Lower survival and higher rates of cirrhosis in patients with ROUX-EN-Y gastric bypass hospitalised with alcohol-associated hepatitis

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ABSTRACT

Objective The incidence of alcohol-associated liver disease (ALD) is increasing, and weight loss surgery is more common due to the obesity epidemic. Roux-en-Y gastric bypass (RYGB) is associated with alcohol use disorder and ALD; however, its impact on outcomes in patients hospitalised for alcohol-associated hepatitis (AH) is unclear.

Design We performed a single-centre, retrospective study of patients with AH from June 2011 to December 2019. Primary exposure was the presence of RYGB. The primary outcome was inpatient mortality. Secondary outcomes included overall mortality, readmissions and cirrhosis progression.

Results 2634 patients with AH met the inclusion criteria; 153 patients had RYGB. Median age of the entire cohort was 47.3 years; median Model for End Stage Liver Disease - Sodium (MELD-Na) was 15.1 in the study group versus 10.9 in the control group. There was no difference in inpatient mortality between the two groups. On logistic regression, increased age, elevated body mass index, MELD-Na >20 and haemodialysis were all associated with higher inpatient mortality. RYGB status was associated with increased 30-day readmission (20.3% vs 11.7%, p<0.01), development of cirrhosis (37.5% vs 20.9%, p<0.01) and overall mortality (31.4% vs 24%, p=0.03).

Conclusions Patients with RYGB have higher rates of readmissions, cirrhosis and overall mortality after discharge from hospital for AH. Allocation of additional resources on discharge may improve clinical outcomes and reduce healthcare expenditure in this unique patient population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The incidences of alcohol use disorder (AUD) and alcohol-associated liver disease (ALD) are increasing in the USA, while the obesity epidemic has resulted in a rise in weight loss surgery (WLS). Although there is an association between AUD and WLS, the impact of WLS on ALD, specifically alcohol-associated hepatitis (AH), is unknown.

WHAT THIS STUDY ADDS

⇒ Patients with a history of roux-en-y gastric bypass (RYGB) surgery who are hospitalised with AH have higher overall mortality, higher readmission rates and cirrhosis following discharge from hospital.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients with RYGB who are hospitalised with AH may need additional resources to prevent readmissions, reduce mortality and for early detection of advanced liver disease after discharge from hospital.

INTRODUCTION

The prevalence of alcohol-associated liver disease (ALD) is increasing, notably in women and patients with low socioeconomic status, and ALD is now the leading indication for liver transplantation in the USA.[1–3] Alcohol-associated hepatitis (AH) is defined by the American Association for the Study of Liver Diseases (AASLD) as a clinicopathologic syndrome of jaundice (onset within 8 weeks), associated with elevated liver enzymes (hepatocellular pattern with AST/ALT> 1.5; AST and ALT <400 IU/L) occurring in an individual with ongoing/recent alcohol use.[4] AH represents a major cause of morbidity, mortality and healthcare utilisation, particularly within the first year of diagnosis.[5] The incidence of AH increased by 30% over an 8-year period in 2013 and is expected to increase further due to the spike of ALD observed in the context of the recent COVID-19 global pandemic.[6 7]

The obesity epidemic is a public health crisis in the USA, directly impacting the incidence of diabetes mellitus (DM), coronary artery disease (CAD) and cerebrovascular disease.[8] Weight loss surgery (WLS) is the most effective intervention for the management of obesity by inducing rapid, durable weight loss and has also been shown to improve long-term survival.[9 10] Roux-en-Y

gastric bypass (RYGB) surgery—division of the stomach into a small pouch with formation of an anastomosis to the jejunum—was the standard of care in WLS until 2013 with the advent of the sleeve gastrectomy.[11 12] RYGB results in significant loss of body weight, improvement of hepatic steatosis and can treat hypertension and type 2 DM.[13–15] However, long-term studies have shown that RYGB is also associated with gastrointestinal ulcers, dumping syndrome and chronic nutritional deficiencies, which can result in high rates of hospitalisations and the need for repeat surgery.[16–18]

WLS is associated with alcohol use disorder (AUD) and ALD.[19–21] Prospective studies show that patients with WLS have an increased risk for the development of AUD, particularly patients with RYGB.[22 23] Furthermore, patients with a history of RYGB are at increased risk of mortality from alcohol and drug use.[24] While the relationship between AUD and WLS is well established, the impact of RYGB surgery on clinical outcomes specifically in patients with AH remains largely unknown. In patients hospitalised for AH, two database studies have shown that the presence of RYGB results in a higher risk of 30-day hospital readmission.[25 26]

We aimed to evaluate the impact of RYGB on mortality, hospital readmissions and diagnosis of cirrhosis following an initial hospitalisation for AH. Due to the increased risk of mortality related to AUD and long-term complications associated with RYGB, we hypothesised that patients with a history of RYGB admitted to hospital for AH would have lower inpatient and overall survival, more frequent readmissions and higher instances of cirrhosis following discharge from hospital.

