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Original Article

Post-cholecystectomy syndrome: A cohort study from a single private tertiary center

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الملخص

أهداف البحث: على الرغم من أن متلازمة ما بعد استئصال المرارة من المضاعفات المعروفة جيدا، الإ ان هناك تقارير قليلة من المملكة العربية السعودية. إن تأثير تكميم المعدة او التصوير الوراثي للقنوات الصفراوية والبنكرياس بالمنظار على الإصابة بمتلازمة ما بعد استئصال المرارة غير معروف. لقد هدفنا الى قياس العوامل المحتملة التي تؤثر على تطور متلازمة ما بعد استئصال المرارة، مثل مدة الأعراض، الأمراض المصاحبة، جراحة السمنة السابقة، ادخال دعامة تصوير القنوات الصفراوية والبنكرياس بالمنظار، التدخل الجراحي، التحول الى الفتح ومعدل المضاعفات.

طرق البحث: هذه دراسة جماعية محتملة، دراسة قائمة على الملاحظة أجريت في مركز جامعي خاص واحد. قمنا بتضمين١٦٧ مريضا خضعوا لعملية جراحية لمرض المرارة في الفترة من أكتوبر ٢٠١٩ الى يونيو ٢٠٢٠. تم تصنيف المرضى الى مجموعتين وفقاً لحالة متلازمة ما بعد استئصال المرارة الخاصة بهم إيجابية/ سلبية

النتائج: كان تسعة وثلاثون مريضا إيجابيا لمتلازمة ما بعد استئصال المرارة (٢٣,٣٪). لم يكن هناك فرق كبير بين المجموعتين فيما يتعلق بالعمر، الجنس، مؤشر كتلة الجسم، التقييم الشخصي لدرجة الصحة العامة للمريض، التدخين، الأمراض المصاحبة مدة الأعراض، جراحة السمنة السابقة، التصوير الوراثي للقنوات الصفراوية بالمنظار، ادخال الدعامة أو بضع العضلة العاصرة. كان التهاب المرارة المزمن هو التشريح المرضي السائد عند٨٣٪ (١٣٩/١٦٧) من المرضى. تشمل الأسباب الأكثر شيوعا لمتلازمة ما بعد استئصال المرارة ضعف الجهاز الصفراوي والإسهال الناتج عن ملح الصفراء والتهاب المعدة ومرض الجزر المعدي المريئي والحصى المحتجزة. كان المرضى المصابون متلازمة ما بعد استئصال المرارة ٧١,٨٪(٢٨/٣٩), بينما كان الباقون يعانون من متلازمة ما بعد استئصال المرارة

الاستنتاجات: متلازمة ما بعد استئصال المرارة هي اختلاط مهمل يظهر عند ربع المرضى بشكل رئيسي في السنة الأولى. يمكن ان يساعد وعي الجراح في تشخيص المريض والاختيار قبل الجراحة والتعليم. علاوة على ذلك، يبدو ان تاريخ دعامات تصوير القنوات الصفراوية والبنكرياس بالمنظار أو بضع العضلة العاصرة او تكميم المعدة لا علاقة له بتطور متلازمة ما بعد استئصال المرارة

الكلمات المفتاحية: متلازمة ما بعد استئصال المرارة؛ تكميم المعدة؛ امراض المرارة؛ استئصال المرارة بالمنظار؛ تصوير البنكرياس والأقنية الصفراوية بالتنظير الباطني بالطريق الراجع

Abstract

Objectives: Although post-cholecystectomy syndrome (PCS) is a well-recognized complication, there are few reports arising from KSA. The effect of sleeve gastrectomy or endoscopic retrograde cholangiopancreatography (ERCP) stenting on the development of PCS is unknown. We aimed to measure the possible factors affecting the development of PCS, such as symptom duration, comorbidities, previous bariatric surgery, ERCP stent insertion, surgical intervention, conversion to open surgery and complication rate.

