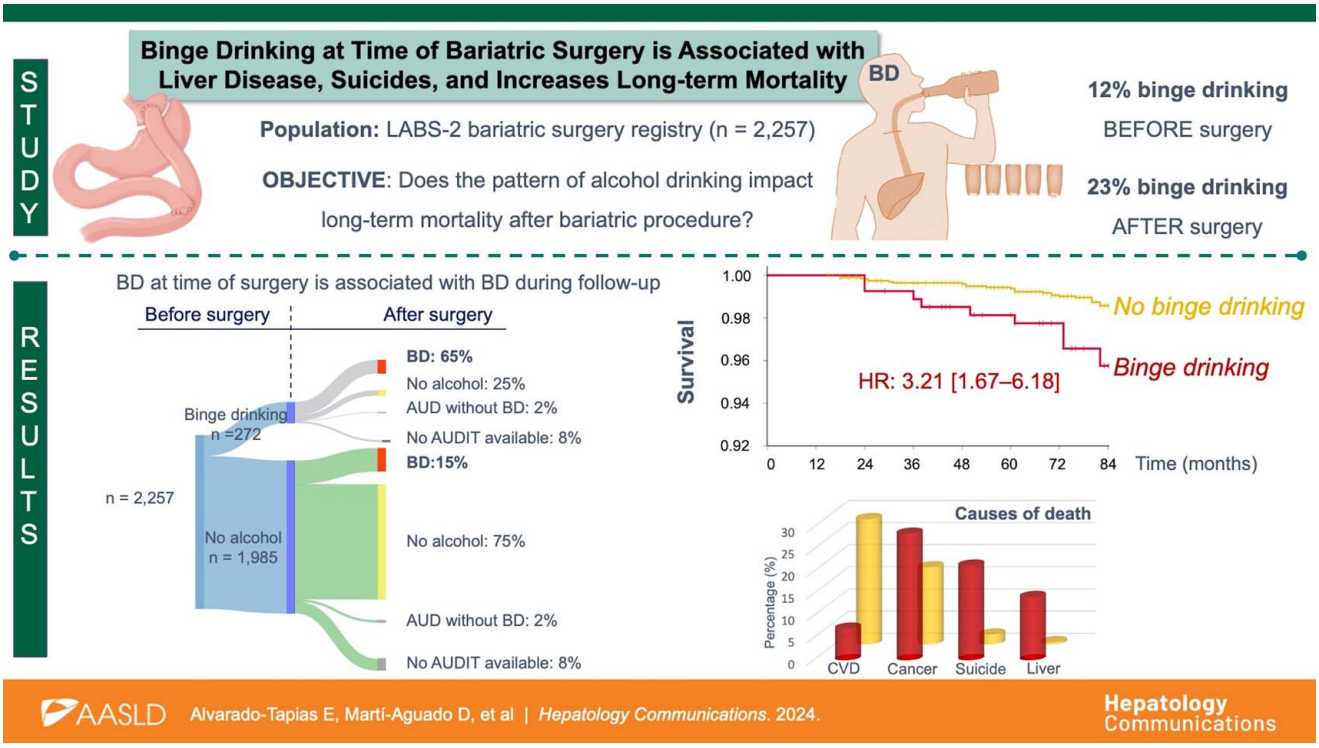
Binge drinking at time of bariatric surgery is associated with liver disease, suicides, and increases long-term mortality

VISUAL ABSTRACT



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ORIGINAL ARTICLE

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Binge drinking at time of bariatric surgery is associated with liver disease, suicides, and increases long-term mortality

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Abbreviations: AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; BD, binge drinking; CVD, cardiovascular disease; LABS-2, Longitudinal Assessment of Bariatric Surgery-2; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; WHO, World Health Organization.

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Abstract

Background and Aims: Alcohol use disorder has been reported in patients undergoing bariatric procedures, but the pattern of alcohol consumption has not been evaluated. We investigated the prevalence, risk factors, and impact of binge drinking (BD) at the time of surgery and during follow-up.

Methods: A prospective, longitudinal study of subjects undergoing bariatric surgery was included in the LABS-2 registry between 2006 and 2009. Participants with AUDIT questionnaire at the time of surgery and a minimum of 12 months follow-up were included. BD was defined as consuming ≥ 5 drinks on at least 1 occasion in the previous month. Liver biopsies were obtained during bariatric procedures in not all cases. Survival analysis was performed with the adjusted Cox regression model and competing risk.

Results: A total of 2257 subjects were included, with a median follow-up of 79 months. The prevalence of BD at time of surgery was 12%, and it raised up to 23% during follow-up. Patients with BD predominantly had a binge eating disorder (OR = 1.35 [95% CI: 1.04–1.76]), regularly consumed fast food [OR = 1.4 (95% CI: 1.07–1.85)] and used other drugs (OR = 2.65 [95% CI: 1.74–4.04]). Within liver biopsies evaluation, BD showed higher hepatic iron deposits (OR = 3.00 [95% CI: 1.25–7.21]). BD at the time of surgery was associated with a higher risk of BD during follow-up (OR = 10.49 [95% CI: 7.86–14.00]) and long-term mortality (HR: 3.21 [95% CI: 1.67–6.18]). Specific causes of death in these patients with BD were liver disease ($p = 0.020$), suicide ($p = 0.015$), neoplasms ($p = 0.034$), and respiratory ($p = 0.025$).

Conclusions: The prevalence of BD in patients undergoing bariatric surgery is high and increases the risk of postoperative liver disease, suicides, and long-term mortality.

INTRODUCTION

Bariatric surgery is the most effective long-term treatment for severe obesity and has shown effectiveness in reducing obesity-related comorbidities and increasing overall survival.[1] Nevertheless, several studies have described an increased risk of alcohol use disorder (AUD) after surgery.[2–4] The Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study, a prospective registry of US adults who underwent bariatric procedures, showed that the prevalence of AUD can double seven years after Roux-en-Y gastric bypass.[2,4] These patients with AUD have a higher risk of developing alcohol-associated liver disease and alcohol-mental disorders.[5]

Several mechanisms have been suggested to explain the association between bariatric surgery and AUD.[6,7] The presence of presurgical binge eating disorders, which are highly prevalent in these patients, can share behavioral similarities with substance use disorders. These conditions can be classified as binge behavioral disorders with a similar neuropsychological profile characterized by heavy episodic intakes (food, alcohol, or drugs)[8] that can progress to an unhealthy stage.[9] Alcohol Use Disorders Identification Test (AUDIT) is a widely validated questionnaire for measuring alcohol-associated problems. Specific AUDIT subscores for alcohol dependence or alcohol-associated harm define AUD as an impaired ability to control alcohol consumption with already established adverse social, occupational, or health consequences.[10] Although AUD, symptoms of alcohol dependence, and alcohol-associated harm do not seem to increase mortality after bariatric surgery, the pattern of alcohol consumption has not been evaluated in this setting.[11] Binge drinking (BD) is a pattern of alcohol consumption defined as consuming 4 or more drinks for females or 5 or more drinks for males on the same occasion on at

least 1 day in the past 30 days.[12,13] The rising prevalence of BD and its association with liver-related disease and death independently of average alcohol intake has raised awareness of the harmful repercussions of this overlooked drinking pattern.[14]

The primary objective of this study was to evaluate the prevalence of BD at the time of bariatric surgery and during follow-up, identify the risk factors associated with this pattern of alcohol consumption, and assess its long-term impact in a well-characterized cohort of the LABS-2 database. The secondary objective was to evaluate liver histological features that differ between patients with and without BD.

