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ORIGINAL ARTICLE

Post endoscopic retrograde cholangiopancreatography cholecystitis: The incidence and risk factors analysis

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Abstract

Background: For decades, endoscopic retrograde cholangiopancreatography (ERCP) has been widely performed as a diagnostic and therapeutic procedure for biliary and pancreatic diseases. Complications of ERCP include pancreatitis, hemorrhage, perforation, cholangitis, and cholecystitis. There are few studies that focus on the incidence of post-ERCP cholecystitis and its potential risk factors.

Methods: A retrospective single-center study was performed in 1345 ERCP procedures after excluding patients with current cholecystitis or post-cholecystectomy between January 2009 and December 2011. Potential risk factors for post-ERCP acute cholecystitis, including age, gender, biochemistry, imaging data, procedures such as endoscopic sphincterotomy (EPT), or endoscopic retrograde biliary drainage (ERBD), were obtained and analyzed by multivariate logistic regression analysis.

Results: Cholecystitis developed after 13 (0.96%) of the 1345 ERCP procedures. Univariate and multivariate logistic regression analyses showed that cystic duct stones (odds ratio [OR] = 198.26; 95% CI, 5.12-7835.44) and ERBD (OR = 37.58; 95% CI, 3.25-445.56) were important potential risk factors for post-ERCP cholecystitis. The percentage of ERBD procedures and cystic duct stones in patients with post-ERCP cholecystitis was 76.9% and 39.8%, respectively. The 13 patients with post-ERCP cholecystitis all received antibiotics, and four of them also received percutaneous gallbladder drainage. All patients recovered without significant clinical event or mortality.

Conclusion: The incidence of post-ERCP cholecystitis was 0.96% in the 1345 ERCP procedures performed. Cyst duct stones and ERBD were found to be risk factors for post-ERCP cholecystitis.

Keywords: Endoscopic retrograde biliary drainage; Endoscopic retrograde cholangiopancreatography; Post-ERCP cholecystitis

1. INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has been widely used as a diagnostic and therapeutic procedure for biliopancreatic system diseases since 1968.[1] The ERCP procedure is complex despite the high efficacy rates and low adverse events reported in several studies. According to past studies, post-ERCP pancreatitis is the most common ERCP-related complication, with an incidence rate ranging between 3.4% and 9.7%.[2–4] Many studies have described the risk factors, pathogenesis, and management of post-ERCP pancreatitis. Other ERCP-related complications include post-ERCP bleeding, cholangitis, cholecystitis, perforation, and duodenoscope-related transmission of infection.[1] However, few studies describe post-ERCP cholecystitis, which is one of the complications of ERCP.

In Freemen's study, newly diagnosed cholecystitis occurred in 11 (0.5%) of the 2347 patients who received ERCP with sphincterotomy,[5] and gallbladder (GB) stones seem to be the only predictor of post-ERCP cholecystitis.[5] Cyst duct obstruction caused by tumor involvement of the cyst duct opening or by fully covered self-expanding metal stent implantation is considered one of the possible risk factors for post-ERCP cholecystitis.[6] However, this hypothesis was not supported by a meta-analysis, which found no obvious differences in the incidence of post-ERCP cholecystitis between covered and uncovered SEMs.[7] The pathogenesis of post-ERCP cholecystitis remains controversial given the scarcity of data on the topic. Therefore, its study may prove beneficial for our understanding the occurrence of post-ERCP cholecystitis and further prophylactic treatment. The aim of this study is to evaluate the incidence of and identify potential risk factors for post-ERCP cholecystitis.

2. METHODS

2.1. Patient enrollment

This was a retrospective, single-center study approved by the Institutional Review Board of the Taipei Veterans General Hospital (2011-10-007IC). Clinical data from 1622 patients

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who received ERCP examination and treatment at Taipei Veterans General Hospital from January 2009 to December 2011 were reviewed. Among these patients, 200 were excluded due to concurrent acute cholecystitis during the ERCP procedure. Furthermore, 69 patients who underwent cholecystectomy before ERCP, and eight patients who had received elective and scheduled cholecystectomy within 1 week following ERCP, were also excluded (Fig. 1). Finally, a total of 1345 patients who underwent an ERCP procedure were included for analysis.

