Type 2 Diabetes: A Risk Factor for Hospital Readmissions and Mortality in Australian Patients With Cirrhosis

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Although there is evidence that type 2 diabetes mellitus (T2D) impacts adversely on liver-related mortality, its influence on hospital readmissions and development of complications in patients with cirrhosis, particularly in alcohol-related cirrhosis (the most common etiological factor among Australian hospital admissions for cirrhosis) has not been well studied. This study aimed to investigate the association between T2D and liver cirrhosis in a population-based cohort of patients admitted for cirrhosis in the state of Queensland, Australia. A retrospective cohort analysis was conducted using data from the Queensland Hospital Admitted Patient Data Collection, which contains information on all hospital episodes of care for patients with liver cirrhosis, and the Death Registry during 2008-2017. We used demographic, clinical data, and socioeconomic characteristics. A total of 8,631 patients were analyzed. A higher proportion of patients with T2D had cryptogenic cirrhosis (42.4% vs. 27.3%, respectively; $P < 0.001$) or nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (13.8% vs. 3.4%, respectively; $P < 0.001$) and an admission for hepatocellular carcinoma (18.0% vs. 12.2%, respectively; $P < 0.001$) compared to patients without T2D. Patients with liver cirrhosis with T2D compared to those without T2D had a significantly increased median length of hospital stay (6 [range, 1-11] vs. 5 [range, 1-11] days, respectively; $P < 0.001$), double the rate of noncirrhosis-related admissions (incidence rate ratios [IRR], 2.03; 95% confidence interval [CI], 1.98-2.07), a 1.35-fold increased rate of cirrhosis-related admissions (IRR, 1.35; 95% CI, 1.30-1.41), and significantly lower survival ($P < 0.001$). *Conclusion:* Among hospitalized patients with cirrhosis, the cohort with T2D is at higher risk and may benefit from attention to comorbidities and additional support to reduce readmissions. (*Hepatology Communications* 2020;4:1279-1292).

An estimated 6% of the adult Australian population had type 2 diabetes mellitus (T2D) in 2017-2018, with the prevalence increasing in association with age and lower socioeconomic status.[(1)] In 2017, T2D contributed to over 11% of all deaths, most commonly in association with cancer, coronary heart disease, and stroke.[(1)] Importantly, in men less than 65 years of age, liver disease was reported as the third most common cause of death (6%) in people with T2D registered with the Australian National Diabetes Services Scheme.[(2)] Despite these data, no guidance about the assessment of liver disease has been provided for general practice management of T2D, apart from the recommendation to "… individually

Abbreviations: adj-HR, adjusted hazard ratio; ALD, alcohol-related liver disease; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICD-10-AM, International Classification of Diseases, Tenth Revision, Australian Modification; IQR, interquartile range; IRR, incidence rate ratios; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PYAR, person-years at risk; T2D, type 2 diabetes.

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assess the need for further investigations such as liver enzyme abnormalities for hepatic steatosis … based upon a clinical risk assessment".[3]

People with T2D have a high prevalence of nonalcoholic fatty liver disease (NAFLD) (40%-70%) and are at increased risk of developing the more severe inflammatory disease nonalcoholic steatohepatitis (NASH), progressive liver fibrosis, and cirrhosis.[4] Patients with other primary causes of chronic liver diseases, including hepatitis C virus (HCV) infection, alcohol-related liver disease (ALD), and hemochromatosis, have a higher risk of disease progression in the presence of metabolic comorbidities, such as insulin resistance, obesity, and steatosis.[5] In a large population-based cohort from the United States (n = 15,866; 11.8% with chronic liver disease) followed for a median period of over 13 years, T2D, metabolic syndrome, and obesity were independent predictors of liver-related mortality in patients with HCV, NAFLD, and ALD.[6] Similarly, in Asian populations, T2D was associated with an increased risk of cirrhosis mortality in both nonviral and viral hepatitis-related cases.[7] The presence of T2D is associated with an increased risk for the development of hepatocellular carcinoma (HCC) and other cirrhosis-related complications in patients with chronic hepatitis B virus (HBV)[8,9] and HCV.[10,11]

Regardless of etiology, most morbidity and mortality from chronic liver disease occurs among people with advanced fibrosis or cirrhosis, who are at risk of developing complications of cirrhosis, including ascites, hepatic encephalopathy, variceal hemorrhage, and HCC. The morbidity and health care costs associated with these complications of cirrhosis are substantial, and recurrent hospital admissions among this patient population are common. In Australia, hospital admissions for cirrhosis increased by 61.7% during 2008-2016, with alcohol misuse a cause or contributing factor for cirrhosis in over half the admissions.[12] Importantly, the burden of T2D as a comorbidity in these patients has also been increasing, with an increase in prevalence of T2D from 13.7% in 2008-2010 to 25.4% in 2014-2016.[12]

Although there is evidence that T2D impacts adversely on liver-related mortality, its influence on hospital readmissions and development of complications in patients with cirrhosis (particularly in ALD, the most common etiological factor among Australian hospital admissions for cirrhosis) has not been well studied. In this population-based study, we examined the association between T2D and patient outcomes (survival and readmission) among patients admitted for cirrhosis in the state of Queensland, Australia. In particular, we examined whether associations differ by patients' sociodemographic features, disease etiology, presence of comorbidity, and complications of cirrhosis at index admission. Given the rising prevalence of T2D and the staggering morbidity and health care costs associated with complications of cirrhosis, this information will have important implications for guiding health service planning and interventions.

Patients and Methods

Using data from the Queensland Hospital Admitted Patient Data Collection, which contains information

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on all hospital episodes of care (public and private) for patients admitted to any Queensland hospital, and the Death Registry, we conducted a retrospective cohort study of people hospitalized for cirrhosis. We identified all hospital admissions for cirrhosis in adults aged 20 years or older during 2008-2017. We excluded admissions where the patient's age or residential location was unknown and interstate or overseas.