METHODS

Study design and participants

This longitudinal observational study was performed using the LABS-2 registry, a prospective cohort of US adults undergoing bariatric surgery at 10 hospitals between 2006 and 2009 (ClinicalTrials.gov: NCT00465829). Participants attended presurgery, 1-month, 6-month, and annual postoperative follow-up assessments for up to 7 years or until 2015, whichever came first. All adults with AUDIT information at the time of bariatric surgery were included. The exclusion criteria were a follow-up of <1 year. The LABS-2 database includes demographical, clinical, analytical, surgical, and follow-up information. The database was supplied by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository.[15] The study was performed in accordance with the Declaration of Helsinki and good clinical practice guidelines. The Institutional Review Boards at each center approved the protocol, and all participants provided informed consent, including a liver biopsy review by the study pathologist. The local Institutional Review Board (University of Pittsburgh) approved the study protocol in May 2019 (STUDY19010143).

Data collection

Preoperative baseline clinical data were collected within 30 days of surgery at in-person visits by study-trained personnel using standardized protocols.[2] Data were collected from patient self-reported information (age, sex, race, educational level, marital and employment status, cigarette smoking, alcohol consumption, and other drugs use), anthropometric measurements (mean arterial pressure, waist circumference, and body mass index) and review of medical records. Educational level was categorized as low (up to high school diploma) and high (some college up to graduate).[16] Comorbidities (metabolic syndrome, arterial hypertension, diabetes, dyslipidemia, sleep apnea, cardiovascular disease [CVD], and chronic kidney disease) were defined using medical records, physical examination, participant interviews, and laboratory values.

The follow-up visits took place in person at the clinical centers. The underlying cause of death was obtained from death certificates and categorized according to the World Health Organization (WHO) Global Burden of Disease Study (Supplemental Table S1, http://links.lww.com/HC9/A997).[17]

Assessment of alcohol consumption and eating behaviors

Participants reported alcohol use, including frequency/quantity of consumption in the previous year. The AUDIT was used to assess alcohol consumption, including BD, through specific subscores.[13] As established by the Substance Abuse and Mental Health Services Administration, BD was defined as 4 or more drinks for women or 5 or more drinks for men on the same occasion on at least 1 day in the past 30 days. Considering this definition, patients with BD were selected if an answer ≥ 3 was obtained for the third question of the AUDIT.[12,13,18] The few patients ($n=67$) who reported daily alcohol consumption defined as AUDIT ≥ 8, but did not referred heavy episodic drinking, were not included in BD category. During follow-up, the AUDIT questionnaire was assessed yearly, allowing the categorization of 4 groups after surgery: (1) no alcohol, (2) BD, (3) AUD without BD, (4) no AUDIT information available.

The self-administered LABS-2 Behavior Form includes a section on eating behaviors and disorders. This study assessed eating behavior, the frequency of eating each type of meal/week (breakfast, lunch, and dinner), the frequency of total snacks/meals per day, the frequency of eating meals at fast food and other restaurants, and the frequency of eating when not hungry or when uncomfortably full.

Eating disorders were defined as previously described using the Diagnostic and Statistical Manual of Mental Disorders-IV.[19] Binge eating disorder was diagnosed by endorsing several items to determine the five criteria defined in the Diagnostic and Statistical Manual of Mental Disorders-IV. Participants reporting evening hyperphagia or nocturnal eating were considered to have night eating syndrome.

Histological evaluation

During surgery, liver biopsies were obtained from some participants according to the local standard of care.[20] Biopsies were routinely stained with hematoxylin-eosin and Masson trichrome. The study pathologist was blinded to clinical and biological data. Biopsy adequacy

was determined by measuring the length of the tissue sample. Features of steatotic liver disease were scored using the NASH Clinical Research Network scoring system.[21] The NAFLD Activity Score was used as a composite measure of liver injury, adding the severity scores of steatosis, lobular inflammation, and ballooning. Inflammation was further evaluated using the Ishak scoring system, and iron deposits (Perls staining) were assessed according to Deugnier criteria.[22,23] In addition to scoring, each biopsy was categorized into histological groups: steatohepatitis (defined as NAFLD Activity Score ≥ 4) and high-risk fibrotic steatohepatitis (defined as fibrosis stage ≥ 2 and NAFLD Activity Score ≥ 4).[24]

Statistical analysis

Continuous variables are expressed as mean (SD) or median (IQR) whenever appropriate. Differences in continuous variables were tested by the ANOVA, Student *t* test, or Wilcoxon signed rank test for independent samples. Categorical variables were presented as frequency and percentage. Differences in the categorical variables were assessed by the χ^2 test or by Fisher exact test. To evaluate differences between studies, tests on the equality of proportions were performed. Time was calculated from the day of surgery to the date of censoring: death or study closure, whichever came first. Time-to-event analysis was conducted using the Kaplan-Meier method. Survival curves were compared using the log-rank test to identify variables at the time of surgery that were associated with mortality. A multivariable Cox proportional hazard regression analysis was performed to determine the independent contribution of each factor to time to death, adjusted by age, sex, body mass index, education level, surgical procedure, smoking, AUD, substance use, and fibrosis score 4 index.[25] A second multivariable Cox time-dependent model was performed with those variables available after surgery during follow-up (BD status, change in body mass index, and diabetes mellitus status). Those variables showing a *p*-value < 0.10 in the univariate analysis were included in the multivariable models. A backward stepwise method was then used to identify independent predictors of mortality. The C-statistic assessed the discriminative ability of the models. The internal validity to assess the robustness of the multivariable model was tested for 500 bootstrap resamples using the "rms" package.[26] The calibration of models was evaluated by the corresponding "slope" using the same package. The Fine and Gray competing risks regression model was used to determine the effect of the explanatory variable (BD) in the risk of each specific cause of death. Finally, a sensitivity analysis was performed using logistic regression analysis and was illustrated with a tornado plot, considering the pattern of alcohol consumption (BD on the *y*-axis) and the range of the outcome (mortality on the x-axis). The reference group was absence of BD at baseline and follow-up. A two-sided *p*-value < 0.05 was considered statistically significant. Missing data were imputed using

