



Original Article

Risk of cholecystectomy in morbidly obese patients after bariatric surgery in Taiwan

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ABSTRACT

Purpose: The anatomic rearrangement of the gastrointestinal tract after bariatric surgery may result in alterations in the bile acid pool and consequently, gallstone disease. We aimed to investigate whether patients undergoing bariatric surgery are at risk of developing gallbladder disease postoperatively.

Patients and methods: We conducted a population-based cohort study by using claims data from the Taiwan National Health Insurance Research Database. The study cohort comprised 4197 patients diagnosed with morbid obesity.

Results: Among the morbidly obese patients, 2698 underwent bariatric surgery. Females and younger subjects were more prevalent in the surgical group than non-surgical group. Bariatric surgery reduced all obesity-related comorbidities. Cox proportional hazards regression was performed, which revealed increased risk of cholecystectomy after bariatric surgery among obese patients (adjusted hazard ratio, 3.43; $p = 0.0165$). After adjusting for sex and age, the incidence of cholecystectomy was increased in the females population (adjusted hazard ratio, 3.74; $p < 0.05$) and in 30–64 years-old-group (adjusted hazard ratio: 3.69, $p < 0.05$). The cumulative incidence rate of cholecystectomy showed an increased tendency in those undergoing bariatric surgery by log-rank test.

Conclusion: Based on the Taiwan database population-based cohort study, bariatric surgery increases the risk of cholecystectomy among morbidly obese patients, especially in the female population and patients aged 30–64 years.

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Introduction

The rapidly increasing incidence of obesity has tripled over the past 20 years [1] and become an emerging worldwide public health problem. Bariatric surgery can aid in body weight loss [2,3,4,5] and is known as the effective treatment for obesity. However, although bariatric surgery has beneficial effects, increasing incidence of gallstone formation [6] and subsequent cholecystectomy were identified [7]. Gallstone formation was documented as

a common adverse effect of rapid body weight loss with diet [8–11] and bariatric surgery [12–18]. Lithogenic changes [10], saturation of bile [19,20], crystallisation-promoting compounds [6], increased cholesterol saturation of bile [10,19,21], and increased amounts of pronucleating proteins and mucin [10,12] have been observed and might be responsible for the defective gallbladder emptying [6,21].

The incidence of asymptomatic gallstone formation was noted to be about 10–25% in diet control [9] and 22–70% in bariatric surgery [14,15,17,22] depending on different follow-up periods. As for the incidence of symptomatic gallstones requiring cholecystectomy, it was about 7–27% [14–17,22,23]. Prophylactic cholecystectomy with bariatric surgery is still controversial. Routine cholecystectomy is suggested in open gastric bypass surgery [17], in cases of abnormal gallbladder or gallstones during opera-

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tion [24], in laparoscopic gastric bypass with safety and feasibility [25]. In contrast, due to the low risk of imperative cholecystectomy [26,27], increased operative time, and doubled hospital stay [25], prophylactic cholecystectomy might not be recommended.

Patients with obesity after bariatric surgery had a fivefold increased risk of symptomatic gallstones disease as compared with the general population [28]. Monitoring gallstones through ultrasound is suggested, and subsequent cholecystectomy is common in obese patients with more than 25% of body weight loss [9]. In addition, more than 25% excess weight loss within the first 3 months after bariatric surgery is the strongest predictor of postoperative cholecystectomy [27]. The rate of cholecystectomy in European patients is 1.45 times higher than in that in African-American patients, but preoperative body mass index (BMI) and sex were not the risk factors [27]. However, gallstones have a positive correlation with BMI, and female patients were more likely to have undergone previous cholecystectomy [29]. Whether female obese patients have a higher rate of cholecystectomy after bariatric surgery needs to be investigated.

