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The journey of MASLD: Tracking resolution, relapse, and predictive factors after sleeve gastrectomy and one-anastomosis gastric bypass, a propensity score-matched cohort study

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ABSTRACT

Aims: To assess the rates and predictors of resolution and relapse of metabolic-dysfunction associated steatotic liver disease (MASLD) in individuals undergoing sleeve gastrectomy (SG) or one-anastomosis gastric bypass (OAGB).

Methods: This observational prospective cohort study involved 1618 propensity score-matched participants (81.5% female) with concurrent MASLD and obesity who underwent SG or OAGB between 2013 and 2023.

Results: In the context of a maximum follow-up of four years with a median follow-up of 2.2 years (IQR: 1.0–3.3), the overall rates of MASLD resolution and relapse were 71.1 per 1000 person-month and 8.7 per 1000 person-month, respectively. These rates were comparable between the SG and OAGB groups. Significant resolution predictors were a lower percentage of hepatic steatosis, a higher percentage of 12-month excess weight loss (EWL %), and younger age. In contrast, an increased percentage of liver steatosis, a higher pre-operative (Pre-Op) fat mass percentage (FM%), and older age were significant predictors of relapse.

Conclusion: This study found no significant differences in MASLD resolution and relapse rates between SG and OAGB. Key factors influencing MASLD outcomes included the percentage of hepatic steatosis, 12-month EWL%, Pre-Op FM%, and age.

1. Introduction

Metabolic-dysfunction associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), was recently defined by the multi-society Delphi consensus in 2023 [1]. MASLD is characterized by the presence of liver steatosis exceeding 5 % along with at least one cardio-metabolic risk factor (CMRF) of metabolic syndrome, with no other acknowledged etiology for liver injury. A systematic review and *meta*-analysis estimated the global prevalence of steatotic liver disease (SLD) to exceed 30 % [2]. SLD encompasses a spectrum from simple fat deposition and steatosis to progression toward steatohepatitis, fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC) [3,4]. Management strategies for MASLD focus on lifestyle alterations, addressing comorbidities, and considering metabolic and bariatric surgery (MBS). However, the U.S. Food and Drug Administration (FDA) has recently approved Rezdiffra (Resmetirom) for the treatment of patients with metabolic dysfunction-associated steatohepatitis (MASH) [5].

While guidelines have provided recommendations for the management of MASLD through MBS in adults [6], and existing data provide insights into liver enzyme status following sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) in individuals with MASLD [7], there is still a lack of understanding regarding the differential effects of various surgical techniques on MASLD outcomes.

Thus, this observational study aims to compare SG versus one-anastomosis gastric bypass (OAGB) in achieving MASLD resolution,

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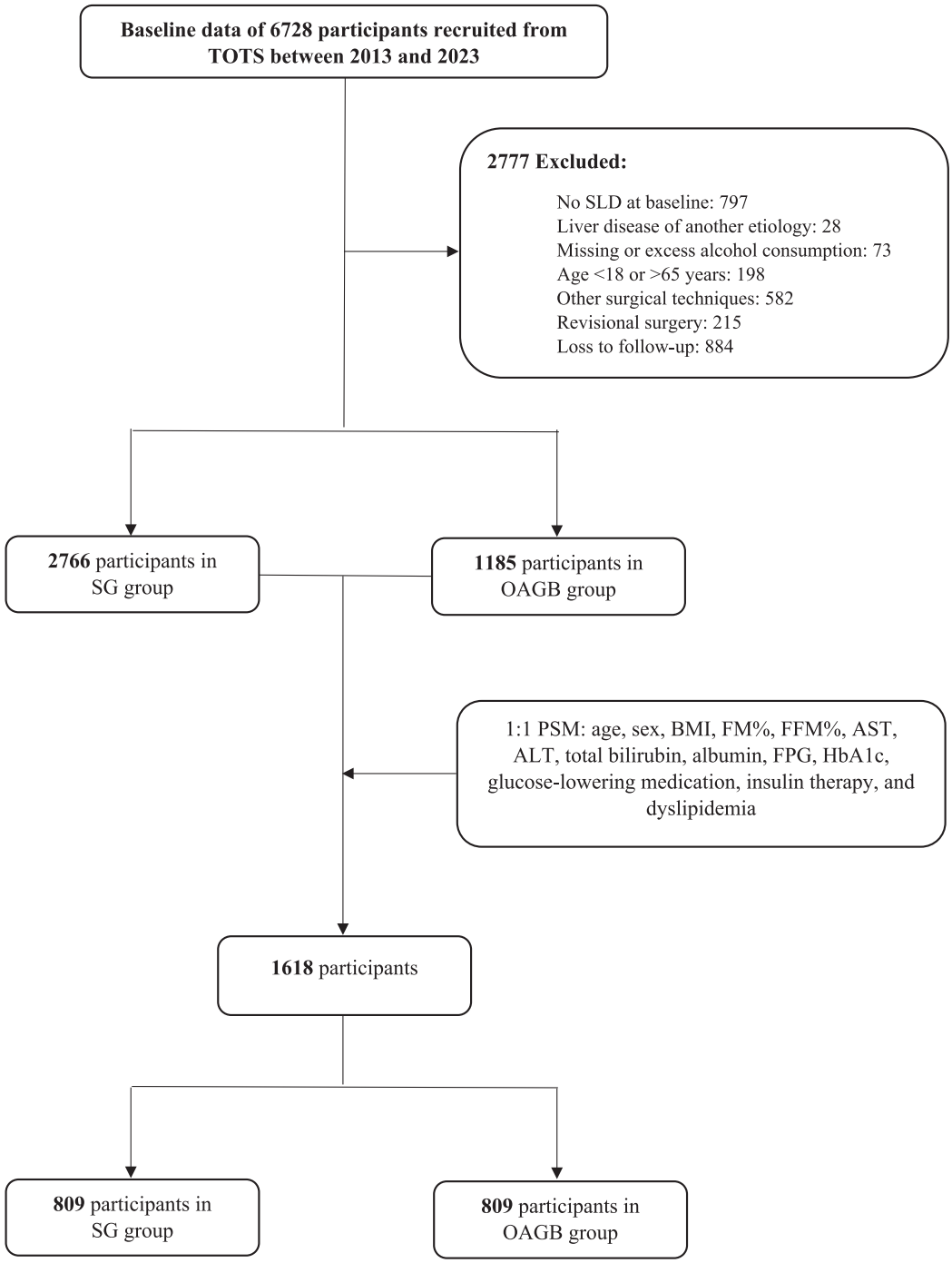

Fig. 1. Study flowchart. TOTS, Tehran obesity treatment study; SLD, steatotic liver disease; PSM, propensity score matching; BMI, body mass index; FM, fat mass; FFM, fat-free mass; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c; SG, sleeve gastrectomy; OAGB, one-anastomosis gastric bypass.

experiencing relapse, and investigating possible predictive factors within a prospective propensity score-matched cohort study.

