Patients with a history of bariatric surgery are 8 years younger at presentation with severe alcoholic hepatitis

Melkebeke, L. van; Broekhoven, A.G.C.; Ostyn, T.; Korf, H.; Coenraad, M.J.; Vangoitsenhoven, R.; ... ; Verbeek, J.

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ORIGINAL CONTRIBUTIONS

Patients with a History of Bariatric Surgery Are 8 Years Younger at Presentation with Severe Alcoholic Hepatitis

Lukas Van Melkebeke[1,2] · Annelotte G. C. Broekhoven[3] · Tessa Ostyn[4] · Hannelie Korf[1] · Minneke J. Coenraad[3] · Roman Vangoitsenhoven[5,6] · Bart Van der Schueren[5,6] · Matthias Lannoo[7] · Hannah Van Malenstein[2] · Tania Roskams[4] · Schalk van der Merwe[1,2] · Frederik Nevens[1,2] · Jef Verbeek[1,2]

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Abstract

Purpose Patients with prior bariatric surgery (BS) are at risk to develop alcohol use disorder (AUD) and alcohol-related liver disease (ALD). Severe alcoholic hepatitis (sAH) is one of the most severe manifestations of ALD with a 28-day mortality of 20–50%. The impact of prior BS on patients presenting with sAH was assessed.

Methods From 01/2008 to 04/2021, consecutive patients admitted to a tertiary referral center with biopsy-proven sAH were included in a database.

Results One hundred fifty-eight sAH patients of which 28 patients had a history of BS (BS group) were identified. Of this BS group, 24 patients underwent a Roux-en-Y gastric bypass (RYGB), 3 a biliopancreatic diversion, 1 an adjustable gastric band, and no patients a sleeve gastrectomy. The proportion of patients with BS increased threefold over time during the study period. Patients in the BS group were significantly younger at diagnosis of sAH (44.3 years vs 52.4 years), were more frequently female, and had a higher body mass index and a higher grade of steatosis on liver biopsy. The correlation between BS and a younger age at diagnosis remained significant in a multivariate regression analysis. There were no differences in disease severity between both groups. Furthermore, there were no differences in corticosteroid response, 28-day, 90-day, or 1-year survival.

Conclusion Prior BS is independently associated with a younger age of presentation with sAH, but is not independently associated with a different disease severity or outcome. These findings support the need for early detection of AUD in patients who underwent BS, in particular RYGB.

Keyword Bariatric surgery; Complications; Epidemiology; Alcoholic hepatitis

Introduction

Bariatric surgery (BS) has been associated with an increased risk of alcohol use disorder (AUD) and alcohol-related liver disease (ALD) [1–3], depending on the type of bariatric surgery performed. Notably, a large prospective multicenter cohort study followed 2348 patients before surgery and annually after Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding (AGB) for up to 7 years [4]. For both RYGB and AGB, the prevalence of regular alcohol drinking (≥2 times a week) doubled in the 7 years post-surgery [4]. However, only for RYGB, the prevalence of AUD increased significantly, from 7% pre-surgery to 16% at year 7. On the other hand, the prevalence of AUD following AGB remained stable between 6 and 8% [4]. The association between sleeve gastrectomy (SG) and AUD was initially less clear, with some studies reporting an increased risk of AUD after SG [5], while others reporting a decreased risk [6, 7]. However, several recent large cohort studies showed an increased risk of AUD after SG, comparable with the increased risk of AUD after RYGB [8–10]. Concerning ALD, one study found a higher risk after RYGB, with a lower risk after SG and AGB, compared to patients undergoing a cholecystectomy [3]. In addition, one study found that patients with prior BS listed

Key Points
- The fraction of sAH patients with prior bariatric surgery (BS) increased over time.
- These patients are significantly younger at diagnosis than those without prior BS.
- Awareness for alcohol-related liver disease in patients with prior BS is necessary.

Lukas Van Melkebeke, Annelotte G.C. Broekhoven, and Tessa Ostyn shared first authorship.

✉ Lukas Van Melkebeke
lukas.vanmelkebeke@kuleuven.be

Extended author information available on the last page of the article

for liver transplantation due to alcohol-related cirrhosis were younger and had a more severe decompensation at time of listing than patients without a prior BS [11].

Alcoholic hepatitis (AH) is an acute form of ALD that ranges from mild to severe disease states and usually presents on a background of cirrhosis [12]. Severe AH (sAH) is defined as a Maddrey discriminant function (MDF) of more than or equal to 32 and/or a model for end-stage liver disease (MELD) score of more than 20 in a patient with prolonged and excessive alcohol abuse and a recent onset of jaundice [13]. sAH typically develops in patients with active AUD or within 3 months of abstinence [12]. sAH is one of the most severe manifestations of ALD with a 28-day mortality of 20–50% [14]. Corticosteroids are the only proven pharmacological therapy with a survival benefit after 28 days, but not after longer follow-up [15]. Response to corticosteroids is determined by calculating the Lille score after 7 days, with a response defined as a score < 0.45 [12]. However, only 50% of patients respond to corticosteroids, with non-responders having a dismal prognosis with a 6-month mortality of 70%.