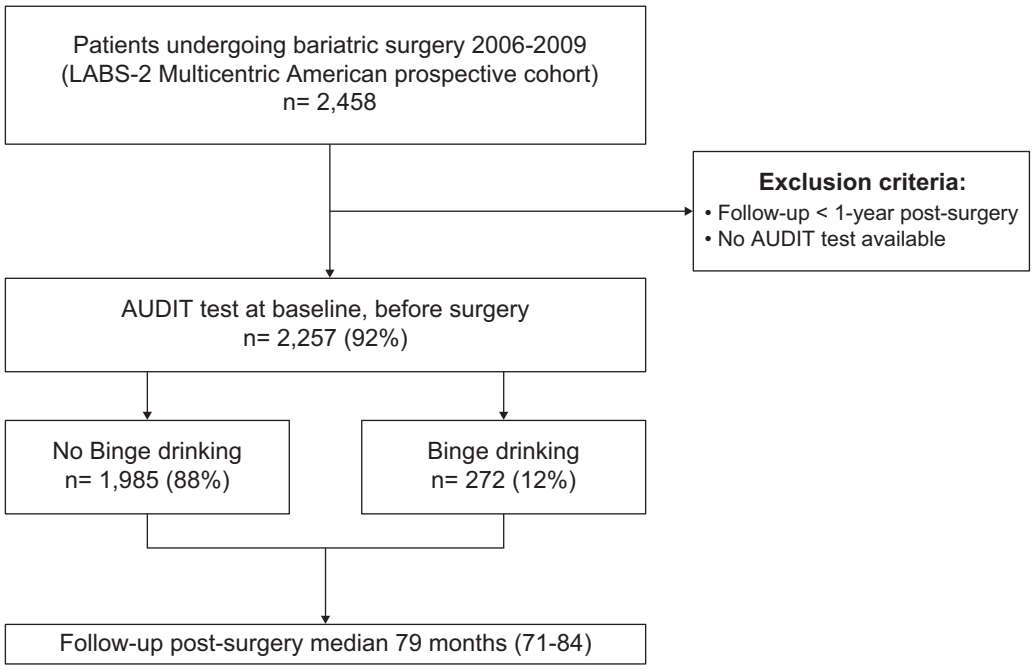

FIGURE 1 Flowchart showing patient selection from the LABS-2 database. Classification into binge drinking or no binge drinking was performed considering the baseline AUDIT test. Abbreviations: AUDIT, Alcohol Disorder Identification Test; LABS-2 Study, Longitudinal Assessment of Bariatric Surgery-2.

TABLE 1 Baseline clinical characteristics and laboratory parameters in both cohorts with and without binge drinking

Characteristics	Binge drinking (n = 272)	No binge drinking (n = 1985)	p
Age (y)	40 ± 10	46 ± 11	< 0.001
Sex, n (%)	—	—	0.020
Female	199 (73)	1572 (79)	—
Male	73 (27)	413 (21)	—
Race, n (%)	—	—	0.050
Hispanic	20 (7)	90 (5)	—
Not Hispanic	252 (93)	1893 (96)	—
Surgery performed, n (%)	—	—	0.979
RYGB	193 (71)	1410 (71)	—
LAGB and others	79 (29)	575 (29)	—
Education level, n (%)	—	—	0.016
Low	47 (17)	470 (24)	—
High	225 (83)	1503 (76)	—
Marital status, n (%)	—	—	0.001
Single	65 (24)	301 (15)	—
Married or living as married	166 (61)	1266 (64)	—
Divorced or separated	39 (14)	359 (18)	—
Widowed	2 (1)	48 (3)	—
Employment status, n (%)	—	—	< 0.001
Employed	218 (81)	1298 (66)	—
Homemaker	11 (4)	92 (5)	—
Disabled	20 (7)	312 (16)	—
Unemployed	11 (4)	86 (4)	—
Retired	6 (2)	143 (7)	—
Other	4 (2)	38 (2)	—
BMI (kg/m^2)	45.4 (41.3–51.1)	46.8 (42.1–52.4)	0.230
MAP (mm Hg)	125 (117–132)	124 (115–133)	0.395
Waist circumference (cm)	130 (121–142)	131 (122–143)	0.793
Smoking, n (%)	23 (9)	73 (4)	< 0.001
Other drugs, n (%)	32 (12)	95 (5)	< 0.001
Sleep apnea, n (%)	110 (40)	979 (49)	0.006
CKD, n (%)	35 (13)	320 (16)	0.180
Diabetes, n (%)	65 (24)	725 (37)	< 0.001
Arterial hypertension, n (%)	160 (60)	1429 (73)	< 0.001
Dyslipidemia, n (%)	63 (27)	615 (38)	0.001
Metabolic syndrome, n (%)	101 (44.1)	899 (57)	< 0.001
Psychiatric medication, n (%)	156 (58)	1075 (55)	0.366
CVD, n (%)	13 (5)	193 (10)	0.003
Glucose (mg/dL)	103.9 ± 38	111 ± 44	0.004
Albumin (g/dL)	4.09 ± 0.4	4.12 ± 0.4	0.247
Platelet count (×10^{-3})	289 ± 71	285 ± 71	0.447
Leukocytes count (×10^{-3})	7.9 ± 2.2	8 ± 3.2	0.988
Bilirrubin (mg/dL)	0.54 ± 0.3	0.55 ± 0.2	0.447
ALT, (U/L)	34 ± 20	32 ± 20	0.108
AST, (U/L)	24 ± 12	25 ± 14	0.506
Alkaline phosphatase (U/L)	77 ± 20	79 ± 24	0.811
AUDIT score medial (IQR)	2 (0–2)	5 (4–5)	< 0.001

Note: Data are presented as mean ± SD, median (quartiles), or frequencies (%). Other surgery procedures include sleeve gastrectomy (n = 55) and biliopancreatic diversion-duodenal switch (n = 17). Psychiatric medication includes treatment for depression and emotional problems.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUDIT, Alcohol Disorder Identification Test; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; LAGB, laparoscopic adjustable gastric band; MAP, RYGB, Roux-en-Y gastric bypass.

the "mice" package in R whenever necessary (m = 5). The statistical analyses were performed using R (v.4.1.3) and the "Tornado" package; SPSS (v.25.0); Graph Pad Prism (v.9.1.1); and sankeymatic.com, statistical packages.

RESULTS

Baseline characteristics

Participants' flowchart is shown in Figure 1. A total of 2257 participants with AUDIT available at the time of bariatric surgery were included. Among them, 12% (n = 272) had BD. Of the 88% (n = 1,985) controls without BD, 3% (n = 67) reported chronic daily alcohol consumption (AUDIT ≥ 8). Baseline characteristics are summarized in Table 1.

