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ORIGINAL ARTICLE

Incidence of Symptomatic Cholelithiasis Following Laparoscopic Roux-en-Y Gastric Bypass Is Comparable to Laparoscopic Sleeve Gastrectomy: A Cohort Study

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Abstract
Background A few comparative studies have assessed the incidence of symptomatic cholelithiasis after laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB). However, they have shown inconsistent results. The present study has been designed based on comparing LSG and LRYGB regarding the incidence of symptomatic cholelithiasis and determining factors related to symptomatic cholelithiasis development after these procedures.
Methods This retrospective cohort study was conducted on 1163 patients aged ≥ 18 years old who underwent LRYGB ($n = 377$) or LSG ($n = 786$) from July 2006 to November 2019. The participants had no previous history of gallstones. A Cox-proportional hazard regression was used to assess associations between the types of procedures and the risk of symptomatic cholelithiasis. The univariable and then multivariable analysis were used to reveal the predictors of symptomatic cholelithiasis.
Results The mean person-time follow-up was 34 months (95% CI: 32.2 to 36.1 months)**.** The incidence of symptomatic cholelithiasis was 8.3% over the follow-up period. There was no significant association between the risk of symptomatic cholelithiasis development and the type of surgical procedure (HR: 1.35, 95% CI: 0.75 to 2.41). Females had a 2.3-fold higher risk of symptomatic cholelithiasis than males, according to the multivariable Cox regression (HR: 2.31, 95% CI: 1.23 to 4.33). In addition, there was an inverse association between the administration of UDCA and the incidence of symptomatic cholelithiasis (HR: 0.13, 95% CI: 0.01 to 0.99). Our findings indicated that age, baseline body mass index (BMI), percentage of weight loss (%WL) after three and six months following surgery, postoperative pregnancy, and obesity-related comorbidities did not predict the risk of symptomatic cholelithiasis.
Conclusion The present study illustrates no significant differences between LRYGB and LSG regarding symptomatic cholelithiasis occurrence. Our findings indicate that administration of UDCA has a protective effect against symptomatic cholelithiasis while, female gender is the main predictor of symptomatic cholelithiasis.

Keywords Cholelithiasis · Gallstones · Sleeve gastrectomy · Gastric bypass · Cholecystectomy · Bariatric surgery

Introduction

Cholelithiasis, the most common biliary tract disease, affects 10 to 15% of adults in developed countries [1]. Evidence indicates that several factors, such as age, sex, genetics, rapid weight loss, dietary habits, pregnancy, health conditions, and some medications, are associated with the development of gallstones [1, 2]. Obesity is also a well-known predictor of cholelithiasis, as the occurrence of gallstones in patients with obesity is fourfold higher than in subjects with normal weight [3]. Besides, bariatric surgery is considered a factor related to predicting gallstones [4]. According to the literature, the incidence of cholelithiasis after bariatric surgery

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ranges from 6 to 52% [3, 5–10]. Rapid weight reduction, alteration in gallbladder motility, an increase in cholesterol passage from the fat mass to the gallbladder, and oversaturation of bile are proposed as possible reasons for developing gallstones post-bariatric surgery [11, 12]. So, prophylactic strategies may be essential to prevent complications and reoperation related to gallstones.

Furthermore, evidence suggests that the risk of cholelithiasis varies depending on the type of bariatric surgery. Accordingly, the incidence of symptomatic and asymptomatic cholelithiasis and complicated gallstones such as common bile duct (CBD) stones is higher in patients who underwent laparoscopic Roux-en-Y gastric bypass (LRYGB) than in those who underwent laparoscopic sleeve gastrectomy (LSG) [11]. Several explanations are proposed for this occurrence, including dysmotility of the gallbladder due to the division of the hepatic branch of the vagus nerve, the difference in time of gastric emptying, and a decrease in postprandial cholecystokinin secretion [13, 14]. Thus, some studies recommend concomitant cholecystectomy during LRYGB to avoid symptomatic cholelithiasis and CBD stones [8, 15]. However, previous research and meta-analyses did not support prophylactic cholecystectomy due to high complications after concomitant surgery, as well as longer hospital stays and operation times [16–18]. A few studies have compared the incidence of symptomatic cholelithiasis between LRYGB and LSG, but they have not shown consistent results [19–21].