As previously reported, we defined an admission for cirrhosis as when a patient was hospitalized for a primary diagnosis of any of the following: 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, portal hypertension, hepatorenal syndrome, gastroesophageal varices, HCC, and unspecified, other, and unspecified cirrhosis of liver.[12] Patients who had any of the above-mentioned diagnoses as "other" diagnosis and a cirrhosis-related diagnosis or procedure as primary diagnosis (e.g., abdominal paracentesis) were also included.[12] See Supporting Information for further details about the definition of an admission for cirrhosis, including the list of International Classification of Diseases, Tenth Revision (ICD-10) diagnosis and procedure codes used.

SELECTION OF CASES AND INDEX ADMISSION

The total data set included 34,678 hospitalization records among 11,448 individual patients with a primary or "other" diagnosis of cirrhosis during 2008-2017. We identified patients with a first hospital admission due to cirrhosis during 2010-2017 (also referred to as index admission) aged 20 years or older. We found 8,917 patients that matched this definition. All patients had a look-back period of 2 years. As approximately 50% of patients with decompensated cirrhosis die within 2 years, the look-back period of 2 years will likely identify the first admission for decompensation for most cases.[13] Patients with an episode of decompensation (hospital admission due to cirrhosis) before the 2-year look-back period are likely to have changed to a compensated stage. Patients with type 1 diabetes (n = 286) were excluded, so data for 8,631 patients were analyzed (1,680 had T2D at index admission).

During the study period, there were changes in the implementation of ICD-10-Australian Modification (AM) in the coding standards for T2D. Before July 2010 and after July 2012, T2D was always coded when documented. From July 2010 through July 2012 (within the ICD-10-AM Seventh Edition), if the patient had T2D but it was not the reason for admission or did not require active intervention or treatment (e.g., commencement, alteration, or adjustment of prescribed diabetes medication; a diagnostic procedure; or increased clinical care and/or monitoring), it was not coded during that episode of care.

MEASUREMENTS

Demographic and health service characteristics and clinical data were obtained from hospital data. Date and cause of death were obtained from the Queensland Death Registry. Patients' residential postcodes at index admission were used to determine the area-based index of relative socioeconomic disadvantage score[14] and remoteness of residence.[15] Code lists for identification of cases, etiology, cofactors, and T2D status were reviewed by four hepatologists and the principal statistical data quality officer, Statistical Services Branch, Queensland Health.[12] Comorbidity at index admission was measured using the Charlson comorbidity index (Charlson index)[16] using validated coding algorithms.[17] All diseases listed in the Charlson index as primary or other diagnosis were analyzed (excluding liver disease and HCC). Data are reported for the Charlson index disease categories. Length of hospital stay was calculated by adding all days the patient was an admitted patient during one hospital stay.

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). Categorical variables are presented as numbers and percentages, and the chi-square test was used to compare groups. All *P* values are two-sided. The rate of readmission was calculated using person-years at risk (PYAR) as a denominator. Poisson regression was undertaken to compare rate of readmission by T2D status (incidence rate ratios [IRRs] and 95% confidence intervals [CIs] were reported). The vce(robust) option was

used to obtain robust standard errors for the parameter estimates.

Cumulative overall survival and time to readmission estimates by T2D status were calculated using the Kaplan-Meier method (log-rank statistic). All cases were followed until date of death, date of first readmission, or December 31, 2017, whichever came sooner. The survival time for patients who died on index admission was counted as a half day. Multivariable Cox regression analysis reported in terms of hazard ratios (HRs) with associated 95% CIs was used to assess the differences by T2D status with respect to timing of hospital readmission and survival. We built five models, namely for time to cirrhosis 30- and 90-day readmission, noncirrhosis 30- and 90-day readmission, and death. Regarding the latter, informed by our previous work,[12] we included factors in the main effects model that could influence overall survival, such as patients' sociodemographic features, disease etiology, presence of comorbidity, and complications of cirrhosis at index admission. When the overall model was statistically significant, a least absolute shrinkage and selection operators (LASSO) penalized regression Cox proportional hazards model was used to identify the set of variables that had the strongest association with the survival outcome. The LASSO procedure was used due to the high number of predictors and potentially complex patterns of collinearity among predictor variables. Variables included in the model were checked to ensure that they adhered to the assumption of proportional hazards over time (Schoenfeld residuals). The vce(robust) option was used to obtain robust standard errors for the parameter estimates to control for mild violation of underlying assumptions.

ETHICS APPROVAL

This study was approved by the Human Research Ethics Committees of Queensland Health (HREC/17/QPAH/23; HREC/2018/QMS/43571) and QIMR Berghofer Medical Research Institute (P3506).

Results

Between January 1, 2008, and December 31, 2017, a total of 8,917 people with cirrhosis aged 20 years or older were admitted to a public or private hospital in Queensland. Of these, 1,680 (18.8%) were coded as having T2D at index admission, 6,951 (77.9%) as not having T2D, and 286 (3.2%) as having type 1 diabetes. Therefore, data for 8,631 patients were included in the study. After index admission, 783 patients who did not have T2D (11.3% of the non-T2D cohort) were diagnosed with T2D (this was taken into account in the multivariable analyses).

SOCIODEMOGRAPHIC FEATURES

Clinical and demographic characteristics at the time of the first hospitalization record of each patient are summarized in Table 1. Compared to patients without T2D, patients with T2D were older (68.4% were 60 years or older vs. 44.1%; $P < 0.001$), 9.1% identified themselves as Indigenous Australians (vs. 6.7% non-Indigenous; $P < 0.001$), and a higher proportion lived in the most disadvantaged areas (31.3% vs. 27.6%; $P = 0.019$). Regarding country of birth, 29.3% of patients with T2D were born overseas (17.4% born in Europe, 5.1% New Zealand and other Oceanic countries, 3.9% Asia, 1.4% Africa and the Middle East, and 2.1% other countries) compared to 25.4% without T2D (13.8%, 4.9%, 3.9%, 1.6%, and 1.7%, respectively; $P = 0.011$).

