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ORIGINAL ARTICLE

The Clinical Relevance of Prior Metabolic and Bariatric Surgery in Alcohol-Related Liver Disease in a Nationwide Belgian Liver Transplant Population

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ABSTRACT

Background and Aims: Patients with a history of metabolic and bariatric surgery (MBS) are susceptible to developing alcohol use disorder. Outcome after transplantation for alcohol-related liver disease (ALD) has not been studied in-depth.

Methods: We included adult patients who underwent a liver transplantation (LT) in Belgium between 1 January 2013 and 31 December 2022 for ALD. We captured all patients with a history of MBS prior to developing ALD, and included non-MBS patients for comparison.

Results: We identified 39 patients who underwent MBS before developing ALD, and included 443 non-MBS patients with an LT for ALD as controls. The median time between MBS and diagnosis of severe liver disease was 7.2 years. MBS patients were 9 years younger at the time of transplantation ($p < 0.001$). Pre-LT hepatocellular carcinoma was more prevalent in the non-MBS group ($p < 0.001$), while severe bacterial infections occurred more frequently in those with prior MBS. Importantly, patients with MBS had a lower survival after LT in age- and sex-adjusted Cox regression analysis (HR 2.205, $p = 0.023$). Liver disease was listed in

Abbreviations: ALD, Alcohol-related liver disease; AUD, Alcohol use disorder; ELTR, European liver transplant registry; HCC, Hepatocellular carcinoma; LT, Liver transplantation; MASLD, Metabolic dysfunction-associated steatotic liver disease; MBS, Metabolic and bariatric surgery; MELD, Model for end-stage liver disease; RYGB, Roux-en-Y gastric bypass; SG, Sleeve gastrectomy.

70.0% versus 13.3% of patients as the main cause of death. Liver-related mortality was linked to alcohol use relapse post-LT, with significantly more MBS patients experiencing relapse (30.8% vs. 13.3%, $p = 0.003$).

Conclusion: Following MBS, excessive alcohol use can progress to end-stage ALD and need for LT. These patients present at a younger age, with more signs of hepatic decompensation, and can be at a higher risk for post-LT mortality, especially liver-related death.

1 | Introduction

The global prevalence of alcohol use disorder (AUD) is 5.1%, with the highest levels in Europe and the Americas [1]. Excessive alcohol consumption is a well-established risk factor for numerous diseases. As such, AUD was the seventh leading risk factor leading to premature death [2]. At least 35% of patients with AUD will develop alcohol-related liver disease (ALD), and alcohol is responsible for up to 60% of cirrhosis cases in Europe and the Americas [1, 3].

Obesity is another major health burden worldwide, affecting 13% of the world population, and is associated with cardiometabolic diseases such as hypertension, diabetes mellitus and metabolic dysfunction-associated steatotic liver disease (MASLD) [4]. Despite breakthroughs in the pharmacological treatment of obesity, metabolic and bariatric surgery (MBS) remains the most effective treatment to obtain durable long-term weight loss, thereby reducing mortality compared to age-, sex- and BMI-matched controls [5]. Many different procedures exist, with the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) being by far the most commonly performed in recent years.

Changes in food preferences, food reward perception and gut hormone signalling are major contributors to the effects of MBS [6]. Patients voluntarily restrict consumption of calorie-dense foods following RYGB [7]. Studies in humans and animals have indicated altered responses to food rewards after MBS, with changes in the prefrontal cortex, striatal area and signalling via gut-derived orexigenic and anorexigenic hormones such as ghrelin and glucagon-like peptide-1 [8]. These same mechanisms are now harnessed to treat obesity pharmacologically.

In contrast to reduced food craving following MBS, multiple studies have demonstrated that these patients are at increased risk for AUD [9–12]. Risk factors are a younger age at surgery, and a higher pre-MBS alcohol consumption [10]. Interestingly, comparative studies show a doubling of the risk for AUD following RYGB, while SG tends to decrease the risk of new-onset AUD [13, 14].

AUD following MBS can conceivably promote the progression of ALD. One precipitating factor might be that MBS alters the pharmacokinetics of alcohol digestion and uptake [6]. Specifically, blood alcohol concentrations increased faster and peaked higher, with a higher area under the curve for alcohol concentration over time, in patients who had undergone RYGB compared to controls [15, 16]. The effects of two standard beverages were comparable to those of four drinks in controls, and might be considered equivalent to an episode of binge drinking [17], which can affect liver health.