2.2. Definition of post-ERCP acute cholecystitis

The diagnosis of post-ERCP acute cholecystitis followed the Tokyo Guidelines 2018 comprising diagnostic criteria and severity grading of acute cholecystitis (Table 1).[8] We reviewed medical charts to investigate and confirm signs of inflammation and imaging results within 2 weeks after ERCP. A combination of the presence of local signs of inflammation and one of either systemic signs of inflammation or imaging confirmation was needed for the diagnosis of acute cholecystitis.[8]

2.3. Data collection

Patients' age, gender, body temperature, laboratory data before ERCP, including serum total bilirubin, gamma-glutamyl transpeptidase (γ-GT), alanine aminotransferase (ALT), white cell count, and differential cell count, indications for ERCP, and the finding and diagnosis of post-ERCP were recorded. Therapeutic ERCP procedures, including endoscopic sphincterotomy (EPT) or endoscopic papilla balloon dilatation (EPBD) with stone extraction, endoscopic retrograde biliary drainage (ERBD) with stent insertion, and nasobiliary drainage, were also recorded. All patients underwent imaging, including abdominal CT and/or abdominal sonography before ERCP. The diagnosis of cystic duct, common bile duct/common hepatic duct (CBD/CHD) stones, and GB stones was confirmed by abdominal sonography, CT scan before ERCP, and cholangiogram during ERCP.

2.4. Statistical analysis

All data were expressed as mean ± standard deviation, and calculations were performed with SPSS v.21.0 (IBM, Armonk, New York, USA). Results were compared between groups, depending on the type of data analyzed, using either Chi-square test, Fisher's exact test, or Student's *t*-test, as appropriate. Continuous variables were transformed into categorical variables, with cut-off points determined by the Receiver Operating Characteristic (ROC) curve in logistic regression analysis. Univariate and multivariate logistic regressions were performed to evaluate the risk factors of acute cholecystitis after ERCP. All *p*-values were two-tailed, and a *p*-value below 0.05 was considered statistically significant. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated.

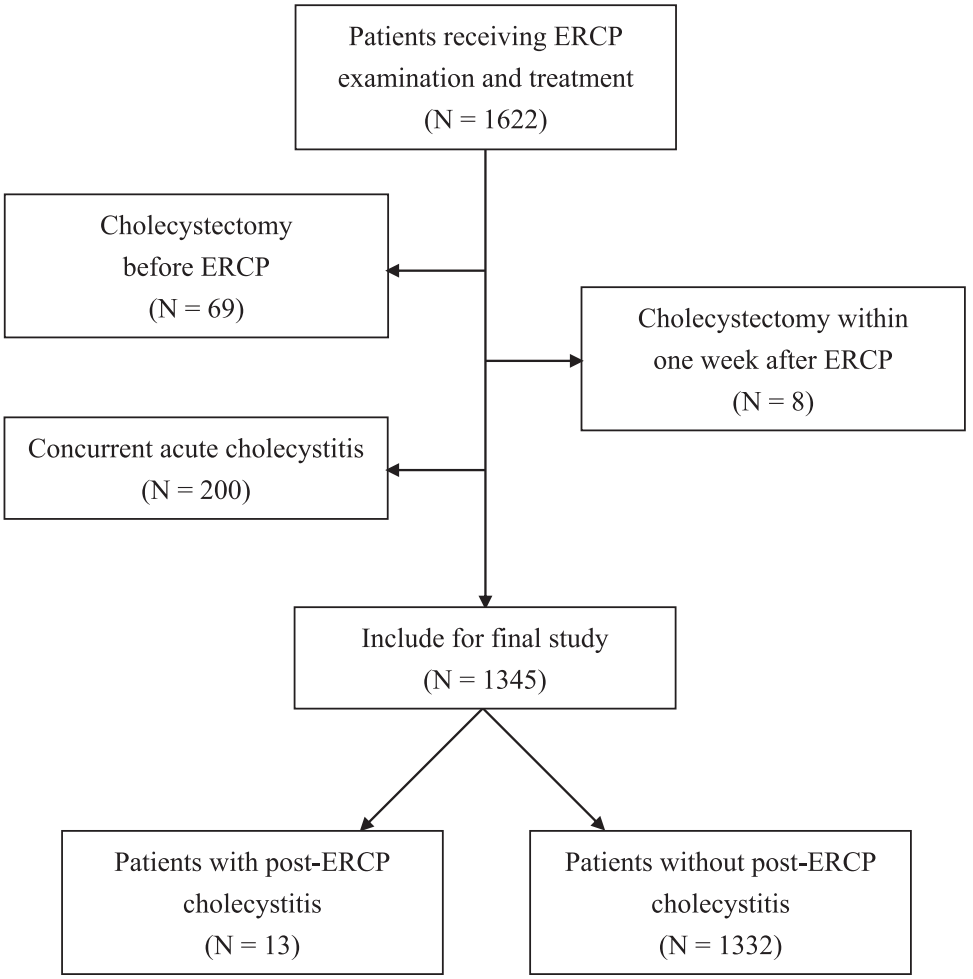

Fig. 1 Flowchart of study subjects based on the inclusion and exclusion criteria. ERCP = endoscopic retrograde cholangiopancreatography.