ETIOLOGY

With the exception of HBV and metabolic liver disease, the distribution of cirrhosis etiology varied significantly by diabetic status (Table 2). A lower proportion of patients with T2D had alcohol-related cirrhosis (36.7%) compared to patients without T2D (52.8%; $P < 0.001$). Fewer patients with T2D had HCV (11.1%) compared to patients without T2D (21.4%; $P < 0.001$). Notably, a higher proportion of patients with T2D had cryptogenic or unspecified cirrhosis (42.4%) compared to patients without T2D (27.3%; $P < 0.001$) and NAFLD/NASH (13.8% with T2D vs. 3.4% without T2D; $P < 0.001$).

Among patients with T2D, there was a significant decrease in the proportion of patients admitted for alcohol-related cirrhosis and an increase in cryptogenic/unspecified cirrhosis during 2010 and 2017 compared to patients without T2D (both $P < 0.001$; Fig. 1). The proportion of T2D patients admitted with alcohol-related

TABLE 1. PATIENT SOCIODEMOGRAPHIC AND HEALTH SERVICE CHARACTERISTICS AT INDEX HOSPITAL ADMISSION BY T2D STATUS

	No T2D (n = 6,951)	T2D (n = 1,680)	Total (n = 8,631)	*P* Value
Age				
20-29 years	113 (1.6%)	3 (0.2%)	116 (1.3%)	<0.001
30-39 years	399 (5.7%)	34 (2.0%)	433 (5.0%)	
40-49 years	1,115 (16.0%)	128 (7.6%)	1,243 (14.4%)	
50-59 years	2,255 (32.4%)	365 (21.7%)	2,620 (30.4%)	
60-69 years	1,741 (25.0%)	592 (35.2%)	2,333 (27.0%)	
70 years and over	1,328 (19.1%)	558 (33.2%)	1,886 (21.9%)	
Sex				
Male	4,660 (67.0%)	1,153 (68.6%)	5,813 (67.4%)	0.210
Female	2,291 (33.0%)	527 (31.4%)	2,818 (32.6%)	
Marital status*				
Married/de facto	3,115 (47.5%)	869 (56.2%)	3,984 (49.2%)	<0.001
No partner	3,441 (52.5%)	678 (42.8%)	4,119 (50.8%)	
Country of birth†				
Australia	5,160 (74.6%)	1,184 (70.7%)	6,344 (73.8%)	0.011
Overseas	1,758 (25.4%)	490 (29.3%)	2,248 (26.2%)	
Indigenous status‡				
Non-Indigenous	6,466 (93.3%)	1,527 (90.9%)	7,993 (92.8%)	<0.001
Indigenous	466 (6.7%)	152 (9.1%)	618 (7.2%)	
Rurality of residence				
Major city	4,168 (60.0%)	1,001 (59.6%)	5,169 (59.9%)	0.100
Inner regional	1,541 (22.2%)	357 (21.3%)	1,898 (22.0%)	
Outer regional	1,078 (15.5%)	265 (15.8%)	1,343 (15.6%)	
Remote/very remote	164 (2.4%)	57 (3.4%)	221 (2.6%)	
Socioeconomic advantage and disadvantage				
Q1 most affluent	998 (14.4%)	205 (12.2%)	1,203 (13.9%)	0.019
Q2	1,174 (16.9%)	270 (16.1%)	1,444 (16.7%)	
Q3	1,332 (19.2%)	318 (18.9%)	1,650 (19.1%)	
Q4	1,531 (22.0%)	362 (21.5%)	1,893 (21.9%)	
Q5 most disadvantaged	1,916 (27.6%)	525 (31.3%)	2,441 (28.3%)	
Hospital sector				
Public hospital only	5,217 (75.1%)	1,242 (73.9%)	6,459 (74.8%)	0.34
Private hospital only or mix	1,734 (24.9%)	438 (26.1%)	2,172 (25.2%)	
Insurance status§				
Insured	2,022 (29.4)	526 (31.5)	2,548 (29.8)	0.10
Not insured	4,852 (70.6)	1,145 (68.5)	5,997 (70.2)	

*Marital status missing for 528 patients.
†Country of birth missing for 39 admissions.
‡Indigenous status missing for 20 admissions.
§Insurance status missing for 86 admissions.
Abbreviation: Q, income quintile.

cirrhosis was 44.5% in 2010-2012 compared to 33.4% in 2015-2017 ($P < 0.001$), while the proportion of T2D patients admitted with cryptogenic/unspecified cirrhosis was 36.8% in 2010-2012 and 46.1% in 2015-2017 ($P = 0.005$). Among patients without T2D, the prevalence of ALD, NAFLD/NASH, and HBV did not change over time. The proportion of patients admitted with cryptogenic/unspecified cirrhosis significantly increased between 2010-12 (25.3%) and 2015-17 (29.7%; $P < 0.001$). Similarly, the proportion of patients with HCV cirrhosis significantly between 2010-12 (18.0%) and 2015-17 (23.1%; $P < 0.001$).

TABLE 2. PRESUMED ETIOLOGY, COMORBIDITIES, CIRRHOSIS-RELATED COMPLICATIONS, AND HEALTH SERVICE FACTORS AT INDEX ADMISSION BY T2D STATUS