Methods: This was a prospective cohort and observational study conducted at a single, private tertiary center. We included 167 patients who underwent surgery for gallbladder disease between October 2019 and June 2020. The patients were classified into two groups according to their PCS status (PCS+ *vs.* PCS−).

Results: Thirty-nine patients were PCS+ (23.3%). There was no significant difference between the two groups with regards to age, gender, BMI, ASA score, smoking, comorbidities, duration of symptoms, previous bariatric surgery, ERCP, stent insertion or sphincterotomy. Chronic cholecystitis was the predominant histopathology in 83% (139/167) of patients. The most frequent

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causes of PCS included biliary system dysfunction, bile salt-induced diarrhea, gastritis, gastroesophageal reflux disease, and retained stones. Overall, 71.8% (28/39) of patients had incident PCS; the remaining patients had persistent PCS.

Conclusions: PCS is a neglected complication that was observed in 25% of patients mainly in the first year. Surgeon awareness can assist with patient diagnosis, preoperative selection and education. Furthermore, the history of ERCP stenting, sphincterotomy, or sleeve gastrectomy seems to be unrelated to PCS development.

Keywords: Endoscopic retrograde cholangiopancreatography (ERCP); Gallbladder disease; Laparoscopic cholecystectomy (LC); Post-cholecystectomy syndrome (PCS); Sleeve gastrectomy

Introduction

Laparoscopic cholecystectomy (LC) is the most routine form of abdominal surgery used to treat symptomatic gallbladder stones (GBS). Laparoscopic cholecystectomy can modify the physiological and hormonal response of the gastrointestinal system in response to eating. Subsequently, a group of patients can experience symptoms post-operatively and remain unhappy with regards to the surgical outcome. Post-cholecystectomy syndrome (PCS) denotes a group of unrelated symptoms that are not recognized or unmasked by surgical gallbladder removal. The causes can be classified as a biliary or non-biliary source from the stomach, esophagus, pancreas and blood vessels. Although this syndrome has been described in older females, is prevalent among young with varied incidence rates.[1,2] Post-cholecystectomy syndrome differs between countries; in KSA, the incidence of PCS is 19.8% but in other countries, can reach 54%, with symptoms that persist after surgery; alternatively, new symptoms can develop after surgical intervention.[2–5] The onset of PCS can occur immediately after the postoperative period and is classified as early biliary PCS; this is caused by retained or missed duct stones, biliary injury or leaks. Late biliary PCS commences months or years after LC and is triggered by recurrent stones, system dysfunction or stricture. This disease creates a significant burden on the health care system; the average treatment costs for one center is \$32,300 ± 26,172 per annum.[2] However, there are no data regarding preoperative risk stratification that can predict PCS.[1] Furthermore, little is known about the effect of ERCP stenting, laparoscopic sleeve gastrectomy (LSG) or conversion to open surgery on emerging PCS. We hypothesized that prolonged symptom durations, stent insertion, previous bariatric surgery, and conversion to open surgery can induce the development of PCS.

Materials and Methods

Patients

Patient evaluation and data collection were prospectively performed at a single, private tertiary center, Dr. Soliman Fakeeh Hospital (Jeddah, KSA). We enrolled 167 consecutive patients who underwent an operation for gallbladder disease in our institution between October 2019 and June 2020. We excluded pediatric patients (aged less than 14 years) and patients who had undergone cholecystectomy combined with other surgeries. Data were recorded before surgery and immediately after surgery and patients were followed up in the outpatient clinic. The diagnosis of PCS was confirmed by a clinical examination carried out by a surgeon or gastroenterologist after ruling out other pathologies by laboratory tests, ultrasonography (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and endoscopy (gastroduodenoscopy or ERCP). According to the persistence of symptoms, the patients were classified into two groups: PCS (+) and PCS (−).

The measured outcomes included factors that might affect the development of PCS, such as symptom duration, comorbidities, previous bariatric surgery, ERCP, stent insertion, surgical intervention, conversion to open, and complication rate.

