International Surgery Journal
Baghel AS et al. Int Surg J. 2022 Oct;9(10):1720-1725
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20222596

Original Research Article

Clinical presentation and surgical outcome among patients having single and multiple gallstones: a prospective study

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Received: 12 August 2022
Revised: 08 September 2022
Accepted: 13 September 2022

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ABSTRACT

Background: Outcome of laparoscopic cholecystectomy is determined by an array of factors including patient & gallstone-related variables. Number of gallstones influences pathophysiology of disease thereby influencing outcome of surgery. This study was aimed at investigating clinical, haematological, radiological features and surgical outcomes among patients having single and multiple gallstones.
Methods: Single centre, hospital-based, prospective, observational study involving 60 patients undergoing LC. Data pertaining to clinical, hematological, radiological variables and surgical outcomes were collected and analysed.
Results: Mean duration of symptoms (m/c- pain) was significantly shorter among participants having multiple gallstones (p=0.034). There was no statistically significant difference among participants having single and multiple stones regarding any of clinical signs and symptoms (p>0.05). Mean GB wall thickness among patients having single and multiple gallstones was 3.27 mm and 4.18 mm (p=0.038). Difference in proportion of patients having pericholecystic collections was statistically significant (p=0.019). Mean duration of surgery among participants with single and multiple stones was 57 minutes and 71 minutes, respectively (p=0.012). On intraoperative examination, adhesion was noted in 20% of participants with single stone and 35% of participants in multiple stones group (p=0.029). Conversion rate to OC was 12% in multiple stones group and only 3.4% of participants with single stone (p=0.028). Adjusted odds ratio for conversion to OC was 3.39 (95% CI 1.98-7.89) for patients having multiple gallstones.
Conclusions: Although patients having single and multiple gallstones have similar clinical features, findings of ultrasonography and surgical outcomes may differ significantly.

Keywords: Multiple gallstones, Difficult laparoscopic cholecystectomy, Clinic-radiological factors, Gallstones, Cholecystectomy

INTRODUCTION

Within a decade since the first case was conducted in the year 1989, Laparoscopy Cholecystectomy (LC) had become the gold standard for managing many ailments of the gallbladder.[1] Further, ever since its introduction, LC's technique has undergone several drastic changes reflecting the needs of the patients, concerns of the surgeons, and advancements in the technology.[1,2] Today, the gold standard technique for managing most gallbladder pathologies is four-port LC(1,2). Given its minimally invasive approach, Laparoscopic cholecystectomy is associated with less postoperative pain, reduced need for postoperative analgesia, shortened hospital stay (24-48 hours) and quicker return to full activity (within 1 week) in comparison to open cholecystectomy (OC).[1,2] Laparoscopic cholecystectomy is also associated with better cosmetic outcomes

reflecting higher satisfaction among patients in comparison to open cholecystectomy.[3] Nevertheless, LC, despite its wide acceptance, increasing popularity and cost-effectiveness, has challenges of its own.[4,5] In addition to the systemic risks of anaesthetic and surgery, common complications associated with laparoscopic cholecystectomy include bleeding, visceral injury, diarrhoea, retained gallstones, and injury to the bile ducts.[4,5]

In many instances, the LC takes more time to complete, or there are complications, including injury to surrounding organs etc.[6] Moreover, sometimes the procedure needs to be converted into open cholecystectomy or the number of ports (in case of 3 or fewer ports) needs to be increased.[7,8] There are many reasons for the same(8). The most fundamental approach to prevent such complications is to perform a thorough check-up of the patients to detect undiagnosed illnesses. With the advancement in radiography, ultrasonography- and pathology, it has become possible to minimize the incidence of such complications.[7,8]

One of the factors affecting the outcome and complications during and after LC is the number of gallstones inside the gallbladder. It is postulated that the number of stones influences the development of associated pathology in and around the gallbladder.[9] This results in the development of complications during and after LC. The research on the impact of the number of stones on clinical presentation and surgical outcome is controversial.[10,11]

Many researchers suggest that the 'solitary' gallstone is more dangerous than multiple but smaller gallstones.[9,12-14] Mofti et al reported solitary gallbladder stone is associated with increased risks of developing mucocele, empyema, gallbladder perforation and postoperative complications.[12,13] Jalali et al also reported that the prognosis of solitary stones is worse in comparison to multiple gallstones.[14] Whereas other studies suggest that multiple stones are more harmful.[15,16] The inflammation and the pathological factors influenced by the number of stones in GB are associated with higher odds of conversion of LC to OC.[10,11] Thus, this study was conducted to investigate and identify clinical, haematological, radiological factors and surgical outcomes associated with single versus multiple gallstones.