Patients with BD were more frequently male (OR: 1.39 [95% CI: 1.05–1.86]), younger (OR: 0.95 [95% CI: 0.94–0.96]), smokers (OR: 2.42 [95% CI: 1.49–3.93]), and consumed other drugs (OR: 2.65 [95% CI: 1.74–4.04]). Participants without BD showed higher rates of metabolic syndrome (OR:1.40 [95% CI: 1.08–1.82]), arterial hypertension (OR:1.79 [95% CI: 1.39–2.33]), diabetes (OR:1.83 [95% CI:1.37–2.46]), dyslipidemia (OR:1.49 [95% CI:1.11–2.00]), CVD (OR: 2.15 [95% CI:

TABLE 2 Eating behaviors and disorders of those with binge drinking versus no binge drinking

Eating behaviors	Binge drinking (n = 272)	No binge drinking (n = 1985)	*p*
Eat breakfast, lunch, and dinner regularly (d/wk), median (IQR)	6 (5-7)	6 (5–7)	0.186
Eat breakfast, lunch, and dinner regularly (6–7/wk), n (%)	99 (37)	826 (42)	0.101
Fast food meals/wk, median (IQR)	2 (1–4)	2 (0–4)	0.008
Eat fast food regularly (≥ 4/wk), n (%)	87 (32)	490 (25)	0.015
Binge eating, n (%)	98 (36)	586 (29)	0.026
Meals/snacks per day, n (%)	—	—	0.110
1–4	100 (37)	835 (43)	—
5–6	136 (51)	850 (44)	—
≥ 7	32 (12)	245 (13)	—
Eat in restaurant regularly (6–7/wk), n (%)	40 (15)	240 (13)	0.297
Restaurant meals/week, median (IQR)	2 (1–4)	2 (0–4)	0.117
Frequency of eating large amounts, n (%)	—	—	0.965
Less than once/week	68 (48)	460 (48)	—
Once/week	29 (21)	185 (20)	—
More than once/week	37 (26)	269 (28)	—
Nearly every day	7 (5)	41 (4)	—
Frequency of eating when not hungry, n (%)	—	—	0.023
Rarely	43 (16)	456 (23)	—
Occasionally	98 (36)	720 (37)	—
Frequently	94 (35)	584 (30)	—
Nearly every day	36 (13)	204 (10)	—
Frequency of eating when uncomfortably full, n (%)	—	—	0.001
Rarely	60 (22)	650 (33)	—
Occasionally	114 (42)	758 (39)	—
Frequently	78 (29)	422 (21)	—
Nearly every day	19 (7)	144 (7)	—
Night eating syndrome, n (%)	43 (16)	282 (14)	0.520
Working late nights interfere with meals, n (%)	67 (25)	380 (19)	0.036

Note: Data are presented as median (quartiles) or frequencies (%).

1.21–3.82]), and sleep apnea (OR: 1.43 [95% CI: 1.11–1.85]). No differences were observed between groups regarding anthropometric measurements and liver tests.

Regarding sociodemographic characteristics, individuals with a high education level who are single and currently employed were more likely to belong to the BD group (Table 1). Additionally, patients with BD had a higher prevalence of binge eating (OR: 1.35 [95% CI: 1.04–1.76]) and more frequent episodes of eating fast food per week (OR: 1.41 [95% CI: 1.07–1.85]). BD was associated with several eating behaviors, including eating when not hungry, when uncomfortably full, or working late night shifts that disrupt regular meals (Table 2).

Pattern of alcohol consumption during follow-up

Up to 2079 (92%) patients had at least 1 AUDIT questionnaire completed during follow-up, of whom n = 46 died. The prevalence of BD after surgery was 23% (n = 482), twice as much as before surgery. Among patients with BD at the time of surgery, 71% (n = 177) continued BD, and 1.6% (n = 4) reported chronic daily alcohol consumption (AUD without BD) during follow-up. Within participants without alcohol consumption at the time of surgery, 17% (n = 305) reported BD and 1.8% (n = 32) AUD during follow-up (Figure 2). BD at the time of surgery was associated with a higher risk of BD after surgery (OR = 10.49 [95% CI: 7.86–14.00]).

Histological evaluation

A total of 271 patients underwent liver biopsy during the bariatric procedure. Of these, liver appearance was normal in 53% (n = 143), and the leading indication for liver biopsy was per study protocol (64%). Tissue samples were mainly obtained from the left lobe (80%) and had a median biopsy length of 13 (9–17) mm. Overall, steatotic droplets predominantly located in