The aim of this study was to estimate the incidence of gallstone-related cholecystectomy after bariatric surgery compared with morbid obesity without bariatric surgery. We also wanted to stratify the relationship of sex and age in cholecystectomy in obese patients who underwent or did not undergo bariatric surgery.

Material and methods

Data sources

We conducted a nationwide population-based cohort study using data from the National Health Insurance Research Database (NHIRD). The National Health Insurance program in Taiwan was launched on March 1, 1995, by the National Health Insurance Administration (NHIA), providing coverage for more than 23.03 million residents in Taiwan (approximately 99.2% of the population). The NHIA releases identification-encrypted data to the National Health Research Institute (NHRI) to establish the NHIRD. The Longitudinal Health Insurance Database 2000 (LHID2000), used in this study, contains medical information of 1 million beneficiaries randomly sampled from the registry of all beneficiaries in 2000. Claims data in the LHID2000 were extended from January 1, 1996, to December 31, 2011. Age- and sex-related distributions in the original claims data and the sampled data do not differ significantly. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes was used for diagnoses.

The NHRI scrambles patient identification and replaces it with surrogate numbers to ensure privacy. Furthermore, data confidentiality is maintained in accordance with NHIA and NHRI data regulations. Because the NHIRD contains de-identified secondary data for research, our study was exempted from obtaining the informed consent from participants. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

Study population and outcomes

Patients aged ≥ 20 years and < 100 years newly diagnosed with morbid obesity (ICD-9-CM, 278.01) underwent bariatric surgery (ICD-9-CM, 43.82, 43.89, 44.31, 44.38, 44.39, 44.68, 44.69, 44.95, and 44.99) between January 1, 2000, and December 31, 2010, were recruited. Patients who underwent cholecystectomy and those who did not (OP code, 51.22 and 51.23) were analysed, and those with newly diagnosed obesity who underwent bariatric surgery not between 2000 and 2010, those less than 20 years or older than 100 years or missing information on sex or age, and those with diagno-

sis of accepted cholecystectomy treatment before the index date were excluded. Patients with morbid obesity were identified using ICD-9-CM codes, with at least three outpatient visits within 1 year or one admission diagnosis during the study period. The diagnostic accuracy of morbid obesity was confirmed through the registration files of the Registry for Catastrophic Illness Patient Database, a subset of the NHIRD [30].

Potential confounders

We systematically identified the potential confounders for morbid obesity by referring to the ICD-9-CM codes in the claims data. The identified confounding factors were sex, age, insurance premium, level of urbanisation, residential area, occupation, comorbidities, and medications. The comorbidities associated with MACEs were hypertension (HTN) (ICD-9-CM, 401–405), hyperlipidemia (ICD-9-CM, 272), diabetes mellitus (DM) (ICD-9-CM, 250, 357.2, 362.01, 362.02, and 366.41), chronic kidney disease (CKD) (ICD-9-CM, 581–588, 403–404, 285.21, and 250.4), coronary artery disease (CAD) (ICD-9-CM, 411–414), congestive heart failure (CHF) (ICD-9-CM, 428), stroke (ICD-9-CM, 430–438), asthma (ICD-9-CM, 493), chronic obstructive pulmonary disease (COPD) (ICD-9-CM, 490–492, 494, and 496), and peripheral arterial occlusive disease (PAOD) (ICD-9-CM, 440–444). Propensity scores were calculated by multivariate logistic regression using the baseline covariates. The baseline characteristics of both cohorts were compared and then further matched by standardised mean differences, calculated as the difference in means or proportions of a variable divided by a pooled estimate of the standard deviation of the variable.

Statistical analyses

Differences in demographic characteristics and comorbidities between the study (with cholecystectomy) and comparison (without cholecystectomy) cohorts were examined using the chi-square test for non-continuous variables and two-sample t-tests for continuous variables. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated for each variable using Cox proportional hazards regression. Difference in the incidence of MACEs between the study and comparison cohorts was estimated using Kaplan–Meier curves by performing the log-rank test. Statistical analyses were performed using the SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, USA), and the level of significance was set at 0.05.