METHODS

Study design, location, duration and outcome

This was a hospital-based, single-centre, prospective, observational study conducted at the department of general surgery, L. N. medical college, Bhopal a tertiary care institute. The total duration of the study was 17 months; from September 2020 to February 2022. Primary outcome parameters were the surgical outcomes (difficult LC or conversion to OC) among participants. Secondary objectives were to study the clinical, radiological, and intraoperative findings among the patients identified to have single and multiple gallstones.

Sample size

Using the prescribed formula for proportion the minimum required sample size for this study was calculated as 60. Sample size is calculated using following formula:

$$n = [DEFF * Np(1-p)]/[(d2/Z21-\alpha/2 * (N-1) + p * (1-p)]$$

Where p=expected prevalence; p=4.0% (17) ; $Z^2_{1-\alpha/2}$=standard normal deviation; Confidence interval =95%; d=desired precision = 0.05 for 95% CI; DEFF-design effect=1; n=Minimum required sample size= 60. **C**

Inclusion criteria

A patient presenting with acute or chronic cholecystitis with cholelithiasis undergoing laparoscopic cholecystectomy and fulfilling the mentioned selection criteria like; patients with symptomatic gall stones confirmed by USG, asymptomatic patients diagnosed during USG for other conditions, age≥18 years, no bleeding/clotting abnormalities and Patients giving consent to participate in the study.

Exclusion criteria

Exclusion criteria for current study were; the patient did not consent to participate in the study and women patients who were pregnant.

A bi-lingual (Hindi and English) consent form was drafted following the prescribed guidelines for research on human participants. The contents of the consent form were explained to all the prospective participants. All the questions from participants about the study, procedure, follow-up, and data privacy were answered. The participants were informed and explained that they have the right to withdraw from the study at any point in time.

Data collection

The data were collected in a paper-based proforma. The proforma had three parts as follows: Demographics and Clinical details, Pathological and Radiological findings and Pre-, Intra-, and postoperative details. There were two sources of data.

First was the interview with the participants containing details about the demographic details, clinical history, symptoms, and previous treatments (if any). The second source of the data reported contains details about clinical examination, laboratory and radiographic findings. Ultrasonographic parameters assessed were as follow: the

number of stones; the size of gall stones; Gallbladder wall thickness; Common bile duct and intrahepatic biliary radicals status.

Statistical analysis

The primary outcome was the surgical outcome and incidence of intraoperative complications among patients having single and multiple gallstones. We aimed to identify from the collected data the clinical, pathological, radiological factors and surgical outcomes were significantly different among patients having single and multiple gallstones. The data were analysed using Stata 17.1 version. For the interval and ratio data types, the author calculated the mean, median, mode, and standard deviation.[18] For the nominal and ordinal data, the author calculated the frequency, percentage, and proportion. The interval and the ratio data variables were analysed using a student's t-test test. Categorical variables were analysed using chi-square (χ^2) tests, $p < 0.05$ was considered statistically significant.[19]

RESULTS

To recruit the participants for the present study we approached a total of 67 participants: 6 patients were excluded, 1 patient refused to participate, and the remaining 60 patients were enrolled in the present study. Details about the selected characteristics of the participants is given in (Table 1). Overall, there were 17 male and 43 female participants, and the mean age of the participants was 48.6 years. The mean age of the participants who had single and multiple gallstones was 49.1 years and 48. 19 years (p=0.813). The duration of symptoms (most commonly pain) was significantly shorter among participants having multiple gallstones (p=0.034).

Table 1: Selected characteristics of participants (n=60).

Variable	Single (n=29)	Multiple (n=31)	P value
Gender			
Female	22 (75.86)	21 (67.74)	0.485
Male	7 (24.14)	10 (32.26)	
Age			
Mean (±SD)	49.1 (15.30)	48.19 (14.78)	0.813
Median	49	48	NA
Duration of symptoms (months)			
Mean (±SD)	9.7 (7.64)	8.3 (3.11)	0.034
Median	10	8	NA
Location of Pain			
RHC	26 (89.66)	30 (96.77)	0.269
Epigastric	3 (10.44)	1 (3.23)	
Characteristics of Pain			
Colicky	26 (89.66)	27 (87.10)	0.758
Dull	3 (10.44)	4 (12.90)	

Table 2: Clinical signs and symptoms among the participants (n=60).