To date, no data have been published on the relationship between BS and severe alcoholic hepatitis (sAH). Moreover, it is unknown whether sAH patients with a history of BS are phenotypically different from those without prior BS. Based on the published literature concerning liver transplantation for ALD in patients with previous BS [11], the hypothesis is that a history of bariatric surgery could also lead to the development of sAH at a younger age and might be associated with a more severe disease course. Therefore, the aim of this study is to assess the differences in disease characteristics at presentation, response to corticosteroids, and survival between patients presenting with sAH with or without a history of bariatric surgery.

Methods

Study Population

From March 2008 to April 2021, consecutive adult patients admitted to the tertiary liver unit of the University Hospitals Leuven and diagnosed with sAH were included in a prospective database aimed at evaluating the clinical course of patients with sAH. Diagnosis of sAH was based on clinical and biochemical data in combination with histological confirmation on transjugular biopsy at admission [16]. Exclusion criteria were as follows: (1) inconclusive biopsy results, (2) concomitant causes of liver disease (e.g., hepatitis B, hepatitis C, primary biliary cholangitis, auto-immune hepatitis), (3) presence of hepatocellular carcinoma, (4) previous liver transplantation. All patients were considered for treatment with corticosteroids, according to current guidelines [12]. Patients with clinical signs of decompensated cirrhosis, such as ascites, spontaneous bacterial peritonitis, or variceal bleeding, were treated according to current international guidelines [12]. The study protocol adhered to the ethical guidelines of the Declaration of Helsinki and approval was obtained from the Ethics Committee of the University Hospitals Leuven.

Data Collection

Demographic data, comorbidities, and patient history were collected from date of biopsy (time zero) onwards. Metabolic and cardiovascular risk factors were defined as the presence of at least one of the following: diabetes (pharmacological treatment or HbA1c ≥ 6.5%), hypertension, hyperlipidemia, history of stroke, history of ischemic cardiac injury, or a history of peripheral vascular disease. Furthermore, information was collected regarding complications of sAH (i.e., hepatic encephalopathy, ascites, infection), laboratory values, and performance scores (i.e., Child Pugh score, MELD score, MDF, CLIF-AD (acute decompensation) score, and CLIF-ACLF (acute-on-chronic liver failure) score). The MDF is calculated based on the serum bilirubin and the prothrombin time, was developed in 1978, and has traditionally been used in guidelines and clinical trials to discriminate between moderate and severe AH [17]. The MELD score is based on the serum bilirubin, the serum creatinine, and the INR [18]. It predicts 3-month survival across liver diseases and is also used to prioritize and stratify patients for liver transplantation [18]. Infection was defined as having a positive culture of blood, urine, or ascites, having > 250 polymorphonuclear cells/mm^3 in ascites, or having lesions on chest radiography compatible with infection. Ascites was grouped in three groups: (1) no ascites on ultrasound, (2) ascites only on ultrasound, (3) ascites on ultrasound and clearly present on a standard clinical examination.

All transjugular liver biopsies were reviewed by an expert liver pathologist (T.R), blinded for clinical outcome, to assess the presence of cirrhosis, presence of either parenchymal or ductular bilirubinostasis, grade of steatosis, polymorphonuclear infiltration, ballooning, Mallory bodies, and activity score according to the recently published SALVE grading system [19].

In the follow-up, information on the use of corticosteroids (within 1 month of the biopsy), development of infection, development of ACLF (as defined by EASL-CLIF) [20], liver transplantation, relapse of alcohol use, and survival were collected. Survival was defined as being dead or transplanted. Relapse of alcohol use was defined as self-reported active drinking at last time of follow-up and was only measured for patients with a survival of more than 90 days. Response to corticosteroid therapy was assessed at day 7 of corticosteroid therapy using the Lille Model [21].

Statistical Analysis

Data were reported as mean ± standard deviation when normally distributed and as median with interquartile range when not normally distributed. Categorical variables were reported as counts and percentage. Group comparisons were performed using Student's *t*-test, Wilcoxon rank sum test, and Fisher's exact test, according to the type of data. A log-rank test was used to compare overall survival. A multivariate linear model was performed with age as the dependent variable and sex, body mass index (BMI), cirrhosis, and steatosis as the independent variables. These independent variables were selected based on the results of the comparison between the bariatric surgery and non-bariatric surgery group. A univariate logistic-regression analysis was performed with 90-day survival as the dependent variable. Specifically for the relation between the Lille score and 90-day survival, the survival was calculated with the start date of corticosteroids as day 0. A multivariate logistic-regression analysis for 90-day survival was performed using age, BS, and MELD score as the independent variables. The independent variables were selected based on the results of the univariate logistic regression. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using the R-software environment (Version 4.0.3).

Results

Characteristics of the Full Cohort of Patients with sAH

In total, 158 sAH patients were included, of which 28 (17.8%) had a history of bariatric surgery (BS group) and 130 not (non-BS group). The median follow-up after presentation with sAH was 12.2 (2.3–55.2) months. Baseline characteristics of the full cohort are listed in Table 1. The mean age of the total group was 51.1 ± 10.4 years, with 88 (56.1%) males. The median MDF was 53.7 (39.3–74.0) and the median MELD score was 24.0 (21.1–28.0).