Table 1

The diagnostic criteria for acute cholecystitis

A. Local signs of inflammation, etc.
(1) Murphy's sign, (2) RUQ mass/pain/tenderness
B. Systemic signs of inflammation, etc.
(1) Fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings
Imaging findings characteristic of acute cholecystitis
Definite diagnosis: one item in A + one item in B + C

CRP = C-reactive protein; RUQ = right upper abdominal quadrant; WBC = white blood cell.

3. RESULTS

3.1. Patient characteristics

A total of 1,622 patients who underwent diagnostic or therapeutic ERCP between January 2009 and December 2011 were consecutively screened. After excluding 277 patients, 1,345 patients with a mean age of 67.1 years were enrolled, 706 (52%) of whom were male and 639 (48%) of whom were female. A total of 13 (0.96%) out of 1,345 ERCP procedures resulted in post-ERCP acute cholecystitis. No significant differences were found in age, sex, total serum bilirubin, γ-GT, ALT, white blood count, differential cell count, presence of acute pancreatitis, cholangitis, GB stones, CBD/CHD stones before ERCP, procedure of EPBD, and EPT during ERCP between patients with and without post-ERCP cholecystitis (Table 2). However, patients with cystic duct stone and ERBD during ERCP had a higher rate of post-ERCP cholecystitis than those without cystic duct stone and ERBD (Table 2). Of the 10 patients with post-ERBD cholecystitis, eight received metal stents (partially covered self-expandable metal stents; BONASTENT; Standard Sci-Tech, Seoul, Korea), and two patients received plastic stents (Advanix; Boston Scientific, Marlborough, MA, USA).

The 13 patients who experienced post-ERCP cholecystitis received medical treatment that included IV fluids and empirical antibiotics; four of these patients also underwent percutaneous GB drainage, and none of them received cholecystectomy. No significant clinical event or mortality after treatment of post-ERCP cholecystitis was found in all 13 patients.

Table 2

The clinical data between patients with post-ERCP cholecystitis and patients without post-ERCP cholecystitis

Parameters	Patients with post-ERCP cholecystitis (N = 13)	Patients without post-ERCP cholecystitis (N = 1332)	*p*
Age (y/o)	69.7 ± 10.9	67.1 ± 11.0	0.408
Sex (male), n (%)	5 (38.5)	701 (52.6)	0.405
White blood count (/mm^3)	9020 ± 3050	8950 ± 4210	0.521
T bilirubin (mg/dL)	6.1 ± 4.3	4.6 ± 4.7	0.255
ALT (U/L)	178 ± 58	151 ± 57	0.087
γ-GT (U/L)	247 ± 104	195 ± 123	0.133
Acute pancreatitis, n (%)	1 (7.7)	191 (14.3)	0.706
Acute cholangitis, n (%)	4 (30.8)	571 (42.9)	0.417
GB stones, n (%)	8 (61.5)	989 (74.2)	0.339
Cystic duct stone, n (%)	4 (30.8)	59 (4.4)	0.002
CBD/CHD stones, n (%)	5 (38.5)	770 (57.8)	0.171
EPBD, n (%)	2 (15.4)	339 (25.5)	0.535
EPT, n (%)	2 (15.4)	398 (29.9)	0.366
ERBD, n (%)	10 (76.9)	285 (21.4)	<0.001

ALT = alanine aminotransferase; CBD/CHD = common bile duct/common hepatic duct; EPBD = endoscopic papillary balloon dilation; EPT = endoscopic sphincterotomy; ERBD = endoscopic retrograde biliary drainage; GB = gallbladder; γ-GT = gamma-glutamyl transpeptidase.

3.2. Univariate and multivariate logistic regression analysis for post-ERCP cholecystitis

We assessed a total of 14 variables, including 11 patient-related factors and three procedure-related factors, in the univariate logistic regression analysis, finding that T bilirubin >5 mg/dL, ALT >160 U/L, γ-GT >200 U/L, cystic duct stones, and ERBD were close to significant ($p < 0.1$) for post-ERCP cholecystitis in the univariate analysis. These five parameters were then selected for multivariate logistic regression analysis to predict the occurrence of post-ERCP cholecystitis, showing that cystic duct stone (OR = 198.26; 95% CI, 5.12-7835.44; $p = 0.005$) and ERBD procedure (OR = 37.58; 95% CI, 3.25-445.56; $p = 0.004$) were important risk factors for post-ERCP cholecystitis (Table 3).

4. DISCUSSION

Contrasted with post-ERCP pancreatitis, post-ERCP cholecystitis is one of the more rare adverse events associated with ERCP. A handful of studies have discussed post-ERCP cholecystitis;[9–12] however, as far as we know, our study is one of the few that explores the incidence and risk factors of post-ERCP cholecystitis. Our retrospective study showed that 0.96% (13 patients) of the 1345 patients developed post-ERCP cholecystitis, consistent with results of previous studies.[5,13] We found that 10 of the 13 patients with post-ERCP cholecystitis had ERBD with stenting, and four of the 13 patients with post-ERCP cholecystitis had cystic duct stones. Multivariate analysis revealed that cystic duct stones and ERBD were significant independent predictive factors for post-ERCP cholecystitis.