2. Methods

2.1. Study design and participants

This study was conducted in the context of the Tehran Obesity Treatment Study (TOTS) between 2013 and 2023. The TOTS is an ongoing, single-institutional, prospective cohort study initiated in March 2013 that enrolls eligible patients referred to our specialized medical center (at 51° 24′ E, 35° 42′ N) to undergo MBS (with more details available elsewhere) [8]. MBS indications were a BMI $\geq$ 35 Kg/m^2 or a BMI of 30–34.9 Kg/m^2 accompanied by metabolic disturbance. Each individual underwent comprehensive multidisciplinary pre-operative (Pre-Op) evaluations, and treatment decisions were made based on an integrative approach. Informed consent was obtained from all participants.

A total of 6728 individuals were recruited from the original TOTS for their first MBS. Participants were excluded if they lacked evidence of liver steatosis at baseline (N = 797), had liver disease of another etiology (liver-related cancers, liver fibrosis, viral hepatitis, autoimmune liver

Table 1
Baseline characteristics of study participants.

Variables	Before PSM				After PSM			
	Total N = 3951	SG N = 2766	OAGB N = 1185	*P*-value	SG N = 809	OAGB N = 809	*P*-value	SMD
Age, years	40.2 ± 10.9	39.9 ± 11.1	40.8 ± 10.5	**0.012**	40.5 ± 11.3	40.8 ± 10.6	0.693	0.01
Sex, Female	3073 (77.8)	2100 (75.9)	973 (82.1)	**<0.001**	653 (80.7)	666 (82.3)	0.405	0.03
BMI, kg/m^2	44.5 ± 5.7	44.2 ± 5.5	45.3 ± 6.0	**<0.001**	45.5 ± 6.0	45.3 ± 5.7	0.672	−0.01
WC, cm	124.7 ± 14.4	124.6 ± 14.5	125.2 ± 14.1	0.268	125.6 ± 15.4	125.2 ± 14.5	0.675	−0.01
FM, %	49.9 ± 4.7	49.7 ± 4.7	50.4 ± 4.4	**<0.001**	50.5 ± 4.5	50.5 ± 4.4	0.707	0.01
FFM, %	49.9 ± 5.4	50.1 ± 5.7	49.3 ± 4.5	**<0.001**	49.2 ± 4.7	49.2 ± 4.4	0.952	−0.00
Steatosis status (diagnosed by ultrasound):								
Grade I	1191 (30.1)	836 (30.2)	355 (30.0)	0.240	237 (29.3)	246 (30.4)	0.887	0.017
Grade II	1849 (46.8)	1312 (47.4)	537 (45.3)		383 (47.3)	377 (46.6)		−0.01
Grade III	911 (23.1)	618 (22.3)	293 (24.7)		189 (23.4)	186 (23.0)		−0.00
AST, IU/L	24.3 ± 15.1	24.7 ± 15.7	23.5 ± 13.4	**0.019**	23.7 ± 13.7	23.5 ± 12.8	0.689	−0.01
ALT, IU/L	32.2 ± 24.9	33.0 ± 25.9	30.5 ± 22.1	**0.002**	30.9 ± 21.7	30.3 ± 21.2	0.568	−0.02
ALP, IU/L	184.5 ± 76.2	184.0 ± 73.1	185.7 ± 83.1	0.552	186.9 ± 64.0	183.0 ± 88.7	0.309	−0.03
AST/ALT ratio	0.85 ± 0.36	0.85 ± 0.38	0.86 ± 0.31	0.344	0.88 ± 0.54	0.87 ± 0.31	0.590	−0.01
Total Bilirubin, IU/L	0.69 ± 0.32	0.7 ± 0.33	0.67 ± 0.30	**0.013**	0.68 ± 0.33	0.67 ± 0.30	0.420	−0.02
Albumin, μmol/L	63.5 ± 5.5	63.7 ± 5.4	63.1 ± 5.6	**0.002**	63.3 ± 5.0	63.1 ± 5.6	0.478	−0.02
PT, sec	12.7 ± 2.4	12.7 ± 2.3	12.7 ± 2.6	0.832	12.8 ± 3.4	12.6 ± 1.1	0.169	−0.05
Hyperglycemia	1456 (39.0)	964 (37.0)	492 (43.5)	**<0.001**	334 (41.3)	300 (37.1)	0.083	−0.06
FPG, mmol/L	6.1 ± 2.0	5.9 ± 1.6	6.6 ± 2.7	**<0.001**	6.27 ± 2.00	6.24 ± 2.13	0.781	−0.01
HbA1c, % (mmol/mol)	5.9 ± 1.2 (41.2 ± 13.4)	5.7 ± 1.0 (39.6 ± 10.9)	6.2 ± 1.5 (44.8 ± 17.4)	**<0.001**	6.0 ± 1.23 (42.2 ± 13.5)	6.0 ± 1.25 (42.3 ± 13.7)	0.858	0.00
Glucose-lowering medication	633 (17.2)	352 (13.8)	281 (25.1)	**<0.001**	157 (19.4)	153 (18.9)	0.801	−0.01
Insulin therapy	136 (3.4)	45 (1.6)	91 (7.7)	**<0.001**	28 (3.5)	27 (3.3)	0.891	0.02
TyG index	8.9 ± 0.5	8.9 ± 0.5	9.0 ± 0.6	**<0.001**	8.9 ± 0.58	8.9 ± 0.56	0.381	0.03
HTN	1403 (37.5)	964 (37.0)	439 (38.8)	0.290	299 (37.0)	273 (33.7)	0.176	−0.04
SBP, mmHg	123.5 ± 11.8	123.4 ± 12.0	124.0 ± 11.4	0.144	124.5 ± 13.2	123.8 ± 11.0	0.249	−0.04
DBP, mmHg	80.0 ± 7.0	80.0 ± 7.3	80.0 ± 6.3	0.951	80.6 ± 7.2	80.3 ± 6.0	0.410	−0.02
Anti-hypertensive treatment	918 (24.9)	614 (24.0)	304 (27.1)	**0.043**	201 (24.8)	194 (24.0)	0.685	−0.01
Hypertriglyceridemia	2109 (57.2)	1149 (56.30	660 (59.2)	0.105	433 (53.7)	462 (57.2)	0.146	0.05
Triglyceride* mmol/L	1.65 (1.23–2.22)	1.64 (1.21–2.1)	1.67 (1.2–2.3)	0.191	1.62 (1.20–2.15)	1.69 (1.25–2.30)	0.067	0.02
Lipid-lowering treatment	635 (17.3)	403 (15.7)	232 (20.7)	**<0.001**	144 (17.8)	143 (17.7)	0.948	−0.00
Dyslipidemia	2565 (69.3)	1763 (68.1)	802 (72.1)	**0.016**	558 (69.0)	564 (69.7)	0.746	0.01
HDL-C, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.885	1.2 ± 0.3	1.2 ± 0.3	0.865	0.00
Current smokers	401 (10.6)	304 (11.4)	97 (8.6)	**0.009**	76 (9.6)	62 (8.0)	0.255	−0.04