Characteristics of Bariatric Surgical Procedures

Of the 28 patients in the BS group, 24 (85.8%) underwent RYGB, 3 (10.7%) underwent biliopancreatic diversion (BPD), and 1 (3.6%) patient underwent AGB. No patients were identified with a history of SG. The mean time between the BS and the presentation with sAH was 8.8 ± 4.0 years. All RYGB procedures were performed between 04/2003 and 08/2018. The BPD procedures were performed between 07/1998 and 07/2011. The gastric banding was performed in 03/2004. The bariatric surgical procedures followed earlier published protocols (RYGB [22], AGB [22], BPD [23]).

Proportion of Patients with a History of BS Over Time

The proportion of patients with BS increased significantly over time: 4 (8%) within the first 5 years, 11 (19%) within the following 5 years, and 13 (28%) during the last 4 years ($p = 0.02$) of the study inclusion period (Fig. 1). The proportions of patients who underwent RYGB also increased significantly over time (supplementary Fig. 1).

Comparison of Baseline Characteristics of the BS Group and Non-BS Group

The patients in the BS group were significantly younger at presentation with sAH (44.3 ± 8.1 years versus 52.4 ± 10.3 years, $p < 0.001$), were more frequently female (19 (70%) versus 50 (38.5%), $p = 0.002$), and had a higher BMI (29.7 ± 4.9 versus 26.6 ± 5.0, $p = 0.003$) than patients without prior BS (Table 1).

No differences were found in the rates of presence of metabolic risk factors, complications of cirrhosis at admission (portal hypertension (i.e., hepato-portal venous pressure gradient > 11 mmHg), ascites, and hepatic encephalopathy), infection, or ACLF (Table 1). Biochemically, no differences were found for individual tests (white blood cell (WBC) count, bilirubin, protrombine time (PT), albumin, creatinine, or C-reactive protein (CRP)), nor for MDF or MELD score (Table 1).

Histologically, the patients in the BS group had a significantly higher grade of steatosis ($p = 0.008$) and less frequently cirrhosis ($p = 0.03$) compared to the non-BS group (Table 1). No differences were found in ballooning, Mallory bodies, polymorphonuclear (PMN) infiltration, or bilirubinostasis (parenchymal and ductular) between both groups, all markers of disease activity and/or severity (Table 1).

Using a multivariate linear model, the association between age and a history of bariatric surgery remained statistically significant after correction for sex, BMI, cirrhosis, and steatosis ($p < 0.001$).

A subgroup analysis excluding patients who underwent BPD and AGB yielded comparable results (supplementary table 1). Only the borderline significant difference in cirrhosis between the two groups became insignificant.

Comparison of Disease Course and Survival in the BS Group and Non-BS Group

Response to corticosteroids, measured with the Lille score at 7 days, was not different between both groups (Table 2). The development of infection or ACLF (for those patients without ACLF at baseline) within 90 days was not higher in

