Int J Clin Exp Med 2019;12(4):4487-4492
www.ijcem.com /ISSN:1940-5901/IJCEM0085664

Original Article

The risk factors for gallstone recurrence in patients with laparoscopic gallbladder-preserving cholelithotomy: a retrospective study of 297 patients

Garba Seydou Aliou*, Gang Zhao, Jing Li Cai, An Hua Huang, Hai Dong Li, Kan Ding, Rui Qi Ye, Hai Hu*

*Department of Gallbladder Diseases Center Affiliated Shanghai East Hospital of Tongji University School of Medicine, Shanghai 200120, People's Republic of China. *Equal contributors.*

Received September 18, 2018; Accepted February 13, 2019; Epub April 15, 2019; Published April 30, 2019

Abstract: Background: Stone recurrence is a major problem in the treatment of gallstones with gallbladder preservation. This study aimed to elucidate the possible risk factors of gallstone recurrence after laparoscopic gallbladder-preserving cholelithotomy (LGPC). Method: A total of 297 patients who underwent LGPC for gallstones at Shanghai East Hospital from January 1, 2013 to December 31, 2013 were retrospectively studied to determine the recurrence rate and the surgery's possible risk factors. Following the LGPC, the patients were followed-up for 3 years. The first follow-up visit was 4 months after the LGPC, and thereafter a follow-up visit was carried out every 6 months. During each visit, the patients were clinically examined to look for signs of relapse, and an abdominal ultrasonography (USG) was performed to confirm the presence or absence of disease. The risk factors associated with gallstone recurrence were identified through a questionnaire, which recorded information such as age, sex, body mass index (BMI), duration of disease course, family history of gallstones, comorbid conditions (e.g, hyperlipidemia, diabetes, and hypertension), history of tauroursodeoxycholic acid (TUDCA) intake, physical activity after LGPC, and preference for fatty food. Results: During the 3 years of follow-up, gallstone recurrence was detected in 26 of the 297 (8.75%) LGPC patients. The maximum recurrence rate was found at the 1-year duration period (11 patients), followed by 3 years, 2 years, 6 months, and 4 months in 5, 4, 3, and 3 patients respectively. The risk factors associated with gallstone recurrence included a preference for fatty food, reduced physical activity and a long course of gallstone disease (>4 years). Other demographic factors (sex, age, BMI, family history of gallstones, a history of medication, and concomitant disease) had no significance on the recurrence of gallstones. Conclusion: The overall recurrence rate of gallstones after LGPC was 8.75% during 3-years of follow-up visits. The associated risk factors were a preference for fatty food, reduced physical activity, and long disease course. We suggest that the use of LGPC in patients with gallstones should be considered carefully because of stone recurrence. In addition, long term follow-up visits after LGPC are highly recommended. The present study was limited by the relatively short duration of the follow-up visits.

Keywords: Laparoscopic gallbladder-preserving cholelithotomy, gallstones, recurrence, risk factors, tauroursodexycholic acid, follow-up

Introduction

Cholelithiasis is prevalent worldwide and with increasing morbidity in recent years [1]. Laparoscopic cholecystectomy (LC) is regarded as the most effective therapeutic approach for gallstone patients [2-4]. Nevertheless, studies in the past have reported some disadvantages with LC, such as post-cholecystectomy syndrome, bile duct injuries, and an increased risk of colon cancer in the long term [5-8]. Therefore, laparoscopic gallbladder-preserving cholelithotomy (LGPC) is being practiced to avoid these complications. LGPC helps to preserve gallbladder function advancements in its technique, and the equipment makes the procedure more effective and safer than before [9]. Nonetheless, LGPC also has some drawbacks, among which the most common is the recurrence of gallstones. Here, we evaluated the recurrence rate of gallstones after LGPC. In addition, we identified the risk factors associated with disease relapse.