METHODS
Study population and patient characteristics
By interrogating the electronic health record (EHR) at the University of Minnesota Medical Center from June 2011 to December 2019, we identified all patients who carried the discharge diagnosis of AH without a history of cirrhosis. We included all patients above the age of 18 and excluded those with incomplete records. We defined AH using AASLD guidelines, which further categorises AH as 'possible AH' (clinically diagnosed with potential confounding factors), 'probable AH' (clinically diagnosed without potential confounding factors) and 'definite AH' (clinically diagnosed and biopsy proven evidence of AH).[4] A large sample of patient records were carefully reviewed to ensure that the diagnosis of AH was accurate. Patients with AH and a history of RYGB (study group) were compared with those diagnosed with AH without a history of RYGB (control group). Baseline characteristics as well as clinical features, hospital course and follow-up were extracted from the EHR. Patients were excluded from analysis if they did not meet criteria for probable or definite AH, if they were below 18 years of age, if they ever had a diagnosis code consistent with cirrhosis prior to admission or if medical records pertaining to

comorbidities, laboratory investigations and outcomes were missing or incomplete.

Outcomes
The primary outcome of our study was inpatient mortality after admission for AH. Secondary outcomes included overall mortality, 30-day readmissions and diagnosis of cirrhosis after discharge.

Statistical analysis
Patient demographic and clinical characteristics were summarised using median (range) for continuous and count (percentage, %) for categorical variables, overall and by RYGB status. C-square tests were used to evaluate associations on categorical variables by group. The association of RYGB on the differences in time to inpatient mortality was assessed using Kaplan-Meier curves, where participants without the event were censored at the date of data collection, 28 June 2021. Time to overall mortality and progression to cirrhosis were also assessed using Kaplan-Meier curves, again with censoring on 28 June 2021. The impact of RYGB on the differences in inpatient mortality was assessed using logistic regression models, adjusted for demographic characteristics that may strongly affect clinical course such as age, sex, race, body mass index (BMI), CAD, DM, and peripheral artery disease. Finally, all p values are two sided and considered at 0.05 for statistical significance. Analyses were conducted in R (R Core Team (2021), V.4.0.4).

RESULTS
Patient characteristics
2634 patients had an International Classification of Diseases (ICD) -9 or -10 code for AH over the study period. A total of 153 (5.8%) patients were in the RYGB group, in which 127 (83%) patients were women compared with 883 (35.6%) patients in the control group. The median age was 47.5 years in both groups and the majority of patients were white (85.2% in the RYGB group and 89% of controls). The median BMI ($31.3 \, kg/m^2$ vs $25.7 \, kg/m^2$) was higher in the RYGB group compared with controls. Obstructive sleep apnoea (8.5% vs 2.9%) and hypertension (49% vs 44.3%) were more common in the RYGB group, while the presence of DM (1.3% vs 1.3%) and CAD (0.7% vs 0.8%) were similar between the groups (table 1).

Regarding severity of liver disease, complications such as ascites (65.3% vs 63.3%) and hepatic encephalopathy (13.1% vs 8%) were higher in the RYGB group. The median MELD-Na (Model for End Stage Liver Disease - Sodium) at presentation was higher in the RYGB group (15.1 vs 10.9); in addition, more patients in the RYGB group had a MELD-Na score >20 (32.1% vs 19.9%, χ^2 test p=0.03). Renal replacement therapy was more common in 7.2% of patients in the RYGB group compared with 4.4% patients in the control group. Endotracheal intubation (2.6% vs 6.7%) and steroid therapy (6.5% vs 7.5%) were more common in the control group (table 1).