It is also crucial to recognize the risk factors for the development of symptomatic cholelithiasis in patients who undergo bariatric surgery. However, it can provide opportunities for high-risk patients to receive preventive therapy. Investigations have found several factors, such as gender, rate of weight loss, and obesity-related comorbidities, that may predict the risk of gallstone development [2, 19, 22]. Nevertheless, these factors are contradictory [23].

Therefore, the present study was designed to compare the incidence of symptomatic cholelithiasis between LSG and LRYGB and to determine predictors of symptomatic cholelithiasis after these procedures.

Materials and Methods

The present retrospective study was conducted using prospectively collected data. The National Institutes of Health (NIH) guidelines defined indications for bariatric surgery as body mass index (BMI) ≥ 40 kg/m^2, or ≥ 35 kg/m^2 with at least one comorbidity [24]. All patients were between 14 and 70 years old, with no significant mental health disorders, and did not have an addiction to alcohol and/or drugs. We generally recommended LRYGB for patients with a higher BMI, in the presence of several comorbidities, and for patients with severe gastroesophageal reflux disease (GERD). On the contrary, high-risk patients, e.g., patients with cardiac disease or organ transplantation, and patients with multiple medications taken for any illness, including psychiatric disorders or arthritis (except metabolic disorders), underwent LSG.

In our center, a total of 1356 patients underwent LRYGB ($n = 463$) and LSG ($n = 893$) between July 2006 and November 2019. A preoperative workup, including a blood test and abdominal ultrasonography, was performed for all the patients. If there was a pre-existing gallstone on the abdominal ultrasonography, simultaneous cholecystectomy was performed during LRYGB and LSG. All surgeries were performed by a single surgeon (K.T). In LRYGB, the pouch volume was 25–30 mL, and the Roux-en-Y limb was 150–200 cm long (50 cm biliopancreatic limb and 100–150 cm alimentary limb). In LSG, a 36-Fr bougie was used for calibration, and the staple line was reinforced by resewing. Postoperatively, ursodeoxycholic acid (UDCA) was not prescribed for these patients. However, we placed our patients who underwent LRYGB on UDCA 300 mg twice a day starting in January 2016 and those who underwent LSG from December 2019. Patients' follow-up was done at one week, three, six, and twelve months after surgery and annually afterward in our outpatient center. At each visit, we recorded the patients' weight and the occurrence of postoperative complications. If patients had symptoms suggesting cholelithiasis, including episodic, stable, and severe right upper abdomen or epigastric pain, shoulder or back pain, and vomiting, postoperative abdominal ultrasonography was performed to confirm gallstones.

In the present study, patients who had a prior cholecystectomy and those who were diagnosed with gallstones during preoperative workup were excluded from the study ($n = 165$). We also excluded adolescents aged < 18 years old ($n = 25$) and patients who passed away during the first 30 days after surgery ($n = 3$). Finally, 1163 adult patients (LRYGB = 377 and LSG = 786) were included in the analysis. In the LRYGB group, 123 patients were put on UDCA, but none of the patients in the LSG group were. The primary goal of the study was to compare the incidence of symptomatic cholelithiasis between LRYGB and LSG, and the secondary outcome was to determine factors associated with the incidence of symptomatic cholelithiasis.

Statistical Analysis

Statistical analyses were conducted using SPSS software (version 20.0; IBM Corporation, Armonk, NY, USA). The association between types of procedures and the incidence of symptomatic cholelithiasis was examined using Cox-proportional hazard regression. The person-time follow-up duration was calculated from the day of surgery to the date of cholelithiasis development, loss of follow-up, or the end of follow-up. It was shown as the mean and 95% confidence interval (95% CI). The risk of symptomatic cholelithiasis incidence after LRYGB and LSG was reported as a hazard ratio (HR) and 95% CI. The first model was adjusted for UDCA administration, age, and sex. The second model was further adjusted for baseline BMI and percentage of weight loss (%WL). The third model was further adjusted for pregnancy and preoperative comorbidities. The LRYGB was defined as a reference group. The Kaplan–Meier analysis, using a log-rank test, was conducted to compare the frequency of symptomatic cholelithiasis events between the two procedures. The univariable Cox regression analysis was performed to determine independent factors that could predict symptomatic cholelithiasis. Type of surgery, age, sex, UDCA, baseline BMI, %WL after three and six months, previous bariatric surgery, pregnancy, type 2 diabetes, hypertension, dyslipidemia, fatty liver, sleep apnea, psychiatric disorders, and hyperuricemia were considered as independent variables. Then, the variables with a P value < 0.2 are inserted into a multivariable Cox regression analysis. The significant level was determined as a P value < 0.05.