PSM, propensity score matching; SMD, standard mean difference; BMI, body mass index; WC, waist circumference; FM, fat mass; FFM, fat-free mass; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c; TyG index, Triglyceride-glucose index calculated as Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SG, sleeve gastrectomy; OAGB, one-anastomosis gastric bypass.
Data are presented as mean ± SD or n (%).
* Data presented as Median (IQR).

disease, primary biliary cirrhosis, drug-induced liver disease, biliary obstruction, hemochromatosis, and Wilson's disease) (N = 28), missing or excess alcohol consumption (N = 73), were under the age of 18 (N = 112), or over the age of 65 (N = 86). Additionally, those who underwent other types of surgery (N = 582) or revisional surgery (N = 215) were excluded. Instances of loss to follow-up (N = 884) further contributed to the refinement of the dataset. Eventually, 3951 (SG = 2766, OAGB = 1185) individuals entered the study analysis, which following adjustments for propensity score matching (PSM), 809 individuals remained per group, totaling 1618 participants (Fig. 1).

2.2. Measurements

Trained investigators collected Pre-Op and post-operative (Post-Op) required data during the scheduled visits under the study protocol [8]. Anthropometric measurements were obtained according to World Health Organization (WHO) guidelines [9], and body composition was evaluated using a portable bioelectrical impedance analyzer (InBody 370, Biospace, Seoul, Korea). Pre-Op and follow-up blood samples and biochemical measures were collected between 7 and 9 a.m. following an overnight fast of 12 to 14 h.

2.3. Surgical techniques

Following a comprehensive patient evaluation and consultation, the surgeon thoroughly informed the patient about the procedure, expected outcomes, and potential complications. All surgeries were conducted laparoscopically by the same surgical team under general anesthesia at three university-affiliated hospitals. SG involved the resection of approximately 80 % of the stomach with the aid of a 36-F bougie inserted through a gastric tube. OAGB was performed using a 160-cm biliopancreatic limb.

2.4. Follow-up and Post-Op care

The Post-Op care team consisted of an obesity specialist, a nutritionist, and a sports medicine physician. Patients were instructed to follow a liquid diet for the first two weeks after discharge, transitioning to a semi-solid diet for an additional four weeks before resuming their regular dietary regimen. Additionally, all subjects adhered to a calorie-restricted diet (10–35 % of calories from protein) and daily vitamin and mineral supplements for approximately 12 months. Dietary adjustments were made according to patients' clinical and biochemical evaluations. Biochemical measurements were also performed 6, 12, 24, 36, and 48 months following the operation. Participants were advised to engage in Post-Op physical activities, such as aerobic and resistance exercises, for