Variable	Single (n=29)	Multiple (n=31)	P value
Symptoms			
Vomit	6 (20.69)	4 (12.90)	0.419
Fever	1 (3.45)	4 (12.90)	0.185
Dyspepsia	18 (62.07)	19 (61.29)	0.951
Sign			
Icterus	0 (0.0)	2 (6.45)	0.164
Tenderness	17 (58.62)	16 (51.61)	0.586
Mass	0 (0.0)	0 (0.0)	NA
Murphy's sign	3 (10.34)	4 (12.90)	0.758

As can be inferred from (Table 2), the most common symptom among the participants was dyspepsia reported by 37 (58.3%) participants followed by vomiting reported by 10 (16.7%) participants.

Further, the most common clinical sign among the participants was tenderness (mostly localised to the RHC region) 33 (55.0%) followed by murphy's sign 7 (11.7%). There was no statistically significant difference among the participants having single and multiple stones regarding any of the clinical signs and symptoms (p>0.05).

Table 3: Laboratory parameters among participants (n=60).

Variable	Single Mean (SD)	Multiple Mean (SD)	P value
TLC	8113.6 (3007.37)	8820 (3885.48)	0.029
Platelet Count	2.9 (0.87)	2.14 (0.34)	0.073
Urea	22.4 (4.46)	25.71 (6.70)	0.057
Creatinine	0.61 (0.14)	0.79 (0.19)	0.042
BMI	29.1 (1.01)	28.72 (0.67)	0.076

The laboratory parameters among the participants is depicted in (Table 3). Among the several clinical parameters measured as part of clinical evaluation, only the difference between TLC and creatinine levels was statistically significant (p<0.05).

The USG findings among the participants is mentioned in (Table 4). The mean GB wall thickness among patients having single and multiple gallstones were 3.27 mm and 4.18 mm, respectively, this difference was statistically significant (p=0.038).

The difference in the proportion of patients having pericholecystic collections was also statistically significant (p=0.019).

Table 4: USG findings among the participants (n=60).

Variable	Single	Multiple	P value
USG findings			
GB wall thickness	3.27 (0.59)	4.18 (0.70)	0.038
Pericholecystic adhesion	2 (6.90)	6 (19.35)	0.019
Impacted gallstone	4 (13.79)	3 (9.68)	0.084

The intraoperative findings, complications, and outcomes of the LC is depicted in (Table 5). The mean duration of surgery among the participants with single and multiple stones was 57 minutes and 71 minutes, respectively (p= 0.012). On intraoperative examination of the operative field, adhesion was noted in 20% of participants with a single stone and 35% of participants in the multiple stones group (p=0.029). Of the total 31 participants with multiple stones, 12% required conversion to OC in comparison to only 3.4% of participants with a single stone. The difference in the proportion of participants requiring conversion to OC was statistically significant (p=0.028). The adjusted odds ratio (multiple variable logistic regression) for conversion to OC was 3.39 (95% CI 1.98-7.89) for patients having multiple gallstones.

Table 5: Surgical outcomes among the participants (n=60).

Variable	Single	Multiple	P value
Duration of surgery	57.62 (21.19)	71.1 (29.13)	0.012
Adhesions	6 (20.69)	11 (35.48)	0.029
Bile leakage	3 (10.34)	8 (25.81)	0.048
Bleeding	0 (0.0)	1 (3.23)	0.068
Injury to CBD	0 (0.0)	1 (3.23)	0.063
Frozen Callot's triangle	1 (3.45)	3 (9.68)	0.039
Conversion to OC	1 (3.45)	4 (12.90)	0.028

DISCUSSION

As mentioned earlier, LC has become the gold standard for the management of several gallbladder pathologies. However, in many cases, the LC is either not feasible or it is unsuccessful and needs to be converted into OC. A systematic review by Rothman et al identified several risk factors related to either patients or gallbladder pathology that increases the odds of encountering difficulty during LC. More importantly, many of these factors could be identified preoperatively by eliciting a medical history, clinical examinations, and radiological investigations including USG. One such factor is the number of gallstones inside the gallbladder.[8] There are several theories and proposed pathological mechanisms that explain why some patients have a single gallstone whereas others develop multiple gallstones.[9-11,20] Moreover, these pathological mechanisms are not limited to the gallbladder cavity/lumen alone but also extend to the surrounding anatomical structures. Hence, the number of gallstones could also influence the surgical outcome(s) of LC. Gallstones irritate the mucosa, leading to mucosal hyperemia and transmural inflammation.[10,11,20] There is a release of cytokines, arachidonic metabolites, and oxygen free radicals from the macrophages.[10,11,20] Soon, a fibrin matrix is formed, which gradually matures into organized fibrous adhesions.[21] Vrako and Weichel have also observed the presence of periductal inflammation in the form of oedema, hyperemia, and petechiae on the outer surface of the bile duct in patients with asymptomatic CBD stones.[22] In this regard, we studied the clinical features, laboratory parameters, and radiological findings among a total of 60 patients diagnosed to have solitary and multiple gallstones.