Patients and methods

From January 1, 2013 to December 31, 2013, a total of 297 patients with gallstones under-

went LGPC at Shanghai East Hospital. Upon institutional review board approval, a retrospective study of these 297 patients was conducted. Patient information was collected through a questionnaire, and the data included demographic records (age and sex), BMI, family history of gallstones, hyperlipidemia, diabetes, hypertension, TUDCA, reduced physical activity after LGPC, preference for fatty food after LGPC, and onset and duration of gallstone disease. After successful LGPC, the recurrence rate and the procedure's risk factors were evaluated. Patients were selected for LGPC according to the following inclusion criteria: (1) the patient had a strong desire to preserve the gallbladder; (2) the thickness of gallbladder wall was <3 mm; and (3) there was a gallbladder volume reduction of >30% and the common bile duct was not dilated. The exclusion criteria included suspicion of gallbladder malignancy, porcelain gallbladder, acute cholecystitis, obstructive jaundice and severe coagulation function abnormalities.

Patient follow-up

All patients were followed-up with for 3 years. The first follow-up visit was 4 months after the LGPC, and the visits occurred on a biannual basis. During the follow-up, the patients were clinically examined, and abdominal USG was performed. We investigated the possible factors that could affect gallstone recurrence, including age, sex, BMI stratification, family history of gallstones, the number of gallstones, concomitant diseases (hyperlipidemia, hypertension, diabetes, coronary heart disease, chronic hepatitis), physical activity, dietary habit (a preference for fatty food), history of operations, TUDCA (taken or not), and the course of the gallstone disease. Gallstone recurrence was defined based on USG findings showing the presence of sludge or gallstones in the gallbladder.

Statistical analysis

The data were analyzed using SPSS 20.0 software. Patients were stratified according to the possible factors associated with stone recurrence, and the statistical significances of the differences in the recurrence rate were assessed using a chi-square test. Univariate and multivariate logistic regression models were used to explore the risk factors of gallstone recurrence. A two-sided $P<0.05$ was considered statistically significant.

Results

A total of 297 patients (male = 101 and female = 196) participated in this study. Of 297 gallstone patients successfully treated with LGPC, 3 patients were found to have gallstone recurrence at the first follow-up visit (4 months after LGPC). Similarly, 3, 11, 4, and 5 patients had disease recurrence at the 6-month, 1-year, 2-year, and 3-year follow-up visits, respectively. Therefore, in total, 26 patients had disease recurrence, with an 8.75% overall recurrence rate at 3 years. Furthermore, we studied the risk factors associated with the gallstone recurrence rate and found the following three major risk factors: a preference for fatty food, reduced physical activity, and long disease course. Of these three major risk factors, a preference for fatty food showed the greatest risk ($P = 0.01$) followed by reduced physical activity ($P = 0.01$) and disease course >4 years ($P = 0.056$).

Other demographic factors (e.g., sex, age, BMI, family history of gallstones, history of medication, concomitant diseases) had no effect on the recurrence of gallstones. Interestingly, our results found that TUDCA treatment had no role in gallstone recurrence; rather, it was a protective factor ($P = 0.019$). **Table 1** shows the characteristics of all 297 patients and the univariate logistic regression analysis of possible risk factors.

Regarding comorbid conditions, we found that they were present in 89 patients, with hyperlipidemia present in 33, hypertension in 54, diabetes in 24, and coronary heart disease in 10 patients. Furthermore, 7 patients had a history of hepatitis B, and 91 patients had a surgical history. Self-reported physically inactive participants ($P = 0.030$) and fatty food lovers ($P = 0.012$) after LGPC were the two most significant independent factors for gallbladder recurrence (**Table 2**).

