BMC Surgery

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Efficacy of ursodeoxycholic acid in reducing the necessity of cholecystectomy due to pre-existing and subsequently formed gallstones in patients who underwent laparoscopic sleeve gastrectomy

Muhammed Taha Demirpolat[1*], Muhammet Oğuz Celikkaya[1], Suleyman Cağlar Ertekin[2], Fatih Basak[1] and Abdullah Sisik[3]

Abstract

Background In this study, we aimed to investigate whether ursodeoxycholic acid (UDCA) would reduce the necessity of cholecystectomy in patients diagnosed with asymptomatic gallstones after laparoscopic sleeve gastrectomy (LSG) and in patients diagnosed with asymptomatic gallstones before LSG.

Methods Between July 2020 and November 2022, at least 2-year follow-ups of patients who underwent LSG for obesity were retrospectively analyzed. Patients with pre-existing asymptomatic gallstones during preoperative evaluation, those with UDCA treatment (group 1), and observation group (group 2). Patients with newly formed gallstones in postoperative outpatient clinic follow-up, those with UDCA treatment (group A), and those without UDCA treatment (group B).

Results A total of 425 patients included. At the end of the first year, patients who had newly formed gallstones after LSG had a higher total weight loss percentages (TWL%) (39.8 ± 6.1) compared to those who did not develop gallstones (37.9 ± 7.4), which were statistically significant ($p = 0.004$). Among patients who developed gallstones postoperatively, UDCA treatment was associated with a significantly lower cholecystectomy rate in patients with newly formed gallstones postoperatively ($p = 0.025$), while no significant difference was shown in patients with preoperative gallstones ($p = 0.631$).

Conclusion UDCA is a promising option for reducing the need for cholecystectomy in patients with post-LSG gallstones, but it appears ineffective for pre-existing gallstones.

Keywords Ursodeoxycholic acid, Gallstones, Laparoscopic sleeve gastrectomy, The necessity of cholecystectomy

*Correspondence:
Muhammed Taha Demirpolat
dr_mtd23@hotmail.com
[1] Department of General Surgery, University of Health Sciences, Umraniye Education and Research Hospital, Istanbul, Turkey
[2] Department of General Surgery, Altınbas University, Istanbul, Turkey
[3] Health Sciences Faculty, Gedik University, Istanbul, Turkey

Introduction

Surgery remains the most effective and sustainable method for treating obesity, which negatively impacts multiple organs and systems, leading to serious health complications. Various metabolic and bariatric surgery (MBS) procedures have been developed, with laparoscopic sleeve gastrectomy (LSG) being one of the most commonly performed. LSG facilitates effective and sustainable weight loss; however, this rapid weight loss may lead to both symptomatic and asymptomatic gallstone formation [1, 2].

Gallstone formation is notably more prevalent among individuals with obesity compared to those without. The prevalence of gallstones is approximately 10–20% in non-obese patients and 30–50% in obese patients. These gallstones can result in complications such as pancreatitis and cholecystitis, potentially necessitating cholecystectomy. Additionally, the rapid weight loss associated with metabolic and bariatric surgery (MBS) may further increase the risk of cholesterol gallstone formation in obese patients, leading to complications that may require cholecystectomy [3–5].

Sen et al. [6] reported that gallstones developed in about one in four patients and symptomatic gallstones in around one in ten patients by the end of the first postoperative year among obese patients who underwent LSG. Similarly, Manatsathit et al. [7] found that gallstones formed in nearly half of the patients with obesity after LSG, with symptomatic gallstones developing in 22.9% of those cases. Consequently, both obesity and MBS are closely linked to gallstone formation [8].

The pathophysiology underlying the elevated incidence of gallstones following MBS is not yet fully understood. It is hypothesized that increased levels of arachidonic acid and prostaglandins in bile lead to enhanced secretion of mucin and calcium from the gallbladder, contributing to gallstone incidence. By the end of the first year post-MBS, weight loss typically peaks, and the risk of gallstone formation is highest during this period [2–4, 8].