Surgery techniques

Standard laparoscopic cholecystectomy is the procedure of choice in our institution to manage gallbladder disease. However, the decision for open surgery or laparoscopy depends on the surgeon's preference and the patient's clinical condition. This study was conducted in a private hospital, and all surgeries were performed by qualified expert surgeons at the consultant level.

Statistical analyses

The normality of data was tested by skewness, kurtosis z-value and the Shapiro−Wilk test. Variables are described by frequency and percentages if categorical and by means and standard deviations if continuous. The demographic and clinical variables of the two groups were compared by the Fisher's exact test with two-sided verification and the Pearson's χ^2 test, or an unpaired Student's t-test, depending on the nature of the data. A p-value of less than 0.05 was considered statistically significant. A Kaplan−Meier survival estimate plot was used to show the PCS interval post-LC. Data were analyzed by SPSS software (version 25, SPSS Inc., Chicago, IL).

Results

Characteristics of the PCS+ and PCS− groups

Of the 167 patients who underwent cholecystectomy, 39 were PCS+ (23.3%); 65% (107/167) of the patients were female. There was no statistically significant difference between the two groups in terms of age, sex, body mass index

Table 1: Demographics and clinical features of the study patients according to post-cholecystectomy syndrome (PCS) status.

Variables	Values as mean ± SD or No. of patients (%)		
	PCS (+) (n = 39)	PCS (−) (n = 128)	*p*-value[a]
Age at surgery, year	41.5 ± 12.7	41.7 ± 13.9	*0.927*
BMI	29.7 ± 7.0	30.6 ± 7.3	*0.468*
Sex			*0.251*
Male	11 (28.2)	49 (38.3)	
Female	28 (71.8)	79 (61.7)	
ASA score			*0.766*
I + II + III	39 (100)	127 (99.2)	
IV + V	0 (0)	1 (0.8)	
Diabetes			*0.552*
Yes	9 (23.1)	24 (18.8)	
No	30 (76.9)	104 (81.3)	
Comorbidities			*0.276*
Yes	20 (51.3)	53 (41.4)	
No	19 (48.7)	75 (58.6)	
Smoking			*0.669*
Yes	7 (17.9)	27 (21.1)	
No	32 (82.1)	101 (78.9)	
Biliary pancreatitis			*0.986*
Yes	4 (10.3)	13 (10.2)	
No	35 (89.7)	115 (89.8)	
Obstructive jaundice			*0.958*
Yes	5 (12.8)	16 (12.5)	
No	34 (87.2)	112 (87.5)	
WBC (u/L)	7.8 ± 3.3	8.9 ± 6.6	*0.333*
HB (g/dl)	12.4 ± 1.5	13.9 ± 9.0	*0.363*
Albumin (g/dl)	3.3 ± 0.5	3.6 ± 0.6	*0.544*
Total bilirubin (mg/dl)	09 ± 1.5	0.8 ± 1.7	*0.519*
Alkaline phosphatase (U/I)	106 ± 99	103 ± 70	*0.870*
SGOT/AST (U/I)	78 ± 71	71 ± 104	*0.268*
SGPT/ALT (U/I)	111 ± 152	95 ± 162	*0.875*
Creatinine (mg/dl)	1.1 ± 1.9	1.8 ± 1.7	*0.491*
INR	0.9 ± 0.6	0.9 ± 0.2	*0.518*

[a] Pearson's χ^2 test or Fisher's exact test and independent t-test; SD, standard deviation; ASA, American society of anesthesiologist score.

(BMI), American Society of Anesthesiologists ASA score, diabetes, comorbidities, smoking, and laboratory findings. Variables such as symptom duration, previous bariatric surgery, ERCP, stenting, sphincterotomy, and surgical outcome were not significantly related to PCS. Thirty-one patients, 9/39 (23%) in PCS+ group *vs* 22/128 (17.2%) in the PCS− group underwent LSG; there was no significant difference between the two groups with this respect ($p = 0.408$), thus implying that LSG has no effect on the development of PCS. Clinical and demographic data are demonstrated in Table 1.