Results

A total of 4922 adults aged ≥ 20 years were hospitalised for morbid obesity in 2000–2010. Of these, 3064 and 1858 were diagnosed with morbid obesity with and without bariatric surgery, respectively. After exclusion of the diagnosed date of accepted cholecystectomy treatment before the index date, we finally recruited 2689 morbidly obese patients who underwent bariatric surgery in the study cohort and 1499 morbidly obese patients who did not undergo bariatric surgery in the comparison cohort (Fig. 1). The number of female patient is significant higher in the study than the comparison cohort (63.4% vs. 52.8%, $p < 0.0001$) (Table 1). The mean age was significant younger in the study cohort as compared with that in the comparison cohort (32.9 ± 9.1 vs. 44.1 ± 15.1 , $p < 0.0001$). The basic demographic characteristics, like as HTN, hyperlipidemia, DM, CAD, CHF, stroke, CKD, COPD, and PAOD, were significantly lower in the study cohort compared with those in the comparison cohort ($p < 0.0001$). The means (median) of follow-up period were 2.41 (2.02) years and 3.77 (3.38) years for the study and comparison cohort, respectively.

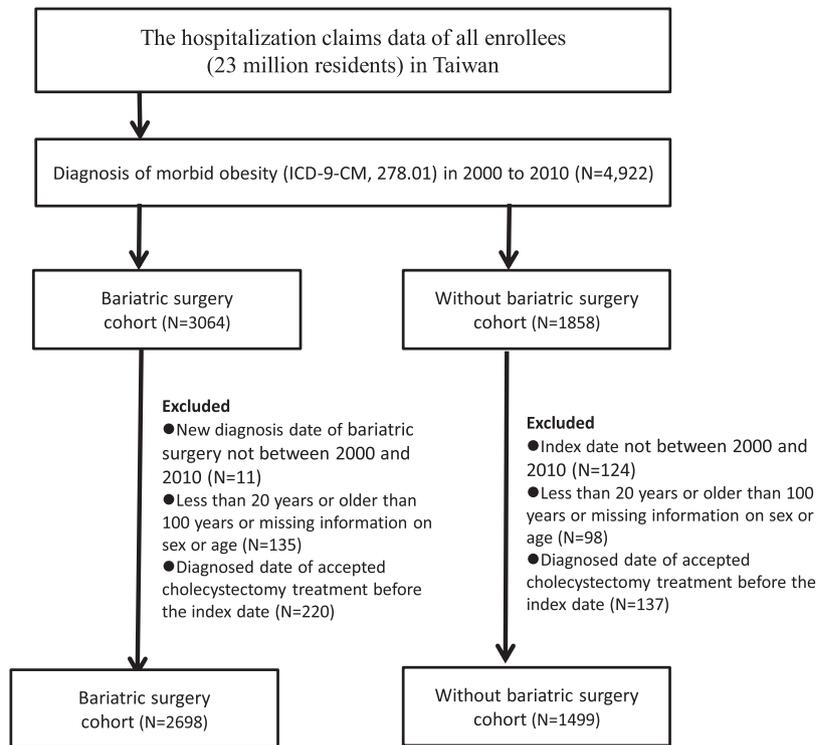


Fig. 1. Flowchart of the patient selection process in the study (morbid obesity with bariatric surgery) and comparison cohort (morbid obesity without bariatric surgery).

Table 1
Demographic characteristics of morbidly obese patients who underwent and did not undergo bariatric surgery.