There is currently no consensus regarding the routine performance of concomitant cholecystectomy (CC) during LSG in patients with obesity and asymptomatic gallstones. Furthermore, there is a lack of sufficient studies addressing the management of gallstones that develop postoperatively. If the risk of gallstone-related complications and the need for cholecystectomy can be minimized in patients who develop gallstones after LSG, it may protect patients from both surgical stress and the potential morbidity and mortality associated with cholecystectomy [6, 8, 9].

Ursodeoxycholic acid (UDCA) is believed to prevent gallstone formation by reducing both the intestinal absorption and bile secretion of cholesterol. UDCA has been reported to inhibit gallstone formation related to weight loss following LSG and has also demonstrated efficacy as a gallstone dissolving agent [10, 11].

In this study, we aimed to evaluate the efficacy of UDCA in reducing the need for cholecystectomy in patients with asymptomatic gallstones, whether pre-existing or developed post-LSG.

Materials and methods

Study population and setting

Between July 2020 and November 2022, patients who underwent LSG for obesity at the General Surgery Clinic of Health Sciences University Umraniye Training and Research Hospital and had at least 2 years of clinical follow-up were retrospectively analyzed. Patients who underwent previous cholecystectomy, patients with asymptomatic gallstones larger than 1 cm, patients who underwent CC, and patients who were performed other types of MBS were excluded. Patients who underwent LSG and had asymptomatic gallstones smaller than 1 cm were included. A biliary disease (biliary pancreatitis, acute cholecystitis, choledocholithiasis, cholangitis, or biliary colics) that necessitates a hospital visit or admission was defined as symptomatic gallstone. The study was approved by the ethics committee of the tertiary health institution (29.04.2024/242359507). All patients were operated on by the same team, and our surgical technique was described in our previous study [1].

Data collection

Demographic data, including age, gender, preoperative weight, height, and body mass index (BMI) were collected. The weight and percentage of total weight loss (TWL%) were recorded at the end of the first postoperative year. For each patient, abdominal ultrasonography was performed in addition to clinical evaluation and laboratory tests in the last month preoperatively and at the 3rd, 6th and 12th months postoperatively and this follow-up program is our standardized clinical protocol for MBS patients. To ensure homogeneity, the same ultrasound device was used and all abdominal ultrasound procedures were performed by the same radiologist team (in our hospital, abdominal ultrasound procedures have been performed by gastrointestinal radiologists and validated among themselves). Among patients with asymptomatic gallstones with and without UDCA treatment, patients necessitating cholecystectomy due to symptomatic gallstones were recorded. This study was a retrospective analysis of prospectively recorded data.

BMI was calculated using the formula kg/m^2. TWL% was calculated with the formula [100 x (initial weight – first year weight) / initial weight] [1].

Study groups

Patients with gallstones who underwent LSG between July 2020 and September 2021 were not prescribed UDCA both preoperatively and postoperatively. However, we changed this protocol. Patients with pre-existing and newly developed gallstones who underwent LSG after September 2021 were prescribed UDCA. After September 2021, UDCA 1000 mg/day for 6 months was prescribed to patients with pre-existing gallstones and to patients with newly developed gallstones during post-LSG outpatient clinical follow-up. The recommended UDCA treatment dose for dissolving gallstones is 8–12 mg/kg/day (refer to product guidelines). Accordingly, the UDCA treatment dose for patients with pre-existing and subsequently developed gallstones was considered as 1000 mg/day in the clinical protocol. Patients who have symptoms despite UDCA treatment underwent cholecystectomy. In our clinical protocol, no patient has been prescribed prophylactic UDCA after LSG.

Patients were divided into two groups according to both preoperative and postoperative gallbladder status:

– For patients with pre-existing asymptomatic gallstones during preoperative evaluation:

  Those with UDCA treatment (group 1), patients with pre-existing gallstones preoperatively after September 2021.
  Those without UDCA treatment (group 2), patients with pre-existing gallstones preoperatively in September 2021 an before.

– For patients with newly formed gallstones in postoperative follow-up:

  Those with UDCA treatment (group A), patients with newly Formed gallstones after September 2021.
  Those without UDCA treatment (group B), patients with newly Formed gallstones in September 2021 and before.