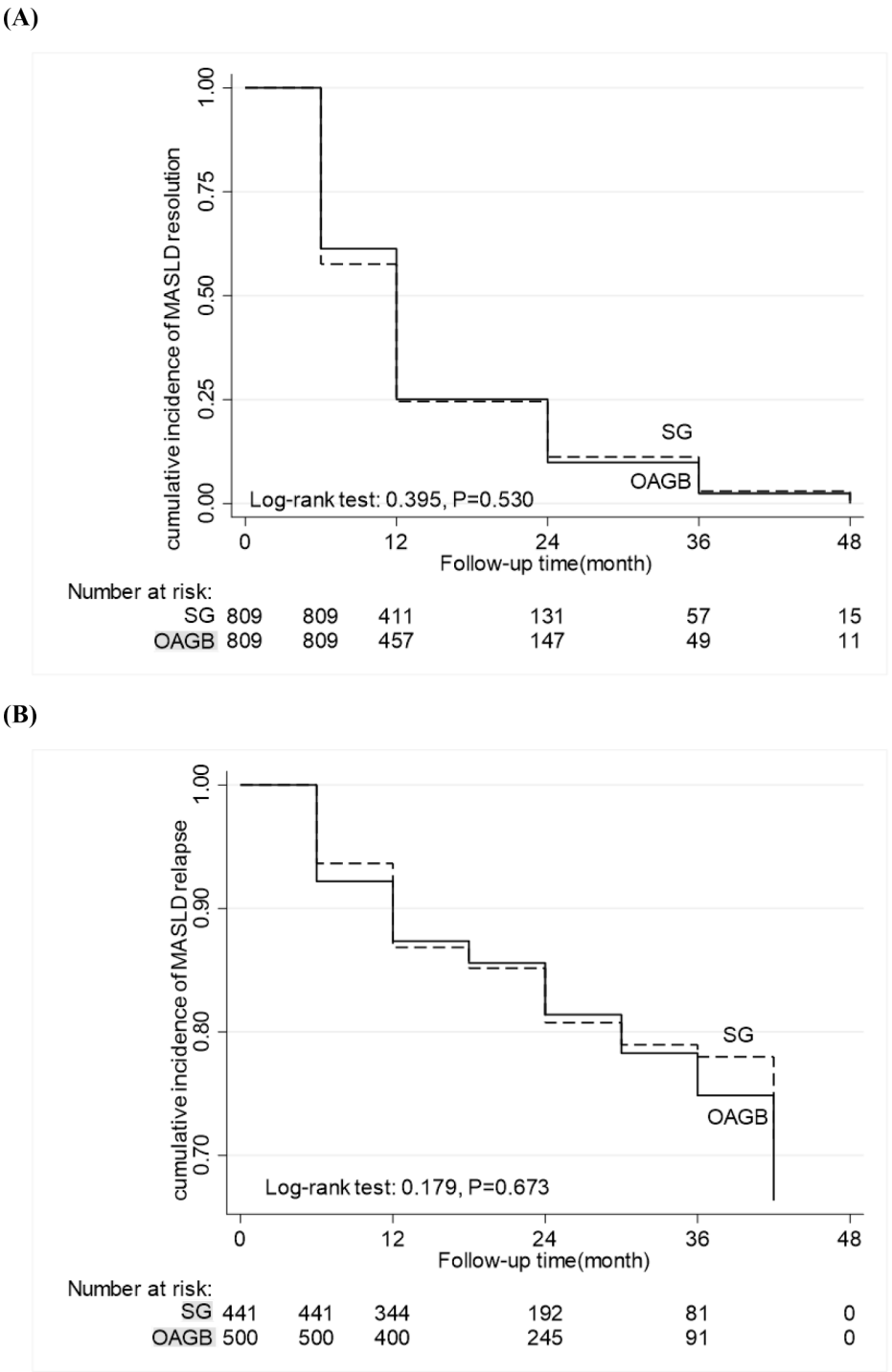

Fig. 2. Kaplan-Meier curves for the cumulative incidence of MASLD resolution (Fig. 2 (A)) and relapse (Fig. 2 (B)) based on the type of surgery over the maximum follow-up of four years. MASLD, metabolic-dysfunction associated steatotic liver disease; SG, sleeve gastrectomy; OAGB, one-anastomosis gastric bypass.

at least 30 min daily. Although adherence to the protocol, including dietary guidelines, supplementation, and physical activity, was encouraged, it was not rigorously supervised.

2.5. Definitions

Established guidelines were used to define MASLD [1]. It is defined as the presence of liver steatosis (identified by imaging or biopsy) accompanied by at least one of the five CMRFs in the absence of excessive alcohol consumption or any other recognized underlying cause of liver steatosis. Excess alcohol consumption is defined as >20 g/day in females and >30 g/day in males. CMRFs include: 1) BMI $\geq$ 25 Kg/m^2, or waist circumference (WC) >90 cm (for both male and female, as an ethnicity adjusted equivalent) 2) fasting plasma glucose (FPG) $\geq$ 5.6 mmol/L (100 mg/dL), or HbA1c $\geq$ 5.7 % (39 mmol/L), or treatment for type 2 diabetes, 3) BP $\geq$ 130/85 mmHg, or anti-hypertensive drug treatment, 4) plasma triglycerides (TG) $\geq$ 1.70 mmol/L (150 mg/dL), or lipid-lowering treatment, and 5) high-density lipoprotein cholesterol (HDL-C) $\leq$ 1.0 mmol/L (40 mg/dL) (male)/ $\leq$ 1.3 mmol/L (50 mg/dL) (female), or lipid-lowering treatment. Resolution was defined as the absence of steatosis in imaging or biopsy, regardless of metabolic status or the presence of steatosis without any associated CMRFs. Relapse was

Table 2
Hazard ratios for incident MASLD resolution and relapse during 4 years of follow-up.

	Variables	Total	SG	OAGB
RESOLUTION	**Number of person-month**	19,836	9756	10,080
	Number of incident remission	1424	707	717
	Incidence rate (per 1000 person-month) (95 % CI)	71.7 (68.1–75.6)	72.4 (67.3–78.0)	71.1 (68.1–75.6)
	HR (95 % CI)	–	Ref.	0.97 (0.88–1.08)
RELAPSE	**Number of person-month**	19,392	8999	10,392
	Number of incident relapse	169	76	93
	Incidence rate (per 1000 person-month) (95 % CI)	8.7 (7.4–10.1)	8.4 (6.7–10.5)	8.9 (7.3–10.9)
	HR (95 % CI)	–	Ref.	1.06 (0.78–1.44)

HR, hazard ratio; MASLD, metabolic-dysfunction associated steatotic liver disease; SG, sleeve gastrectomy; OAGB, one-anastomosis gastric bypass; CI, confidence interval.

identified when a patient, having previously achieved resolution, subsequently met the criteria for MASLD again. Excess weight loss percentage (EWL%) was calculated as [(Initial Weight) − (Postop Weight)]/[(Initial Weight) − (Ideal Weight)] × 100, and total weight loss percentage (TWL%) was calculated as: [(Initial Weight) − (Postop Weight)]/[(Initial Weight)] × 100 [10]. As a surrogate for insulin resistance, the triglyceride-glucose (TyG) index was defined as Ln [fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2] [11].

2.6. Statistics

Normally distributed continuous variables were reported as mean ± standard deviation (SD). Skewed continuous variables were presented as median and interquartile range (IQR) 25–75, and categorical baseline characteristics were expressed using the frequency (percentage). Differences in baseline characteristics between the surgical groups were assessed using the independent *t*-test for normally distributed continuous variables, the Mann-Whitney *U* test for skewed continuous variables, and the Chi-square test for categorical variables. A PSM analysis was performed to overcome deviations caused by baseline imbalance. A logistic regression model was used to calculate propensity scores. Propensity scores were calculated based on clinically important variables and factors concerning survival, including age, sex, BMI, percent fat mass (FM%), percent fat-free mass (FFM%), aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, albumin, FPG, HbA1c, glucose-lowering medication, insulin therapy, and dyslipidemia. To show the degree of adjustment for PSM, we calculated standardized mean differences (SMD) for all variables before and after PSM to show the size of differences in patient characteristics between the two groups. The SMD <0.2 showed proper matching.

All participants with MASLD were included and followed for 6, 12, 24, 36, and 48 months following the surgery. If the patients met the MASLD resolution criteria at each Post-Op visit, they were placed in the resolution group; otherwise, they were assigned to the persistent MASLD group. From the surgery date until the first visit when resolution was observed, the time of MASLD resolution was calculated (months 6, 12, 24, 36, and 48 after surgery). Patients initially assigned to the MASLD resolution group who re-developed MASLD during follow-up visits over the four-year period, were reassigned to the relapse group; otherwise, they were assigned to the MASLD resolution without relapse group. The MASLD relapse analysis only included patients who received at least one follow-up visit after the resolution occurred. Hazard ratios (HRs) for incident MASLD resolution and relapse during the maximum follow-up of four years were investigated after PSM.

When evaluating the effect of surgical technique on the resolution and relapse of MASLD, we analyzed an idealized scenario with matched surgical groups. We included the entire study population before applying PSM for univariate and multivariate analyses, thereby considering the surgical technique as a real-world variable. This

Table 3
Univariate and multivariate hazard ratios for the potential predictors of MASLD resolution.