Variable	Undergoing bariatric surgery				P value ^b
	No		Yes		
	N	%	N	%	
Malabsorptive procedures	–	–	1657	61.42	
Restrictive procedures	–	–	2312	85.69	
Sex					<0.0001
Female	791	52.77	1711	63.42	
Male	708	47.23	987	36.58	
Age at baseline, years					<0.0001
20–29 years	287	19.15	1258	46.64	
30–64 years	1046	69.78	1439	53.34	
65–100 years	166	11.07	1	0.04	
Mean(SD)	44.09(15.06)		32.92(9.08)		<0.0001 ^a
Comorbidities					
HTN	745	49.7	239	8.86	<0.0001
Hyperlipidemia	323	21.55	105	3.89	<0.0001
DM	529	35.29	166	6.15	<0.0001
CAD	260	17.34	66	2.45	<0.0001
CHF	254	16.94	38	1.41	<0.0001
Stroke	122	8.14	37	1.37	<0.0001
CKD	132	8.81	23	0.85	<0.0001
COPD	147	9.81	35	1.3	<0.0001
PAOD	29	1.93	4	0.15	<0.0001

The means (median) of the follow-up periods were 2.41 (2.02) years and 3.77 (3.38) years for the study and comparison cohorts, respectively.

Abbreviations: HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CHF, congestion heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.

^a t-Test.

^b Chi-square test.

In univariate analyses (Table 2), covariates such as female sex, age, HTN, hyperlipidemia, DM, CAD, CHF, stroke, CKD, COPD, and PAOD did not significantly increase the risk of cholecystectomy. Undergoing bariatric surgery had the trend to increase the rate of

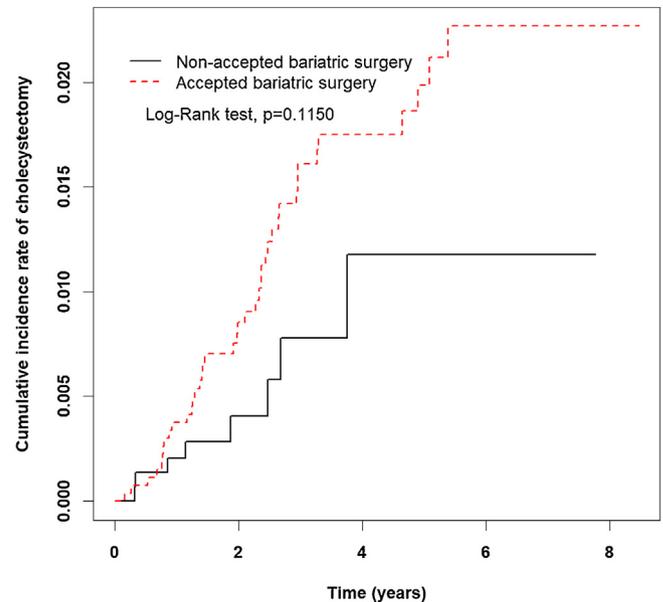


Fig. 2. Cumulative incidence of cholecystectomy according to morbid obesity with bariatric surgery or without bariatric surgery during the follow-up period.

cholecystectomy. In multivariate analyses using Cox proportional hazards regression, undergoing bariatric surgery exerted a significantly increased rate of cholecystectomy after adjusting for the potential confounders of age, sex, and all comorbidities (adjusted HR = 3.43; 95% CI, 1.25–9.4; p = 0.0165).

In Fig. 2, Kaplan–Meier curves of the study and comparison cohort, estimated by conducting the log-rank test, had the trend of increasing cumulative incidence of cholecystectomy in the study cohort, morbid obese patient who underwent bariatric surgery (p = 0.1150).

Table 2
Cox model with HR and 95% CIs of cholecystectomy associated with receiving bariatric surgery among morbidly obese patients.