Therefore, the patient groups compared represented different time periods. Group 2 and group B consisted of patients in whom we performed the previous treatment protocol, while group 1 and group A consisted of patients after the change of the treatment protocol.

Outcome measures

The primary objective of the study was to determine whether UDCA prevents the necessity of cholecystectomy for patients with newly developed gallstones after LSG.

The secondary objective of the study was to determine whether UDCA prevents the necessity of cholecystectomy for patients with pre-existing asymptomatic gallstones before LSG.

Statistical analysis

Data were analyzed using SPSS (IBM Corp., Armonk, NY, USA), version 20. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as frequencies and percentages.

The choice of statistical tests was based on the characteristics of the data. For normally distributed variables, comparisons between groups were made using the independent samples t-test, which is appropriate for comparing means between two groups. For non-normally distributed data, the Mann–Whitney U test was used. This non-parametric test is suitable for comparing the distributions of two independent groups when the data do not meet the assumptions of normality. Categorical variables were compared using the chi-square test or Fisher's exact test, as needed, for examining the association between groups. The correlation of TWL% and gallstone formation was analyzed by Receiver Operating Characteristics (ROC) analysis and the area under the curve (AUC) was calculated. The TWL% value with the highest sum of sensitivity and specificity for gallstone formation was determined by Youden's index.

Additionally, no analysis was conducted to control for potential confounders such as metabolic or genetic factors influencing gallstone formation within this study. Addressing these potential confounders would require more complex study designs, such as multivariate regression models, which were not employed in this retrospective analysis. A p-value of < 0.05 was considered statistically significant.

Results

In this retrospective cohort study, out of 476 patients who met the inclusion criteria, 51 were excluded for various reasons, and 425 patients were included in the final analysis. The flowchart (Fig. 1) shows both the included-excluded patients and the management of LSG patients diagnosed with gallstones at preoperative and postoperative clinical follow-ups.