Table 1 Patient characteristics

Patient characteristics	RYGB+AH	AH only
Number of patients (%)	153 (5.8)	2481 (94.2)
Median age at admission, years (range)	47.5 (20.6, 77.0)	47.5 (20.3, 90.7)
Female gender (%)	127 (83.0)	883 (35.6)
BMI, kg/m^2 (range)	31.3 (15.1, 65.5)	25.7 (10.8, 63.9)
Race:		
White (%)	127 (85.2)	2108 (89.0)
Black/African (%)	19 (12.8)	143 (6.0)
Native American/Alaskan (%)	3 (2.0)	93 (3.9)
Diabetes mellitus (%)	2 (1.3)	32 (1.3)
Hypertension (%)	75 (49.0)	1099 (44.3)
Coronary artery disease (%)	1 (0.7)	19 (0.8)
Hyperlipidemia (%)	23 (15.0)	443 (17.9)
Peripheral artery disease (%)	1 (0.7)	28 (1.1)
Median ICU length of stay, days (range)	2.0 (0.0, 28.0)	2.0 (0.0, 82.0)
Median overall length of stay, days (range)	4.0 (1.0, 33.0)	4.0 (1.0, 89.0)
Hepatic encephalopathy (%)	20 (13.1)	199 (8.0)
Ascites (%)	100 (65.4)	1570 (63.3)
Variceal haemorrhage (%)	0 (0.0)	25 (1.0)
Laboratory parameters – median (range)		
Haemoglobin, g/dL	11.7 (4.2, 16.7)	13.7 (2.8, 20.9)
White blood cell count, 10^9/L	7.4 (1.0, 35.8)	7.3 (0.0, 44494.0)
Platelet count, 10^9/L	167.0 (27.0, 678.0)	155.0 (2.0, 633.0)
Aspartate aminotransferase, U/L	177.0 (22.0, 14896.0)	170.0 (8.0, 24377.0)
Alanine aminotransferase, U/L	82.5 (17.0, 4232.0)	94.0 (7.0, 15552.0)
Total bilirubin, mg/dL	1.7 (0.2, 33.7)	1.4 (0.1, 51.1)
Sodium, mMol/L	135.0 (111.0, 149.0)	136.0 (104.0, 155.0)
Creatinine, mg/dL	0.7 (0.3, 13.0)	0.8 (0.3, 16.2)
International normalised ratio, INR	1.2 (0.8, 8.4)	1.1 (0.8, 9.3)
Total protein, mg/dL	7.0 (3.6, 10.0)	7.5 (0.0, 10.8)
Albumin, g/dL	3.2 (1.0, 10.0)	3.7 (0.5, 12.0)
Phosphorus, mg/dL	2.6 (0.5, 8.6)	2.7 (0.2, 12.7)
Median Model for End Stage Liver Disease, MELD-Na (range)	15.1 (6.4, 48.2)	10.9 (6.4, 53.9)
MELD-Na>20, N (%)	35 (32.1)	317 (19.9)
Steroid use (%)	10 (6.5)	187 (7.5)
Endotracheal intubation (%)	4 (2.6)	166 (6.7)
Renal replacement therapy (%)	11 (7.2)	108 (4.4)

BMI, body mass index; ICU, Intensive Care Unit; MELD-Na, Model for End Stage Liver Disease - Sodium
AH, alcohol-associated hepatitis; RYGB, Roux-en-Y gastric bypass.