	Univariate HR (95 % CI)	Multivariate HR (95 % CI)
Age, (years)	**0.996 (0.993–0.999)** *	**0.996 (0.992–1.000)** *
Sex (Ref: male)	0.98 (0.91–1.06)	–
BMI, (kg/m^2)	**0.987 (0.981–0.992)** *	–
WC, (cm)	0.99 (0.99–1.00)	–
FM, (%)	**0.990 (0.983–0.9970)***	–
FFM, (%)	**1.009 (1.003–1.015)** *	–
Steatosis status (Ref: Grade I)		
Grade II	**0.86 (0.79–0.92)***	**0.87 (0.80–0.95)***
Grade III	**0.77 (0.70–0.85)***	**0.79 (0.71–0.88)***
AST, (IU/L)	0.998 (0.995–1.000)	–
ALT, (IU/L)	0.998 (0.997–1.000)	–
ALP, (IU/L)	0.99 (0.99–1.00)	–
AST/ALT ratio	1.04 (0.95–1.12)	–
Total Bilirubin, (IU/L)	1.00 (0.90–1.11)	–
Albumin, (μmol/L)	1.07 (0.98–1.18)	–
PT, (sec)	1.00 (0.98–1.01)	–
Hyperglycemia (Ref: no)	0.93 (0.87–1.00)	–
FPG, (mmol/L)	0.999 (0.998–1.000)	–
HbA1c, (%)	**0.97 (0.94–0.99)***	–
Glucose-lowering medication (Ref: no)	0.92 (0.84–1.01)	–
Insulin therapy (Ref: no)	0.93 (0.78–1.12)	–
TyG index	0.95 (0.90–1.01)	–
HTN (Ref: no)	0.94 (0.87–1.01)	–
SBP, (mmHg)	0.998 (0.995–1.000)	–
DBP, (mmHg)	0.996 (0.991–1.001)	–
Anti-hypertensive treatment (Ref: no)	0.93 (0.86–1.01)	–
Hypertriglyceridemia (Ref: no)	0.97 (0.90–1.04)	–
Triglyceride, (mmol/L)	1.00 (0.99–1.00)	–
Lipid-lowering treatment (Ref: no)	0.95 (0.86–1.04)	–
Dyslipidemia (Ref: no)	1.02 (0.95–1.10)	–
HDL-C, (mmol/L)	1.000 (0.997–1.002)	–
12-month TWL, (%)	**1.005 (1.000–1.011)** *	–
12-month EWL, (%)	**1.005 (1.003–1.007)** *	**1.004 (1.001–1.006)** *
Surgery type (Ref: GB)	**1.11 (1.03–1.19)***	–
Current smokers (Ref: no)	1.03 (0.92–1.15)	–
Education (Ref: ≤ 12 years)	1.04 (0.97–1.11)	–

MASLD, metabolic-dysfunction associated steatotic liver disease; HR, hazard ratio; BMI, body mass index; WC, waist circumference; FM, fat mass; FFM, fat free mass; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c; TyG index, Triglyceride-glucose index calculated as Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TWL, total weight loss; EWL, excess weight loss. The univariate and multivariate analyses presented in this table are conducted on the total population before applying propensity score matching.
* P-value < 0.05.