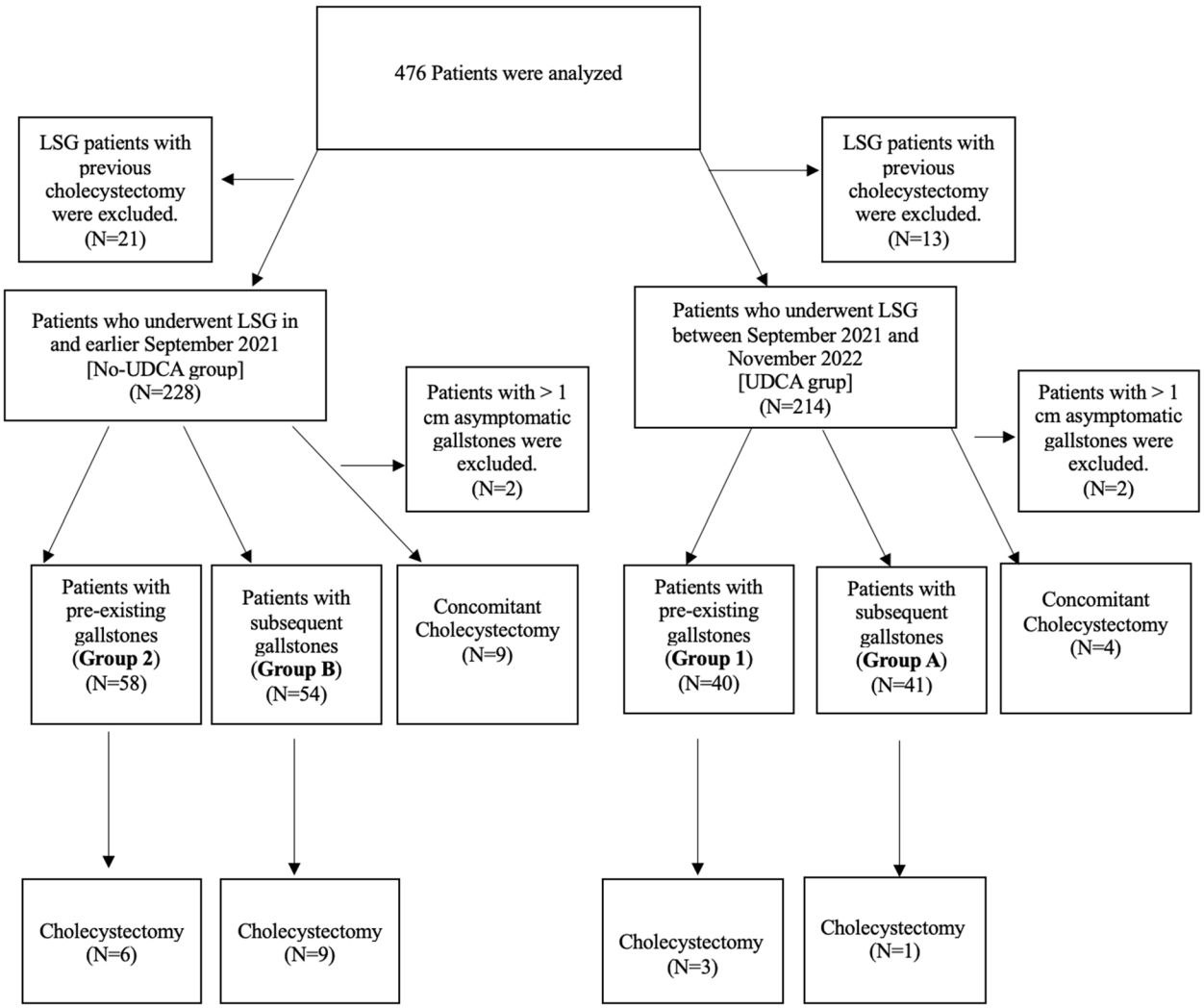

Fig. 1 Flowchart of management of pre-existing gallstones and newly developed gallstones in LSG

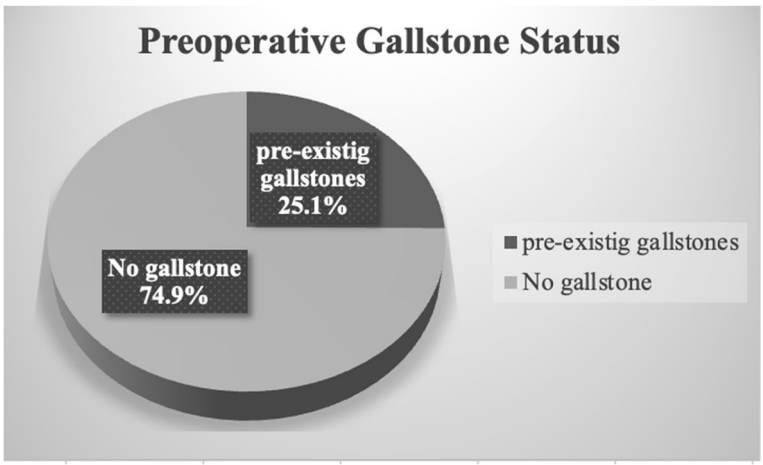

Fig. 2 Preoperative gallstones status

Table 1 Effect of UDCA on preoperative gallstones

	Group 1[a]	Group 2	*P*-value
Patients with pre-existing gallstones preoperatively			
Operated, *n (%)*	3 (7.5%)	6 (10.3%)	0.631
No operation needed	37	52	

Preoperative: Before bariatric surgery, UDCA: Ursodeoxycholic acid

[a] Used for 6 months following LSG, UDCA have been prescribed for patients having gallbladder stone sludge or stones with lower than 1 cm in size

Preoperative gallstones status

Of 476 patients, 34 (7.1%) were performed CC. Of 442 patients, 115 (25,1%) had preoperative gallstones (Fig. 2), but 13 of them underwent CC for symptomatic gallstones, and 2 were excluded because their gallstones were > 1 cm. Of the 98 patients with preoperative asymptomatic < 1 cm gallstones, 9 (9.1%) patients required cholecystectomy due to progression to symptomatic gallstones during follow-up. Three of these nine patients were in group 1, and six were in group 2. There was no significant difference in comparison of the groups ($p = 0.631$) (Table 1).