Still, there is a relative paucity of data on ALD post-MBS. We have previously reported that hospitalised patients with ALD and prior MBS are more prone to develop acute-on-chronic liver disease, resulting in a lower transplant-free survival [18]. Furthermore, the proportion of patients presenting with alcohol-related hepatitis who have a history of MBS seems to steadily increase, as reported in a tertiary Belgian centre [19]. We have also published that ALD in MBS patients can necessitate liver transplantation (LT) [20]. A recurring finding from these studies is that MBS patients with ALD are predominantly female, and present with severe liver disease at a significantly younger age.

However, an important limitation of these studies was their monocentric design, resulting in a small sample size, limiting generalizability. Therefore, in this study, we aimed to capture all patients transplanted for ALD in Belgium in a 10-year timeframe, through a nationwide cohort in collaboration with the European Liver Transplant Registry (ELTR). Patient characteristics, disease severity and outcomes were compared to a large group of patients who received a LT for ALD without a history of MBS.

2 | Patients and Methods

2.1 | Study Design

In this ELTR-endorsed study, adult patients who underwent a single-organ LT for ALD in Belgium between 1 January 2013 and 31 December 2022 were evaluated for inclusion. We captured all patients with a history of MBS prior to developing ALD, and included a convenience sample of non-MBS patients from the same cohort as for comparison. Controls were recruited from the participating centres proportionally to the number of MBS patients identified in those centres. MBS patients and controls were not matched for age and sex, as we aimed to evaluate differences in these demographic characteristics between the two patient populations. The ALD control group included patients with mixed ALD/MASLD; this subgroup was studied separately in a secondary analysis. We refrained from using the term metALD [21] for patients with mixed ALD/MASLD, as both the alcohol intake and metabolic profile fluctuated over time. A second cohort of MASLD patients were also included for comparison. Patients were followed up until June 2024.

ALD was suspected upon documentation of regular consumption of > 21 alcoholic drinks per week for males and > 14 for females in the presence of clinical, biochemical and/or radiological signs of liver disease. The main exclusion criteria were the presence of another liver disease potentially contributing to

Summary

- Surgical procedures to promote weight loss, including the gastric bypass, are known to increase the risk of alcohol overuse and alcohol use disorder.
- In this study, we show that these patients can develop alcohol-related liver disease which necessitates a liver transplantation.
- Notably, we show that these patients have a worse prognosis after transplantation.

listing for LT (viral or autoimmune hepatitis, hemochromatosis, cholestatic liver disease, Wilson's disease, etc.), except for MASLD. For patients with a history of MBS, those who had signs or symptoms of advanced liver disease prior to or at the time of MBS were excluded. Only data at the time of first LT were included.

The study protocol was approved by the ELTR (31/03/2020), the Ghent University Hospital Ethical Review Board (06/04/2021, reference BC-09379), and subsequently by the ethical committees of the participating centres. The study was conducted according to the principles of the Declaration of Helsinki.

2.2 | Data Collection

We recorded demographic, biochemical and clinical data, comorbidities, cause of death and date of death or last follow-up. In patients with prior MBS, weight at surgery, the timeline relative to liver disease diagnosis, and type of procedure were also recorded. Alcohol consumption during drinking periods was based on self-reporting. Data were collected from the ELTR database, supplemented with standardised retrospective data retrieval from the electronic medical records at each centre. Because of this, there were no missing data in key variables including diagnosis, history of MBS, alcohol use relapse and date of death/last follow-up. Data were stored and transferred in REDCap.

2.3 | Statistical Analysis

Continuous variables are presented as median (interquartile range (IQR)) and were analysed using the Mann–Whitney *U* or Kruskal–Wallis test. Categorical variables are presented as *n* (%) and were analysed by the chi^2 or Fisher's exact test. Post-transplant survival was modelled using Cox regression analysis with prior MBS, sex, age at transplantation ± diabetes as covariates. The Cox regression graphs were modelled with the age set at 60, the median of the study population. A sensitivity analysis was performed whereby the main analyses were repeated after excluding patients transplanted for ALD + HCC. A two-tailed p value < 0.05 was considered statistically significant. Statistical analysis and graphical presentation were performed using SPSS 29.0 (SPSS Software, IBM Corp., NY, USA) and GraphPad Prism 9.5 (GraphPad Software Inc., Boston, USA).