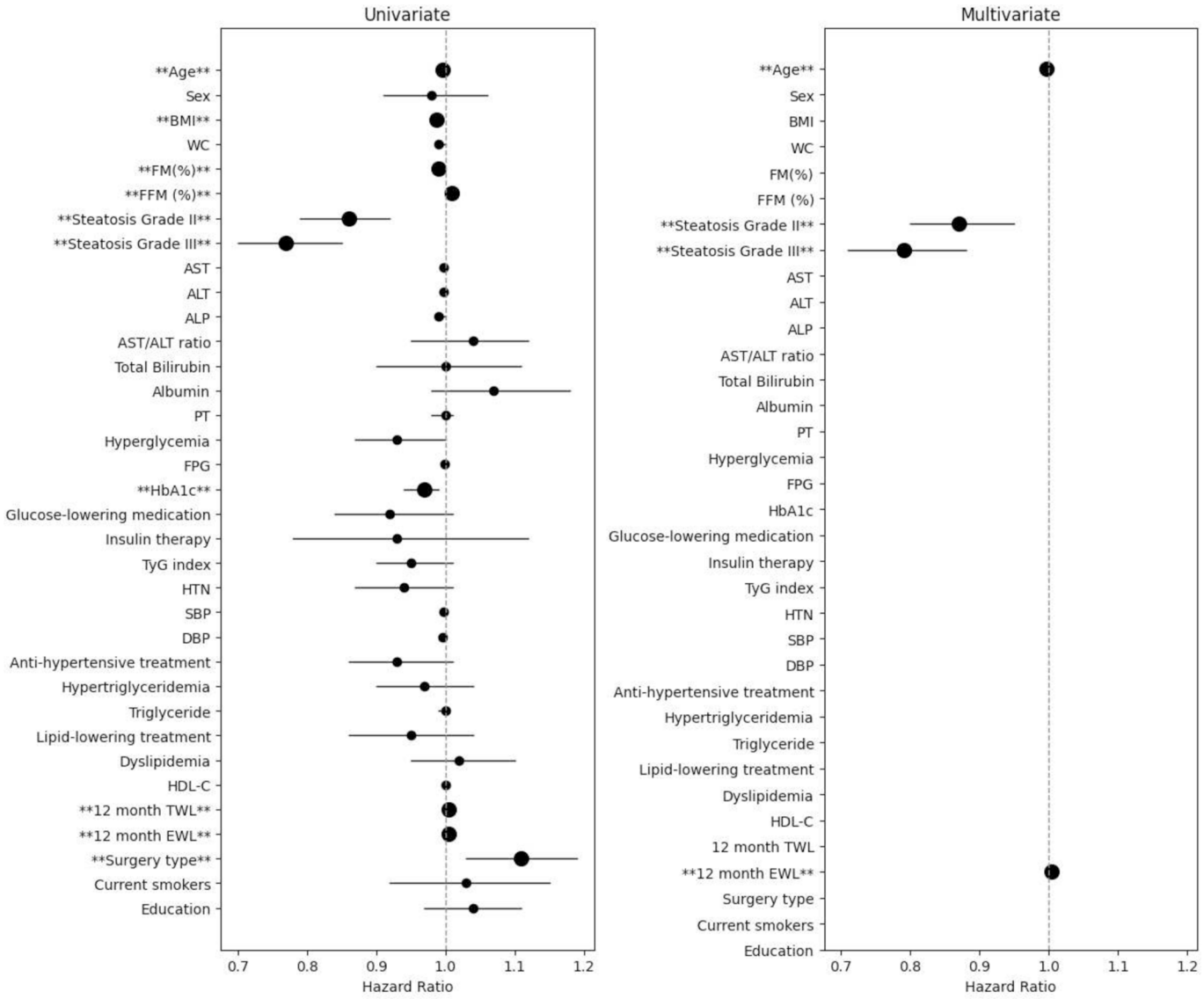

Fig. 3. Forest plots showing the univariate and multivariate hazard ratios for the potential predictors of MASLD resolution. Hazard ratios (HR) with 95 % confidence intervals (CI) are presented for each variable. MASLD, metabolic-dysfunction associated steatotic liver disease; BMI, body mass index; WC, waist circumference; FM, fat mass; FFM, fat-free mass; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c; TyG index, Triglyceride-glucose index calculated as Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TWL, total weight loss percentage; EWL, excess weight loss percentage. The univariate and multivariate analyses presented in this figure are conducted on the total population before applying propensity score matching. The vertical reference line (at HR = 1) indicates no effect. Statistical significance ($p < 0.05$) is indicated by asterisks on both sides of the variable name and an increased marker size.

methodology allowed for a more robust and clinically relevant assessment of the impact of surgical approaches on MASLD outcomes. Univariate Cox proportional hazard regression analysis explored the relationship between potential predictors and the outcomes of interest (MASLD resolution or relapse). The univariate model's significance threshold for variable selection was set at an alpha level of 0.2. Risk factors for MASLD resolution or relapse were evaluated by calculating HRs using a stepwise backward Cox proportional hazards regression model. The Stata version 14.0 (Stata Corp. LLC, TX, USA) was used for the analysis. P-values less than 0.05 were considered statistically significant using a two-tailed test.

3. Results

An overall sample of 3951 participants with MASLD were considered eligible for this study, including 2766 undergoing SG and 1185 undergoing OAGB. Before applying PSM, the groups had statistically significant differences in demographics, body composition, biochemical measures, dyslipidemia, and glycemic and smoking status. After conducting 1:1 PSM, 1618 participants (809 in each surgical group) remained. The matched participants showed no significant differences and were well-balanced, as indicated by the balance diagnostics; the SMD was below 0.20 for all variables (Table 1).

In this study, 1424 participants (707 undergoing SG and 717 undergoing OAGB) experienced MASLD resolution during the maximum follow-up of four years and the median follow-up of 2.2 years (IQR: 1.0–3.3). The cumulative incidence of MASLD resolution was 0.93 (95 % CI: 0.91–0.94) in the SG group and 0.93 (95 % CI: 0.92–0.95) in the OAGB group. The log-rank test produced a value of 0.395, indicating no statistically significant difference between the surgical groups (P = 0.530) (Fig. 2(A)). The overall incidence rate (IR) for MASLD resolution through the maximum follow-up of four years was 71.1 per 1000 person-

Table 4
Univariate and multivariate hazard ratios for the potential predictors of MASLD relapse.

	Univariate HR (95 % CI)	Multivariate HR (95 % CI)
Age, (years)	**1.02 (1.01–1.03)***	**1.02 (1.01–1.03)***
Sex (Ref: male)	**1.292 (1.007–1.658)***	–
BMI, (kg/m^2)	**1.017 (1.001–1.033)***	–
WC, (cm)	1.00 (0.99–1.01)	–
FM, (%)	**1.03 (1.01–1.05)***	**1.02 (1.00–1.05)***
FFM, (%)	**0.96 (0.94–0.98)***	–
Steatosis status (Ref: Grade I)		–
Grade II	**1.36 (1.07–1.71)***	**1.32 (1.04–1.67)***
Grade III	**1.329 (1.005–1.759)***	1.32 (0.99–1.75)
AST, (IU/L)	0.99 (0.98–1.00)	–
ALT, (IU/L)	0.996 (0.992–1.001)	–
ALP, (IU/L)	1.000 (0.998–1.001)	–
AST/ALT ratio	**1.27 (1.04–1.54)***	–
Total Bilirubin, (IU/L)	1.24 (0.908–1.706)	–
Albumin, (μmol/L)	1.09 (0.83–1.43)	–
PT, (sec)	0.95 (0.87–1.04)	–
Hyperglycemia (Ref: no)	0.87 (0.71–1.07)	–
FPG, (mmol/L)	1.001 (0.999–1.003)	–
HbA1c, (%)	1.01 (0.94–1.09)	–
Glucose-lowering medication (Ref: no)	1.07 (0.83–1.38)	–
Insulin therapy (Ref: no)	1.24 (0.77–1.99)	–
TyG index	1.07 (0.90–1.26)	–
HTN (Ref: no)	0.97 (0.79–1.20)	–
SBP, (mmHg)	0.998 (0.989–1.006)	–
DBP, (mmHg)	1.00 (0.98–1.01)	–
Anti-hypertensive treatment (Ref: no)	**1.28 (1.03–1.60)***	–
Hypertriglyceridemia (Ref: no)	1.03 (0.84–1.26)	–
Triglyceride, (mmol/L)	1.00 (0.99–1.00)	–
Lipid-lowering treatment (Ref: no)	1.23 (0.95–1.58)	–
Dyslipidemia (Ref: no)	0.95 (0.77–1.18)	–
HDL-C, (mmol/L)	1.00 (0.99–1.01)	–
12-month TWL, (%)	**0.97 (0.96–0.98)***	–
12-month EWL, (%)	**0.986 (0.981–0.992)***	–
Surgery type (Ref: OAGB)	0.93 (0.75–1.14)	–
Current smokers (Ref: no)	0.75 (0.53–1.08)	–
Education (Ref: ≤ 12 years)	**0.73 (0.60–0.89)***	–

MASLD, metabolic-dysfunction associated steatotic liver disease; HR, hazard ratio; BMI, body mass index; WC, waist circumference; FM, fat mass; FFM, fat-free mass; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c; TyG index, Triglyceride-glucose index calculated as Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TWL, total weight loss; EWL, excess weight loss. The univariate and multivariate analyses presented in this table are conducted on the total population before applying propensity score matching.

* P-value < 0.05.

month (95 % CI: 68.1–75.6), which corresponds to 88 % of the participants. The IRs for SG and OAGB were 72.4 per 1000 person-month (95 % CI: 67.3–78.0) and 71.1 per 1000 person-month (95 % CI: 68.1–75.6), respectively. However, the hazard ratio (HR) for MASLD resolution did not differ significantly between the surgical groups (Table 2).