Table 1 Preoperative characteristics of participants based on surgical procedures

Characteristics	LRYGB (n = 377)	LSG (n = 786)	P value
Age (yr)	37.4 ± 10.4	37.4 ± 10.3	0.98
Female (%)	276 (73.2)	618 (78.6)	0.04
Weight (kg)	126 ± 26	110 ± 18	< 0.001
BMI (kg/m^2)	45.7 ± 7.3	40.0 ± 4.7	< 0.001
History of bariatric surgery	38 (10.1)	20 (2.5)	< 0.001
UDCA	123 (32.6)	–	< 0.001
Type 2 diabetes	91 (24.1)	130 (16.5)	0.002
Hyperlipidemia	166 (44.0)	300 (38.2)	0.05
Hypertension	98 (26.0)	116 (14.8)	< 0.001
Sleep apnea	143 (37.9)	217 (27.6)	< 0.001
Psychiatric disorders	127 (33.7)	187 (23.8)	< 0.001
Fatty liver	290 (76.9)	542 (69.0)	0.005
Hyperuricemia	33 (8.8)	53 (6.7)	0.21

Data were presented as mean ± SD for continuous variables and count (%) for non-continuous variables

BMI: body mass index; UDCA: ursodeoxycholic acid

Results

In the present retrospective cohort study, 1163 patients who underwent LRYGB (32.4%) or LSG (67.6%) and did not have preoperative cholelithiasis were included. The mean person-time follow-up was 34.1 months (32.2 to 36.1 months). It was 47.6 months (43.6 to 51.8 months) in LRYGB and 27.7 months (25.8 to 29.6 months) in LSG. The lower follow-up rate in the LSG group compared to the LRYGB group was due to two reasons: 1) the patient moved to another country, and 2) the patient refused to accept follow-up procedures for personal reasons. In the present study, 123 patients who underwent LRYGB were treated with UDCA. Preoperative characteristics of patients based on surgical procedures are presented in Table 1.

The preoperative prevalence of gallstones was 12.4% (n = 165). At the end of the follow-up period, 96 patients (8.3%) experienced symptomatic cholelithiasis and underwent laparoscopic cholecystectomy. Symptomatic cholelithiasis was found in 8.5% of patients who underwent LRYGB (n = 32) and 8.1% of those in the LSG group (n = 64). After removing patients who had revisional bariatric surgery (n = 58), the incidence was 8.1%. The mean time to develop symptomatic gallstones was 23.8 months (18.4 to 29.2 months) [37.7 months (25.1 to 50.5 months) in LRYGB and 16.8 months (12.6 to 21.1 months) in LSG]. A total of 56.2% of events occurred during the first year, and 43.8% of cases were observed one year post-surgery (P = 0.01). The incidence of symptomatic cholelithiasis was 9.5% (n = 85) in females and 4.1% (n = 11) in males (P = 0.005). Six cases of symptomatic cholelithiasis developed following pregnancy (12.5%).

The hazard ratio (95% CI) for the incidence of symptomatic cholelithiasis based on surgical procedures is presented in Table 2. There was no significant association between the types of surgical procedures and the risk of symptomatic cholelithiasis (HR: 1.35, 95% CI: 0.75 to 2.41). When we excluded patients with a history of a prior bariatric procedure, the hazard ratio (95%) for symptomatic cholelithiasis did not change significantly (HR: 1.45, 95% CI: 0.81 to 2.57). The Kaplan–Meier analysis indicated that the time to develop symptomatic cholelithiasis incidence is similar between the two procedures (Log rank = 2.49, P = 0.11) (Fig. 1).

Factors associated with the risk of symptomatic cholelithiasis are presented in Table 3. Age, baseline BMI, %WL three and six months after surgery, postoperative pregnancy, and baseline obesity-related comorbidities were not associated with the incidence of symptomatic cholelithiasis. However, there was an inverse association between the administration of UDCA and the incidence of symptomatic cholelithiasis (HR: 0.13, 95% CI: 0.01 to 0.99). In addition, we found a positive association between female gender and the risk of symptomatic cholelithiasis (HR: 2.31, 95% CI: 1.23 to 4.33). The Kaplan–Meier curves of cholelithiasis incidents in females and males, and patients who were placed on UDCA and those who were not, are presented in Figs. 2 and 3, respectively.