Table 1 Baseline characteristics in full cohort, BS group, and non-BS group

	Full cohort ($n = 158$)	BS group ($n = 28$)	Non-BS group ($n = 130$)	p - value (BS vs non-BS)
Clinical data				
Age (years)	51.1 ± 10.4	44.3 ± 8.1	52.4 ± 10.3	p < **0.001**
Sex (male)	88 (56.1%)	8 (29.6%)	80 (61.5%)	p = **0.002**
HVPG > 11 mmHg	143 (92.9%)	24 (85.7%)	119 (94.4%)	$p = 0.12$
Ascites				$p = 0.89$
Absent	25 (15.8%)	5 (17.9%)	20 (15.4%)	
Present on ultrasound	72 (45.6%)	13 (46.4%)	59 (45.4%)	
Clinically present	61 (38.6%)	10 (35.7%)	51 (39.2%)	
Hepatic encephalopathy				$p = 0.98$
Grade 0	95 (61.0%)	18 (64.3%)	77 (59.2%)	
Grade 1	35 (22.2%)	6 (21.4%)	29 (22.3%)	
Grade 2	23 (14.6%)	4 (14.3%)	19 (14.6%)	
Grade 3	5 (3.2%)	0 (0.0%)	5 (3.8%)	
Infection (at baseline)	57 (36.1%)	14 (50%)	43 (33.1%)	$p = 0.13$
BMI	27.1 ± 5.1	29.7 ± 4.9	26.6 ± 5.0	p = **0.003**
Metabolic or cardiovascular risk factor	46 (29.1%)	9 (32.1%)	37 (28.5%)	$p = 0.82$
Histological data				
Steatosis				p = **0.007**
< 5%	18 (11.4%)	0 (0.0%)	18 (14.0%)	
5–33%	35 (22.2%)	5 (17.9%)	30 (23.3%)	
33–66%	40 (25.3%)	4 (14.3%)	36 (27.9%)	
> 66%	64 (40.5%)	19 (67.9%)	45 (34.9%)	
Cirrhosis	156 (98.7%)	26 (92.9%)	130 (100%)	p = **0.03**
PMN infiltration				$p = 0.92$
Mild	26 (16.6%)	4 (14.3%)	22 (17.1%)	
Moderate	46 (29.3%)	9 (32.1%)	37 (28.7%)	
Severe	85 (54.1%)	15 (53.6%)	70 (54.2%)	
Mallory bodies				$p = 0.17$
Mild	28 (17.7%)	2 (7.1%)	26 (20.0%)	
Severe	130 (82.3%)	26 (92.9%)	104 (80.0%)	
Ballooning				$p = 0.47$
Mild	14 (8.9%)	1 (3.6%)	13 (10.1%)	
Severe	143 (91.1%)	27 (96.4%)	116 (89.9%)	
Parenchymal bilirubinostasis	148 (93.7%)	26 (92.9%)	122 (93.8%)	$p = 0.69$
Ductular bilirubinostasis	65 (41.1%)	11 (39.3%)	54 (41.5%)	$p = 1.00$
Activity score (SALVE)				$p = 1.00$
3	4 (2.5%)	0 (0.0%)	4 (3.1%)	
4	153 (97.5%)	28 (100%)	125 (96.9%)	
Biochemical data				
WBC count (10^9/l)	9.6 (5.84–13.5)	10.0 (5.7–13.0)	9.6 (5.9–10.6)	$p = 0.88$
Neutrophil count (10^9/l)	7.0 (3.7–11.1)	7.5 (3.6–10.4)	6.9 (3.7–11.5)	$p = 0.88$
Sodium (mmol/l)	134.4 ± 5.7	134.7 ± 5.5	134.3 ± 5.8	$p = 0.78$
Creatinine (mg/dl)	0.76 (0.57–1.25)	0.72 (0.56–1.08)	0.78 (0.59–1.25)	$p = 0.54$
Albumin (g/l)	27.6 (24.8–31.3)	27.1 (21.8–31.8)	27.7 (24.9–31.2)	$p = 0.55$
Bilirubin (mg/dl)	12.8 (7.0–22.6)	13.2 (6.2–21.0)	12.8 (7.1–22.9)	$p = 0.60$
PT	20.4 (17.6–24.9)	21.0 (18.1–25.3)	20.2 (17.6–24.1)	$p = 0.55$
CRP (mg/l)	31.3 (13.7–48.7)	21.4 (11.3–43.7)	32.5 (15.4–49.7)	$p = 0.22$

Table 1 (continued)

	Full cohort ($n = 158$)	BS group ($n = 28$)	Non-BS group ($n = 130$)	p - value (BS vs non-BS)
Scoring systems				
MDF	53.7 (39.3–74.0)	56.3 (37.8–75.2)	53.6 (40.6–70.9)	$p = 0.71$
MELD score	24.0 (21.1–28.0)	23.3 (20.7–29.9)	24.0 (21.1–27.6)	$p = 0.97$
CLIF-AD score	58.3 ± 9.5	56.1 ± 10.1	58.7 ± 9.3	$p = 0.21$
CLIF-ACLF				$p = 0.37$
Grade 0	94 (59.5%)	15 (53.6%)	79 (60.8%)	
Grade 1	18 (11.4%)	5 (17.9%)	13 (10.0%)	
Grade 2	31 (19.6%)	7 (25.0%)	24 (18.5%)	
Grade 3	15 (9.5%)	1 (3.6%)	14 (10.8%)	

BS, Bariatric surgery; *HVPG*, hepato-venous portal gradient; *MDF*, Maddrey discriminant function; *non-BS*, non-bariatric surgery; *PMN*, polymorphonuclear; *WBC*, white blood cells. Significant p-values are marked in bold

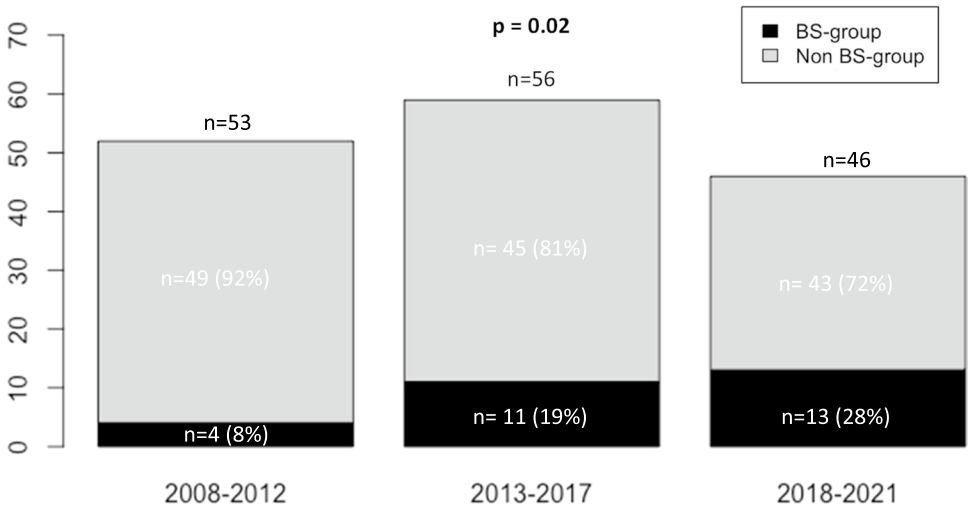

Fig. 1 Patients in the bariatric surgery group per time-interval

Table 2 Comparison of disease course and survival in BS group versus non-BS group