	No T2D (n = 6,951)	T2D (n = 1,680)	Total (n = 8,631)	*P* Value
Presumed Etiology				
Alcohol	3,669 (52.8%)	616 (36.7%)	4,285 (49.6%)	<0.001
Cryptogenic	1,897 (27.3%)	712 (42.4%)	2,609 (30.2%)	<0.001
HCV	1,488 (21.4%)	186 (11.1%)	1,674 (19.4%)	<0.001
NAFLD/NASH	233 (3.4%)	232 (13.8%)	465 (5.4%)	<0.001
HBV	333 (4.8%)	68 (4.0%)	401 (4.6%)	0.19
Metabolic liver disease*	98 (1.4%)	20 (1.2%)	118 (1.4%)	0.49
Autoimmune liver disease†	214 (3.1%)	29 (1.7%)	243 (2.8%)	0.003
Inflammatory liver disease unspecified	69 (1.0%)	30 (1.8%)	99 (1.1%)	0.006
Comorbidities‡				
Cancer (excluding HCC)	420 (6.0%)	142 (8.5%)	562 (6.5%)	<0.001
Renal disease	259 (3.7%)	256 (15.2%)	515 (6.0%)	<0.001
Congestive heart failure	318 (4.6%)	152 (9.0%)	470 (5.4%)	<0.001
Acute myocardial infarction	33 (0.5%)	22 (1.3%)	55 (0.6%)	<0.001
Peripheral vascular disease	47 (0.7%)	22 (1.3%)	69 (0.8%)	0.009
Cerebrovascular disease	52 (0.7%)	22 (1.3%)	74 (0.9%)	0.025
Dementia	50 (0.7%)	27 (1.6%)	77 (0.9%)	<0.001
Complications of cirrhosis				
Ascites	2,390 (34.4%)	563 (33.5%)	2,953 (34.2%)	0.50
Gastrointestinal bleeding	2,460 (35.4%)	587 (34.9%)	3,047 (35.3%)	0.73
HCC	851 (12.2%)	302 (18.0%)	1,153 (13.4%)	<0.001
Hepatic encephalopathy	345 (5.0%)	77 (4.6%)	422 (4.9%)	0.52
Jaundice	50 (0.7%)	14 (0.8%)	64 (0.7%)	0.62
Hepatorenal syndrome	222 (3.2%)	54 (3.2%)	276 (3.2%)	0.97
Spontaneous bacterial peritonitis§	209 (3.0%)	56 (3.3%)	265 (3.1%)	0.49
Health service factors				
Referral source				
Emergency department	3,349 (50.0%)	758 (47.3%)	4,107 (49.5%)	0.025
Outpatient clinic or other	1,528 (22.8%)	398 (24.8%)	1,926 (23.2%)	
Private medical practitioner	1,344 (20.1%)	307 (19.2%)	1,651 (19.9%)	
Other	472 (7.1%)	139 (8.7%)	611 (7.4%)	
Length of hospital stay				
1 day	1,893 (27.2%)	363 (21.6%)	2,256 (26.1%)	<0.001
2-4 days	1,406 (20.2%)	365 (21.7%)	1,771 (20.5%)	
5-9 days	1,596 (23.0%)	374 (22.3%)	1,970 (22.8%)	
10-19 days	1,160 (16.7%)	292 (17.4%)	1,452 (16.8%)	
20-29 days	389 (5.6%)	120 (7.1%)	509 (5.9%)	
30+ days	507 (7.3%)	166 (9.9%)	673 (7.8%)	

*Metabolic liver disease included hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency.
†Autoimmune liver disease included primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis.
‡Data not shown for Charlson index disease categories where prevalence of exposure was <3% or $P \geq 0.05$, namely peptic ulcer disease, hemiplegia, connective tissue disease, pulmonary disease, and acquired immune deficiency syndrome.
§ICD-10-AM code for acute or unspecified peritonitis.

CIRRHOSIS COMPLICATIONS

A higher proportion of patients with T2D (18.0%) had an admission for HCC compared with patients without T2D (12.2%; $P < 0.001$) (Table 2). In both patients with and without T2D, ascites (34.2%) and gastrointestinal bleeding (35.3%) were the most frequent complications of cirrhosis; there was no difference in the prevalence of other cirrhosis complications between the two groups.