ERCP and surgical outcome

ERCP was performed in 13.8% (23/167) of patients. In the PCS+ and PCS− groups, 17.9% (7/39) and 12.5% (16/112) of patients required ERCP, respectively. Of the 23 patients who underwent ERCP, a stent was inserted in 18 patients (78%); sphincterotomy was performed in the remaining patients. Urgent cholecystectomies were performed in 10.7% of patients (18/167) and the rate of conversion to open surgery was 3% (5/167). Surgical parameters were comparable between the two groups. No significances

Table 2: The effects of key factors on the development of PCS.

Variables	Values as mean ± SD or No. of patients (%)		
	PCS (+) (n = 39)	PCS (−) (n = 128)	*p*-value[a]
Duration of complaint			*0.157*
Less than 6 weeks	25 (64.1)	66 (51.5)	
More than 6 weeks	14 (35.9)	62 (48.5)	
Sleeve gastrectomy			*0.408*
Yes	9 (23.1)	22 (17.2)	
No	30 (76.9)	106 (82.8)	
GB wall thickness (mm)	3.6 ± 1.4	3.6 ± 2.1	*0.974*
ERCP			*0.387*
Yes	7 (17.9)	16 (12.5)	
No	32 (82.1)	112 (87.5)	
Stent insertion			*0.374*
Yes	6 (15.4)	12 (9.4)	
No	33 (84.6)	116 (90.6)	
Surgery sitting			*0.570*
Elective	36 (92.3)	113 (88.3)	
Urgent/ER	3 (7.7)	15 (11.7)	
Operative approach			*0.688*
Laparoscopy	38 (97.4)	124 (96.9)	
Lap. converted to open	1 (2.6)	4 (3.1)	
Operative time (min)	63 ± 30	65 ± 38	*0.799*
Bleeding > 100 ml			*0.399*
Yes	0 (0)	4 (3.2)	
No	39 (100)	124 (96.8)	
Drain			*0.202*
Yes	0 (0)	7 (5.5)	
No	39 (100)	121 (94.5)	
Wound infection			*0.552*
Yes	1 (2.6)	2 (1.6)	
No	38 (97.4)	126 (98.4)	
Collection			*0.414*
Yes	1 (2.6)	1 (0.8)	
No	38 (97.4)	127 (99.2)	
Stump leak			
Yes	0 (0)	0 (0)	
No	39 (100)	128 (100)	
CBD injury			
Yes	0 (0)	0 (0)	
No	39 (100)	128 (100)	
Pulmonary Embolism	0	1 (0.78)	
Chronic cholecystitis (histopathology)			*0.467*
Yes	35 (89.7)	109 (85.2)	
No	4 (10.3)	19 (14.8)	
Re-visit to theater	0	0	
Length of stay (days)	2.5 ± 1.7	2.4 ± 1.5	*0.668*
30 days readmission			*0.625*
Yes	2 (5.1)	4 (3.1)	
No	37 (94.9)	124 (96.9)	
30 days mortality	0	0	

[a] Pearson's χ^2 test or Fisher's exact test and independent t-test; SD, standard deviation.