Postoperative gallstones status

During the follow-up period, 97 out of 329 patients (29.4%) developed gallstones postoperatively (Fig. 3), but 2 of them were excluded because their gallstones were > 1 cm. Comparison of patients who developed gallstones with those who did not showed no significant differences in terms of age, gender, height, preoperative weight, and preoperative BMI. However, a significant difference was observed in TWL%, weight at the end of the first year, and BMI at the end of the first year. At the end of the first year, patients who newly developed gallstones following LSG had a higher TWL% (39.8 ± 6.1), lower weight (73.4 ± 11.5), and lower BMI (27.3 ± 3.9) compared to those who did not develop gallstones (37.9 ± 7.4, 77.3 ± 13.9, and 28.7 ± 4.4), which were statistically significant ($p = 0.004$, $p = 0.028$, $p = 0.006$, respectively) (Table 2). Additionally, among patients with new-onset postoperative gallstones, those who received UDCA showed a significantly lower rate of cholecystectomy compared to those who did not ($p = 0.025$) (Table 3).

The analysis aimed to determine the optimal cut-off value of total weight loss percent (TWL%) for predicting postoperative gallstone formation. Using ROC analysis, a cut-off value of 25.0% was identified as the optimal threshold, providing a balance between sensitivity and specificity. At this cut-off, the sensitivity was 37.3%, and the specificity was 81.4%, with a Youden's Index of 18.7. The area under the curve (AUC) for the Receiver Operating Characteristics (ROC) analysis was 0.602 (95%CI = 0.536 to 0.668), with an asymptotic significance (p-value) of 0.004, indicating the model's discriminatory ability was statistically significant (Fig. 4).

These findings suggest that a TWL% cut-off of 25.0% offers the most clinically relevant balance, enabling effective discrimination between patients at risk of developing gallstones postoperatively and those who are not. A detailed summary of sensitivity, specificity, Youden's Index, AUC, and p-value for all tested thresholds is presented in Table 4.

Discussion

In the past, some surgeons have performed CC during MBS for patients with gallstones detected during preoperative evaluation [12, 13]. Nowadays, many surgeons suggest that CC is unnecessary for patients with asymptomatic gallstones undergoing LSG. Controversy remains as to whether CC should be performed for patients with preoperative gallstones. The management of LSG patients with postoperatively formed gallstones is also still unclear [6, 8, 14]. There may be differences in the risks of gallstone development between the various weight-loss procedures, such as a simple restrictive surgery or the more complex restrictive-malabsorptive surgery [15]. There is a significant increase in serum bile acid after laparoscopic Roux-en-Y gastric bypass, but there is no significant change in serum bile acid level after LSG, so the mechanism for gallstone formation following LSG is still unclear. Increased cholesterol saturation and increased biliary mucin concentration in the gallbladder are suggested to facilitate gallstone formation. UDCA helps in preventing gallstone formation by decreasing cholesterol saturation in bile, increasing bile flow through the gallbladder, and preventing cholesterol crystal formation, the first step in gallstone formation [4, 8, 15, 16].

The present study provides insights into the management of gallbladder issues in patients who underwent LSG. Among the 442 patients, a significant portion (25.1%) presented with preoperative gallstones. Despite concerns that pre-existing gallstones may impact postoperative outcomes, we observed no significant differences in key variables such as age, gender, baseline weight, height, or BMI between patients with and without preoperative gallstones. Among patients with asymptomatic < 1 cm pre-existing gallstones who were managed conservatively, we found no significant difference in the necessity of cholecystectomy between the groups with and without UDCA treatment (group 1, and group 2). The percentage of patients without preexisting gallstones and with newly developed gallstones post-LSG was 29.4%. The development of postoperative gallstones was associated with a notable effect on weight loss outcomes. Patients who newly developed gallstones following LSG had a significantly higher TWL% compared to