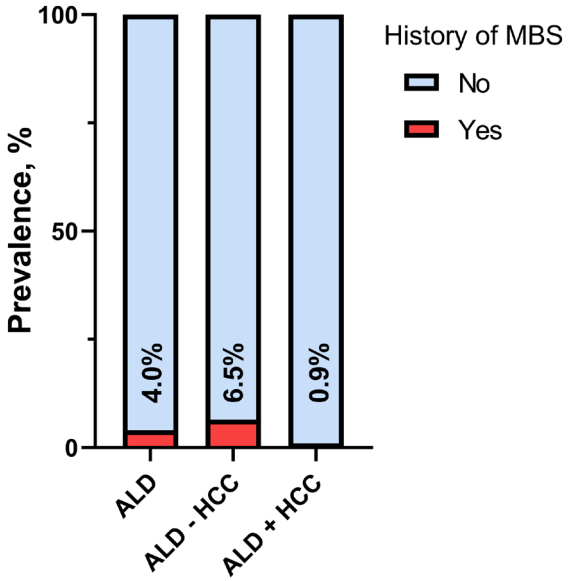

FIGURE 1 | The prevalence of prior MBS in the Belgian ALD transplant population stratified by whether concomitant HCC was present.

3 | Results

3.1 | Patient Characteristics

We identified 39 patients who underwent MBS before developing ALD, and subsequently received a LT at a Belgian centre between 2013 and 2022. The median time between MBS and diagnosis of severe liver disease was 7.2 years. RYGB was by far the most commonly performed surgical procedure (82.1%).

We collected data from 443 non-MBS patients with an LT for ALD as controls, out of a total of 930 non-MBS patients who were transplanted for ALD in Belgium during the study period. Thus, the prevalence of prior MBS in the total Belgian sample of LT for ALD was 4.02% (39/969) (Figure 1). There was marked regional variation in prevalence however, with 7.18% and 1.63% of patients being transplanted in Flanders and Brussels/Wallonia having a history of MBS, respectively.

The demographic and clinical patient characteristics are displayed in Table 1. As in previous studies, patients with prior MBS were significantly younger compared to the concurrent cohort (median 53 vs. 62 years, $p < 0.001$), and the proportion of women was significantly higher than in the non-MBS group (48.7% vs. 18.1%, $p < 0.001$). Body weight at time of listing did not differ between both groups ($p = 0.208$). Alcohol consumption per week, during drinking periods, was equal between both groups ($p = 0.956$). Data on the duration of AUD were not available in our dataset.

Liver function was impaired to a greater degree in those having undergone weight loss surgery, as evidenced by an increased MELD score (median 20 vs. 15, $p < 0.001$). As such, patients with prior MBS spent less time on the waiting list (median 43 vs. 144 days, $p < 0.001$), and the time between diagnosis and listing was shorter as well (median 12 vs. 19 months, $p = 0.017$)

TABLE 1 | Characteristics of patients transplanted for alcohol-related liver disease.

Baseline characteristic	No history of MBS ($n=443$)	History of MBS ($n=39$)	p
Age at transplantation, year	62 (57–66)	53 (45–60)	**<0.001**
Sex, female	80 (18.1)	19 (48.7)	**<0.001**
MELD score at listing	15 (10–22)	20 (14–25)	**0.001**
Type of MBS			
Roux-en-Y gastric bypass		32 (82.1)	
Sleeve gastrectomy		3 (7.7)	
Gastric banding		2 (5.1)	
Other type of MBS		2 (5.1)	
Body weight at MBS		128 (110–142)	
Body weight at listing	81 (70–92)	70 (67–86)	0.208
Diabetes pre-LT	51 (26.8)	4 (16.0)	0.243
Diabetes post-LT (pre-existing or new-onset)	71 (37.8)	4 (16.0)	**0.032**
Pre-LTx Complications of cirrhosis (actual or history)			
Ascites	221 (67.4)	33 (91.7)	**0.003**
Encephalopathy	156 (47.6)	23 (63.9)	0.063
Non-bleeding varices	150 (45.7)	17 (47.2)	0.865
Variceal bleeding	65 (19.8)	5 (13.9)	0.392
Hepatocellular carcinoma	211 (47.6)	4 (10.3)	**<0.001**
Severe bacterial infections	69 (21.0)	19 (52.8)	**<0.001**
Hepatorenal syndrome	54 (16.5)	11 (30.6)	**0.036**
Alcohol-related hepatitis	31 (9.5)	4 (11.1)	0.748
Complications after liver transplantation			
Biliary complications	101 (30.9)	13 (36.1)	0.522
Primary non-function	6 (1.8)	1 (2.8)	0.696
CMV reactivation	47 (14.4)	5 (13.9)	0.937
Liver steatosis	37 (11.3)	1 (2.8)	0.112
Relapse alcohol use	59 (13.3)	12 (30.8)	**0.003**