Discussion

Gallstone recurrence is a major disadvantage for all gallstone treatments, including LGPC, that preserve the gallbladder *in situ* and avoid the complications caused by traditional LC [10-12]. Hence, considering the previously reported

Table 1. Characteristics of the patients (n = 297) and univariate logistic regression analysis of the possible risk factors

Variables	Total (*n*)	Stone recurrence post L-GPC n (%)	OR	95% CI	*P value*
Age (year)					
≤60	236	21 (8.9%)	1		
>60	61	5 (8.2%)	0.91	0.33-2.53	0.863
Sex					
Male	101	8 (7.9%)	1		
Female	196	18 (9.2%)	1.18	0.49-2.81	0.715
With hyperlipidemia					
No	264	22 (8.3%)	1		
Yes	33	4 (12.1%)	1.52	0.49-4.71	0.471
With hypertension					
No	243	20 (8.2%)	1		
Yes	54	6 (11.1%)	1.39	0.53-3.66	0.500
History of operation					
No	203	18 (8.9%)	1		
Yes	88	8 (9.1%)	1.03	0.43-2.46	0.951
Taking TUDCA					
No	97	14 (14.4%)	1		
Yes	200	12 (6.0%)	0.38	0.17-0.85	0.019*
Reduced physical activity after L-GPC					
No	249	17 (6.8%)	1		
Yes	48	9 (18.8%)	3.15	1.31-7.56	0.010*
Preference for fatty foods after L-GPC					
No	133	5 (3.8%)	1		
Yes	164	21 (12.8%)	3.76	1.38-10.26	0.010*
Stone number					
<3	233	20 (8.6%)	1		
≥3	64	6 (9.4%)	1.10	0.42-2.87	0.840
Stone Sizes					
<15	183	14 (7.7%)	1		
≥15	114	12 (10.5)	0.01	0.41-2.71	0.914
Course of disease pre-LPGCL					
≥1 m	89	4 (4.5%)	1		
2 m-6 m	67	7 (10.4%)	2.48	0.70-8.85	0.162
7 m-3 y	86	6 (7.0%)	1.59	0.43-5.88	0.483
4 y-10 y	41	6 (14.6%)	3.64	0.97-13.71	0.056
>11 y	14	3 (21.4%)	5.80	1.14-29.38	0.034*
Diabetes					
No	273	24 (8.8%)	1		
Yes	24	0	0.00	0.000	0.998

*P<0.05 i.e., statistically significant values.

high recurrence rate, the efficacy of LGPC remains in doubt [13].

Nonetheless, in this study the overall recurrence rate of 8.75% over 3 years was much lower than the values reported in previous studies, which were 27.33% in 3 years [14] and 30% in 7 to 12 months [15]. A study with a follow-up period of 10 years reported an increasing trend of the recurrence rate from 9.57% at the 1-year

Table 2. Multivariate logistic regression analysis of gallstone recurrence

Variables	Total (*n*)	Stone recurrence post LGPCL n (%)	OR	95% CI	*P value*
Taking TUDCA					
No	97	14 (14.4%)	1		
Yes	200	12 (6.0%)	0.36	0.15-0.86	0.022*
Reduced physical activity after L-GPC					
No	249	17 (6.8%)	1		
Yes	48	9 (18.8%)	2.97	1.11-7.93	0.030*
Preference for fatty foods after LGPC					
No	133	5 (3.8%)	1		
Yes	164	21 (12.8%)	3.86	1.35-11.08	0.012*
BMI					
<25	250	8 (7.6%)	1		
≥25	47	18 (14.9%)	1.20	1.04-1.38	0.111
Family history of gallstones					
No	215	16 (7.4%)	1		
Yes	82	10 (12.2%)	1.73	0.75-3.98	0.199

*P<0.05 i.e., statistically significant values.

follow-up to 43.21% at the 10-year follow-up [14]. This signifies the importance of longer follow-up visits after LGPC. Furthermore, the time period of the follow-up visits needs to be optimized, lest a patient undergoing LGPC require life-long follow-ups, thereby making this treatment approach unsuitable. It is quite unpredictable when a patient might develop a recurrence, thus subjecting the patient to a lifelong risk of developing the disease again.