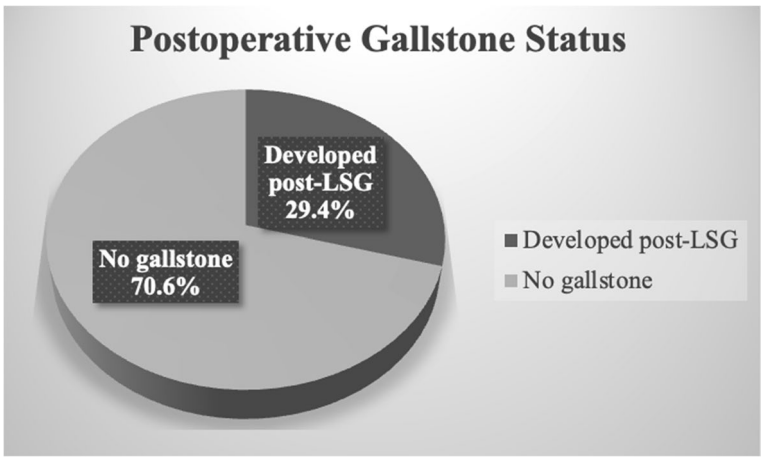

Fig. 3 Postoperative gallstones status

those who did not develop gallstones. This difference (39.8% vs. 37.9%) suggests that higher postoperative TWL% may be a contributing factor to the formation of gallstones. The incidence of gallstone formation is significantly increased in patients with TWL% > 25% after LSG. At this threshold, the sensitivity and specificity of TWL% for predicting gallstone formation were 37.3% and 81.4%, respectively. UDCA administration played a key role in managing patients who newly developed gallstones. For those who were diagnosed postoperatively with sludge or small gallstones, UDCA use was associated with a significantly lower rate of cholecystectomy compared to those who did not receive the medication. This finding underscores the potential benefit of UDCA in preventing the need for surgical intervention in postoperative patients. Interestingly, for patients who had preoperative gallstones, UDCA use did not appear to reduce cholecystectomy rates, suggesting that UDCA may be more effective in preventing complications arising from newly developed gallstones rather than managing pre-existing ones.

Although the incidence of gallstones in MBS candidates can reach nearly 50%, there is still no consensus on the optimal management of these patients [12, 13, 17]. In a study of 86 experts from 36 countries, 57% of experts agreed that CC should not be recommended for LSG patients with preoperative gallstones unless they are symptomatic [18]. In their study of 312 patients with gallstones who underwent LSG, Yardimci et al. [8] recommended only follow-up for patients with asymptomatic gallstones. In our study, the rate of LSG candidates with gallstones was 25.1%, and 13 (11.5%) of them underwent CC for symptomatic gallstones. The rate of postoperative symptomatic gallstones in LSG patients treated with UDCA compared to those not treated with UDCA was also not significantly different.

In a meta-analysis of 2513 patients, Fearon et al. [19] found that UDCA significantly reduced symptomatic and asymptomatic gallstone formation after MBS. Similarly, there are meta-analyses showing that prophylactic

Table 2 Postoperative gallstones status in laparoscopic sleeve gastrectomy patients without pre-existing gallstones

	Newly diagnosed—Postoperative gallstone status		
	Yes, *n* = 95	**No, Gallbladder intact, *n* = 232**	***P*-value**
Age, *Mean* ± *SD*	37.2 ± 11.1	37.8 ± 10.3	0.642
Gender, M/F, *n/n*	15/80	40/194	0.871
Baseline			
Height, *Mean* ± *SD*	163.7 ± 7.2	163.8 ± 8.4	0.825
Weight, *Mean* ± *SD*	122.2 ± 16.2	124.7 ± 17.9	0.344
BMI, *Mean* ± *SD*	45.5 ± 5.3	46.4 ± 5.1	0.150
First year			
Weight, *Mean* ± *SD*	73.4 ± 11.5	77.3 ± 13.9	**0.028**
BMI, *Mean* ± *SD*	27.3 ± 3.9	28.7 ± 4.4	**0.006**
TWL%, *Mean* ± *SD*	39.8 ± 6.1	37.9 ± 7.4	**0.004**

Postoperative: After bariatric surgery, BMI: Body Mass Index, TWL: Total Weight Loss