	BS group ($n = 28$)	Non-BS group ($n = 130$)	p-value
Received corticosteroids	19 (67.9%)	86 (66.2%)	$p = 1.00$
Lille score	0.11 (0.07–0.42)	0.27 (0.12–0.60)	$p = 0.23$
Corticosteroid response	14 (73.7%)	56 (65.9%)	$p = 0.60$
Infection at 90d	19 (67.9%)	84 (64.6%)	$p = 0.83$
ACLF at 90d	4 (26.7%)	30 (38.0%)	$p = 0.56$
Active alcohol use at last FU	10 (41.7%)	37 (43.0%)	$p = 1.00$
LTX at last FU	4 (14.3%)	11 (8.5%)	$p = 0.31$
28-day survival	27 (96.4%)	118 (90.8%)	$p = 0.47$
90-day survival	24 (85.7%)	90 (69.8%)	$p = 0.10$
1-year survival	13 (54.2%)	67 (54.5%)	$p = 1.00$

ACLF, Acute-on-Chronic Liver Failure; *BS*, bariatric surgery; *LTX*, liver transplantation; *non-BS*, non-bariatric surgery

patients with a prior BS (Table 2). Furthermore, relapse of self-reported alcohol use at last follow-up was also comparable between both groups (Table 2). Lastly, mortality was not significantly different at 28 days, 90 days, 1 year, or at last follow-up ($p = 0.40$) (Table 2). We specifically assessed variables associated with 90-day survival, given that most of the clinical improvement from sAH occurs within the first 3 months (Table 3) [24]. In the univariate analysis, age, creatinine, bilirubin, PT, MDF, MELD score, and CLIF-ACLF grade were negatively associated with 90-day survival, but a history of bariatric surgery was not. Specifically in the patients treated with corticosteroids, the Lille score (as a measure of response to corticosteroids) was highly correlated with survival (OR 0.46, 95%CI 0.36–0.59, $p < 0.001$). Due to the fact that multiple variables assessed in the univariate analysis were not independent (e.g., bilirubin and MDF), we only assessed MELD score (the score most strongly correlated with survival), age, and bariatric surgery (as variable of interest) in the multivariate analysis. In this multivariate analysis, age and MELD score remained significantly and negatively correlated with 90-day survival (Table 3).

A subgroup analysis excluding patients who underwent BPD and AGB yielded comparable results (supplementary table 2 and 3).

Discussion

While bariatric surgery is a clear risk factor for AUD [1–3], there is less information about the association of bariatric surgery and ALD. Furthermore, it is unclear whether sAH patients with a history of BS are phenotypically different from those without prior BS. In this study, it is shown that the rate of prior BS in sAH patients is increasing over time and that a history of BS in sAH patients is independently associated with a younger age at presentation. However, prior BS is not independently associated with a different disease severity and outcome in patients with sAH.

sAH patients with a history of BS were almost a decade younger at presentation. This in combination with the threefold increase in the proportion of sAH patients with prior BS over the last 15 years, reaching 28% in the last 4 years of the study period, underscores the relevance of these findings. The increase in the proportion of sAH patients with prior BS can partly be explained by the increase of the number of bariatric surgeries (+ 80% between 2010 and 2017 in Belgium) [25]. RYGB remains an efficient and popular type of BS, and it was the most performed bariatric procedure in the University Hospitals Leuven and Belgium during most of the study period (63–67% between 2009 and 2017) [25]. Sleeve gastrectomy on the other hand is a relatively newer procedure, which only accounted for 10% of all BS procedures in 2009, and has since then steadily increased to more than 35% in 2017 [25]. In line with these data and the observed lag time of 8 years after BS to develop sAH, the vast majority (85.8%) of sAH patients in the BS group underwent RYGB, and no patients had sleeve gastrectomy.

There are several possible explanations for the relation between bariatric surgery and the development of ALD, of which anatomic alterations leading to altered alcohol metabolism are probably the most important one. RYGB results in rapid alcohol absorption through direct dumping of alcohol in the jejunum. In addition, due to the loss of gastric alcohol dehydrogenase, a part of alcohol metabolism is lost. This results in faster and higher peak serum alcohol levels in RYGB [26–28], which might put the patient at increased