Note: Data are presented as *n* (%) or median (IQR). Data on pre- and post-LTx complications (except for HCC and relapse alcohol use) are missing in 114 patients without history of MBS and 3 with MBS.
Abbreviations: CMV, cytomegalovirus; MBS, metabolic and bariatric surgery; MELD, Model For End-Stage Liver Disease. *p* values indicating statistical significance ($p < 0.05$) are shown in bold.

(Figure S1). The latter was not due to differences in the time between diagnosis and abstinence (0 (0–12) vs. 0 (−1–10) months, $p=0.148$).

Several complications, including ascites, hepatorenal syndrome and severe bacterial infections were more prevalent in the MBS group (Table 1). Conversely, HCC was significantly less common (10.3% vs. 47.6%, $p<0.001$). Post-transplant complications occurred at equal rates in the two groups. Notably, post-transplant alcohol use relapse occurred in more than twice as many patients with prior MBS (30.8% vs. 13.3%, $p=0.003$).

We next stratified ALD and mixed ALD/MASLD separately, and included a MASLD cohort as additional controls (Table S1). MASLD patients were, in accordance with the literature, older and more female, with a higher proportion of patients having diabetes mellitus. ALD and ALD/MASLD patients had similar characteristics, except for a higher body weight and higher rate of transplantation for HCC in the latter. These findings are broadly comparable to those of a recent report comparing these three groups [22]. The group of ALD patients with a history of MBS was younger and leaner than all other groups, with the lowest prevalence of diabetes and HCC, and the highest rate of alcohol use relapse after transplantation.

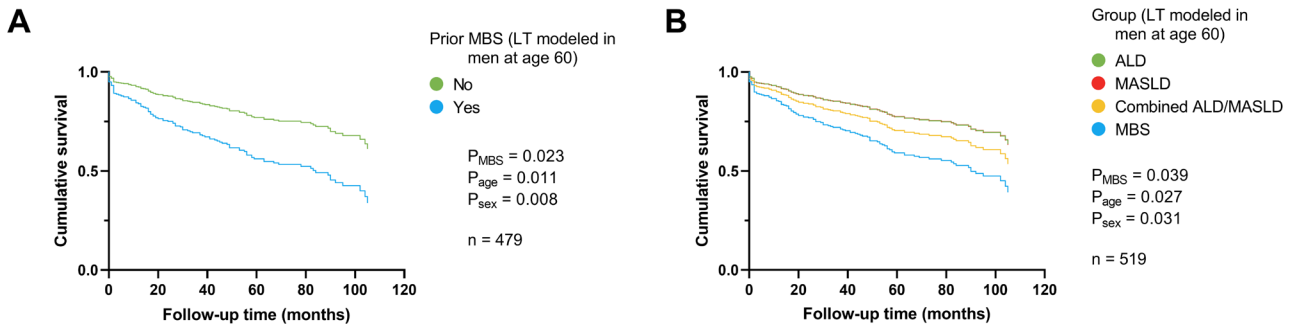

FIGURE 2 | Modelled post-transplant survival. Cox proportional regression analysis with ALD patients (with or without concomitant MASLD) as controls (A), and controls stratified as ALD, mixed ALD/MASLD and MASLD (B). Data are graphed for a modelled age of 60 and male sex at the time of transplantation.

3.2 | Survival

Patients were followed up for a median of 4.6 (IQR 2.3–7.0) years, during which time 22.4% of patients died. Since patients with a history of MBS were significantly younger and more likely female, which might be confounding factors, we performed Cox regression analysis with MBS, sex and age as cofactors. Age ($p = 0.011$) and sex ($p = 0.008$) were associated with survival. Importantly, MBS significantly increased the risk of death (hazard ratio (HR) MBS = 2.205 (95% CI 1.11–4.37), $p = 0.023$) (Figure 2A). When comparing the survival of ALD, MASLD, mixed ALD/MASLD and ALD + MBS patients, we found that ALD and MASLD patients had overlapping modelled survival curves. In contrast, survival in mixed ALD/MASLD patients was non-significantly lower ($p = 0.347$). As in the main analysis, patients with ALD and a history of MBS had a significantly lower survival compared to ALD patients (HR compared to ALD = 2.058 (95% CI 1.036–4.086), $p = 0.039$) (Figure 2B). Including diabetes as a cofactor did not affect the results (Figure S2).