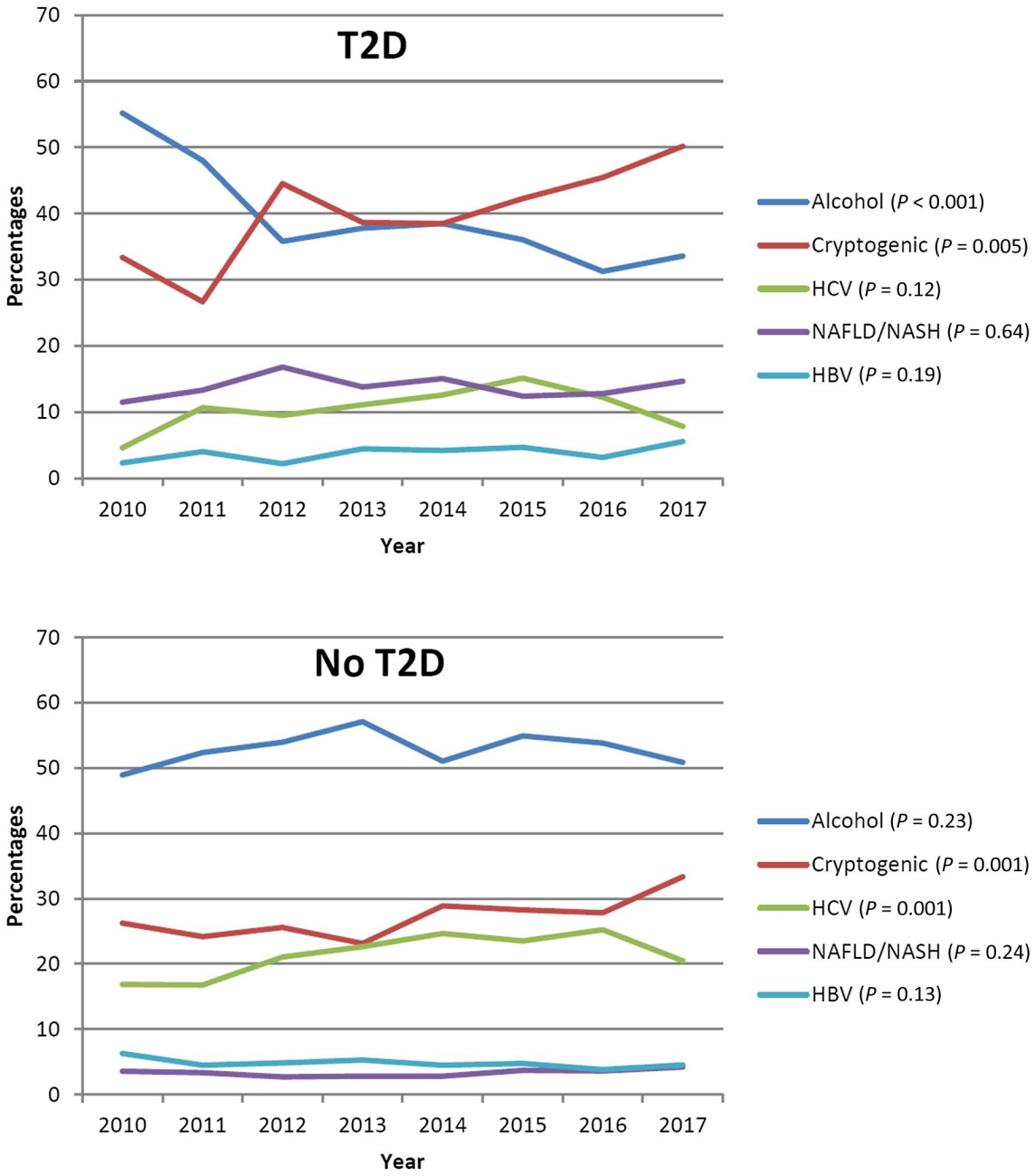

FIG. 1. Trends in prevalence of liver disease etiology among patients with and without T2D when first hospitalized for cirrhosis during 2008-2017. Pearson chi-squared test for the difference between the average proportion in 2008-2010 and 2015-2017.

COMORBIDITIES

Patients with T2D had a significantly higher prevalence of Charlson index-related disease groups, such as cancer (including primary cancers or metastasis, excluding HCC), renal disease, congestive heart failure, acute myocardial infarction, peripheral and cerebrovascular disease, and dementia (Table 2).

BURDEN OF CARE

Length of hospital stay varied significantly by diabetic status, with fewer patients with T2D having 1-day admissions compared to patients without T2D (21.6% vs. 27.2%, respectively; $P < 0.001$) (Table 2). The median length of hospital stay was 6 (range, 1-11) days compared to 5 (range, 1-11) for patients without T2D ($P < 0.001$).

Once discharged, patients with T2D had more readmissions than patients without T2D, whether for liver disease (28.6 per 10,000 PYAR vs. 21.1 per 10,000 PYAR, respectively) or other reasons (120.2 per 10,000 PYAR vs. 59.2 per 10,000 PYAR, respectively). Patients with T2D had double the rate of noncirrhosis-related admissions (IRR, 2.03; 95% CI, 1.98-2.07) and 1.35-fold the rate of cirrhosis-related admissions (IRR, 1.35; 95% CI, 1.30-1.41) compared to patients without T2D.

In view of the higher proportion of patients with T2D having an admission for HCC compared with patients without T2D, we examined the prevalence of procedures for HCC in readmissions. Of 61,731 readmissions, 1.46% of patients had a procedure for HCC (n = 904; 1.24% of patients with T2D vs. 1.53% without diabetes; P = 0.011), suggesting that the higher rate of readmission among patients with T2D is not driven by HCC treatment.

30- AND 90-DAY READMISSION

The median time from index admission to the first readmission during the follow-up period was 164 days (interquartile range [IQR], 24-701). For patients with T2D, this was 123 days (IQR, 21-491), and for patients without T2D, this was 178 days (IQR, 25-766) (log-rank test, P = 0.0004).

There were no disparities in time to 30- and 90-day cirrhosis-related readmission by T2D status, reflected in the unadjusted and adjusted hazard rates. Regarding noncirrhosis readmission, patients with T2D were 34% more likely to have a 30-day readmission (HR, 1.34; 95% CI, 1.18-1.53) and 28% more likely to have a 90-day readmission (HR, 1.28; 95% CI, 1.15-1.42) compared to patients without T2D. In multivariable analysis, the disparities in noncirrhosis readmissions between patients with and without T2D were explained by differences in demographic and clinical characteristics (Table 3).

The strongest predictors of 30-day noncirrhosis readmissions were presence of non-HCC cancer (adjusted [adj] HR, 2.26; 95% CI, 1.82-2.82), longer hospital stay (e.g., HR, 2.99; 95% CI, 2.30-3.87 for 20+ days vs. 1 day), renal disease (adj-HR, 1.67; 95% CI, 1.32-2.12), and patients who identified themselves as Indigenous (adj-HR, 1.48; 95% CI, 1.19-1.85). Similarly, the strongest predictors of 90-day noncirrhosis readmissions were non-HCC cancer (adj-HR, 2.37; 95% CI 1.98-2.83), longer hospital stay (adj-HR, 2.37; 95% CI, 1.98-2.83 for 10-19 days vs. 1 day), renal disease (adj-HR, 1.65; 95% CI, 1.36-2.00), and patients who identified as Indigenous (adj-HR, 1.48; 95% CI, 1.25-1.76).

SURVIVAL

At the end of the follow-up period, a higher proportion of patients with T2D had died compared to patients without T2D (56.8% vs. 52.0%, respectively; P < 0.001). This disparity was reflected in the unadjusted hazard rate, which was 36% higher for patients with T2D compared to their counterparts (HR, 1.36; 95% CI, 1.27-1.46). The major cause of death in both groups was cirrhosis or cirrhosis-related complications (63.2% for patients with T2D vs. 66.3% for patients without T2D; P = 0.076). The proportion of patients who died from T2D, heart, cerebral, and peripheral vascular diseases was higher in patients with T2D (9.0%) compared to their non-T2D counterparts (4.8%; P < 0.001).

The median time from index admission to death was 1.0 year (IQR, 0.18-2.49) for patients with T2D and 1.6 years (IQR, 0.33-3.77) for patients without T2D. Across 1-, 2-, and 5-year survival estimates, patients with T2D had a significantly lower survival compared to patients without T2D with cirrhosis (Fig. 2).

