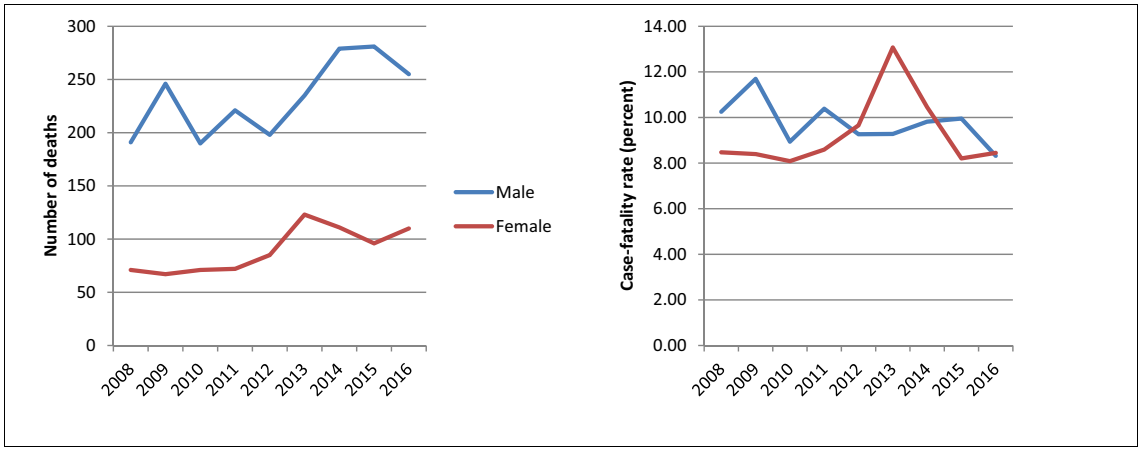

Fig. 4. Number of hospital deaths and case-fatality rate (percent) for liver cirrhosis by year and gender, Queensland, 2008 to 2016.

Table 3
Predictors of in-hospital mortality among 30,327 admissions (main analysis) and excluding 1-day admissions (N = 18,178).