Table 2 Hazard ratio (95% CI) for symptomatic cholelithiasis incident based on surgical procedures

Symptomatic cholelithiasis	LRYGB ($n=377$)	LSG ($n=786$)	P value
Number of cases (%)	32 (8.5)	64 (8.1)	0.84
Mean follow-up (month)	47.6	27.7	< 0.001
Model 1	1	1.12 (0.70 to 1.78)	0.62
Model 2	1	1.42 (0.83 to 2.41)	0.19
Model 3	1	1.35 (0.75 to 2.41)	0.30

Model 1: adjusted for UDCA, age and sex

Model 2: additional adjustment for baseline BMI and %weight loss

Model 3: additional adjustment for postoperative pregnancy and preoperative comorbidities

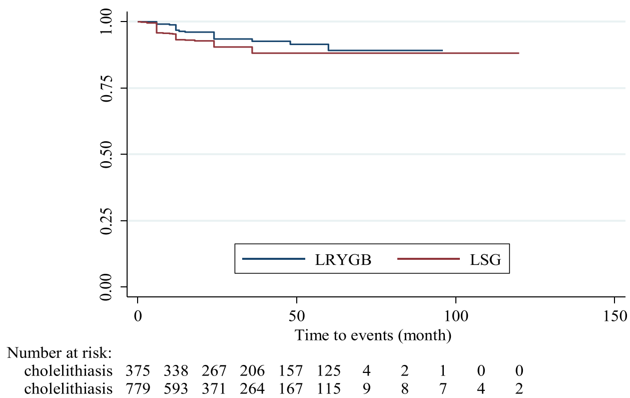

Fig. 1 Kaplan–Meier curves of cholelithiasis incident based on surgical procedures. (Log rank = 2.49 and $P=0.11$)

Discussion

In the present retrospective study, patients who underwent LRYGB did not show a higher risk of symptomatic cholelithiasis than those who underwent LSG. There was no significant relationship between age, baseline BMI, postoperative %WL, pregnancy, preoperative comorbidities, and the incidence of symptomatic cholelithiasis. However, an inverse association between UDCA administration and a positive association between the female gender and the postoperative incidence of symptomatic cholelithiasis was observed.

Several studies have indicated that the rate of gallstone occurrence in patients who have undergone bariatric surgery is higher than in the general population. This phenomenon may be related to the use of ultrasonography as a diagnostic tool to examine gallstone formation. The quality of abdominal ultrasound depends on body fat mass,

Table 3 Univariable and multivariable Cox regression to determine predictors of symptomatic cholelithiasis

Cholelithiasis incident	Univariable regression		Multivariable regression	
	HR (95%) CI	P value	HR (95%) CI	P value
Type of Procedure	1.40 (0.90 to 2.15)	0.12	1.11 (0.71 to 1.73)	0.64
Gender	2.34 (1.25 to 4.40)	0.008	2.31 (1.23 to 4.33)	0.009
Age	1.00 (0.82 to 1.21)	0.99	–	–
Baseline BMI	1.01 (0.87 to 1.18)	0.80	–	–
Ursodeoxycholic acid	0.12 (0.01 to 0.90)	0.04	0.13 (0.01 to 0.99)	0.04
%WL after 3 month	0.98 (0.93 to 1.04)	0.55	–	–
%WL after 6 month	1.00 (0.96 to 1.03)	0.99	–	–
History of bariatric surgery	1.12 (0.49 to 2.57)	0.77	–	–
Postoperative pregnancy	0.88 (0.38 to 2.02)	0.76	–	–
T2D	0.93 (0.54 to 1.59)	0.79	–	–
Hypertension	0.70 (0.40 to 1.24)	0.23	–	–
Dyslipidemia	0.86 (0.57 to 1.31)	0.50	–	–
Sleep apnea	1.11 (0.72 to 1.72)	0.61	–	–
Hyperuricemia	0.83 (0.36 to 1.90)	0.66	–	–
Psychiatric disorders	1.25 (0.82 to 1.92)	0.29	–	–
Fatty liver	1.08 (0.69 to 1.68)	0.73	–	–