In multivariable analysis, the disparity in survival between patients with T2D compared to without T2D (unadjusted HR, 1.36; 95% CI, 1.27-1.46) was mostly explained by differences in comorbidities and sociodemographic characteristics. Adding etiology (adj-HR, 1.43; 95% CI, 1.34-1.54), complications including HCC (adj-HR, 1.30; 95% CI, 1.21-1.39), and hospital service factors (adj-HR, 1.29; 95% CI, 1.20-1.39) one at a time did not strongly alter the HR. Adding comorbidities (adj-HR, 1.16; 95% CI, 1.08-1.25) and sociodemographic characteristics (adj-HR, 1.18; 95% CI, 1.10-1.26) one at a time decreased the HR substantially. Adding comorbidities and sociodemographic characteristics (adj-HR, 1.06; 95% CI, 0.98-1.14) explained the survival deficit. The final (full model; Table 3) adj-HR was 1.02 (95% CI, 0.94-1.11). The strongest predictors of mortality were presence of hepatorenal syndrome (adj-HR, 3.04; 95% CI, 2.51-3.67), non-HCC cancer (adj-HR, 2.64; 95% CI, 2.33-2.98),

TABLE 3. RESULTS FROM COX REGRESSION MODELS EXAMINING PREDICTORS OF MORTALITY, 30- AND 90-DAY CIRRHOSIS READMISSION, AND NONCIRRHOSIS READMISSION AMONG 8,631 PATIENTS

		Mortality	30-day cirrhosis readmission	30-day non-cirrhosis readmission	90-day cirrhosis readmission	90-day non-cirrhosis readmission
		Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)
T2D status	T2D (vs. no T2D)	1.36 (1.27-1.46)	0.98 (0.84-1.14)	1.34 (1.18-1.53)	1.06 (0.94-1.19)	1.28 (1.15-1.42)
		Adjusted HRs (95% CI)	Adjusted HRs (95% CI)	Adjusted HRs (95% CI)	Adjusted HRs (95% CI)	Adjusted HRs (95% CI)
T2D status	T2D (vs. no T2D)	1.02 (0.94-1.11)	0.99 (0.84-1.16)	1.12 (0.96-1.32)	1.07 (0.94-1.21)	1.06 (0.93-1.19)
Socio-demographic factors						
Age	20-29 years	0.34 (0.19-0.62)	1.12 (0.60-2.11)	1.18 (0.70-2.00)	n/s	1.14 (0.74-1.75)
	30-39 years	0.97 (0.79-1.18)	1.17 (0.87-1.58)	1.09 (0.81-1.47)	n/s	1.18 (0.94-1.48)
	40-49 years	ref*	ref*	ref*	n/s	ref*
	50-59 years	1.31 (1.17-1.47)	0.88 (0.73-1.07)	1.00 (0.82-1.21)	n/s	1.02 (0.88-1.19)
	60-69 years	1.70 (1.50-1.91)	1.02 (0.84-1.25)	1.16 (0.94-1.43)	n/s	1.19 (1.01-1.40)
	70 years and over	2.57 (2.26-2.92)	1.00 (0.80-1.24)	1.26 (1.01-1.56)	n/s	1.45 (1.23-1.72)
Gender	Male (vs. female)	1.06 (0.99-1.14)	1.17 (1.02-1.34)	n/s	1.14 (1.03-1.27)	
Marital status	No partner (vs. Married/De Facto)	1.10 (1.03-1.18)	n/s	0.90 (0.80-1.02)	n/s	0.87 (0.79-0.95)
Country of birth	Overseas (vs. Australia)	0.92 (0.85-0.99)	n/s	0.77 (0.66-0.89)	n/s	0.82 (0.74-0.92)
Indigenous status	Indigenous (vs. Non-Indigenous)	1.16 (1.01-1.32)	n/s	1.48 (1.19-1.85)	n/s	1.48 (1.25-1.76)
Rurality of residence	Major city	ref*	n/s	ref*	ref*	ref*
	Inner regional	1.12 (1.03-1.22)	n/s	0.94 (0.80-1.10)	1.05 (0.92-1.20)	0.94 (0.84-1.06)
	Outer regional	1.15 (1.05-1.27)	n/s	0.81 (0.67-0.97)	1.19 (1.04-1.37)	0.89 (0.78-1.02)
	Remote/Very remote	1.11 (0.91-1.35)	n/s	1.00 (0.70-1.42)	0.97 (0.71-1.32)	0.93 (0.70-1.25)
Socioeconomic advantage and disadvantage	Q1 most affluent	ref*	n/s	ref*	ref*	n/s
	Q2	1.03 (0.92-1.17)	n/s	0.87 (0.70-1.07)	1.11 (0.93-1.33)	n/s
	Q3	1.04 (0.93-1.17)	n/s	0.92 (0.75-1.13)	1.10 (0.92-1.31)	n/s
	Q4	1.04 (0.93-1.17)	n/s	0.94 (0.77-1.16)	1.09 (0.91-1.30)	n/s
	Q5 most disadvantaged	1.02 (0.91-1.15)	n/s	0.84 (0.68-1.03)	0.95 (0.80-1.14)	n/s
Hospital sector	Private (vs. public)	n/s	1.28 (1.09-1.51)	1.15 (0.98-1.34)	1.32 (1.16-1.51)	1.15 (1.02-1.29)
Insurance status	Insured (vs. not)	n/s	n/s	n/s	n/s	n/s
Presumed aetiology						
Alcohol		1.03 (0.94-1.13)	1.20 (1.03-1.40)	0.71 (0.59-0.84)	1.14 (1.02-1.29)	0.80 (0.70-0.92)
Cryptogenic		0.94 0.87-1.03)	n/s	0.83 (0.71-0.98)	n/s	0.85 (0.76-0.96)
HCV		1.13 (1.03-1.24)	n/s	0.90 (0.75-1.07)	n/s	n/s
NAFLD/NASH		0.80 (0.69-0.92)	n/s	0.74 (0.56-0.99)	n/s	n/s
HBV		0.75 (0.63-0.89)	n/s	n/s	n/s	n/s
Metabolic liver disease[†]		n/s	n/s	0.72 (0.42-1.22)	n/s	0.78 (0.52-1.16)
Autoimmune liver disease[‡]		0.82 (0.66-1.02)	n/s	n/s	n/s	n/s