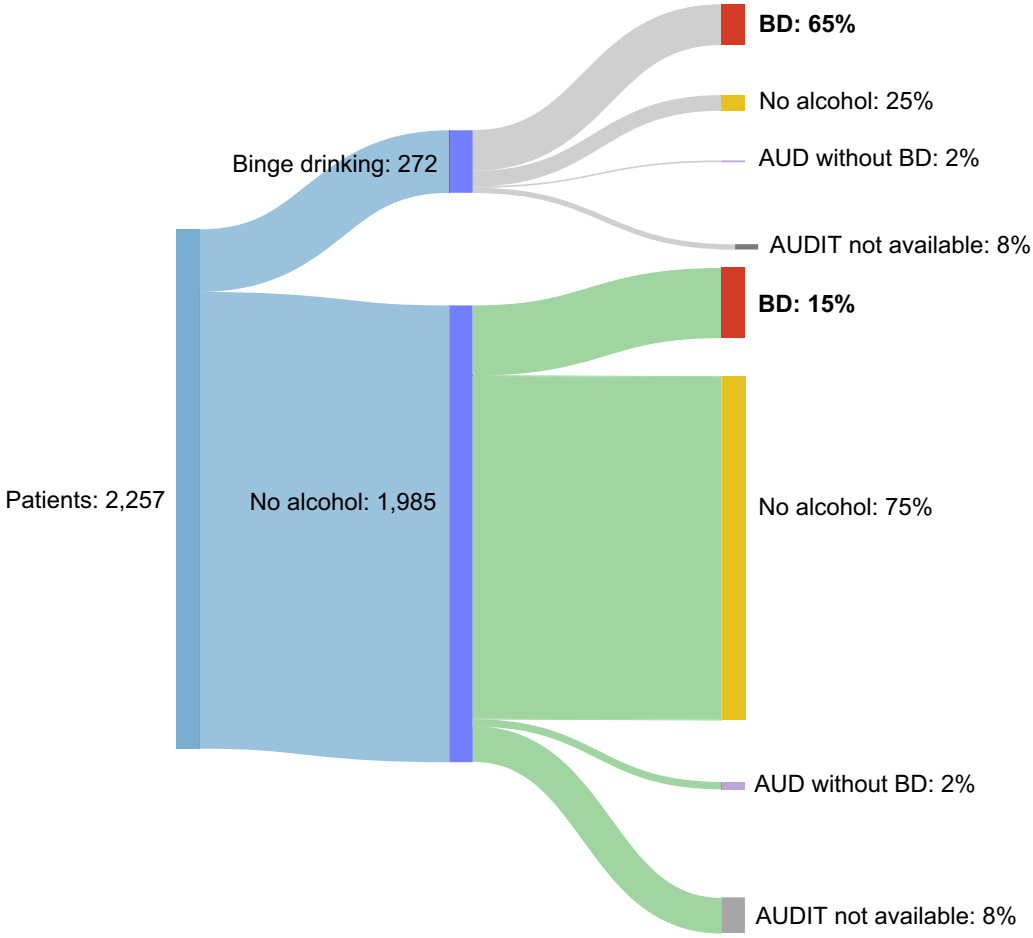

FIGURE 2 Sankey diagram of a pattern of alcohol consumption at the time of surgery and during follow-up in all the patients included. Data are presented as numbers and proportions (%). Abbreviations: AUD, alcohol use disorder; AUDIT, alcohol disorder identification test; BD, binge drinking.

zone 3 (66%), 31% (n = 84) showed features of steatohepatitis, and 48% (n = 131) had any stage of fibrosis. The prevalence of patients with BD with histological information was 12% (n = 33). Histological differences between patients with and without BD are summarized in Supplemental Table S2, http://links.lww.com/HC9/A997. Both groups shared similar histological features except for iron deposits (Supplemental Figure S1, http://links.lww.com/HC9/A997). Perls staining was performed in 184 patients (68%). BD had a higher iron overload (OR: 3.00 [95% CI: 1.25–7.21]), mainly due to mesenchymal deposits in the sinusoidal cells.

Survival analysis

Median follow-up after bariatric surgery was 79 months (71–84). During this study period, 60 patients died, mainly due to CVD (23%) and neoplasms (19%) (Supplemental Table S2, http://links.lww.com/HC9/A997). Mortality was seen primarily in participants with Roux-en-Y gastric bypass (82%). BD at the time of surgery was associated with higher long-term mortality (5.1% vs. 2.3%, $p = 0.007$; Figure 3A).

The cause of death differed substantially between patients with and without BD (Figure 3B). The most common causes of death in the BD group were neoplasms (29%), suicide (21%), respiratory (21%), and liver disease (14%). Suicide prevalence in BD group was 1.1% (n = 3/272), significantly higher compared to previously described rates of 0.3% in meta-analysis of bariatric surgery cohorts[27] and 0.02% in the US general population, with the same age, sex, race distribution, and time period (Supplemental Figure S2, http://links.lww.com/HC9/A997).[28] Participants with BD at the time of surgery had significantly more deaths due to suicide ($p = 0.015$), liver disease ($p = 0.020$), neoplasms ($p = 0.034$), and respiratory ($p = 0.025$). Supplemental Table S3, http://links.lww.com/HC9/A997, shows the subdistribution HR for the main causes of mortality.

Predictors of mortality and sensitivity analysis

Univariate and multivariate analysis of the baseline factors predicting mortality at the time of surgery is shown in Table 3. Final adjusted multivariate model included the following variables: BD (HR: 3.21 [95%

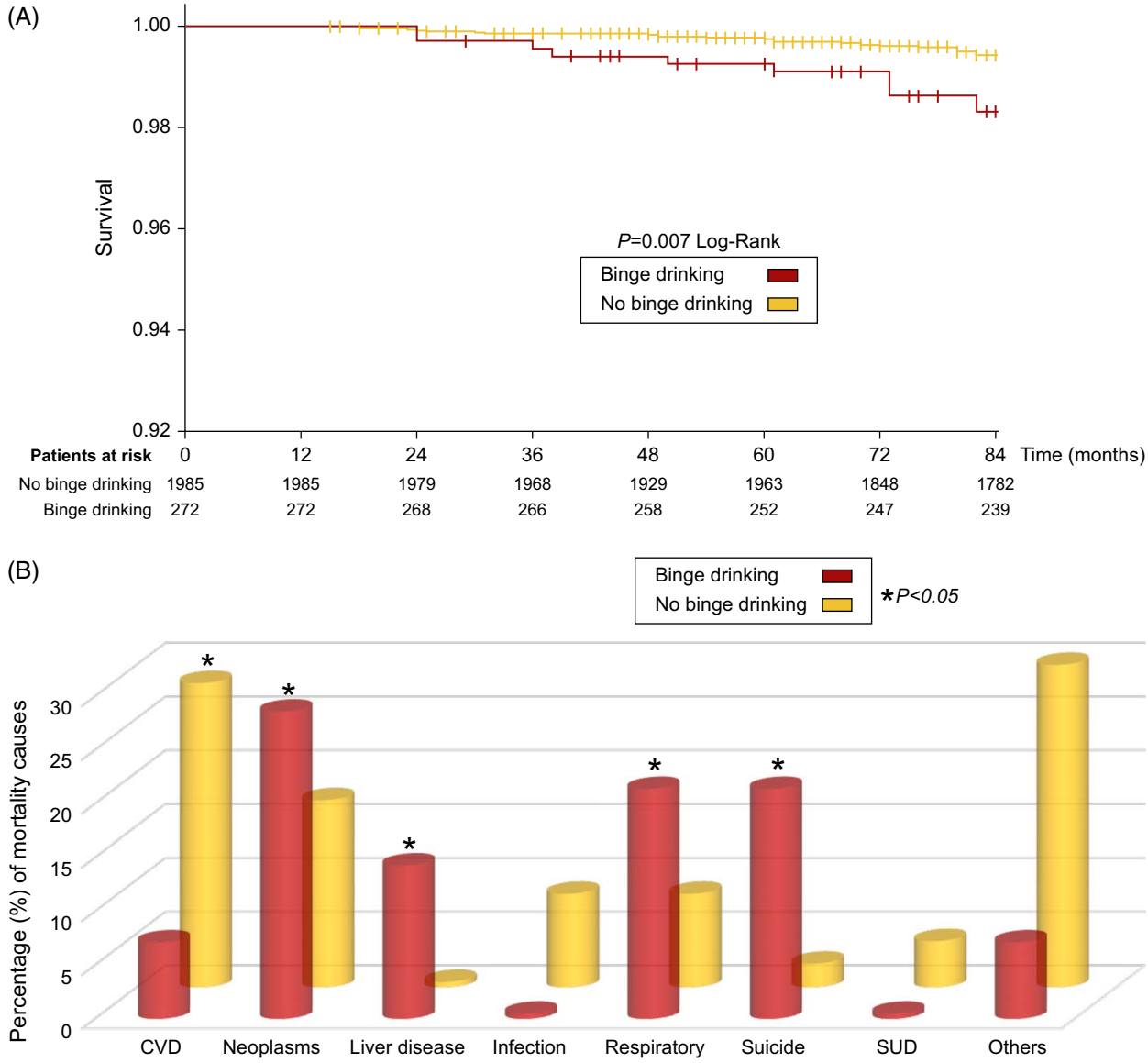

FIGURE 3 (A) Kaplan-Meier plot showing the overall cumulative probability of survival in patients with binge drinking versus no binge drinking patients. The probability of survival was calculated according to KM survival analysis and compared by Log-rank. (B) Causes of mortality in patients with binge drinking versus no binge drinking. Patients with no binge drinking had a higher prevalence of mortality due to cardiovascular disease ($p = 0.030$). Patients with binge drinking had a higher prevalence of mortality due to liver disease ($p = 0.020$), suicide ($p = 0.015$), neoplasms ($p = 0.034$), and respiratory ($p = 0.025$). Abbreviations: CVD, cardiovascular disease; SUD, substances use disorders.