Primary outcome

The inpatient mortality rate was similar between the RYGB group and the control group (2.6% vs 2.7%, respectively). The Kaplan-Meier estimates of inpatient survival were also similar between the two groups (log-rank p=0.82) (figure 1A). After controlling for confounders, the presence of RYGB did not affect the risk of inpatient mortality (OR 0.53, 95% CI 0.13 to 1.73, p=0.33). Increased age at admission (OR 1.05, 95% CI 1.03 to 1.08, p=0.00), increased BMI (OR 1.05, 95% CI 1.01 to 1.09, p=0.02), MELD-Na >20 (OR 5.88, 95% CI 2.82 to 12.61, p=0.00) and need for haemodialysis (OR 14.86, 95% CI 7.61 to 29.91, p=0.00) were all associated with increased inpatient mortality (table 2). In patients with MELD-Na >20, the Kaplan-Meier estimates of inpatient survival did
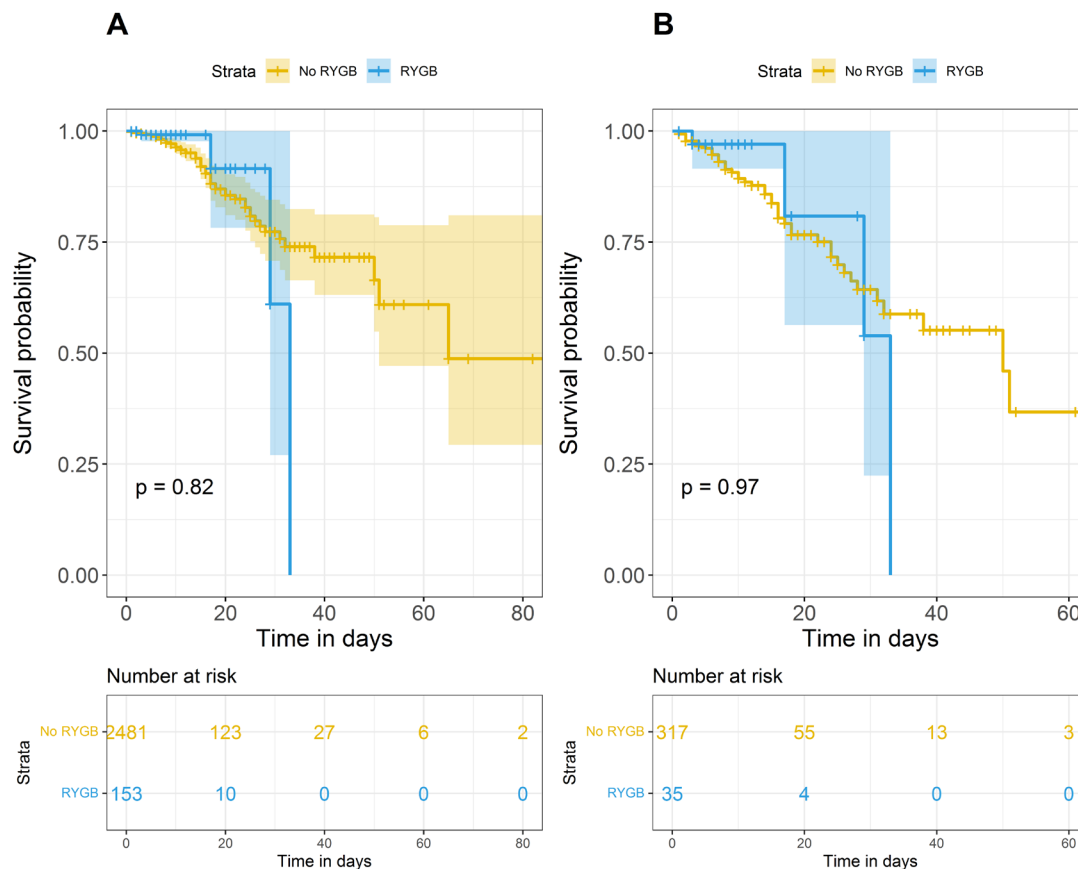
Figure 1 A: Kaplan-Meier Estimates of Inpatient Mortality Following Admission for AH. B: Kaplan-Meier Estimates of Inpatient Mortality Following Admission for AH in Patients with MELD-Na>20. AH, alcohol-associated hepatitis; RYGB Roux-en-Y gastric bypass.

not differ between the RYGB and control groups (log-rank p=0.97) (figure 1B).

Secondary outcomes
Overall mortality
The median follow-up time from date of admission to death was 3.3 years in the RYGB group and 3.6 years in the control group. In the RYGB group, 31.4% patients

Table 2 Odds of inpatient mortality in all patients using a multivariate logistic regression model

Variable	OR	95% CI	P value
RYGB status	0.53	0.13 to 1.73	0.33
Age at admission	1.05	1.03 to 1.08	0.00
Male sex	0.86	0.45 to 1.67	0.66
Black or African American race	0.47	0.06 to 2.02	0.37
Native American race	0.90	0.19 to 3.20	0.89
BMI	1.05	1.01 to 1.09	0.02
Peripheral artery disease	4.52	0.66 to 18.61	0.06
MELD-Na>20	5.88	2.82 to 12.61	0.00
Hemodialysis	14.86	7.61 to 29.91	0.00

BMI, body mass index; MELD-Na, Model for End Stage Liver Disease - Sodium; RYGB, Roux-en-Y gastric bypass.

died, compared with 24% in the control group. The Kaplan-Meier estimates of overall survival were 86.3%, 83.4% and 67.2% at 1, 2 and 5 years in the RYGB group, respectively, and 88.4%, 84.3% and 74.8% at 1, 2 and 5 years in the control group, respectively (log-rank p=0.03) (figure 2A). In patients with MELD-Na >20, the Kaplan-Meier estimates of overall survival were 74.3%, 67.8% and 41.6% at 1, 2 and 5 years in the RYGB group, respectively, and 57.7%, 52.6% and 42.1% at 1, 2 and 5 years in the control group, respectively (log-rank p=0.51) (figure 2B).