Our data showed that age and sex were irrelevant to gallstone recurrence, which is consistent with the findings of a previous report [14]. However, the number of gallstones, previously considered as the primary risk factor [14], appeared to be independent in this study. This outcome may be due to the advancement in LGPC technique and equipment in such a way that the cholelithotomy is more easily performed and with fewer residual gallstones [9]. Other factors, such as obesity (BMI>25), a family history of gallstones, concomitant diseases, and history of operations appeared to have no impact (P>0.05) on gallbladder recurrence. The intensified perioperative care for obese patients or patients with hyperlipidemia, hypertension, diabetes or other diseases may contribute to the improved prognosis of gallstone disease. Moreover, the multidisciplinary team (MDT) effort for gallstone disease and other clinical departments, including endocrinology, the hypertension clinic, and cardiology may also lower the recurrence rate of gallstones in patients with comorbid conditions [16].

Previous studies demonstrated that dietary habits play a pivotal role in the pathogenesis of gallstone formation. Food high in fat and cholesterol increase serum cholesterol levels and hepatic cholesterol levels that are major components of gallstone formation [17, 18]. In our study as well, a preference for fatty food was one of the major risk factors associated with gallstone recurrence. Nevertheless, reduced physical activity also raised the risk of gallstone recurrence because it has a direct effect on colon motility [19] and a reduction in insulin resistance [20]. Moreover, the long duration of gallstone disease (>4 years) that usually leads to poor gallbladder function also contributes to an increased gallstone recurrence rate [10]. TUDCA acts as a litholytic agent by reducing the absorption of intestinal cholesterol; it has been suggested for gallstone treatment for years [20-22]. Nevertheless, since only a minority of patients are amenable to taking TUDCA, the effectiveness of TUDCA remains unclear [22, 23]. Notably, a multivariate logistic regression analysis showed that taking TUDCA after LGPC was a protective factor and could help to decrease the recurrence rate of gallstones [24].

Conclusion

The risk factors associated with the recurrence of gallstones were patient preference of fatty

food, reduced physical activity, and the long course of gallstone disease. Other demographic factors-such as sex, age, BMI, family history of gallstones, and a history of operations and concomitant diseases-showed no effect on the recurrence of gallstones. LGPC in patients with gallstones should be considered carefully because of stone recurrence. In addition, long-term follow-up visits after LGPC are highly recommended. The present study was limited by the relatively short duration of the follow-up visits.

Acknowledgements

The authors acknowledge the staff and doctors of the Department of Gallbladder Diseases Center Affiliated Shanghai East Hospital of Tongji University for their kind help and assistance in this study. This work was supported by the National Natural Science Foundation of China under Grant number (91570577).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hai Hu, Department of Gallbladder Diseases Center Affiliated Shanghai East Hospital of Tongji University School of Medicine, Shanghai 200120, People's Republic of China. Tel: (+86) 13386057031; E-mail: haihulc@hotmail.com

References

[1] Kasahara Y, Umemura H, Shiraha S, Kuyama T, Sakata K, Kubota H. Gallstone ileus. Review of 112 patients in the Japanese literature. Am J Surg 1980; 140: 437-440.

[2] Sain AH. Laparoscopic cholecystectomy is the current "gold standard" for the treatment of gallstone disease. Ann Surg 1996; 224: 689-690.

[3] Soper NJ, Stockmann PT, Dunnegan DL, Ashley SW. Laparoscopic cholecystectomy. The new 'gold standard'? Arch Surg 1992; 127: 917-21.

[4] Begos DG, Modlin IM. Laparoscopic cholecystectomy: from gimmick to gold standard. J Clin Gastroenterol 1994; 19: 325-30.

[5] Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. Lancet 2006; 368: 230-239.