CI: 1.67–6.18]), age (HR: 1.03 [95% CI: 1.01–1.06]), diabetes (HR: 1.84 [95% CI: 1.05–3.22]), chronic kidney disease (HR: 2.05[95% CI: 1.17–3.62]), and sleep apnea (HR: 1.99 [95% CI: 1.11–3.57]) (Figure 4). All of these baseline factors were independently associated with higher long-term mortality after bariatric surgery, with BD showing the highest HR (Supplemental Figure S3, http://links.lww.com/HC9/A997). The multivariate Cox model obtained a C-index of 0.759 for mortality risk prediction. After internal validation, the model showed robustness in the results with a C-index of 0.734 and a slope of 0.823.

The Cox-time–depending analysis included patients with available information during follow-up (n = 2,079). BD before and after surgery was independently associated with mortality (HR = 2.71 [95% CI: 1.24–5.92]) with a C-index of 0.616 and a slope of 0.962 (Supplemental Table S4, http://links.lww.com/HC9/A997). There was a total of 7 deaths among patients with BD before and after surgery, n = 2 due to liver disease. The sensitivity analysis illustrated with the tornado plot shows how BD before and after surgery produces the largest range of mortality (Figure 5).

In the subpopulation with liver biopsy, histological features were analyzed as predictors of mortality

TABLE 3 Baseline predictors of mortality after bariatric surgery

Characteristics	Univariate analysis	*p*	Multivariate analysis	*p*
Sex (female)	1.46 (0.83–2.55)	0.191	—	—
Surgery (RYGB)	1.77 (0.92–3.41)	0.080	—	—
Education level (low)	1.74 (1.01–2.99)	0.051	—	—
FIB-4	1.09 (0.99–1.21)	0.082	1.04 (0.87–1.25)	0.631
Age at surgery	1.06 (1.03–1.08)	< 0.001	1.03 (1.01–1.06)	0.019
BMI (kg/m^2)	1.03 (0.99–1.06)	0.110	—	—
Binge drinking	2.24 (1.23–4.07)	0.001	3.21 (1.67–6.18)	0.001
AUD	1.71 (0.94–3.12)	0.082	0.99 (0.13–7.76)	0.991
Smoking	1.5 (1.05–1.77)	0.024	1.53 (0.90–2.60)	0.111
Ilicit drugs	1.24 (0.45–3.41)	0.682	1.20 (0.41–3.45)	0.736
Sleep apnea	2.78 (1.58–4.87)	< 0.001	1.99 (1.11–3.57)	0.021
CKD	2.92 (1.72–4.96)	< 0.001	2.05 (1.17–3.62)	0.014
Diabetes mellitus	2.81 (1.68–4.71)	< 0.001	1.84 (1.05–3.22)	0.033
Arterial hypertension	1.49 (0.80–2.75)	0.211	—	—
Dyslipidemia	2.77 (1.35–5.68)	0.010	—	—
Metabolic syndrome	2.49 (1.33–4.66)	0.011	—	—
CVD	2.29 (1.20–4.42)	0.012	—	—

Note: Data are presented as HR and CI 95%.
Internal validation after bootstrap (500 samples); C-index 0.734; slope 0.823.
Abbreviations: AUD, alcohol use disorder; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; FIB-4, fibrosis score 4; RYGB, Roux-en-Y gastric bypass.

(Supplemental Table S5, http://links.lww.com/HC9/A997). In the multivariable model, adjusted by age, sex, and surgical procedure, the following histological features were retained as independent predictors of mortality: fibrosis (HR: 3.76 [95% CI: 13.63–1.038]), portal inflammation (HR: 5.06 [95% CI: 15.35–1.67]), and mesenchymal iron overload (HR: 4.72 [95% CI: 22.23–1.00]).

DISCUSSION

The present study reveals a high prevalence and clinical impact of BD in subjects undergoing bariatric surgery. BD occurs at the time of surgery in 12%, particularly in young and single males with a high education level, consumers of cigarettes and other drugs, and with binge eating disorders. Importantly, BD prevalence increases up to 23% after surgery. Patients with BD have a higher risk of long-term mortality after surgery.

Despite the well-known beneficial effects of bariatric surgery, an increased risk of AUD after surgery has been described.[2,4] Clinicians are usually unaware of this risk, probably due to under-reported alcohol consumption. Alcohol is the most frequently consumed substance among young adults, including those with severe obesity.[29] Furthermore, when young adults

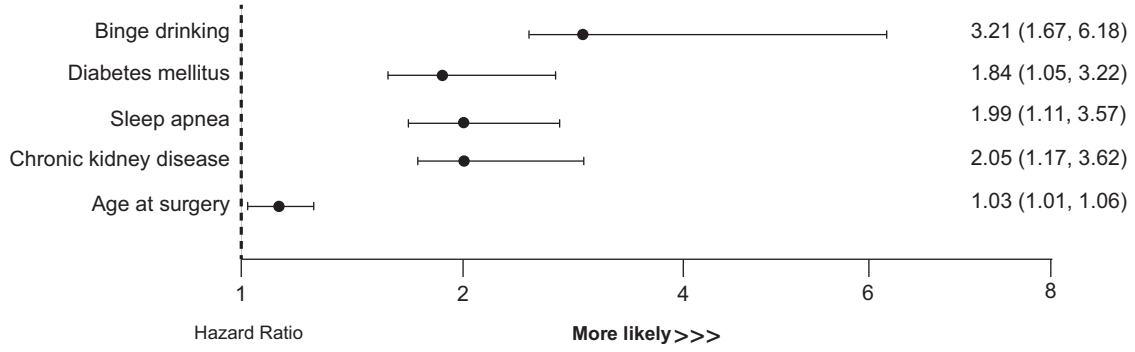

FIGURE 4 Predictive factors of mortality after bariatric surgery. The final adjusted multivariate Cox model identified the significant main factors at the time of surgery that were independent predictors of mortality. All the results are expressed as an HR with a 95% CI. The multivariate Cox model, after internal validation, showed robustness of the results with a C-index of 0.734 and a slope of 0.823.