30-day readmissions
The instances of 30-day readmissions were higher in the RYGB group compared with the control group (20.3% vs 11.7%, χ^2 test p<0.01). Among these patients readmitted within the first 30 days, the number of rehospitalisations was similar between both groups (table 3).
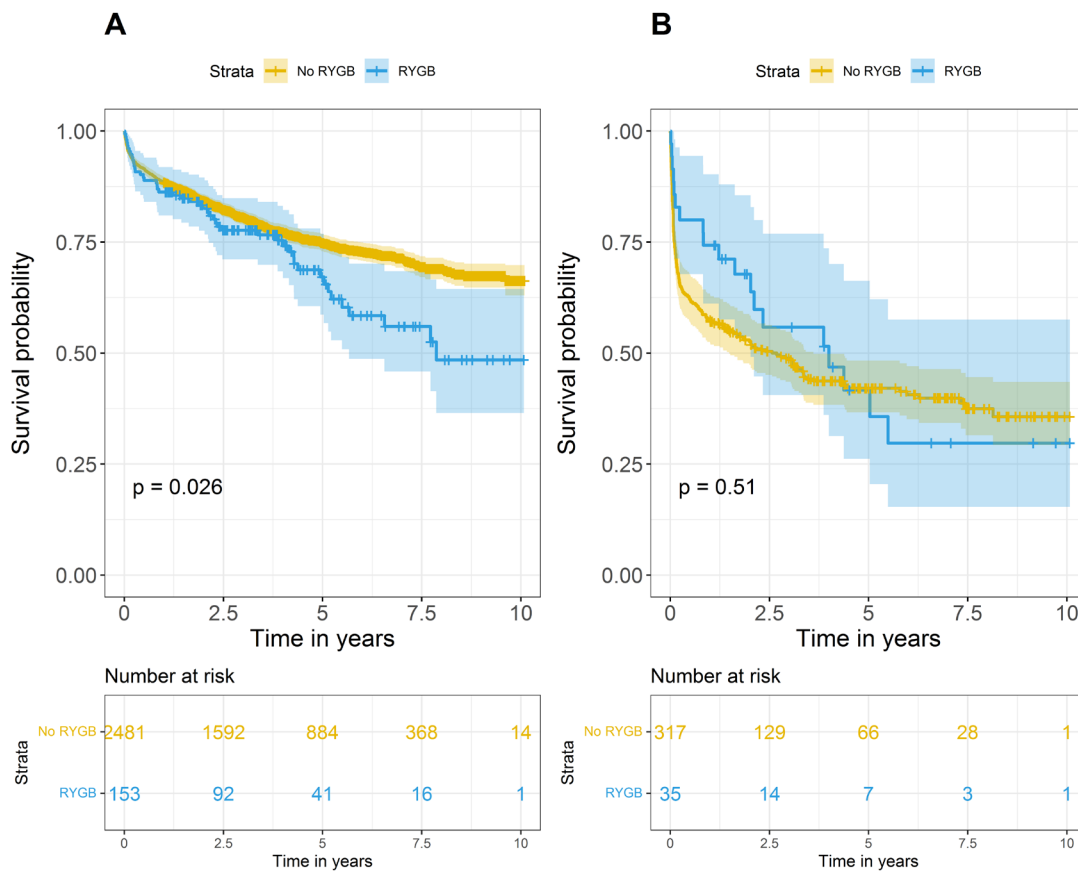
Development of cirrhosis
Cirrhosis was diagnosed in 57 (37.5%) patients in the RYGB group following discharge from hospital compared with 518 (20.9%) patients in the control group. The median time to diagnosis of cirrhosis was 2.4 (0, 10.0) years in the RYGB group compared with 3.7 (0, 10.1) years in the control group. The Kaplan-Meier estimates for diagnosis of cirrhosis were 28.9%, 34.7% and 38.9%

Figure 2 A: Kaplan-Meier Estimates of Overall Mortality Following Admission for AH. B: Kaplan-Meier Estimates of Overall Mortality Following Admission for AH in Patients with MELD-Na>20. RYGB, Roux-en-Y gastric bypass.

at 1, 2 and 5 years in the RYGB group, respectively, and 15.1%, 17.6% and 21.5% at 1, 2 and 5 years in the control group, respectively (log-rank p<0.01) (figure 3).