Table 3 Variables predicting 90-day survival

	Univariate analysis	*p*-value	Multivariate analysis	*p*-value
Age	0.99 (0.98–0.99)	**< 0.001**	0.98 (0.98–0.99)	**< 0.001**
Bariatric surgery	1.15 (0.96–1.38)	0.10	1.04 (0.88–1.23)	0.623
Sex	1.00 (0.87–1.15)	0.96		
BMI	0.99 (0.98–1.01)	0.34		
Infection	0.97 (0.84–1.12)	0.68		
Portal hypertension	0.92 (0.75–1.12)	0.40		
PMN infiltration	0.98 (0.89–1.08)	0.67		
Cirrhosis	1.27 (0.69–2.36)	0.44		
Creatinine	0.90 (0.84–0.98)	**0.01**		
Bilirubin	0.99 (0.98–0.99)	**0.002**		
PT	0.99 (0.98–0.99)	**0.004**		
MDF	0.99 (0.99–0.99)	**< 0.001**		
MELD score	0.98 (0.97–0.99)	**< 0.001**	0.98 (0.97–0.98)	**< 0.001**
CLIF-ACLF grade	0.89 (0.83–0.94)	**< 0.001**		

Data presented as odds ratio (95% CI interval); *MDF*, Maddrey discriminant function; *PT*, prothrombin time. Significant *p*-values are marked in bold

and accelerated risk for developing liver damage in case of prolonged excessive alcohol use. In contrast, AGB and SG both preserve (at least partially) gastric alcohol dehydrogenase function and do not bypass a part of the small bowel, which also might explain the lack of SG patients in the cohort. In addition, patients who undergo BS are at risk for having metabolic-associated fatty liver disease (MAFLD). In combination with AUD, MAFLD can be a contributive factor leading to ALD and possibly sAH [3]. Lastly, central nervous system changes after bariatric surgery, such as an increased reward sensitivity for alcohol, can also contribute to the increased risk of AUD and ALD [29]. Overall, these findings indicate the need for increased awareness for AUD and ALD in patients who have had BS and in particular RYGB. A pre-operative alcohol addiction screening as part of a comprehensive psychological assessment is important and is already a requirement for reimbursement of the BS procedure since 2007 in Belgium [30]. Furthermore, the multiple year lag time between BS and the development of sAH indicates the need for follow-up and awareness also beyond the immediate post-operative period.

In the University Hospitals Leuven, and in all the associated hospitals, BS is not performed in patients with active AUD. BS is only performed after careful multidisciplinary consideration, including specific validated questionnaires (AUDIT) and extensive interviewing by psychologist, dietician, and physician. All patients in this cohort had an active AUD at presentation or became abstinent only recently (within 3 months). The data about the amount of alcohol used at presentation with sAH cannot be considered a reliable marker for the amount of alcohol used in the years between the BS procedure and the presentation with sAH, and was therefore not included in the statistical analysis. Due to the design of this study, there is no data about the duration, patterns, and exact levels of alcohol use in the period before the BS procedure and in the period between the BS procedure and presentation with sAH. Therefore, it is not possible to determine if AUD developed before or after the bariatric surgery and no definite conclusions can be made concerning pathophysiology underlying the age difference between the BS and non-BS group at presentation with sAH.

The higher rate of females within the BS group compared with the non-BS group can be explained by the fact that BS is predominantly performed in women (71.3% in Belgium, 77.1% worldwide) [25, 31]. The fact that women are more prone than men to developing ALD in the presence of AUD might be a contributive factor [32]. No differences were found in disease severity (clinically or histologically) or response to corticosteroids between the BS and non-BS group. Both the histological grade of steatosis on liver biopsy and the BMI were significantly higher in the BS group. This might be a reflection of co-incident MAFLD in these patients with prior BS, supporting the idea that co-incident MAFLD could be a contributing factor to the development of ALD in these patients. On the other hand, the presence of other systemic metabolic risk factors was similar between both groups. Nevertheless, it is important to note that even in patients with ALD and MAFLD, ALD is the primary driver of liver damage [33]. Of note, the association between a history of BS and younger age at sAH presentation was independent from the histological grade of steatosis and BMI. Differences in levels of patterns of alcohol use as steatogenic factor might be another explanation for the observed difference.

While specific data on the impact of BS on presentation and outcome of sAH are not published to date, a recent study found that patients with prior BS listed for transplantation due to alcohol-related liver cirrhosis were significantly younger than those without. Somewhat in contrast with the findings in this study, listed ALD patients with prior BS had a more severe decompensation at presentation and a shorter interval between diagnosis and transplantation [11]. However, only a limited number of patients with prior BS ($n=11$) were included in this study. The fact that their patient population was only recruited at the moment of listing for transplantation also makes these findings susceptible for selection bias.

BS was not an independent risk factor for mortality in this study, in contrast to the established risk factors age, severity of liver disease (MDF, MELD, CLIF-ACLF), and the Lille score [21, 34]. A trend to a better survival in sAH patients with prior BS was observed at 90 days (85.7% vs 69.8%, $p=0.10$). It is possible that this observation might become statistically significant in larger cohort or multicenter studies. However, this potential better survival at 90 days seems to be driven by their younger age. In multivariate analysis, correcting for the observed age difference between patients with and without prior BS, this trend to better survival at 90 days was lost. The observation that survival is similar in patients with and without BS at the same age is also important for pharmacological trial design and randomization, in particular given the relatively high and increasing proportion of patients with sAH and prior BS.