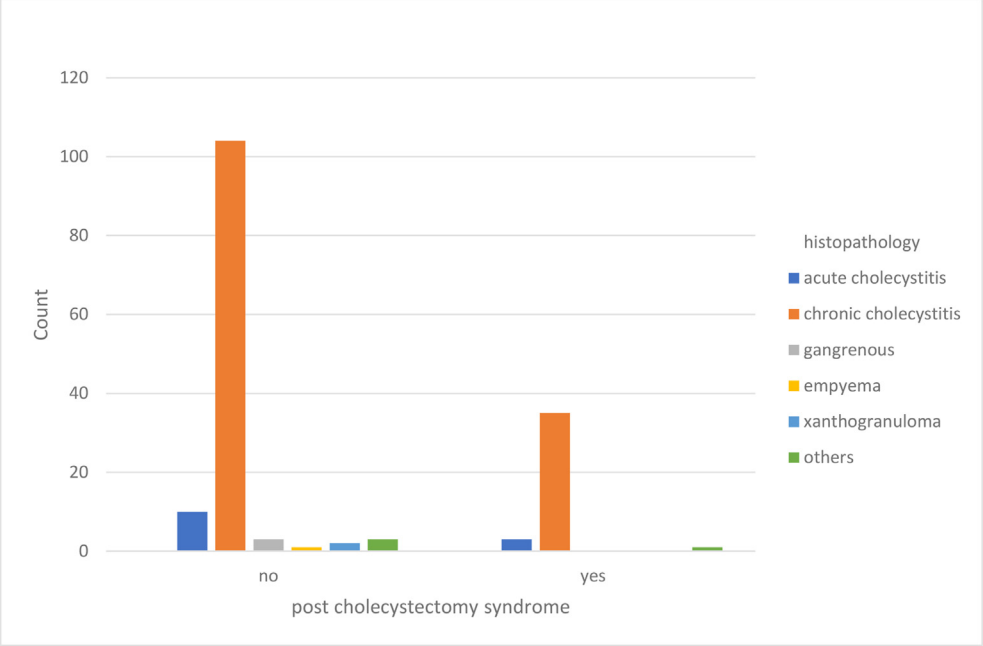

Figure 1: Histopathology of 167 cholecystectomies.

differences were evident between the two groups in terms of surgery-related complications, such as wound infection, collection, bleeding, the need for drains, biliary system injury or cystic stump leakage (Table 2).

Histopathology results

Chronic cholecystitis was observed in 83% of patients (139/167); the remaining patients suffered from acute cholecystitis, adenomyosis, gangrenous, empyema, mucocele and xanthogranuloma. Histopathological analysis did not reveal an incidental finding of malignant tumors or dysplasia (Figure 1). Since chronic cholecystitis implies prolonged symptoms, no statistical difference was evident between specific pathological findings and PCS.

Causes of PCS

Over an average follow-up period of 18 months (2–32 months), 39 patients complained of persistent symptoms.

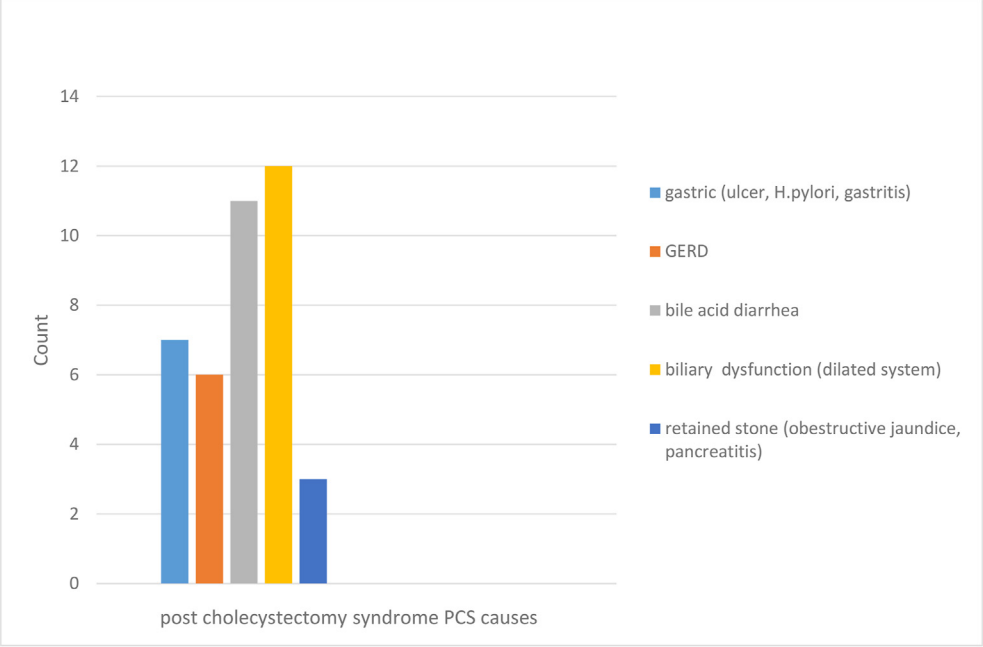

Figure 2: Causes of post-cholecystectomy syndrome in 39 patients.