Most of the acute cholecystitis is caused by stone-induced obstruction of biliary outflow; 90% of acute cholecystitis is associated with GB stones, and cystic duct stones is one of the common causes of biliary obstruction.[14] Intraluminal pressure of the GB is increased if the cystic duct is obstructed—and sometimes even bile flow is affected—if there is no obvious obstruction of the cystic duct. Post-ERCP cholecystitis may occur if other contributing factors are present, such as infection of bile within the biliary tract. Like other post-ERCP infections, enteric bacteria that enter the biliary tract by a retrograde route following ERCP manipulation will lead to cholecystitis. Contaminated contrast also plays a role in the setting of post-ERCP cholecystitis. Bacterial translocation, contaminated contrast, and poor GB motility all exacerbate the possibility of post-ERCP cholecystitis due to partial or complete obstruction by cystic duct stones. Furthermore, whether the level of obstruction and the size and number of cystic duct stones is an important factor for post-ERCP cholecystitis requires further study.

ERBD includes plastic stent placement, metallic stent insertion, and nasobiliary drainage. Cholecystitis occurred after stent placement for unresectable malignant biliary obstruction has been studied, including its incidence, risk factors, and differences between covered and uncovered stents.[9,12,15] In fact, a higher

Table 3

The possible risk factors associated with post-ERCP cholecystitis by multivariate logistic regression analysis

	Adjusted OR	95% CI	*p*
T bilirubin >5 mg/dL	0.54	0.23-3.61	0.389
ALT >160 U/L	1.36	0.27-6.78	0.686
g-GT >200 U/L	1.87	0.28-13.77	0.504
Cystic duct stone	198.26	5.12-7835.44	0.005
ERBD	37.58	3.25-445.56	0.004

ALT = alanine aminotransferase; ERBD = endoscopic retrograde biliary drainage; ERCP = endoscopic retrograde cholangiopancreatography; *g*-GT = γ-glutamyltransferase.

proportion of patients are diagnosed with post-ERCP cholecystitis after stent insertion, with an incidence rate between 4% and 9.7%.[6,9,10,15] In our study, there were 10 (3.38%) incidences of post-ERCP cholecystitis in 295 ERBD procedures. The previous studies reported that risk factors involving acute cholecystitis after stent placement included an obstruction across the cystic duct orifice by the tumor and the presence of GB stones.[10,15] Isayama's study showed that only tumor involvement of the orifice of the cystic duct was a risk factor for cholecystitis.[10] In our study, stent insertion was a significant independent predictive factor for cholecystitis, but gallstone and GB cancer were not found to contribute to post-ERCP cholecystitis.

Post-ERCP cholecystitis developed after placement of both an uncovered and a covered metal stent,[7] but Fumex et al.[9] showed a higher risk of cholecystitis with covered metal stents. The possible explanation was stent insertion-induced cystic duct obstruction. Both tumor growth across the cystic duct orifice and stent insertion were the factors contributing to cystic duct obstruction, which then progressed to cholecystitis. However, when researchers assessed the association of stent and cholecystitis, they observed the occurrence of cholecystitis for several weeks or months after stent insertion. In our study, cholecystitis was diagnosed within 2 weeks after stent insertion. The cause of early cholecystitis was more likely due to the cystic duct obstruction or compression by stent rather than tumor growth. The comorbidity, including specific malignancy, such as cholangiocarcinoma or pancreatic cancer, was also not discussed in this cohort. The effect of different types of malignancy after stent insertion also affects late cholecystitis if the longer outcome is followed.

Our study had some limitations. First, the retrospective nature of the study might underestimate the incidences of post-ERCP cholecystitis due to lack of evidence for true diagnosis. Second, due to the low incidence of post-ERBD cholecystitis, further analysis for the type or brand of stent (covered or uncovered metal stent or plastic stent) was not performed in this retrospective study. Third, the data of comorbidities, especially malignancies like cholangiocarcinoma or pancreatic cancer, were not analyzed as risk predictors of post-ERCP cholecystitis. In addition, some risk factors were also excluded from the analysis (e.g., duration of ERCP procedure, amount of contrast used for cholangiography). Therefore, a prospective study with a larger population of patients that investigates whether prophylactic antibiotics for prevention of post-ERCP cholecystitis is effective needs further study.

In conclusion, our study showed that the incidence of post-ERCP cholecystitis was not high (0.96%), and that cystic duct stones and ERBD were risk factors associated with post-ERCP cholecystitis. More attention should be paid to these risky patients, although this particular ERCP complication is uncommon in our daily practice.

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