Although strict clinical and histological diagnostic criteria were applied and patients were treated according to current guidelines, this novel data concerning increase in proportion of patients presenting with sAH and prior BS and their significantly younger age need to be validated in external cohorts. Finding significant differences in survival of sAH patients remains a particular challenge, since very large cohorts are needed for sufficient power [24] .

In conclusion, the proportion of sAH patients with prior BS increased significantly in our cohort. These patients are significantly younger at presentation suggesting an accelerated disease course to sAH, but have a similar disease severity. These findings indicate the need for early detection of

AUD in order to prevent sAH in patients who underwent BS and that these patients should not be excluded from clinical trials. Prospective studies from the timepoint of different types of BS are needed to decipher the exact risk factors and related pathophysiology leading to ALD and sAH in these patients.

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Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare no competing interests.

Statement of Human Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. King WC, Chen JY, Mitchell JE, et al. Prevalence of alcohol use disorders before and after bariatric surgery. JAMA. 2012;307(23):2516–25. https://doi.org/10.1001/JAMA.2012.6147.
2. Conason A, Teixeira J, Hsu CH, et al. Substance use following bariatric weight loss surgery. JAMA Surg. 2013;148(2):145–50. https://doi.org/10.1001/2013.JAMASURG.265.
3. Kim HP, Jiang Y, Farrell TM, et al. Roux-en-Y gastric bypass is associated with increased hazard for de novo alcohol-related complications and liver disease. J Clin Gastroenterol. 2021. https://doi.org/10.1097/MCG.0000000000001506.
4. King WC, Chen JY, Courcoulas AP, et al. Alcohol and other substance use after bariatric surgery: prospective evidence from a US multicenter cohort study. Surg Obes Relat Dis. 2017;13(8):1392–402. https://doi.org/10.1016/J.SOARD.2017.03.021.
5. Ibrahim N, Alameddine M, Brennan J, et al. New onset alcohol use disorder following bariatric surgery. Surg Endosc. 2019;33(8):2521–30. https://doi.org/10.1007/S00464-018-6545-X.
6. Östlund MP, Backman O, Marsk R, et al. Increased admission for alcohol dependence after gastric bypass surgery compared with restrictive bariatric surgery. JAMA Surg. 2013;148(4):374. https://doi.org/10.1001/JAMASURG.2013.700.
7. Thereaux J, Lesuffleur T, Czernichow S, et al. Long-term adverse events after sleeve gastrectomy or gastric bypass: a 7-year nationwide, observational, population-based, cohort study. Lancet Diabetes Endocrinol. 2019;7(10):786–95. https://doi.org/10.1016/S2213-8587(19)30191-3.
8. Maciejewski ML, Smith VA, Berkowitz TSZ, et al. Association of bariatric surgical procedures with changes in unhealthy alcohol use among US veterans. JAMA Netw Open. 2020;3(12):e2028117. https://doi.org/10.1001/JAMANETWORKOPEN.2020.28117.
9. Strømmen M, Bakken IJ, Klöckner C, et al. Diagnoses related to abuse of alcohol and addictive substances after gastric bypass and sleeve gastrectomy: a nation-wide registry study from Norway. Surg Obes Relat Dis. 2020;16(4):464–70. https://doi.org/10.1016/J.SOARD.2019.12.011.
10. Miller-Matero LR, Orlovskaia J, Hecht LM, et al. Hazardous alcohol use in the four years following bariatric surgery. Psychol Health Med. 2022;27(9):1884–90. https://doi.org/10.1080/13548506.2021.1930075.
11. Lefere S, Stroobant L, Verhelst X, et al. Bariatric surgery patients are at risk for alcoholic liver disease with need for liver transplantation. Obes Surg. 2020;30(11):4659–64. https://doi.org/10.1007/S11695-020-04806-8.
12. Thursz M, Gual A, Lackner C, et al. EASL Clinical Practice Guidelines: management of alcohol-related liver disease. J Hepatol. 2018;69(1):154–81. https://doi.org/10.1016/j.jhep.2018.03.018.
13. Seitz HK, Bataller R, Cortez-Pinto H, et al. Alcoholic liver disease. Nat Rev Dis Primers. 2018;4(1):1–22. https://doi.org/10.1038/s41572-018-0014-7.
14. Sarin SK, Sharma S. Predictors of steroid non-response and new approaches in severe alcoholic hepatitis. Clin Mol Hepatol. 2020;26(4):639–351. https://doi.org/10.3350/cmh.2020.0196.
15. Van Melkebeke L, Korf H, Tsochatzis E, et al. Treatment of severe alcoholic hepatitis: a systematic review. Curr Opin Pharmacol. 2021;60:91–101. https://doi.org/10.1016/J.COPH.2021.06.011.
16. Singal A, Louvet A, Shah V, et al. Grand rounds: alcoholic hepatitis. J Hepatol. 2018;69(2):534–43. https://doi.org/10.1016/J.JHEP.2018.05.001.
17. Maddrey WC, Boitnott JK, Bedine MS, et al. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology. 1978;75(2):193–9.
18. Morales-Arráez D, Ventura-Cots M, Altamirano J, et al. The MELD score is superior to the Maddrey discriminant function score to predict short-term mortality in alcohol-associated hepatitis: a global study. Am J Gastroenterol. 2022;117(2):301–10. https://doi.org/10.14309/AJG.0000000000001596.
19. Lackner C, Stauber R, Davies S, et al. Development and prognostic relevance of a histologic grading and staging system for alcohol-related liver disease. J Hepatol. 2021;75(4):810–9. https://doi.org/10.1016/J.JHEP.2021.05.029.
20. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144(7). https://doi.org/10.1053/J.GASTRO.2013.02.042
21. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology. 2007;45(6):1348–54. https://doi.org/10.1002/hep.21607.
22. Lannoo M, Dillemans B. Laparoscopy for primary and secondary bariatric procedures. Best Pract Res Clin Gastroenterol. 2014;28(1):159–73. https://doi.org/10.1016/J.BPG.2013.11.013.
23. Scopinaro N, Gianetta E, Civalleri D, Bonalumi U, Bachi V. Bilio-pancreatic bypass for obesity: II Initial experience in man. Br J Surg. 1979;66(9):618–20. https://doi.org/10.1002/BJS.1800660906.
24. Mathurin P, Thursz M. Endpoints and patient stratification in clinical trials for alcoholic hepatitis. J Hepatol. 2019;70(2):314–8. https://doi.org/10.1016/j.jhep.2018.11.005.