BMI: body mass index; T2D: Type 2 diabetes; WL: weight loss

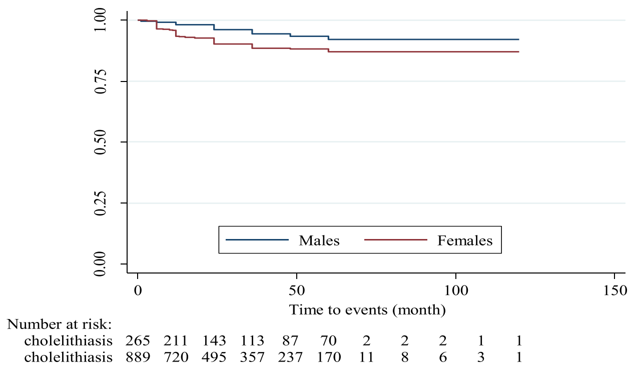

Fig. 2 Kaplan–Meier curves of cholelithiasis incident in males and females (Log rank = 5.61 and $P = 0.01$)

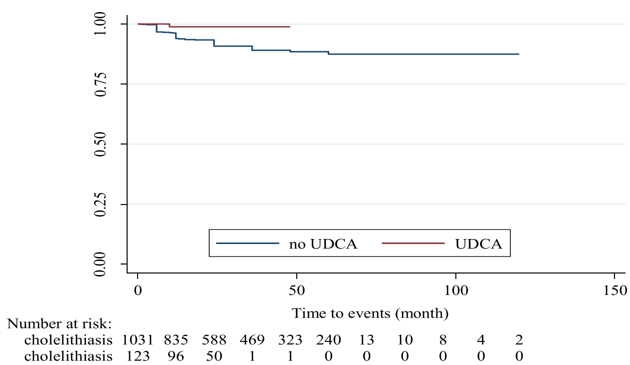

Fig. 3 Kaplan–Meier curves of cholelithiasis incident in patients who were placed on UDCA and those who were not (Log rank = 6.09 and $P = 0.01$)

and its accuracy diminishes as adiposity rises [25]. Therefore, postoperative weight loss by improving the quality of ultrasonography may lead to better detection of gallstones not visualized in patients with morbid obesity. In addition, preoperative ultrasound screening is not routine in some practices, and this may explain the higher incidence of newly diagnosed symptomatic cholelithiasis postoperatively. Chen et al. [26], in a cohort study, indicated that the risk of gallstones is comparable between patients who underwent bariatric surgery and patients with obesity. Still, it is higher than the general population overall. Accordingly, obesity, but not bariatric surgery, may be responsible for a higher incidence of cholelithiasis in patients who have undergone bariatric surgery compared to the general population.

Previous studies with at least 12-month follow-up have reported the incidence of symptomatic cholelithiasis ranged from 3 to 15.7% after LRYGB [27–31] and 0.9 to 23% after LSG [12, 13, 22, 32–34]. The incidence rate observed in this study is in agreement with those studies. It is supposed that the incidence of gallstone formation in LRYGB is higher than LSG due to the difference in time for gastric pouch clearing and the difference in cholecystokinin levels after a meal. Still, our results did not confirm this hypothesis.

A few studies ($n = 6$) investigated the relationship between the types of procedures, i.e., LRYGB and LSG, and the risk of symptomatic cholelithiasis, and showed inconsistent findings [19–21, 35–38]. Coupaye et al. [19], in a prospective study, have reported no significant differences between the types of procedures and the occurrence of symptomatic cholelithiasis. Two other retrospective studies also showed that there was no significant relationship between the types of procedures (LRYGB and LSG) and the risk of symptomatic gallstones [21, 35]. In contrast, Mishra et al. [20], over a 6-year follow-up, revealed that the incidence of symptomatic cholelithiasis after LRYGB (4.9%) is higher than LSG (1.9%). Following the latter study, Tsirline et al. [38] and Sneineh et al. [37] demonstrated that the total number of LRYGB-treated patients who underwent cholecystectomy was significantly higher than LSG-treated patients. The reasons for this inconsistency between studies are not clear. However, it may be related to the differences in sample size, duration of follow-up, design of the study, and patient characteristics. In addition, geographical location is also important. Evidence has revealed that the prevalence of gallstones in Asia, particularly in South-Eastern Asia and Africa, is lower than in the USA and Europe [23, 38]. Differences in dietary patterns, such as the consumption of high-fat diets and refined carbohydrates by western countries compared to other countries, may be responsible for this event [26, 39]. Hence, further prospective cohort investigations are essential to make a conclusive decision.