[6] Shao T, Yang YX. Cholecystectomy and the risk of colorectal cancer. Am J Gastroenterol 2005; 100: 1813-1820.

[7] Jaunoo SS, Mohandas S, Almond LM. Postcholecystectomy syndrome (PCS). Int J Surg 2010; 8: 15-17.

[8] Lum YW, House MG, Hayanga AJ, Schweitzer M. Postcholecystectomy syndrome in the laparoscopic era. J Laparoendosc Adv Surg Tech A 2006; 16: 482-485.

[9] Zha Y, Zhou ZZ, Chen XR, Gan P, Tan J. Gallbladder-preserving cholelithotomy in laparoscopic and flexible choledochoscopic era: a report of 316 cases. Surg Laparosc Endosc Percutan Tech 2013; 23: 167-170.

[10] Pauletzki J, Althaus R, Holl J, Sackmann M, Paumgartner G. Gallbladder emptying and gallstone formation: a prospective study on gallstone recurrence. Gastroenterology 1996; 111: 765-71.

[11] Niranjan B, Chumber S, Kriplani AK. Symptomatic outcome after laparoscopic cholecystectomy. Trop Gastroenterol 2000; 21: 144-148.

[12] Bates T, Ebbs SR, Harrison M, A'hern RP. Influence of cholecystectomy on symptoms. Br J Surg 1991; 78: 964-967.

[13] Soreide K. Gallstone disease and cancer risk: finding the bug in the system. Gastroenterology 2017; 152: 1825-1828.

[14] Zou YP, Du JD, Li WM, Xiao YQ, Xu HB, Zheng F, Huang H, Liu HR, Li HC. Gallstone recurrence after successful percutaneous cholecystolithotomy: a 10-year follow-up of 439 cases. Hepatobiliary Pancreat Dis Int 2007; 6: 199-203.

[15] De Caluwe D, Akl U, Corbally M. Cholecystectomy versus cholecystolithotomy for cholelithiasis in childhood: long-term outcome. J Pediatr Surg 2001; 36: 1518-21.

[16] Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. J Long Term Eff Med Implants 2005; 15: 329-38.

[17] Di Ciaula A, Garruti G, Fruhbeck G, De Angelis M, De Bari O, Q-H Wang D, Lammert F, Portincasa P. The role of diet in the pathogenesis of cholesterol gallstones. Curr Med Chem 2017; [Epub ahead of print].

[18] Donald JJ, Cheslyn-Curtis S, Gillams AR, Russell RC, Lees WR. Percutaneous cholecystolithotomy: is gall stone recurrence inevitable? Gut 1994; 35: 692-695.

[19] Liu F, Kondo T, Toda Y. Brief physical inactivity prolongs colonic transit time in elderly active men. Int J Sports Med 1993; 14: 465-467.

[20] Portincasa P, Ciaula AD, Bonfrate L, Wang DQ. Therapy of gallstone disease: what it was, what it is, what it will be. World J Gastrointest Pharmacol Ther 2012; 3: 7-20.

[21] O'Donnell LD, Heaton KW. Recurrence and re-recurrence of gall stones after medical dissolution: a longterm follow up. Gut 1988; 29: 655-658.

[22] Boatright JH, Nickerson JM, Moring AG, Pardue MT. Bile acids in treatment of ocular disease. J Ocul Biol Dis Infor 2009; 2: 149-159.

[23] Yamamoto R, Tazuma S, Kanno K, Igarashi Y, Inui K, Ohara H, Tsuyuguchi T, Ryozawa S. Ursodeoxycholic acid after bile duct stone removal and risk factors for recurrence: a randomized trial. J Hepatobiliary Pancreat Sci 2016; 23: 132-136.

[24] Tan YY, Zhao G, Wang D, Wang JM, Tang JR, Ji ZL. A new strategy of minimally invasive surgery for cholecystolithiasis: calculi removal and gallbladder preservation. Dig Surg 2013; 30: 466-471.