25. Van den Heede K, Ten Geuzendam B, Dossche D, et al. Bariatric surgery in Belgium: organisation and payment of care before and after surgery. Health Servises Research. *Health Serv Res*. 2020;(KCE Reports 329):1–42.
26. Steffen KJ, Engel SG, Pollert GA, Li C, Mitchell JE. Blood alcohol concentrations rise rapidly and dramatically after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2013;9(3):470–3. https://doi.org/10.1016/J.SOARD.2013.02.002.
27. Steffen KJ, Engel SG, Wonderlich JA, Pollert GA, Sondag C. Alcohol and other addictive disorders following bariatric surgery: prevalence, risk factors and possible etiologies. Eur Eat Disord Rev. 2015;23(6):442–50. https://doi.org/10.1002/ERV.2399.
28. Cederbaum AI. Alcohol metabolism. Clin Liver Dis. 2012;16(4):667–85. https://doi.org/10.1016/J.CLD.2012.08.002.
29. Blackburn AN, Hajnal A, Leggio L. The gut in the brain: the effects of bariatric surgery on alcohol consumption. Addict Biol. 2017;22(6):1540–53. https://doi.org/10.1111/adb.12436.
30. Van den Heede K, Ten Geuzendam B, Dossche D, et al. *Obesitaschirurgie: Organisatie En Financiering van Zorg Voor En Na de Operatie – Synthese*.; 2020.
31. Ramos A, Fasmbs F, Kow L, et al. *The IFSO Global Registry 5th IFSO Global Registry Report*.; 2019.
32. Kezer CA, Simonetto DA, Shah VH. Sex differences in alcohol consumption and alcohol-associated liver disease. Mayo Clin Proc. 2021;96(4):1006–16. https://doi.org/10.1016/J.MAYOCP.2020.08.020.
33. Moreno C, Sheron N, Tiniakos D, Lackner C, Mathurin P. "Dual aetiology fatty liver disease": a recently proposed term associated with potential pitfalls. J Hepatol. 2021;74(4):979–82. https://doi.org/10.1016/j.jhep.2020.11.004.
34. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med. 2015;372(17):1619–28.

Authors and Affiliations

Lukas Van Melkebeke[1,2] · Annelotte G. C. Broekhoven[3] · Tessa Ostyn[4] · Hannelie Korf[1] · Minneke J. Coenraad[3] · Roman Vangoitsenhoven[5,6] · Bart Van der Schueren[5,6] · Matthias Lannoo[7] · Hannah Van Malenstein[2] · Tania Roskams[4] · Schalk van der Merwe[1,2] · Frederik Nevens[1,2] · Jef Verbeek[1,2]

1 Department of Chronic Diseases and Metabolism, Laboratory of Hepatology, KU Leuven, Herestraat 49, Leuven 3000, Belgium

2 Department of Gastroenterology and Hepatology, UZ Leuven, Herestraat 49, Leuven 3000, Belgium

3 Department of Gastroenterology and Hepatology, Leiden University Medical Center, Postbus 9600, Leiden 2300, RC, The Netherlands

4 Department of Imaging and Pathology, Translational Cell and Tissue Research, KU Leuven, Herestraat 49, Leuven 3000, Belgium

5 Department of Endocrinology, UZ Leuven, Herestraat 49, Leuven 3000, Belgium

6 Department of Chronic Diseases and Metabolism, Clinical and Experimental Endocrinology, KU Leuven, Herestraat 49, Leuven 3000, Belgium

7 Department of Abdominal Surgery, UZ Leuven, Herestraat 49, Leuven 3000, Belgium