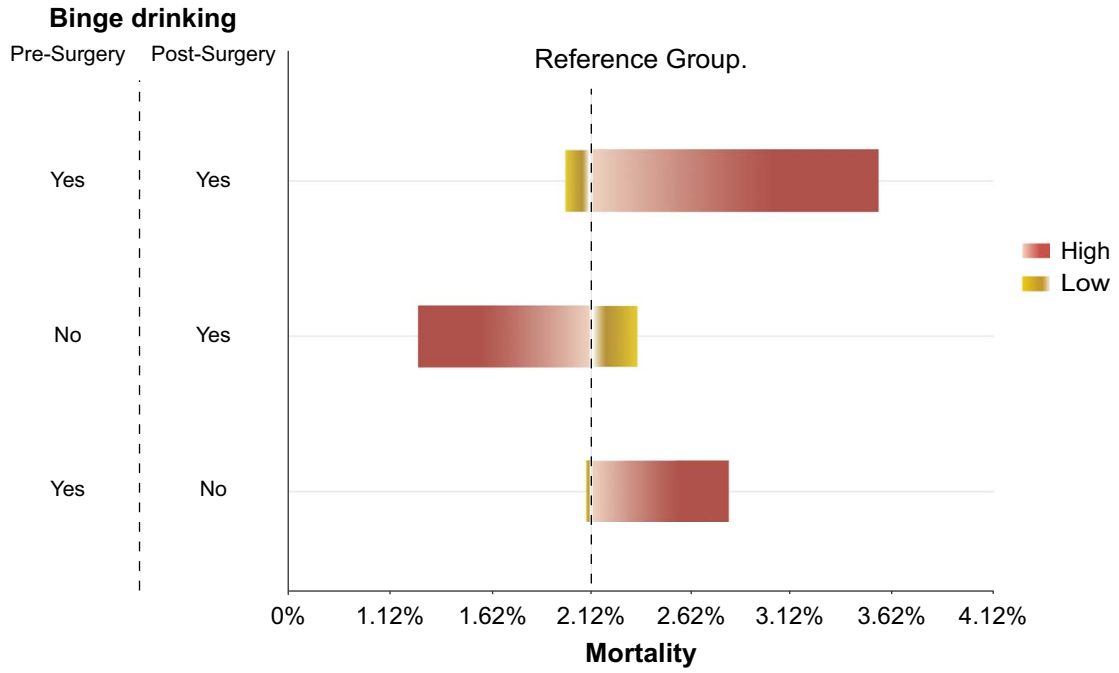

FIGURE 5 Sensitivity analysis of mortality. The sensitivity analysis has been performed using logistic regression analysis and is illustrated with a tornado plot. The specific pattern of binge drinking at baseline and follow-up on the *y*-axis and the range of the outcome mortality on the *x*-axis. The absence of binge drinking at baseline and during follow-up was taken as the reference group represented by the dashed line. In the tornado chart, each bar represents the range of the outcome. Binge drinking before and after surgery produces the largest range of mortality, and it is at the top of the graphic. The other 2 bars become smaller toward the bottom of the chart. As for the colors of the bars, the red color means the result value was produced by the upper limit (high), and the yellow light color means the result value was produced by the lower limit (low).

consume alcohol, they typically drink more per occasion than adults (ie, BD), and 16% also consume other drugs.[30,31] Alcohol use, and BD in particular, are primary contributors to the leading cause of death and/or unintentional injury (including attempting suicide) in young adults.[32] Among patients with severe obesity, both binge behaviors (drinking and eating) frequently co-exist. Actually, it has been postulated that binge eating disorder is a precipitating factor in the onset and aggravation of excessive alcohol consumption. On the other hand, alcohol consumption can also lead to unhealthy and uncontrollable eating behavior.[33] Given these behavioral similarities, we considered it clinically relevant to evaluate BD's prevalence before bariatric surgery and recognize its impact during long-term follow-up.

The study population was obtained from the LABS-2 database. In this cohort, the prevalence of AUD at baseline was previously reported at 7%, which is almost half the prevalence of BD at the time of surgery in our study (12%).[2,4] Different percentages reflect that BD is a bigger problem in young adults undergoing bariatric surgery, and special attention should be paid to identify and treat them. Our results align with other studies of bariatric cohorts reporting a rate of 14% BD prior to surgery.[34] In addition, risk factors associated with BD were young males, high education level, single, currently employed, smoking, and consumption of other drugs. Other studies share these risk factors, identifying patients in whom a careful evaluation should be performed and, if appropriate, referred for substance use disorder treatment.[34] Interestingly, these risk factors associated with presurgery BD are shared by those reported to increase the incidence of postsurgery AUD symptoms.[2] Contrary to low education level and unfavorable socioeconomic position, which has been previously associated with NAFLD, high educational level and employment were associated with BD.[16]

Recently, a relationship between addictive behaviors, such as impulsive alcohol and food consumption, has been described in patients undergoing bariatric surgery.[35] These addictive behaviors arise in individuals with specific psychological, cognitive, and social characteristics that make them more vulnerable to developing binge episodes. The LABS-2 cohort has a substantial proportion of patients with problematic eating behaviors, especially binge eating. Higher odds of having a binge eating disorder are related to college degree, AUD symptoms, taking psychiatric medications, and depressive symptoms.[19] The relationship between alcohol and eating can be partially explained by our results, which show that BD, rather than AUD, is the condition behind the binge behavioral disorders association. This hypothesis is supported by previous studies showing that binge eating predicts incident alcohol use after bariatric surgery.[36] In our study, BD was also associated with other eating behaviors and disorders, including eating fast food. Both impulsive

alcohol and food consumption have been associated with depressive symptomatology, anxiety, substance abuse, and suicide attempts.[37] On the other hand, patients without BD had higher rates of metabolic syndrome, arterial hypertension, diabetes, dyslipidemia, sleep apnea, and CVD, all of which are common metabolic risk factors.[38]

In the present study, we also found that 12% of patients with liver biopsy performed during surgery also had BD disorder. Iron overload can be present in both NAFLD and alcohol-associated liver disease.[39] Patients with BD had a higher iron overload, mainly due to mesenchymal deposits in the sinusoidal cells. This association can be related to several mechanisms: (1) increased iron absorption and dysregulation of iron-related proteins mediated by alcohol consumption[40]; (2) ethanol exposure promoting iron absorption by downregulating hepcidin expression, and iron uptake by upregulating the expression of transferrin receptor in hepatocytes; (3) ethanol upregulating iron-dependent cell death namely ferroptosis[40]; (4) systemic inflammation in response to BD.[41]