The cause of death differed between the groups ($p = 0.004$), with liver disease being listed in 70.0% of MBS patients as the main cause of death, whereas the causes of death in the non-MBS controls were evenly divided between sepsis, non-HCC malignancy, HCC, liver disease and other causes (Table 2). Given that alcohol use post-LT negatively impacts patient survival [23] and that the former was more prevalent in the MBS group, we explored whether alcohol relapse was associated with liver disease mortality in our cohort. Indeed, 8/20 (40.0%) of patients who died of liver disease had some degree of alcohol relapse post-LT, compared to 6/87 (6.9%) of those who died of other causes ($p < 0.001$).

3.3 | Sensitivity Analysis

The higher prevalence of LT for HCC in the non-MBS group, for which patients can be listed with a standard exception MELD and without other complications of decompensated cirrhosis, might have impacted the results in this study. We therefore performed a sensitivity analysis, excluding all patients with HCC (Table S2). The prevalence of prior MBS rose to 6.5% of patients transplanted for ALD without HCC (Figure 1).

TABLE 2 | Cause of death in the follow-up after liver transplantation.

Cause of death	No history of MBS ($n = 98$)	History of MBS ($n = 10$)
Cardiovascular disease	6 (6.1)	1 (10.0) **Overall $p = 0.004$**
Sepsis/Infection	19 (19.4)	1 (10.0)
Liver disease	13 (13.3)	7 (70.0)
HCC	13 (13.3)	0 (0.0)
Non-HCC malignancy	18 (18.4)	1 (10.0)
Post-transplant complications	5 (5.1)	0 (0.0)
Other	14 (14.3)	0 (0.0)
Unknown	10 (10.2)	0 (0.0)

Note: Data are presented as *n* (%). MBS, metabolic and bariatric surgery. *p* values indicating statistical significance ($p < 0.05$) are shown in bold.

In accordance with the complete cohort, patients with a history of bariatric surgery remained younger (53 vs. 60 years, $p < 0.001$) compared to non-MBS controls, with a higher proportion of females (48.6% vs. 23.3%, $p = 0.003$). However, the MELD score did not differ between both groups, and ascites and hepatorenal syndrome were no longer more prevalent in patients with a history of MBS. Only a history of severe bacterial infections associated with decompensation, most frequently spontaneous bacterial peritonitis, remained more common in the MBS group (54.5% vs. 34.1%, $p = 0.031$). The time between diagnosis of advanced alcohol-related liver disease and listing ($p = 0.009$), and listing and LT ($p = 0.033$), was still shorter in those with prior bariatric surgery.

Importantly, Cox regression analysis of survival, taking into account age and sex as cofactors again indicated a poorer post-transplant prognosis in MBS patients transplanted for ALD without HCC (HR MBS = 2.56 (1.21–5.40), $p = 0.013$) (Figure S3).

4 | Discussion

In this nationwide Belgian ELTR-supported study, we investigate the prevalence, characteristics and outcome of patients with

prior metabolic and bariatric surgery who then underwent liver transplantation for alcohol-related liver disease. We confirm previous monocentric findings [20] that patients with a history of MBS are younger at transplantation, predominantly female, and have a lower prevalence of HCC. In addition, we report that these patients have a lower long-term survival and higher rate of relapse alcohol use after LT.

We previously showed in a monocentric study of hospitalised patients with ALD that prior MBS was associated with a decreased transplant-free survival, after correction for patient age, with the main cause of death being acute-on-chronic liver failure [18]. Data from the US retrospective cohort study indicate that prior RYGB is associated with an increased long-term mortality in patients presenting with acute alcohol-related hepatitis, whereas the short-term inpatient survival is similar [24]. Our present data indicate that MBS was also independently associated with post-transplant mortality. This relationship remained significant when constraining the analysis to patients without HCC. This excess mortality was mainly liver disease-related. Although our dataset did not allow a more granular examination of the disease course in these patients, one of probably several contributing factors might be alcohol relapse, which was more prevalent in the MBS group and was associated with mortality due to liver disease.