TABLE 3. *Continued*

		Mortality	30-day cirrhosis readmission	30-day non-cirrhosis readmission	90-day cirrhosis readmission	90-day non-cirrhosis readmission
		Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)	Unadjusted HRs (95% CI)
T2D status	T2D (vs. no T2D)	1.36 (1.27-1.46)	0.98 (0.84-1.14)	1.34 (1.18-1.53)	1.06 (0.94-1.19)	1.28 (1.15-1.42)
		Adjusted HRs (95% CI)	Adjusted HRs (95% CI)	Adjusted HRs (95% CI)	Adjusted HRs (95% CI)	Adjusted HRs (95% CI)
T2D status	T2D (vs. no T2D)	1.02 (0.94-1.11)	0.99 (0.84-1.16)	1.12 (0.96-1.32)	1.07 (0.94-1.21)	1.06 (0.93-1.19)
Comorbidities						
Cancer		2.64 (2.33-2.98)	1.17 (0.90-1.51)	2.26 (1.82-2.82)	n/s	2.37 (1.98-2.83)
Renal disease		1.23 (1.08-1.40)	n/s	1.67 (1.32-2.12)	1.33 (1.06-1.67)	1.65 (1.36-2.00)
Congestive heart failure		1.34 (1.17-1.53)	0.68 (0.48-0.96)	1.14 (0.89-1.45)	0.64 (0.48-0.86)	1.20 (0.99-1.46)
Acute myocardial infarct		1.80 (1.19-2.74)	n/s	1.45 (0.68-3.11)	n/s	n/s
Peripheral vascular disease		0.84 (0.58-1.21)	n/s	n/s	n/s	n/s
Cerebrovascular disease		1.83 (1.31-2.57)	n/s	n/s	1.70 (0.98-2.96)	n/s
Dementia		1.37 (1.03-1.81)	n/s	n/s	0.35 (0.13-0.96)	n/s
Complications of cirrhosis						
Ascites		1.37 (1.26-1.48)	2.27 (1.95-2.63)	n/s	2.12 (1.89-2.39)	n/s
Gastrointestinal bleeding		n/s	n/s	n/s	n/s	n/s
Hepatocellular carcinoma		2.42 (2.19-2.69)	2.92 (2.43-3.51)	0.68 (0.55-0.85)	2.81 (2.42-3.26)	0.73 (0.62-0.87)
Hepatic encephalopathy		1.49 (1.27-1.76)	0.81 (0.56-1.16)	0.70 (0.49-1.01)	0.73 (0.54-0.99)	0.86 (0.67-1.11)
Jaundice		1.51 (1.08-2.12)	n/s	1.55 (0.87-2.74)	n/s	n/s
Hepatorenal syndrome		3.04 (2.51-3.67)	n/s	n/s	1.49 (1.00-2.20)	n/s
Spontaneous bacterial peritonitis[§]	1.62 (1.36-1.92)	n/s	1.27 (0.91-1.76)	1.23 (0.90-1.67)	n/s	
Health service factors						
Referral source	Emergency department vs. not	1.40 (1.29-1.52)	1.99 (1.68-2.36)	1.19 (1.02-1.39)	1.80 (1.57-2.05)	1.16 (1.03-1.31)
Length of hospital stay	1 day	ref*	ref*	ref*	ref*	ref*
	2-4 days	1.55 (1.38-1.74)	1.25 (0.97-1.61)	1.81 (1.45-2.26)	1.47 (1.21-1.79)	1.70 (1.45-2.00)
	5-9 days	1.60 (1.42-1.81)	1.35 (1.04-1.75)	2.16 (1.73-2.72)	1.66 (1.35-2.03)	1.97 (1.66-2.34)
	10-19 days	1.82 (1.60-2.08)	1.19 (0.90-1.57)	2.57 (2.03-3.26)	1.35 (1.08-1.69)	2.37 (1.98-2.83)
	20+ days	1.74 (1.49-2.02)	1.04 (0.76-1.43)	2.99 (2.30-3.87)	1.03 (0.79-1.34)	2.25 (1.84-2.77)

Hazard ratio (HR) estimates generated using Cox regression models were adjusted for year of index admission, T2D diagnosis after index admission, and all variables in the table except those marked n/s (variable not selected as a predictor).

*Reference category.

[†]Metabolic liver disease included haemochromatosis, Wilson's disease and Alpha-1 antitrypsin deficiency.

[‡]Autoimmune liver disease included primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis.

[§]ICD-10-AM code for acute or unspecified peritonitis.

	1-year survival estimates (95% CI)	2-year survival estimates (95% CI)	5-year survival estimates (95% CI)
T2D	0.60 (0.57-0.62)	0.49 (0.46-0.52)	0.26 (0.23-0.29)
No T2D	0.67 (0.66-0.68)	0.58 (0.57-0.59)	0.42 (0.40-0.43)
Log Rank test	<0.001	<0.001	<0.001

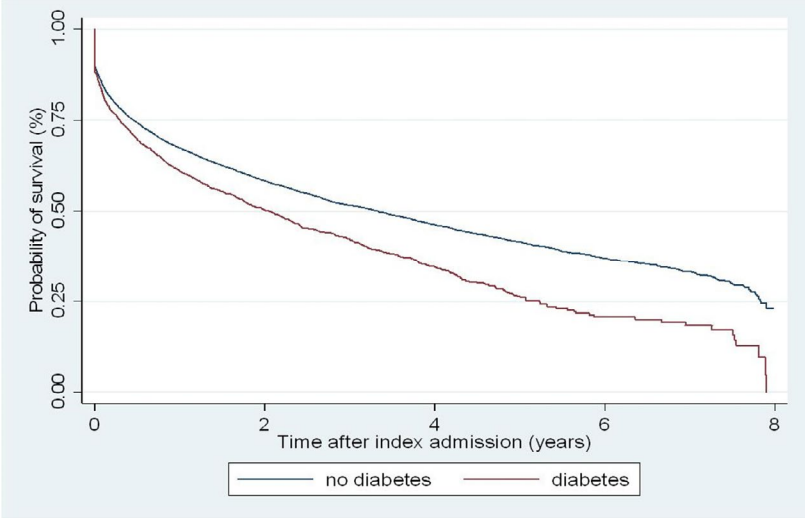

FIG. 2. Relative survival at 1, 2, and 5 years after index admission and cumulative survival (estimated by the Kaplan-Meier method) by T2D status.

older age (adj-HR, 2.57; 95% CI, 2.26-2.92 for 70+ years vs. 40-49 years), and HCC (adj-HR, 2.42; 95% CI, 2.19-2.69).