		N = 30,327				N = 18,178		
Socio-demographic factors		OR	(95%CI)	AOR	(95%CI)	OR (95%CI)	AOR	(95%CI)
Age group	20–29 years	0.47	0.26–0.87	0.58	0.29–1.17	0.63 0.33–1.22	0.61	0.29–1.28
	30–39 years	0.79	0.62–1.01	0.74	0.56–0.97	0.84 0.64–1.09	0.78	0.58–1.05
	40–49 years	ref[§]		ref[§]		ref[§]	ref[§]	
	50–59 years	1.11	0.97–1.27	1.07	0.92–1.24	1.27 1.10–1.46	1.16	0.99–1.36
	60–69 years	1.37	1.20–1.57	1.25	1.07–1.45	1.67 1.45–1.93	1.40	1.18–1.65
	70 years and over	1.94	1.70–2.22	1.63	1.38–1.92	2.39 2.07–2.77	1.81	1.51–2.16
Gender	Female (vs. male)	0.95	0.87–1.03	n/s		0.95 0.86–1.04		
Indigenous status[a]	Indigenous (vs. Non-Indigenous)	0.99	0.86–1.15	0.90	0.75–1.08	0.84 0.72–0.98	0.97	0.80–1.17
Marital status[b]	No partner (vs. Married/De Facto)	1.14	1.06–1.23	1.06	0.97–1.16	0.97 0.89–1.06	1.04	0.94–1.14
Country of birth[c]	Overseas (vs. Australia)	0.98	0.89–1.07	n/s		1.01 0.92–1.12		
Rurality of residence	Major city	ref[§]		ref[§]		ref[§]	ref[§]	
	Inner regional	1.20	1.09–1.32	1.15	1.03–1.30	1.23 1.11–1.26	1.16	1.03–1.32
	Outer regional	1.39	1.25–1.54	1.37	1.21–1.56	1.30 1.16–1.46	1.35	1.18–1.55
	Remote	1.28	0.95–1.73	1.23	0.87–1.74	0.91 0.65–1.27	1.01	0.69–1.47
	Very remote	1.67	1.10–2.53	1.01	0.62–1.66	1.39 0.89–2.16	0.97	0.58–1.62
Socioeconomic advantage and disadvantage[d]	Q1 most affluent	ref[§]		ref[¥]		ref[j]	ref[k]	
	Q2	1.16	1.01–1.34	1.09	0.92–1.28	1.06 0.91–1.24	1.03	0.87–1.23
	Q3	1.28	1.12–1.47	1.08	0.92–1.27	1.22 1.05–1.41	1.12	0.95–1.33
	Q4	1.29	1.13–1.48	1.01	0.86–1.18	1.15 0.99–1.34	1.00	0.84–1.18
	Q5 most disadvantaged	1.40	1.23–1.59	1.10	0.94–1.29	1.16 1.01–1.34	1.05	0.89–1.25
Hospital sector[e]	Private (vs. public)	0.84	0.76–0.92	n/s		1.36 1.22–1.50		
Clinical factors								
Charlson comorbidity index		1.29	1.27–1.31	1.13	1.09–1.17	1.22 1.21–1.24	1.10	1.05–1.16
Charlson comorbidity group	CCI = 0	ref[§]		ref[€]		ref[§]	ref[L]	
	CCI = 1	1.77	1.54–2.03	1.18	1.01–1.39	1.46 1.26–1.70	1.14	0.98–1.33
	CCI = 2	2.45	2.21–2.71	1.24	1.07–1.43	1.81 1.62–2.02	1.04	0.87–1.23
	CCI ≥ 3	5.20	4.72–5.73	1.29	1.02–1.64	3.56 3.20–3.95	1.31	0.98–1.74
Presumed etiology[f, g]								
Alcohol		1.41	1.30–1.52	1.47	1.32–1.64	0.92 0.85–1.01	1.26	1.12–1.41
Cryptogenic or unspecified cirrhosis of liver		0.74	0.68–0.81	n/s		0.85 0.77–0.94		
Chronic HBV		1.07	0.89–1.29	n/s		0.90 0.74–1.10		
Chronic HCV		0.88	0.80–0.96	n/s		0.74 0.67–0.82		
NAFLD/NASH		0.88	0.73–1.06	0.69	0.56–0.86	0.82 0.67–0.99	0.72	0.58–0.91
Metabolic liver disease[h]		1.94	1.44–2.63	n/s		1.40 1.02–1.91		
Autoimmune liver disease[i]		0.91	0.70–1.19	n/s		1.14 0.86–1.52		
Inflammatory liver disease unspecified		1.49	1.04–2.13	n/s		1.27 0.88–1.85		
No etiology recorded		0.89	0.80–0.99	n/s		1.66 1.46–1.88		
Factors obtained during hospital admission								
Complications of cirrhosis[g]								
Ascites		1.40	1.30–1.51	1.43	1.21–1.69	1.23 1.13–1.33	1.39	1.17–1.66
Gastrointestinal bleeding		0.68	0.63–0.74	n/s		0.87 0.79–0.96		
Hepatic encephalopathy		4.17	3.67–4.73	1.94	1.61–2.34	2.66 2.34–3.03	1.88	1.56–2.28
Jaundice		3.61	2.53–5.16	1.82	1.20–2.75	2.29 1.59–3.31	1.74	1.15–2.66
Hepatorenal syndrome		12.05	10.52–13.79	7.24	5.99–8.75	8.38 7.27–9.68	6.71	5.74–8.47
Hepatocellular carcinoma		2.58	2.37–2.82	2.53	2.20–2.91	2.04 1.85–2.25	3.11	2.73–3.55
Acute peritonitis		3.41	2.92–3.98	1.93	1.61–2.33	2.03 1.73–2.38	1.68	1.40–2.03
Length of stay	1 day	0.43	0.37–0.51	0.32	0.27–0.37	- -	–	–
	2–4 days	ref[§]		ref[§]		ref[§]	ref[§]	
	5–9 days	1.43	1.25–1.64	1.61	1.42–1.82	1.61 1.42–1.82	1.43	1.25–1.64
	10–19 days	2.69	2.34–3.10	3.25	2.87–3.68	3.25 2.87–3.68	2.67	2.32–3.07
	20–29 days	4.21	3.52–5.04	5.22	4.47–6.10	5.22 4.47–6.10	4.16	3.48–4.96
	30+ days	3.81	3.21–4.52	5.61	4.85–6.50	5.62 4.85–6.50	3.79	3.20–4.49
Procedures[g]								
Abdominal paracentesis		1.11	1.03–1.20	0.54	0.48–0.61	1.04 0.95–1.13	0.62	0.55–0.71
Endoscopic banding		0.52	0.44–0.61	0.67	0.55–0.81	0.57 0.48–0.67	0.70	0.57–0.86
Transjugular intrahepatic portosystemic shunt		0.89	0.41–1.94	n/s		0.61 0.28–1.32		
Trans-arterial chemoembolization		0.21	0.14–0.32	0.10	0.07–0.16	0.18 0.12–0.28	0.12	0.08–0.19
Liver resection		0.47	0.25–0.88	0.12	0.06–0.23	0.24 0.12–0.49	0.11	0.05–0.22
Liver transplant		0.31	0.17–0.56	0.13	0.07–0.25	0.25 0.13–0.45	0.15	0.08–0.28

n/s, variable not selected as a predictor; ref, reference category; p-values by logistic regression Chi square testing § $p < 0.001$; ¥ $p = 0.555$; € $p = 0.021$; [j] $p = 0.063$; [k] $p = 0.525$; [L] $p = 0.139$.