Variable	Cholecystectomy No. (N = 48)	Crude ^a			Adjusted [†]		
		HR	(95%CI)	p Value	HR	(95%CI)	p Value
Undergoing bariatric surgery							
No	8	1.00	Reference		1.00	Reference	
Yes	40	1.94	(0.9–4.17)	0.0899	3.43	(1.25–9.4)	0.0165
Sex							
Female	32	1.00	Reference		1.00	Reference	
Male	16	0.8	(0.44–1.46)	0.4669	0.81	(0.44–1.5)	0.507
Age							
20–29 years	19	1.00	Reference		1.00	Reference	
30–64 years	27	1.07	(0.59–1.93)	0.8231	1.13	(0.61–2.1)	0.6996
65–100 years	2	1.52	(0.35–6.56)	0.5737	2.26	(0.38–13.33)	0.366
Comorbidities (ref = non-)							
HTN	9	1	(0.48–2.08)	0.9953	1.06	(0.39–2.89)	0.9149
Hyperlipidemia	5	1.30	(0.51–3.28)	0.5849	1.63	(0.55–4.88)	0.3787
DM	6	0.94	(0.4–2.22)	0.8862	1.00	(0.36–2.73)	0.9939
CAD	4	1.37	(0.49–3.82)	0.5463	1.15	(0.31–4.22)	0.8306
CHF	4	1.61	(0.58–4.49)	0.3642	1.83	(0.48–6.92)	0.3733
Stroke	1	0.63	(0.09–4.58)	0.649	0.35	(0.04–2.95)	0.334
CKD	2	1.55	(0.38–6.41)	0.5429	1.63	(0.35–7.6)	0.5349
COPD	3	1.89	(0.59–6.1)	0.2846	1.83	(0.46–7.29)	0.389
PAOD	1	3.91	(0.54–28.41)	0.1777	5.12	(0.63–41.5)	0.1258

Crude HR^a represented relative hazard ratio; adjusted HR[†] represented adjusted hazard ratio; mutually adjusted for accepted bariatric surgery, age, sex, baseline comorbidities (like tables), and drug used in Cox proportional hazard regression.

Abbreviations: HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CHF, congestion heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.

Table 3
Incidence rate and HRs with 95% CIs of cholecystectomy associated with those undergoing bariatric surgery, stratified by age and sex

Variable	Undergoing bariatric surgery						Undergoing vs. not-undergoing bariatric surgery	
	No			Yes			Crude HR	Adjusted HR [‡]
	Event	Person years	IR [†]	Event	Person years	IR [†]		
Total	8	3616	2.21	40	10181	3.93	1.94 (0.90–4.17)	3.43 (1.25–9.40) [*]
Sex								
Female	4	1896	2.11	28	6629	4.22	2.13 (0.74–6.14)	3.74 (1.06–13.14) [*]
Male	4	1720	2.33	12	3552	3.38	1.67 (0.54–5.21)	3.10 (0.65–14.73)
Age group, year								
20–29 years	1	736	1.36	18	5109	3.52	3.00 (0.40–22.3)	2.92 (0.35–24.31)
30–64 years	5	2505	2	22	5068	4.34	2.29 (0.86–6.09)	3.69 (1.13–12.07) [*]
65–100 years	2	374	5.34	0	4	0	–	–

Abbreviations: †IR, incidence rates, per 1000 person-years; HR, hazard ratio; CI, confidence interval.

[‡]Represented adjusted hazard ratio; mutually adjusted for age, sex and baseline comorbidities in Cox proportional hazard regression.

^{*}p-Value <0.05; ^{**}p-value <0.01; ^{***}p-value <0.001.

In **Table 3**, incidence rate and HR of cholecystectomy associated with undergoing bariatric surgery were stratified by sex and age. Female sex and age of 30–64 years had significant a higher adjusted HR.

Discussion

Our study demonstrated a significant increased risk of cholecystectomy in the morbidly obese patients after bariatric surgery compared with those who did not undergo without bariatric surgery. After stratification of age and sex, female and patients aged 30–64 years had a significant higher HR. Morbid obesity after bariatric surgery had the trend of increasing cumulative incidence of cholecystectomy.