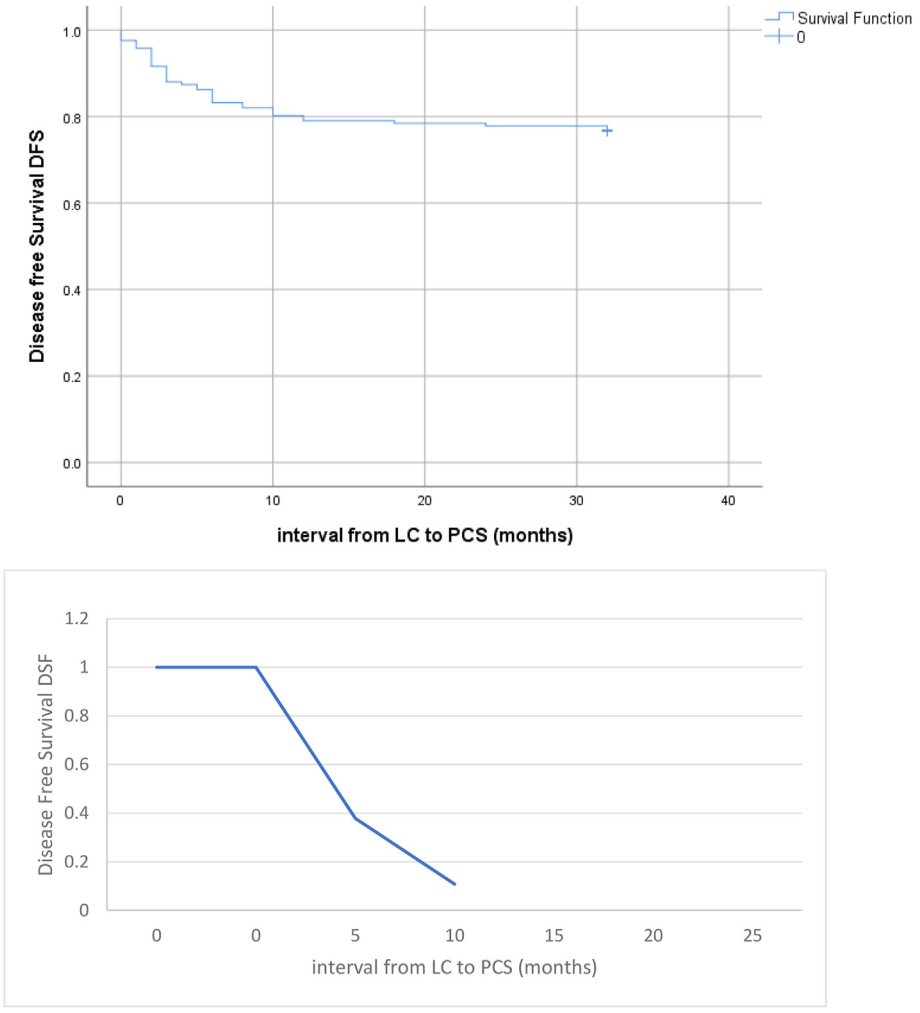

Figure 3: Kaplan–Meier survival estimate plot; 90% of PCS occurred in 10 months post-LC.