Table 3 Effect of UDCA on postoperative gallstones

	Group A[a]	**Group B**	***P*-value**
Patients with Newly diagnosed gallstones postoperatively			
Operated, *n (%)*	1 (2.4%)	9 (16.6%)	**0.025**
No operation needed	40	45	

UDCA Ursodeoxycholic acid, Postoperative: After laparoscopic sleeve gastrectomy

[a] Used for 6 months after diagnose in clinic follow-ups. UDCA have been prescribed for patients having gallbladder stone sludge or stones with lower than 1 cm in size

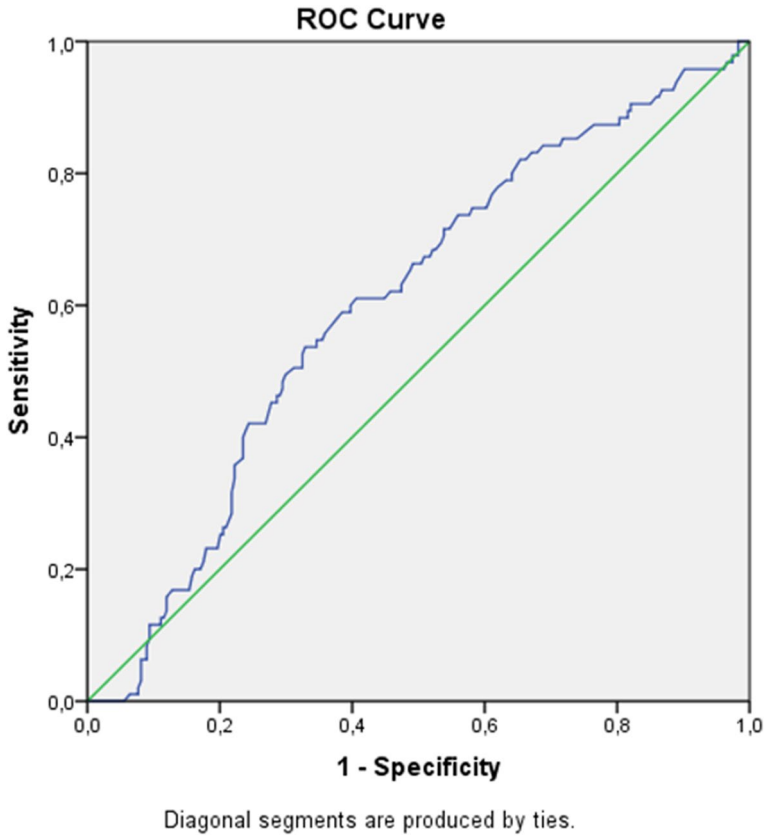

Fig. 4 ROC Curve of TWL% thresholds for predicting Post-LSG gallstone formation

Table 4 Summary of ROC analysis results for TWL%

TWL% Threshold	Sensitivity (%)	Specificity (%)	Youden's Index
12.5	94.9	3.4	-1.7
15.0	91.5	8.9	0.4
17.5	76.3	28.8	5.1
20.0	64.4	47.9	12.3
22.5	49.2	67.8	17.0
25.0	**37.3**	**81.4**	**18.7**
27.5	25.4	89.8	15.2
30.0	13.6	96.6	10.2
32.5	5.1	100.0	5.1

UDCA treatment after MBS reduces the occurrence of symptomatic gallstones and the necessity of cholecystectomy [20, 21]. The use of UDCA for 6 months after LSG decreased the occurrence of postoperative gallstones and significantly higher excess weight loss (EWL%) was found in LSG patients with the newly formed gallstones [22, 23]. In the preoperative examination, Pineda et al. [24] detected gallstones in 58 (34.3%) of 169 patients, and at the end of the 12th month following MBS, they detected newly developed gallstones in 31 (21.2%) of 146 patients. They also found no significant difference in EWL% between patients with and without de novo biliary disease. In our study, the incidence of patients with pre-existing gallstones before LSG was 25.1%, while the percentage of patients with newly developed gallstones after LSG was 29.4%. We found that the use of 1000 mg/day UDCA significantly reduced the necessity of cholecystectomy in patients with newly developed gallstones after LSG. In patients with newly formed gallstones after LSG, we found that TWL% values above 25% caused a significant increase in gallstone formation, therefore this result of current study supported the relationship between weight loss and gallstone formation. This result of our study was different from the findings of Pineda et al. [24]. These different findings between the current study and Pineda et al. may be explained by using different metrics for the analysis of weight loss (TWL% and EWL%, respectively), differences in types of MBS, and the characteristics of the patient populations.