[a] Indigenous status missing for 38 admissions.
[b] Marital status missing for 514 admissions.
[c] Country of birth not stated for 1538 admissions.
[d] Socioeconomic advantage and disadvantage missing for 214 admissions.
[e] Includes 582 admissions that were a mix of private and public.
[f] Could not calculate ORs for Budd-Chiari syndrome, and RFA.
[g] Reference category is no exposure.
[h] Metabolic liver disease included haemochromatosis, Wilson's disease and Alpha-1 antitrypsin deficiency.
[i] Autoimmune liver disease included primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis.

[31]. Therefore, variability in data capture is inevitable, potentially leading to misclassification of presumed etiology, co-factors and comorbidities. Moreover, data accuracy is strongly dependent on clinicians' coding practices and performs worse when the diagnoses are either less overt or considered relatively less "important". With 29% of Australian men and 44% of women obese [7], and obesity being a significant contributing factor in cirrhosis [32], our report of 3.1% patients with a recorded diagnosis of obesity is perhaps an extreme example of failure to capture patient data. The low proportion of admissions associated with hepatic encephalopathy (4.3%) compared to other previous studies where prevalence ranged from 8.8% to 48.8% [3,4,17] is another example of possible inaccurate capture of patient data. There is also the potential for changes in the accuracy of coding and in hospital record coverage over time. However, misclassification and changes over time, if any, are unlikely to be differentially biased when comparing live discharges vs. in hospital deaths. ICD-10 codes for cirrhosis and related complications were validated in the US Department of Veteran Affairs (VA) administrative databases, with positive predictive values for cirrhosis, ascites, varices and HCC ranging from 87.5% to 98.2% [14]. Although the findings may differ in non-VA databases, the validation data suggest high coding accuracy and that these codes reliably identified cirrhosis-related hospital admissions and complications. Furthermore, although HCC can occur without cirrhosis, it typically develops in the presence of advanced liver disease and indicates cirrhosis [14]. Data obtained from the hospital admissions database is inadequate for the assessment of cause of admission or whether it was an urgent vs. planned admission, as it does not provide enough granular detail. Identification of the cause of admission can only be obtained through careful review of a patient's medical records. The available data also do not permit an assessment of the severity of chronic liver disease using the MELD or Child-Pugh scores. This is an important limitation as MELD or Child-Pugh scores are strong predictors of a patient's prognosis [33]. Nevertheless, the data were appropriate for addressing the study aims and demonstrated that healthcare use by patients with cirrhosis is increasing, and this has major resource and economic implications.

Although an assessment of healthcare burden and economic impact was beyond the scope of this study, it is clear that management of the hospitalized cirrhotic patient is expensive as treatment of complications usually requires highly specialized and resource intensive care [2,34]. Thirty-nine percent of admissions required a length of stay greater than four days, and admission rates were highest in males of working age, further reflecting the significant social and economic impacts of decompensated cirrhosis. The latest (fourth) account of the Lancet Standing Commission on Liver Disease in the UK reports that liver disease will soon overtake ischemic heart disease as the leading cause of years of working life lost [35]. Our data highlight the need for greater awareness and emphasis on preventive care in order to reduce the increasing prevalence of cirrhosis and the personal, social and economic burden of its complications. It also highlights the disproportionate impact of liver disease on Indigenous Australians and people from the most socioeconomically disadvantaged areas. Specific plans for prevention (e.g. public health policies discouraging harmful alcohol consumption) and diagnosis of cirrhosis in these groups should be designed by governments to reduce the burden of liver diseases. Our findings from a geographically vast country with a universal healthcare system that does not provide uniform care across rural, regional and metropolitan areas, provide an important contribution to the global perspective on the impact of chronic liver disease.

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Contributors

PCV and EP contributed to the conception and design of the study. EP, RS, PC, and TR assisted with the preparation of coding algorithms for identification of admissions for cirrhosis and etiological factors. PCV and GH performed the data analysis and take responsibility for the integrity and the accuracy of the data. EP drafted the report. All authors contributed to the interpretation of data, revising draft critically for important intellectual content, and approved the final version.

Declaration of Competing Interest

There are no financial disclosures.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.05.007.

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