Discussion

T2D is a common comorbidity that has occurred in almost 20% of patients with hospital admissions for cirrhosis over the last 10 years. This large population-based study has shown that the presence of T2D is associated with adverse patient outcomes, including a 1.36-fold higher mortality, a 1.85-fold higher rate of hospital readmission, and a 1.48-fold higher prevalence of admission with HCC.

Our data concur with studies demonstrating an increased risk of mortality in patients with cirrhosis with T2D compared to patients without T2D.[9,18,19] In our analysis, this association was explained mostly by a higher prevalence of comorbidities and sociodemographic characteristics (mainly older age) among patients with T2D, whereas overall, the presence of hepatorenal syndrome and cancer (HCC or not) were strong predictors of mortality. Understanding the clinical and to a lesser extent sociodemographic differences in hospital admissions for patients with cirrhosis with T2D is necessary to inform risk stratification and management strategies to improve outcomes for these patients. Not unexpectedly, patients with cirrhosis with T2D are older and have more comorbidities, in particular cancer (HCC and other cancers), renal, cardiac and vascular disease, than their counterparts without T2D.

Studies in patients with advanced liver disease[20] and other chronic diseases[21-23] have also found that diabetic status has an increased risk of readmission. In other patient populations, the higher rate of readmission has been attributed to the specific comorbidities and infection-related complications of patients with T2D.[23,24] In our study, the presence of T2D was

associated with a longer hospital stay and a 15% to 39% increased odds of readmission during the follow-up period. When short-term readmission outcomes (30- and 90-day readmission) were examined, there were no disparities in cirrhosis-related readmission by T2D status. In contrast, noncirrhosis readmissions were 28% to 34% more likely in patients with T2D compared to patients without diabetes. Following multivariable analysis, the effect of T2D on noncirrhosis readmission was explained by differences in demographic and clinical characteristics, particularly the presence of non-HCC cancer and renal disease. Because hospitalization costs contribute more than 50% of the economic burden of care for patients with decompensated cirrhosis,[25] patients with T2D may benefit from additional support after discharge with close follow-up of comorbidities (in addition to the liver disease) to reduce the need for readmission.

In our study, while admission to a private hospital was not associated with mortality, it was associated with a 28% to 32% increased odds of readmission for cirrhosis. The reason for this is unclear and needs to be evaluated in future studies.

Our data also confirm the higher prevalence of HCC in patients with cirrhosis with T2D compared to those without T2D. An increasing body of literature indicates that T2D is a risk factor for HCC and that the risk is greater in patients with a longer duration of T2D and with a greater number of comorbid metabolic conditions.[26] A meta-analysis of 21 cohort studies showed that patients with chronic liver disease and T2D had a 1.9-fold increased risk of HCC compared to patients without T2D, independent of alcohol consumption, body mass index, and smoking.[27] Although epidemiologic studies and meta-analyses show a significant association between T2D and HCC among patients with chronic HCV (pooled risk ratio, 2.5), the association has been more variable among individuals with chronic HBV infection.[28] Potential mechanisms contributing to the association with HCC include an effect of T2D on the insulin-like growth factor signaling pathway[29] and accelerated DNA damage through intrahepatic lipid peroxidation and reactive oxygen species formation.[30] Unfortunately in our population-based study, we were unable to examine the impact of obesity[31] or of medications used in the treatment of T2D or metabolic syndrome, such as metformin[32] or statins,[33] which may impact on HCC risk.

In our study, patients with T2D did not have a higher prevalence of other (non-HCC) cirrhosis complications at their index admission. While some studies have reported a higher incidence of decompensation events in patients with both compensated cirrhosis and T2D, data are inconsistent.[9,10,34-37] It is possible that different patient populations, data sources, coding of patient admitted hospital data, and definitions of decompensation events may explain the disparity between studies.

Interestingly, the most common label for cirrhosis etiology among patients with T2D was cryptogenic or unspecified cirrhosis (42.4%), and its prevalence increased substantially from 2010 to 2017. The term cryptogenic cirrhosis is applied when the etiology of cirrhosis remains unidentified by customary clinical, laboratory, or histologic findings.[38] Although NAFLD was reported in only 13.8% of patients with T2D, this is highly likely to be an underrepresentation,[39] and NAFLD may also be the etiological factor for many of the cases of cryptogenic or unspecified cirrhosis in these patients with metabolic comorbidities. Of concern, a recent study suggests that patients with cryptogenic cirrhosis have more hepatic dysfunction and portal hypertension and worse clinical outcomes compared to patients with NASH-related cirrhosis.[40] It will therefore be important for future studies to capture relevant patient data that will assist with determining the etiological contribution of NAFLD to cryptogenic cirrhosis in order to better address its increasing prevalence.

While this study included a population-based sample of patients with cirrhosis and used widely accepted and validated coding algorithms for cirrhosis[12] and comorbidities[17] from linked hospital data that were reviewed by hepatologists and hospital coding personnel, some limitations should be noted. The available data do not permit an assessment of the severity of chronic liver disease using the Child-Pugh or Model for End-Stage Liver Disease scores. This is a key limitation as these scores are strong predictors of a patient's prognosis.[41] Moreover, we could not assess whether severity or stage of cirrhosis varied by T2D status. There is also the potential for misclassification of presumed etiology, comorbidities, cirrhosis complications, and T2D status. Regarding the latter, while most patients categorized as "with T2D" are likely to have been correctly coded as such, patients categorized as "without T2D" may have had T2D that was underreported (e.g., T2D was not the reason for admission

or did not require active treatment in that admission). As a result, this misclassification bias is likely to diminish the true effect of T2D. Nevertheless, our findings demonstrate that the cohort with T2D among hospitalized patients with cirrhosis are at higher risk and may benefit from attention to comorbidities and additional support to reduce readmissions.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1536/suppinfo.