While increased post-transplant alcohol use relapse is a novel finding, this ties in well with the increased risk for AUD overall following MBS. Multiple causes can account for this. First, the documented changes in alcohol pharmacokinetics, especially the more rapid uptake and delivery to the brain, can increase the addictive properties [8, 25]. Second, altered gut-brain axis hormone signalling is likely involved. The most convincing data have been obtained for ghrelin, an orexigenic peptide. Rats consume more alcohol following RYGB than sham-operated obese and lean control rats [26, 27]. The injection of a ghrelin receptor antagonist reduced alcohol consumption in RYGB rats [26]. Since LT does not fundamentally impact either alcohol pharmacokinetics or gut hormone release, these mechanisms conceivably increase the risk of post-transplant alcohol use. Third, psychological mechanisms and risk factors also contribute to the risk of AUD. Depression and anxiety are prevalent in patients undergoing MBS, and their persistence or reappearance after surgery may increase alcohol intake. In a recent systematic review of qualitative studies of patients' own perceptions, four mechanisms were put forward that promoted alcohol use after MBS: psychological problems, alcohol as a coping strategy (often replacing the role that food played before surgery, described in the so-called addiction transfer theory), changes in the physiological response to alcohol, and the lack of information and/or long-term follow-up [28]. Regarding the latter, a standardised follow-up post-LT with specific attention on alcohol use in these patients seems warranted.

As RYGB was the surgical procedure performed in more than 80% of patients, our findings are in line with large epidemiological studies reporting that RYGB but not sleeve gastrectomy increases the risk of alcohol-related health issues [13, 14, 29]. The reasons for this are currently unclear, yet the two procedures differentially impact alcohol absorption and metabolism, and gut hormone release, again leading to the hypothesis that these mechanisms are key [29].

Patients with prior MBS were more frequently listed for decompensated liver disease, as evidenced by higher prevalence of ascites, severe bacterial infections and hepatorenal syndrome. Conversely, HCC was much less prevalent, probably due to the younger age and higher number of female patients in the MBS cohort. Prior MBS might thus accelerate ALD progression, leading to decompensation before HCC has developed. Excluding patients with HCC from the analysis negated the differences in signs of decompensation, with the exception of severe bacterial infections, which remained more prevalent in patients with prior MBS. It is tempting to speculate that by promoting bacterial translocation and/or small intestinal bacterial overgrowth [30], MBS might predispose to bacterial infections and liver disease progression. In a study of patients hospitalised for ALD, we similarly found that infection was a more frequent trigger for decompensation in patients with a history of MBS (manuscript in revision). Malnutrition following MBS in combination with alcohol use might also predispose to post-MBS ALD [31]. These relationships need to be investigated in prospective and mechanistic studies.

This study has several limitations. First of these is the retrospective design, which resulted in interesting variables not being recorded, for instance the duration of AUD or additional granularity on liver disease as a cause of death post-transplant in MBS patients. The evolution of alcohol use post-LT could also not be evaluated at standardised timepoints. These points should be addressed in a prospective study. Second, the sample size of 39 MBS patients is relatively small. Still, this nationwide sample of MBS patients undergoing LT for ALD capturing all patients over a 10-year timeframe is the largest reported so far, and given the large control group, sufficient statistical power was achieved to draw several conclusions. Third, although we detected higher levels of alcohol relapse after transplantation in those with a history of MBS, a quantitative comparison of alcohol intake could not be performed. Alcohol relapse is also a term with various definitions and prevalence estimates in the literature [32]. While no level of alcohol use is seen as safe, the specific risks associated with various patterns of consumption should be investigated further.

In summary, a non-negligeable proportion of patients hospitalised for ALD had a history of MBS in this nationwide cohort. These patients were comparatively young women with signs of liver decompensation and lower prevalence of HCC. Age- and sex-adjusted survival was lower. Liver-related mortality contributed to this, possibly linked to a higher post-transplant relapse alcohol use in MBS patients.

Author Contributions

Sander Lefere, Roberto Ivan Troisi and Anja Geerts participated in research design and data analysis. Sander Lefere and Anja Geerts drafted the manuscript. All authors contributed to data collection and proofread the article.

Disclosure

Work in the lab of SL and AG has received a grant from Inventiva.

Ethics Statement

The study protocol was approved by the ELTR (31/03/2020), the Ghent University Hospital Ethical Review Board (06/04/2021, reference BC-09379), and subsequently by the ethical committees of the participating centres. The study was conducted according to the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.