The cumulative incidence of MASLD relapse was 0.29 (95 % CI: 0.24–0.35) in the SG group and 0.31 (95 % CI: 0.26–0.36) in the OAGB group. Fig. 2(B) illustrates the Kaplan-Meier curves for the cumulative incidence of MASLD relapse throughout the follow-up period. Statistical analysis using the log-rank test yielded a test statistic of 0.179 ($P = 0.673$), indicating no significant difference in MASLD relapse between the two surgical groups. The overall IR for MASLD relapse during the maximum follow-up of four years was 8.7 per 1000 person-month (95 % CI: 7.4–10.1), representing 18 % of the participants who had initially experienced resolution. The relapse IR for those undergoing SG and OAGB were 8.4 per 1000 person-month (95 % CI: 6.7–10.5) and 8.9 per 1000 person-month (95 % CI: 7.3–10.9), respectively. The HRs for relapse were comparable between the SG and OAGB groups. For the patients who experienced relapse, the median time in resolution was 18.0 months, with an IQR of 12.0 to 30.0 months.

In the univariate analysis, several factors were identified as predictors of MASLD resolution, including age, BMI, FM%, FFM%, hepatic steatosis grades II and III (compared to grade I), HbA1c, 12-month TWL %, 12-month EWL%, and surgical technique. After conducting multivariate analysis, a lower percentage of hepatic steatosis, a greater 12-month EWL%, and younger age were retained as significant predictors (Table 3 and Fig. 3).

In the univariate analysis for predictors of MASLD relapse, significant variables included age, sex, BMI, FM%, FFM%, hepatic steatosis grades II and III (compared to grade I), AST/ALT ratio, anti-hypertensive treatment, 12-month TWL%, 12-month EWL%, and education. However, after performing multivariate analysis, an increased percentage of liver steatosis, a higher Pre-Op FM%, and older age remained significant predictors (Table 4 and Fig. 4).

4. Discussion

The results of this study, conducted over a maximum follow-up of four years with a median follow-up of 2.2 years (IQR: 1.0–3.3), revealed no significant differences in the resolution and relapse of MASLD between the propensity score-matched SG and OAGB surgical groups following MBS. Factors predicting the resolution of MASLD included a lower percentage of hepatic steatosis, a higher 12-month EWL%, and younger age. Conversely, predictors of MASLD relapse included a higher percentage of liver steatosis, higher Pre-Op FM%, and older age.

The pathogenesis of MASLD remains incompletely understood; however, the “multiple hit” hypothesis has indeed superseded the traditional “two-hit” model in explaining the complex pathogenesis [12,13]. This updated model considers various factors, such as environmental influences, dietary habits, metabolic dysfunction, obesity, insulin resistance, adipose tissue dysfunction, variations in the intestinal microbiome and gut-liver axis, genetic and epigenetic factors, and oxidative stress.

The American Association for the Study of Liver Diseases (AASLD) practice guidelines recommend a multifaceted approach to managing MASLD. First, lifestyle interventions such as dietary changes and increased physical activity should be implemented to facilitate weight loss. Second, pharmacological treatments, although not explicitly approved for MASLD, Rezdiffra (Resmetirom) has recently been approved by the U.S. FDA due to potential benefits for MASH. Third, MBS is also recommended [5,14]. Results from a prospective study involving 180 participants with severe obesity and biopsy-confirmed MASH who underwent various bariatric surgical techniques (including biliointestinal bypass, gastric banding, RYGB, and SG) displayed promising outcomes [15]. Five years after the surgery, 84 % of the participants achieved resolution of MASH without any worsening of fibrosis, 70.2 % experienced fibrosis reduction compared to baseline, and 56 % showed complete resolution of fibrosis. Additionally, Verrastro et al. conducted a substantial randomized controlled trial to assess the effectiveness of two major bariatric surgical techniques, RYGB and SG, alongside lifestyle modifications and medical therapy, on the histological resolution of MASH [16]. The study, part of the BRAVES cohort, included 288 participants (44 % female) with obesity and histologically confirmed MASH. The results indicated that the probability of achieving MASH resolution was 3.60 times higher in the RYGB group and 3.67 times higher in the SG group than in those undergoing lifestyle modifications.

A study including 100 participants (62 % female) who underwent either SG or RYGB indicated that RYGB was superior to SG for the