At present, bariatric surgery is known for promising long-term body weight loss for morbid obesity patients [4,31] but the increasing rate of gallstone formation owing to body weight loss was the adverse effect and a challenging problem. Nearly 50% of new gallstones after bariatric surgery required emergency cholecystectomy [32]. Although the rate of cholecystectomy associated with post-bariatric surgery is low [26,27], the obese patients who underwent bariatric surgery had an increased risk of symptomatic

gallstones as compared with the general population [26,28]. The highest rate of cholecystectomy after bariatric surgery was 3.7% in the first six months after bariatric procedure [27]. The characteristics of gallstones had more cholesterol and higher cholesterol saturation than the gallbladder sludge from cholecystectomy in patients after bariatric surgery [15]. In addition, our study proposed that the obese patients after bariatric surgery had 3.43-fold increased risk as compared with obese patients who did not undergo bariatric surgery. Routine prophylactic cholecystectomy with bariatric surgery simultaneously is still not recommended. Ursodeoxycholic acid administration was proposed as an alternative medical treatment to prevent gallstone formation after bariatric surgery [33,34], but has a poor compliance [18].

The female population is well known to have two- to three-fold higher rate of gallstones than the male population [35,36]. Especially, female sex has been associated with an increased prevalence of gallstones as are age and BMI [9]. In addition, female morbidly obese patients (BMI >45 kg/m²) had a sevenfold rate of gallstones than general population and had a gallstones incidence of 2%/year [37]. Female patient were more likely to undergo cholecystectomy before bariatric surgery than male patients in the obese and normal population [29]. Bariatric surgery not only is

Table 4

The role of female sex in cholecystectomy after bariatric surgery.

Studied subjects (published studies vs. the present study)	BMI	Cholecystectomy	Factors related to cholecystectomy rate
Morbid obesity (Tsirlina et al., 2013) [27]	45.4 ± 5.3	LRYGB: 10.6%	Female (–)
	43.1 ± 5.0	LAGB: 2.9%	Preoperative BMI (–)
	43.7 ± 6.0	LSG: 3.5%	Excess weight loss >25% within the first 3 months (+)
Obesity (Melmer et al., 2015) [13]	>35	LAGB: 8.6%	Female (+)
Morbid obesity (our current data)		LRYGB and LSG: 40%	Rapid weight loss (+)
		LRYGB and LSG	Female (+) 30–64 years old (+)

BMI, body mass index; LRYGB, laparoscopic Roux-en-Y gastric bypass; LAGB, laparoscopic adjustable gastric band; LSG, laparoscopic sleeve gastrectomy.

a good solution for morbid obesity and decreasing overall mortality [2] but also for decreasing the cancer incidence in female obese patients [31]. Female sex is also another major risk factor of gallstone formation after bariatric surgery [13]. The rate of cholecystectomy after bariatric surgery was increased [13,27], but whether female sex is related to the post-operative cholecystectomy [13] or not [27] is still controversial (Table 4). Our study confirmed that female obese patients had significant higher rate of cholecystectomy after bariatric surgery than male obese patients, especially in the patients aged 30–64 years in Taiwan.

The valuable information of our study was the use of a nationwide data with large sample size and attention to all cholecystectomy in morbidly obese patients after bariatric surgery. Our study also had some limitations. First, the Taiwanese National Health Insurance Research Database did not contain detailed data, regarding body weight and height, so we could not analyse the relationships between the body weight losses, body mass index and cholecystectomy after bariatric surgery. Second, due to the small numbers of cholecystectomy after bariatric surgery, we could not further analyse the differences of cholecystectomy in the morbidly obese patients after bariatric surgery between malabsorptive procedures and restrictive procedures.

Conclusion

Our study demonstrated that bariatric surgery significantly increased the risk of cholecystectomy in the morbidly obese patients post-operatively. After stratification of age and gender, sex and the patients aged 30–64 years had a significant higher HR.

Conflict of interest

The authors declare that they have no conflict of interest.

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