Strengths and limitations

In the literature, there are studies on prophylactic UDCA treatment for the first 6 months postoperatively for the prevention of gallstone formation after LSG [23, 25, 26], but we did not find a study evaluating whether UDCA therapy prevents the necessity for cholecystectomy in patients who didn't receive prophylactic UDCA after LSG and developed gallstones during postoperative clinical controls. To the best of our knowledge, rather than evaluating UDCA's efficacy in preventing postoperative gallstone formation, this is the first study to examine how well it works in preventing newly formed gallstones from transforming into symptomatic and necessitating cholecystectomy.

It is obvious that the use of UDCA for the first 6 months after LSG prevents postoperative gallstone formation. Therefore, prophylactic UDCA use is recommended to prevent the formation of gallstones after LSG [27]. In addition, according to the results of our study, symptomatic gallstones can be prevented by continuing UDCA treatment in patients who develop gallstones despite prophylactic UDCA use in postoperative clinical follow-up. Thus, the incidence of cholecystectomy due to gallstones after LSG can be minimalized.

One limitation of this study is that the data of 13 patients who underwent CC during LSG were not analyzed. This exclusion was necessary to prevent potential bias, as performing cholecystectomy during LSG could impact outcomes related to gallstone formation and the need for future cholecystectomy. Additionally, since the study has a retrospective cohort design, it is inherently subject to limitations such as incomplete or missing data, recall bias, and potential confounding factors that may not have been fully considered. Moreover, the observational nature of the study restricts the ability to establish causality between UDCA use and reduced cholecystectomy rates. Prospective randomized controlled trials would be useful in confirming these findings and investigating other influencing factors. The last abdominal USG was performed at the postoperative 12th month; therefore, there could be patients with developed gallstones between the first and second postoperative years. This can be considered as another limitation of our study. A limitation of the study was that the patients were not tested by the same radiologist. Lastly, the study was conducted in a single center, which may limit the generalizability of the results to broader populations or different clinical settings.

Conclusion

UDCA is a promising option for reducing the need for cholecystectomy in patients with post-LSG gallstones, but it appears ineffective for pre-existing gallstones.

In LSG candidates, pre-existing asymptomatic gallstones can be managed conservatively. It revealed that UDCA treatment for the first 6 months postoperatively did not reduce the necessity for cholecystectomy in LSG patients with pre-existing gallstones.

Multi-center research with larger patient series and prospective randomized studies are needed to determine the effectivity of UDCA to achieve better postoperative outcomes.

Acknowledgements

None.

Informed consent

This study was performed in accordance with the principles of the Declaration of Helsinki. Patient consent was waived by the institutional review board (IRB) of University of Health Sciences Umraniye Training and Research Hospital due to the retrospective nature of the study. Informed consent was obtained from all subjects involved in the study.

Authors' contributions

Conceptualization: M.T.D. methodology: M.T.D. Software: F.B., S.C.E Validation: M.T.D., MOC Formal analysis: M.T.D., M.O.C. Investigation: M.T.D., M.O.C Resources: M.T.D. Data Curation: M.T.D., M.O.C, F.B Writing-Original Draft: M.T.D., A.S Writing-Review & Editing: M.T.D., A.S Visualization: M.T.D., F.B Supervision: M.T.D., S.C.E, A.S Project administration: M.T.D., A.S

Funding

None.

Data availability

The manuscript presents the data. Upon request, the corresponding author can provide the datasets analyzed within this study.

Declarations

Ethical approval and consent to participate

The study was approved by the Ethics Committee of University of Health Sciences Umraniye Training and Research Hospital. Approval of protocol number was (29.04.2024/242359507).

Consent for publications

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 4 November 2024 Accepted: 8 January 2025
Published online: 17 January 2025

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