In our study, the surgical outcomes were worse among the patients having multiple gallstones. Firstly, the meantime for the completion of the surgery was significantly longer among those having multiple stones. Secondly, the adjusted odds ratio for conversion to OC was 3.39 (95% CI 1.98-7.89) among patients with multiple gallstones. These adverse surgical outcomes in part could be attributed to advanced pathology noted among patients having multiple stones viz. thicker GB wall, pericholecystic adhesions, and frozen Calot's triangle. All these factors have been identified by Rothman et al. as determinants for the conversion of LC to OC.[8] In the present study, the distribution of all these three pathological features was significantly higher among the patients having multiple gall stones.

Similar to our study, Raja et al also reported that surgeons encountered greater difficulty during LC among patients having multiple gallstones.[15] In the multiple gallstones, the small floating stones may not remain in constant touch with the gallbladder mucosa, thereby spreading the inflammation to multiple sites inside the gallbladder. Because the gallbladder and extrahepatic bile duct are drained by lymphatic vessels and lymph nodes in Calot's triangle and along the bile duct, its inflammation results in the formation of adhesions around Calot's triangle and the common duct.[23] However, in contrast to our findings, studies from other countries reported that patients having a single gallstone had more difficult LC.[9,12,14] Verma et al also reported that surgeons encountered greater difficulty among patients having a single gallstone because of denser pericholecystic adhesions.[9] However, they also suggested that difficulty encountered during LC can be attributed to the learning curve of surgeons as most cases of difficult LC were encountered during the first 100 cases of LC done by surgical residents.[9] Only 1 patient in our study with a single stone required conversion to OC. The patient had a larger gallstone (4.56 cm) and long-standing symptoms and complaints. Verma et al also reported that patients having larger gallstones had increased odds of conversion to OC.[9] The larger size of the stones in patients with a single stone who required conversion substantiates the

argument that the larger the stone, the greater the chances of development of dense adhesions and consequently a high rate of conversion.

In the present study, only the duration of the chief presenting symptom was significantly shorter among those having multiple gallstones. This may be attributed to the fact that a single stone takes time to increase in size whereas several stones growing in size quickly fills the lumen of GB and causes symptoms. Solitary stones, once they attain considerable size, tend to settle in the dependent part of the gallbladder, Hartmann's pouch. Over time, the stone increases in size, causing stretching of the wall of the gallbladder around it. The constant irritation of the gallbladder sets the stage for accelerated transmural inflammation and pericholecystic adhesions around the porta hepatis.

Similar to all other studies, we did observe any significant difference in the distribution of clinical signs and symptoms among patients having single and multiple gallstones.[9,12,14] Mofti et al reporting the frequency of symptoms, signs, and laboratory parameters were equally distributed among patients with solitary stones than those with multiple gallstones.[12] Similarly, Jalali et al reported that the incidence of chief presenting complaints and radiological findings were similar among those who had solitary stones and those with multiple gallstones.[14] In the present study, the age and sex distribution among the patients were similar among patients having single and multiple gallstones. Other studies have also reported that there is an age difference between the patients with solitary stones and those with multiple gallstones. This age similarity makes one wonder why one patient would develop a solitary gallstone while another would develop multiple stones. Thus, further collaborative and analytic studies are necessary to find out what promotes lithogenesis.

CONCLUSION

Although, patients having single and multiple gallstones have similar clinical signs and symptoms the surgical outcomes may differ significantly. Based on our analysis, we recommend that patients with multiple gallstones should be offered preoperative counselling about the likelihood of a successful outcome and motivated for early surgery. Although laparoscopic cholecystectomy is the gold standard for many gallbladder diseases, the conversion of LC to OC is inevitable in some cases. Moreover, the conversion cannot always be predicted with absolute certainty in every case. Lastly, therefore, every surgeon should be trained in both laparoscopic and open cholecystectomy in case the need arises during the intraoperative period.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Baghel AS, Anand K, Gupta S. Clinical presentation and surgical outcome among patients having single and multiple gallstones: a prospective study. Int Surg J 2022;9:1720-5.