The interval between cholecystectomy and the development of PCS varied between 2 days and 24 months. The most frequent causes were biliary system dysfunction, bile salt-induced diarrhea (BSID), stomach-related factors (gastritis, peptic ulcer, and *Helicobacter pylori* infection) or gastro-esophageal reflux disease. Three patients with retained stones required postoperative ERCP (Figure 2). Early biliary PCS secondary to LC was observed in 14 out of 39 patients (36%); these patients presented with BSID and retained biliary duct stones. Incident PCS was evident in 71.8% of patients (28/39), while the remaining patients had persistent PCS. The Kaplan–Meier survival estimate plot showed that 90% of PCS cases were triggered 10 months post-LC (Figure 3).

Discussion

During the initial ultrasound investigation by a gastro-enterologist, a patient showing abdominal pain and gall-bladder stones will be referred to a surgeon for LC without further workup. Post-cholecystectomy syndrome encom-passes a range of GIT symptoms, such as abdominal pain, dyspepsia, flatulence, vomiting, jaundice and diarrhea that are either persistent or represent new incidents after surgery. Early biliary PCS can arise from a complication after cho-lecystectomy and is considered an incident rather than a persistent symptom, such as biliary duct injury or leakage, retained cystic or common bile duct stones, or BSID.[2] In our data, there was no evidence of inadvertent injury to the biliary system nor any postoperative stump leak. Early PCS presented with BSID in 11 patients and retained stones in three patients. Diarrhea was reported as early as day 2 post-cholecystectomy; this was similar to previous findings.[2] Incident symptoms were documented in 71.8% of PCS cases, thus indicating the need to thoroughly investigate the remaining 29.2% of cases, to diminish symptom persistence and achieve maximum benefits from LC.

Other treatable causes of PCS include the remnant gall-bladder, a large cystic stump[6] or a stump mucocele.[7] Such findings on ERCP or images require referral of the patient to a skilled surgeon for completion of cholecystectomy. Laparoscopic cholecystectomy for remnant stumps is common, but we did not encounter this in our patients. A detailed study must confirm the absence of a lethal underlying disease such as malignancy, vascular pathology or anomaly. For example, a splenic or gastroduodenal

artery aneurysm[8,9] or a choledochal cyst[10] can be masked by PCS. Such rare cases can be fixed by surgical, endoscopic, or endovascular intervention.

Late biliary PCS is due to recurrent stones, biliary system stricture or dysfunction of the sphincter of Oddi. Dysfunction of the biliary system with duct dilation was observed in 30% (12/39) of our patients, while concurrent primary stones were not reported. Saleem et al. previously reviewed 275 patients; of these patients, 219 had no apparent cause, biliary dysfunction was evident in 20 patients, peptic ulcer disease in 11 patients and biliary obstruction in 8 patients.[2] Dysfunction of the sphincter of Oddi is classified by three Milwaukee grades and is diagnosed clinically by persistent biliary pain, altered liver function tests, and >6 mm dilated duct on ultrasound. Furthermore, dysfunction of the sphincter of Oddi can be categorized into dyskinesia (spasm) possibly due to hormones, or stenosis (stricture) secondary to LC, passed stones, pancreatitis and trauma from ERCP.[11] Sphincter of Oddi dysfunction manometry is the standard gold test to differentiate these groups with duct pressure measurement in response to muscle relaxants.[11] Disease-free survival analysis by the Kaplan–Meier plot indicated that 90% of PCS occurs in the first 10 months after surgery. Frequent patient visits to the emergency room or clinic in the first year raises a query regarding the incidence of PCS; the underlying causes must be pursued.

Non-specific symptoms and patient awareness were implied as risk factors for PCS; however, certain factors have yet to be investigated.[5] Patient smoking history and obesity are not apparent risk factors for PCS. Smoking habits existed in 18% of our patients with a BMI of 29.7 (overweight). Conversely, young females appeared to be at high risk for PCS post-LC.[2] The duration of preoperative complaints has been related to PCS, as reported in some previous reviews.[12] When we divided our patients into two categories based on symptom duration and histopathological findings, there was no statistically significant association, as evidenced by Pearson's χ^2 test. The same results were observed for urgent surgery and operative complications, which were reported by others as risk factors for PCS.[1,12,13]