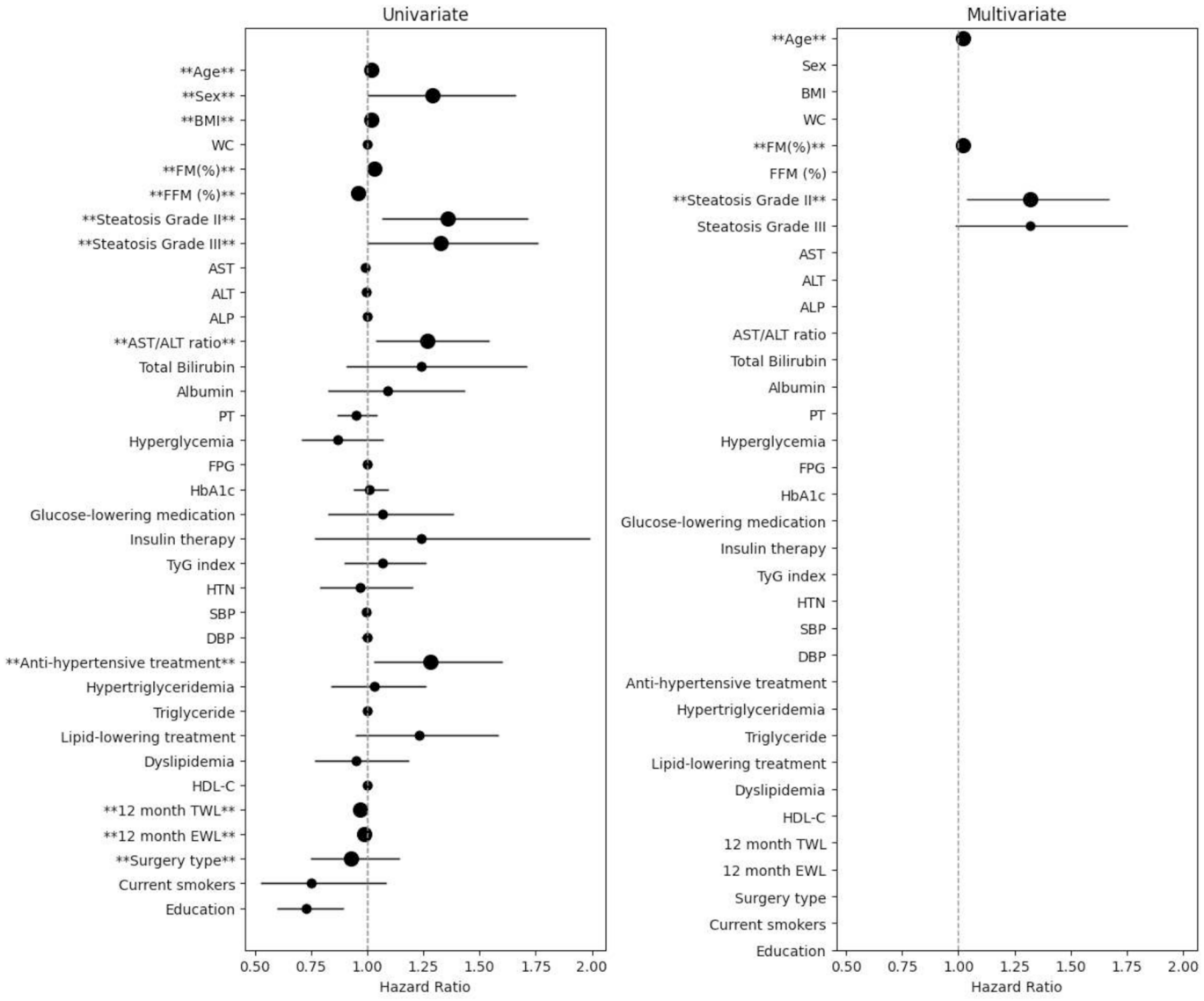

Fig. 4. Forest plots showing the univariate and multivariate hazard ratios for the potential predictors of MASLD relapse. Hazard ratios (HR) with 95 % confidence intervals (CI) are presented for each variable. MASLD, metabolic-dysfunction associated steatotic liver disease; BMI, body mass index; WC, waist circumference; FM, fat mass; FFM, fat-free mass; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT, prothrombin time; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c; TyG index, Triglyceride-glucose index calculated as Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TWL, total weight loss percentage; EWL, excess weight loss percentage. The univariate and multivariate analyses presented in this figure are conducted on the total population before applying propensity score matching. The vertical reference line (at HR = 1) indicates no effect. Statistical significance ($p < 0.05$) is indicated by asterisks on both sides of the variable name and an increased marker size.

improvement or resolution of MASLD after a median follow-up of 12.5 months [17]. In contrast, a matched cohort study of 96 participants (45.8 % female) with severe obesity, type 2 diabetes, and MASLD demonstrated that SG was favored over RYGB in achieving MASLD resolution at three years Post-Op [18]. However, a subsequent *meta*-analysis of 45 studies ultimately concluded that SG and RYGB are equally effective for managing and treating MASLD/MASH [19]. Despite the existing data on MASLD resolution following SG and RYGB, research on OAGB is still limited. In the current matched study, the overall IR for MASLD resolution after MBS through the maximum follow-up of four years was 71.1 per 1000 person-month (reflecting an 88 % resolution rate among participants), with comparable outcomes between SG and OAGB. Furthermore, a lower percentage of hepatic steatosis, a higher 12-month EWL%, and younger age were significant predictors of MASLD resolution.

Drawing from our previous studies indicating that diabetes and hypertension can relapse after initial remission following MBS [20,21], we hypothesize that MASLD may similarly recur as a hepatic manifestation of metabolic syndrome. In this study, we found that the overall IR for MASLD relapse during the maximum follow-up of four years was 8.7 per 1000 person-month, accounting for 18 % of participants who had initially achieved resolution, with no significant differences observed between SG and OAGB. Moreover, a greater degree of liver steatosis, higher Pre-Op FM%, and older age emerged as significant predictors of MASLD relapse. Given that only grade II hepatic steatosis emerged as a significant predictor while grade III did not, we speculate that this may be attributed to the limited number of individuals with grade III hepatic steatosis who achieved MASLD resolution. Consequently, the statistical power for grade III to serve as a significant predictor may have been insufficient.

The main limitations of our study are as follows: 1) Its non-randomized design, which may introduce bias. However, we employed

PSM to address this issue, which has limitations in addressing unmeasured confounders. 2) The lack of liver biopsy and histological data, which are considered the gold standard for assessing chronic liver disease. 3) Due to the dynamic nature of a prospective cohort study, data for each participant at every follow-up time point were not available. While participants were followed for a maximum of four years, the median follow-up duration was 2.2 years (IQR: 1.0–3.3). Nonetheless, our study has notable strengths, including its large prospective design. To our knowledge, it is one of the first observational matched cohort studies to examine the resolution and relapse of MASLD following MBS (specifically SG and OAGB) while also comparing outcomes and identifying predictors over a maximum follow-up of four years.

5. Conclusion

In this prospective matched cohort study with a maximum follow-up of four years conducted within the framework of the TOTS, we witnessed that MASLD resolution and relapse rates were similar among candidates for MBS undergoing SG and OAGB. A lower percentage of hepatic steatosis, higher 12-month EWL%, and younger age were identified as predictors of resolution. In comparison, a higher percentage of liver steatosis, higher Pre-Op FM%, and older age emerged as relapse predictors. To further clarify the long-term effects of various bariatric surgical techniques on MASLD outcomes and to assess whether any specific technique yields superior results, randomized clinical trials with sufficient sample sizes are warranted.

Ethical approval and informed consent

All the procedures performed in the study were approved by the Research Ethics Committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences and were under the ethical standards of the institutional Human Research Review Committee (No. 2ECRIES 93/03/13) and the 1964 Helsinki declaration and its later amendments. Informed written consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Authors' contributions

'SS': Study design, data collection, literature review, manuscript preparation, and the final approval of the manuscript. 'FH' and 'MV': Study design, revising the manuscript, and final approval of the manuscript. 'AK' and 'HT': Study design, performing surgeries, and the final approval of the manuscript. 'MM': Data analysis, data interpretation, and manuscript preparation. 'MB': Study design, data collection, coordination of patients' issues, manuscript preparation, manuscript revision, and final approval. All authors reviewed and approved the final draft.

CRediT authorship contribution statement

Sara Sadeghi: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Farhad Hosseinpanah:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Alireza Khalaj:** Writing – review & editing, Supervision, Methodology. **Maryam Mahdavi:** Writing – review & editing, Supervision, Resources, Methodology, Data curation. **Majid Valizadeh:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Hamidreza Taheri:** Writing – review & editing, Supervision, Methodology. **Maryam Barzin:** Writing – review & editing, Supervision, Resources, Methodology, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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