In the LABS-2 cohort, it was previously shown that AUD was not independently associated with post-operative mortality.[4,11] Despite these previous results, we evaluated mortality and BD. Strikingly, among the 60 reported deaths, 23% had BD. The presence of BD at the time of surgery was associated with a higher risk of BD during follow-up and increased long-term mortality (Figure 5). Other factors independently associated with mortality were age, diabetes, chronic kidney disease, and sleep apnea. These metabolic factors have been previously described, but BD emerges as a novel predictor of mortality.[11,42] The leading causes of death in patients with BD were neoplasms, respiratory and liver disease, and suicide. The distribution of cause-specific death in these subjects is very similar to that in patients with alcohol-associated liver disease.[43] Although we are aware of the low number of deaths in our cohort, they allow us to suggest that the pattern of consumption and the effect of surgery on alcohol metabolism influence the degree of liver damage[5] and the existence of psychiatric comorbidity can increase the risk of suicide.[44] A notable finding is the significantly higher prevalence of suicide in patients with BD compared to other US series of bariatric patients[27] and the general population. These results can be explained from a psychopathological point of view since patients with binge behaviors (BD and binge eating) have predisposition to act impulsively, with an increase in the likelihood of asocial behaviors, intentional injuries, and suicide attempts.[45,46] In line with other series, CVD was the leading cause of mortality in patients without BD.[47] Our study implies the need to increase awareness and an adequate evaluation of mental health disorders related to alcohol in the setting of bariatric procedures before and after surgery.

Recent studies indicate that BD is associated with a rapid passage of pathogen-associated molecular patterns such as lipopolysaccharide to the circulation, leading to systemic, brain, and hepatic inflammation.[41,48] The fact that bariatric surgery increases intestinal permeability and favors bacterial overgrowth[49] could explain the increased susceptibility to the deleterious effects of BD among these patients.

The study has several limitations. Due to its design, there is limited capacity to verify the data quality included by all the participating centers. Although many variables were considered in the models assessing presurgery factors related to postoperative mortality, it is possible that some were missed or not always available in the clinical database. Although the availability of liver biopsies was limited and subject to the surgeon's decision during bariatric surgery, the number of samples analyzed allows for inferring the probable pathophysiological mechanisms involved in the liver damage mediated by the pattern of alcohol consumption. Another limitation is that BD can be under-reported and under-recognized, particularly in patients being treated for medical conditions unrelated to alcohol use; however, the systematical assessment of alcohol consumption with AUDIT can help to minimize this limitation. Likewise, the type of alcohol consumed by the patients was not recorded to study the effects of different types of alcohol, which is an aspect to be clarified in future studies. Finally, the number of deaths was small and underpower for some specific causes.

In conclusion, this study shows a high prevalence of BD in patients undergoing bariatric procedures, which increases mortality risk after surgery due to suicide and liver disease. Given that BD is associated with binge eating, further studies should examine the role of psychological and pharmacological interventions and whether presurgery treatment of alcohol use and eating disorders can improve long-term outcomes.

AUTHOR CONTRIBUTIONS

Edilmar Alvarado-Tapias, David Martí-Aguado, Josepmaria Argemi, and Ramon Bataller: study concept and design. Edilmar Alvarado-Tapias, David Martí-Aguado, Concepción Gómez-Medina, Carlos Fernández-Carrillo, Meritxell Ventura-Cots, Ana Clemente, Rubén Osuna-Gómez, Clara Alfaro-Cervelló, Joaquin Cabezas, Justyna Szafranska, Albert Guinart-Cuadra, and Anna Brujats: data acquisition. Edilmar Alvarado-Tapias, David Martí-Aguado, Josepmaria Argemi, and Ramon Bataller: analysis and interpretation of data. Andreu Ferrero-Gregori: statistical analysis. Edilmar Alvarado-Tapias and David Martí-Aguado: drafting of the manuscript. Edilmar Alvarado-Tapias, David Martí-Aguado, Concepción Gómez-Medina, Andreu Ferrero-Gregori, Justyna Szafranska, Anna Brujats, Rubén Osuna-Gómez, Albert Guinart-Cuadra, Clara Alfaro-Cervelló, Elisa Pose, Meritxell Ventura-Cots, Ana Clemente, Cynthia Contreras, Joaquin Cabezas, Hugo López-Pelayo,

JuanPablo Arab, Josepmaria Argemi, and Ramon Bataller: critical manuscript revision. All authors approved the final version of the article: Edilmar Alvarado-Tapias, David Martí-Aguado, Concepción Gómez-Medina, Andreu Ferrero-Gregori, Justyna Szafranska, Anna Brujats, Rubén Osuna-Gómez, Albert Guinart-Cuadra, Clara Alfaro-Cervelló, Elisa Pose, Meritxell Ventura-Cots, Ana Clemente, Cynthia Contreras, Joaquin Cabezas, Hugo López-Pelayo, JuanPablo Arab, Josepmaria Argemi, and Ramon Bataller.

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CONFLICTS OF INTEREST

Ramon Bataller received lectures fee from Abbvie and Gilead. Hugo López-Pelayo received funds for training from Lundbeck and for elaborating training materials from Advanz Pharma. Joaquin Cabezas consults, advises, is on the speakers' bureau, and received grants from Gilead. He is on the speakers' bureau and received grants from Abbvie. Ramon Bataller is a recipient of NIAAA grants U01AA021908, U01AA020, and NIDDK P30DK120531821. Meritxell Ventura-Cots, Carlos Fernández-Carrillo, Edilmar Alvarado-Tapias, and Ana Clemente are recipients of a scholarship grant for study extension abroad, sponsored by the Spanish Association for the Study of the Liver (AEEH). Meritxell Ventura-Cots is recipient of a Joan Rodes award from the ISCII (JR19/00015) and the PI22/01770 grant from the ISCIII—Fondos Feder. Edilmar Alvarado-Tapias is a recipient of a Joan Rodes award from the ISCII (JR20/00047) and the PI21/01995 grant from the ISCIII- Fondos Feder. David Martí-Aguado is a recipient of the Joan Rodes award ISCIII (JR22/00002) and a scholarship grant for study extension abroad, sponsored by the University of Valencia (UV-RI_MID-1528578). Elisa Pose is a recipient of the PI22/00910 grant from the ISCIII—Fondos Feder. Josepmaria Argemi is a recipient of the PI20/01663 grant from the ISCIII- Fondos Feder and an award from the "Fundación Echebano" (Pamplona, Spain). Hugo López-Pelayo is a recipient of the PI20/00760 grant from the ISCIII—Fondos Feder, 2020I004 grant from Plan Nacional sobre Drogas, and 101045870 from DG Justice-European Commission. The remaining authors have no conflicts to report.

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