DISCUSSION

Increases in the diagnosis of AUD and the obesity epidemic have resulted in rising rates of both ALD and WLS in the USA, making it important to understand the complex relationship between these two entities. In this

Table 3 Rates of 30-day readmissions

	RYGB+AH	AH only
N (%)	153 (5.8)	2480 (94.2)
Readmission 30 days		
No	122 (79.7)	2190 (88.3)
Yes	31 (20.3)	290 (11.7)
Number of readmissions in readmitted patients in the first 30 days		
1	27 (87.1)	246 (84.8)
2	4 (12.9)	38 (13.1)
3	0 (0.0)	6 (2.1)

AH, alcohol-associated hepatitis; RYGB, Roux-en-Y gastric bypass.

single-centre study, a history of RYGB surgery was not associated with an increase in inpatient mortality in patients hospitalised with AH; however, RYGB was associated with 30-day readmissions, higher overall mortality and higher rates of cirrhosis after discharge from hospital.
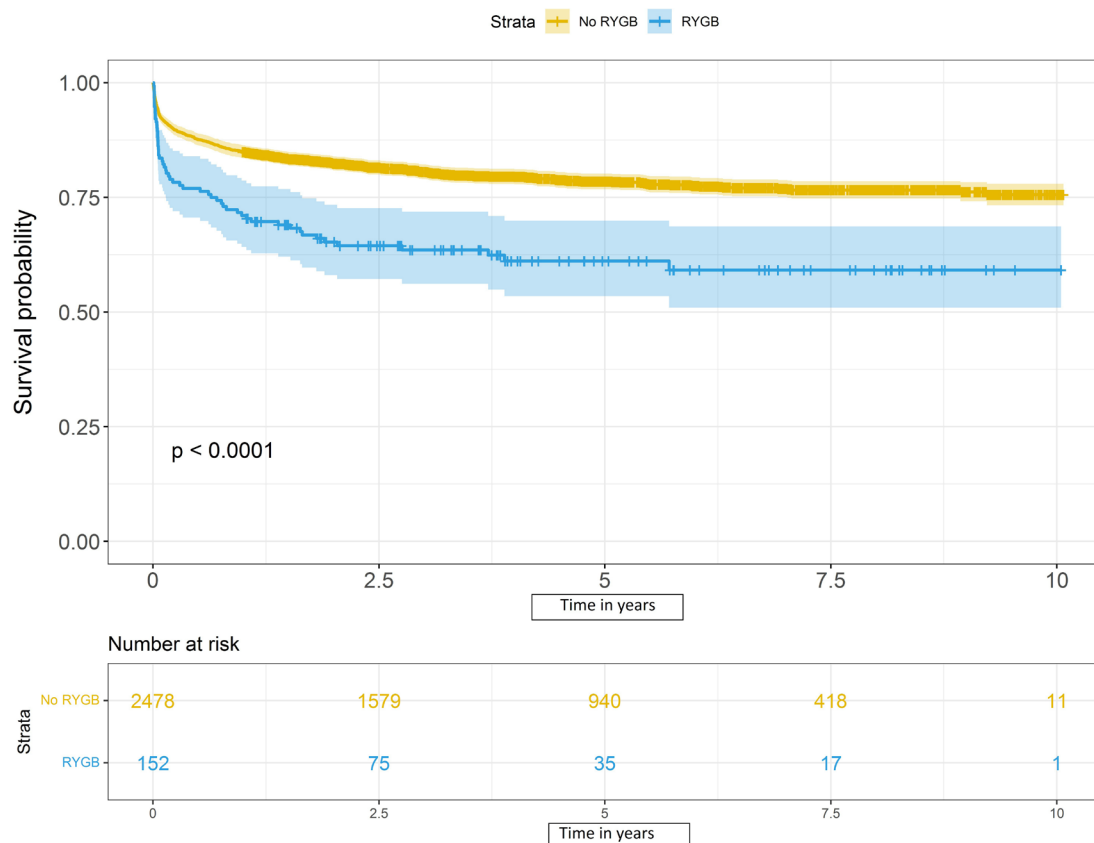
Although we did not observe a significant difference in inpatient mortality between the two groups, RYGB was associated with lower overall survival compared with controls particularly beyond 3 years after discharge from hospital. Despite a history of WLS, patients with a history of RYGB had a higher BMI, which influenced inpatient mortality on multivariate analysis in our study. Obesity is associated with several comorbidities, for example, type II DM, cardiovascular disease and obstructive sleep apnea, which negatively affect patient survival.[27–29] Furthermore, protein-calorie malnutrition, a frequent complication of WLS, is associated with worse clinical outcomes in patients with AH.[30–32] Longer term follow-up may be needed for patients with RYGB who recover from AH to address the associated comorbidities, which may contribute to higher rates of mortality after discharge from hospital.