In the present study, the incidence of gallstones in patients who received UDCA was significantly lower than in those who did not. Our findings are in agreement with previous studies that indicated beneficial effects of UDCA in the prevention of gallstones in patients who underwent bariatric surgery [40–42]. Moreover, the results of a meta-analysis of eight studies also supported the effectiveness of UDCA in reducing cholelithiasis (OR: 0.25, 95% CI: 0.17 to 0.38) [43]. However, Tsirline et al. [30] did not show the protective effect of UDCA against gallstone formation. They investigated 1398 patients who underwent bariatric surgeries by three individual surgeons. Out of those, one surgeon prescribed UCDA 600 mg daily for three to six months for his patients, the second placed his patients on UCDA in 2008 (but not before), and the third did not prescribe it for his patients. They indicated that the rate of cholecystectomy did not differ between patients on UCDA and those without UCDA.

According to our data, the risk of symptomatic gallstone formation in females was 2.3-fold higher than in males after bariatric surgery. Our results agree with some previous studies that demonstrated in patients who underwent bariatric surgery that female gender is a predictor of symptomatic cholelithiasis [20, 23] and asymptomatic cholelithiasis [22, 26]. The female gender is identified as a risk factor for cholelithiasis in the community [25, 29]. This is because female sex hormones, especially estrogen, promote gallstone formation by concentrating the cholesterol content of bile [24]. However, in our study, most patients who underwent bariatric surgery were females (77% of the population), which may have affected the results.

Regarding other predictors of symptomatic cholelithiasis, we did not find any relationship between age, BMI, %WL, and preoperative comorbidities (e.g., diabetes, dyslipidemia, sleep apnea, and fatty liver) and the incidence of symptomatic cholelithiasis. Although identifying significant predictors of symptomatic cholelithiasis plays an essential role in reducing the risk of postoperative complications and reoperations, there is no consensus about them. In our study, despite the fact that the patients who underwent LRYGB had higher baseline weight and %WL, the risk of symptomatic cholelithiasis in these patients was comparable to those who underwent LSG. Although rapid WL was determined as a risk factor for cholelithiasis, the results of previous studies in terms of the association between the rate of WL and gallstones are inconsistent. Some studies have shown that high weight loss is a predictor of symptomatic cholelithiasis [5, 35], but other studies did not report any relationship between weight loss and symptomatic gallstones [21, 33]. This inconsistency may be related to differences in the applied methods for calculating %WL.

We did not find a significant association between preoperative comorbidities and symptomatic cholelithiasis, which is consistent with other series [23, 26, 33, 35]. Despite this, data about the relationship between preoperative hypertension and symptomatic gallstones are controversial [26, 33, 35]. Further assessments are essential to determine the role of hypertension and the rate of weight loss in the development of symptomatic cholelithiasis.

Our study has some strengths and limitations. The main potential of the present study was the large sample size for each group, which increased the validity of the study. In contrast, the lack of randomization was one of our limitations, leading to selection bias. Although randomization was difficult due to differences in selective criteria between the two procedures, we used analytical strategies to compensate for covariates correlated with selection to mitigate such bias. However, further well-designed studies matched by sex, baseline BMI, and obesity-related comorbidities are required. Also, it was a retrospective cohort study, and missing data may have affected the results. Despite the fact that we regularly monitor patients and update our database, we may have missed some cases of symptomatic cholelithiasis handled at other hospitals, especially among those living in other countries. Finally, our findings may not be generalizable to other individuals due to differences in dietary patterns and food cultures, as well as genetic backgrounds across varied groups.

Conclusion

In conclusion, our results illustrated no significant differences in terms of symptomatic cholelithiasis occurrence between LRYGB and LSG. Our findings demonstrated that administration of UDCA has a protective effect against symptomatic cholelithiasis while female gender is the main predictor of symptomatic cholelithiasis. We found no significant relationship between other predefined predictors and the incidence of symptomatic cholelithiasis.

Author's contribution MG and KT contributed to the study conception, data extraction, data analysis, and manuscript drafting. RP and SED contributed to the manuscript drafting. All authors have read and approved the final manuscript.

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Declarations

Conflicts of interest None of authors have any conflict of interest.

Ethical approval The protocol of study was approved by ethical committee of Tehran University of Medical Sciences.

Consent to participate Consent form was obtained from all patients.

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