Although some authors linked ERCP choledochotomy in 20% of PCS cases,[12] most did not elucidate the effect of ERCP stenting, bariatric surgery or conversion to open surgery on evolving PCS. Instrumentation of the biliary duct with a stent can induce Sphincter of Oddi dysfunction SOD and stenosis, thus directly influencing the incidence of PCS[11]; on the other hand, LSG is not precisely related to PCS but has theoretically unforeseen effects. Laparoscopic sleeve gastrectomy is associated with surgical adhesion and can increase the chance of symptomatic and complicated GBS, such as choledocholithiasis, cholangitis and pancreatitis.[14] These complications are considered causes of PCS if patients undergo LC as part of their treatment. However, no previous study has attempted to investigate whether LSG is related to PCS. A variety of bariatric surgeries are performed in our center; however, in our study, 18.5% of patients (31/167) had undergone LSG. In addition, conversion to open surgery can trigger chronic pain in the right upper quadrant.[1] Our data revealed a 3% (5/167) conversion rate mainly due to intraoperative bleeding. There was no significant relationship between ERCP stenting, LSG or conversion to open surgery and PCS. This can be explained by sample size *versus* the reality of no relationship.

The symptoms of PCS can be significant and disturb the quality of life, or they can be minor and be ignored by the patient and physician. The pathophysiological changes noted in PCS are related to duodenogastric and gastroesophageal reflux, SOD and surgical adhesions.[1] Recent studies emphasized the role of the gut microbiome in triggering PCS as the intestinal flora can be altered due to the lack of bile after LC. Gut microbiota dysbiosis refers to an imbalance or lack of healthy microorganisms in the GIT.[15] The abundance of proteobacteria in the stools of patients post-LC might act as a risk factor for chronic pain and diarrhea in individuals with PCS.[16] Whether this dysbiosis specifically results from LC or the antibiotics the patient receives is unclear.[1] Restoring the normal flora with a probiotic regimen is suggested for treating PCS.[17] The treatment of PCS varies and depends on the underlying findings. Many protocols and algorithms have been designed to solve this problem; these begin with dietary modification and medication to improve the quality of life.

Antispasmodic, anticholinergic sedatives, proton pump inhibitors, cholestyramine, and antidiarrheal agents are used for symptomatic control. In addition, some patients require non-invasive radiological drainage or invasive intervention by ERCP stenting for biliary injury or leaks or papillotomy for SOD type I or II, but not type III.[11,13,18] Remnant gallbladder stumps necessitate the completion of cholecystectomy. In addition, one systemic review previously concluded that acupuncture therapy is useful and safe for treating PCS.[19]

Although LC may improve the symptoms of GBS, associated metabolic syndromes might persist; appropriate patient selection is the key.[20] Two current prospective trials [(Dutch Trial Register: NTR7307) and (NTR7267)] aim to answer queries regarding gastrointestinal function related to gallstones and to minimize the wrong surgical indications of LC.[20]

The limitations of our study include the observational nature and the sample sizes used. In addition, we did not focus on PCS treatment but on assessing specific predisposing factors. Here, we provide an analysis of a relationship that exists between PCS and stenting. We also estimated PCS disease-free survival post-LC. In conclusion, PCS is an overlooked complication that is observed in 25% of all cholecystectomy patients. Physician awareness is necessary, and clinical management should be aimed towards appropriate preoperative patient selection, postoperative correction of the underlying cause and symptom control. Patient education regarding physiological changes can help in future treatment once PCS is diagnosed. History of previous ERCP stenting, sphincterotomy or sleeve gastrectomy seems to be unrelated to the development of PCS. Close patient monitoring in the first year is necessary for the early detection and management of PCS.

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Conflict of interest

The author has no conflict of interest to declare.

Ethical approval

The Institutional Review Board at Dr. Soliman Fakeeh Hospital approved the study protocol on July 1, 2021 (approval number: 228/IRB/2021).

Acknowledgments

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