Two recent studies using data from the National Readmissions Database showed that bariatric surgery was associated with higher rate of readmissions in patients with AH: our results show a similar increase in the risk of readmissions for patients with AH who specifically had a history of RYGB.[25 26] Increased readmission rates have

Figure 3 Kaplan-Meier Estimates of Development of Cirrhosis After Discharge from Hospital with AH. RYGB, Roux-en-Y gastric bypass.

contributed greatly to healthcare spending on patients with AH at a time when healthcare costs continue to rise exponentially in the USA.[5 25] Patients with a history of RYGB who require admission to hospital for AH may require closer follow-up on discharge to prevent readmissions. In patients with cirrhosis, one study has shown that early follow-up visits after admission can reduce readmissions and lower short-term mortality.[33]

Our study is the first to examine the relationship between RYGB and the development of cirrhosis in patients with AH. We found that patients with RYGB and AH had higher rates of cirrhosis after discharge from hospital when compared with controls. First-pass alcohol metabolism by gastric alcohol dehydrogenase is significantly reduced in patients with RYGB, while faster gastric emptying results in uncontrolled exposure to and absorption of alcohol through the small bowel.[34 35] As a result, patients with RYGB who ingest alcohol may have higher peak blood alcohol concentrations compared with patients with normal stomach anatomy, which may be more directly toxic to the liver and accelerate the development of cirrhosis.[36] Patients with RYGB may also have concurrent non-alcoholic fatty liver disease hastening the development of cirrhosis after discharge.[37 38] In patients with RYGB, early liver biopsy should be considered after biochemical recovery of AH to identify cirrhosis and determine the need for screening for oesophageal varices and hepatocellular carcinoma. Non-invasive strategies,

such as transient/shear wave elastography or magnetic resonance elastography, may also be considered although data on their accuracy in patients with a history of RYGB are currently limited.[39–42]

In the USA, active AUD is a contraindication to WLS. The American Society for Metabolic and Bariatric Surgery recommends that all patients being considered for WLS are screened for AUD and counselled about the risk of development of AUD after surgery. Patients with AUD may be considered for WLS after undergoing treatment and a period of prolonged abstinence.[43] Our data suggest that reinforcement of preoperative education, ongoing education regarding the risks of alcohol and screening for AUD are important to prevent morbidity and mortality from ALD, AH and potentially cirrhosis in patients with RYGB. Individuals at high risk for AUD may benefit from referral for additional mitigation strategies such as psychoeducation and counselling.[44]

The results from our study should be interpreted with certain limitations. First, the retrospective study design has its inherent flaws, although the granularity of our data is improved compared with large database studies. Second, as a tertiary referral centre, our results may not be generalisable to patients presenting to community hospitals. Third, readmission data may be underestimated as patients discharged from tertiary referral centres may represent to their local hospitals without requiring referral back to the tertiary centre. Fourth, we

used ICD codes to identify patients with AH and cirrhosis; however, each diagnosis of AH was validated with manual chart review and a recent study showed that using ICD diagnosis codes for cirrhosis has a high specificity and a high positive predictive value.[45–47] Finally, details about alcohol use prior to WLS and after hospitalisation for AH were incomplete, an important factor in the development of cirrhosis after discharge.

In conclusion, RYGB did not affect inpatient mortality in patients hospitalised with AH but impacted overall survival, readmissions and rates of cirrhosis after discharge compared with similar patients without RYGB. Providers should recognise these risks and additional resources may be necessary to improve clinical outcomes in this unique population. Further study is needed to develop interventions to reduce readmissions for RYGB patients admitted to hospital with AH and to better understand the impact of alcohol use on liver function in these patients.

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