

Increased Risk of Pyogenic Liver Abscess after Endoscopic Sphincterotomy for Treatment of Choledocholithiasis

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Background and Aim: Endoscopic sphincterotomy (ES) abolished the barrier between the hepatobiliary system and duodenum and might be at risk of pyogenic liver abscess (PLA). We aimed to identify the association factors of PLA in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) procedures for treatment of choledocholithiasis.

Methods: This study was based on the Chung Gung Research Database (CGRD) between January 1, 2001 and December 31, 2018. Those who had an International Classification of Diseases, Ninth and Tenth Revision (ICD9 and ICD10) codes of choledocholithiasis and received ERCP were enrolled. After strict exclusions, 11,697 patients were further divided into the endoscopic sphincterotomy (ES) group (n=7,111) and other ERCP group (n=4,586) for analysis.

Results: Patients receiving ES had significantly higher rates of PLA than those of the other ERCP group (5-year cumulative incidence 2.4% versus 1.7%; 10-year cumulative incidence 3.9% versus 3.2%, log-rank $p=0.0177$). Aging, male gender, surgery for hepato-pancreato-biliary system and hepatobiliary malignancy were significant association factors of PLA. On multivariate analysis, the ES increased the risk of PLA (adjusted hazard ratio [aHR]=1.49; 95% CI=1.12–1.98; $p=0.0058$) but decreased the risks for acute pancreatitis (aHR=0.72; 95% CI=0.60–0.85; $p=0.0002$) and cholangitis (aHR=0.91; 95% CI=0.84–0.99; $p=0.0259$). There was no significant difference about recurrent choledocholithiasis between groups.

Conclusion: This study demonstrated a significant risk of PLA after patients receiving ES compared with the other ERCP group. We should also carefully monitor the association factors of PLA after ERCP treatment of choledocholithiasis including aging, male gender, surgery for the hepato-pancreato-biliary system and hepatobiliary malignancy.

Keywords: pyogenic liver abscess, endoscopic sphincterotomy, choledocholithiasis, endoscopic retrograde cholangiopancreatography

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) is widely applied as the standard management of bile duct stones.^{1,2} Although generally considered safe, ES still carries some risks of complications. The short-term complications include procedural bleeding, pancreatitis, cholangitis, and perforation, whose overall incidence ranges from 2.5–13.1%.^{3–7} As for long-term complications, Oliveira-Cunha et al⁸ reported the incidence of cholangiocarcinoma varied from 0–3.1% between studies, the rate of recurrent

choledocholithiasis from 3.2–22.3%, and low incidence of cholangitis in the absence of recurrent biliary stones.

Pyogenic liver abscess (PLA) is a potential life-threatening infectious disease. Recently, biliary tract diseases including choledocholithiasis, hepatobiliary malignancy, stricture, and congenital biliary anomalies become the predominant etiologies of PLA.⁹ Diabetes mellitus (DM), underlying hepatobiliary or pancreatic disease, and gastrointestinal cancers with biliary tract involvement are well-known risk factors for PLA.^{10–12} Prior ES procedure promotes duodenal-biliary reflux and may induce ascending bacterial colonization or even infection of the common bile duct (CBD).^{13,14} Theoretically, ES might be associated with development of PLA. To date, there has been a lack of comprehensive study associating the risk of PLA with ES.

Therefore, we conducted a population-based, cohort study from the Chang Gung Research Database to analyze the risk of PLA among patients undergoing an ES procedure, as well as other complications including pancreatitis, cholangitis, and recurrence of CBD stones.

Methods

Compliance with Ethical Requirements

The study protocol was approved by the Institutional Review Board and the Ethics Committee of Chang Gung Memorial Hospital at Taoyuan in Taiwan (permitted number 201900919B0C601). This study was performed in accordance with relevant guidelines and regulations. The Ethics Committee waived the requirement for informed consent for this study, and the data were analyzed anonymously. This study was performed in accordance with the Declaration of Helsinki.

Data Sources

We collected the patient data from the Chang Gung Research Database (CGRD), the largest hospital system in Taiwan. The CGRD is a de-identified database based on detailed medical records including outpatient and inpatient treatment, laboratory data, interventional procedures, and prescription of medication. The diseases are identified based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for data before 2016 and ICD-10-CM for data thereafter. To protect the patients' privacy, the data are encrypted and de-identified when entered into the CGRD and can be further decrypted for medical

information if needed. According to a previous validation study,¹⁵ the CGRD contains more severe comorbidities and higher prevalence of certain diseases than in the Taiwanese National Health Insurance Research Database. Therefore, the CGRD is more convincing in studying complicated or rare diseases.

Study Cohort, Inclusion, and Exclusion Criteria

The identifications of disease according to codes of ICD-9-CM or ICD-10-CM based on ≥ 1 claim of inpatients or ≥ 1 claims of outpatients in 1 year are shown in [Supplementary Table S1](#). Those who had procedure codes including endoscopic sphincterotomy or endoscopic sphincterotomy with stone removal (56031B, 56033B, 56040B) were classified as endoscopic sphincterotomy (ES) group. Those who did not receive ES, but had other endoscopic retrograde cholangiopancreatography (ERCP) procedures such as endoscopic papillary balloon dilation, endoscopic nasobiliary drainage or endoscopic retrograde biliary drainage and endoscopic retrograde pancreatic drainage (33033B, 33024B, 56032B, 56020B, 56021B) were classified as the other ERCP group. Those who had a combination of ES and other therapeutic procedures were classified as the ES group. [Figure 1](#) showed a schematic flowchart of the study design. The cohort of patients with choledocholithiasis and received ERCP procedures was identified between January 1, 2001 and December 31, 2018. Those aged < 18 years old, with a history of receiving ERCP procedure, pyogenic liver abscess, amebic liver abscess, alcoholism, history of surgery for hepatopancreato-biliary system and malignancy including hepatocellular carcinoma (HCC), malignant neoplasm of gallbladder and extrahepatic bile ducts, malignant neoplasm of small intestine including duodenum and malignant neoplasm of pancreas were excluded before the index of choledocholithiasis. The eligible patients were then divided into the endoscopic sphincterotomy (ES) group ($n=7,111$) and other ERCP group ($n=4,586$) for further analysis.

Study Outcomes

The definition of primary and secondary outcomes is shown in [Supplementary Table](#). The primary outcome was the occurrence of liver abscess. All patients were followed from the index hospital admission to liver

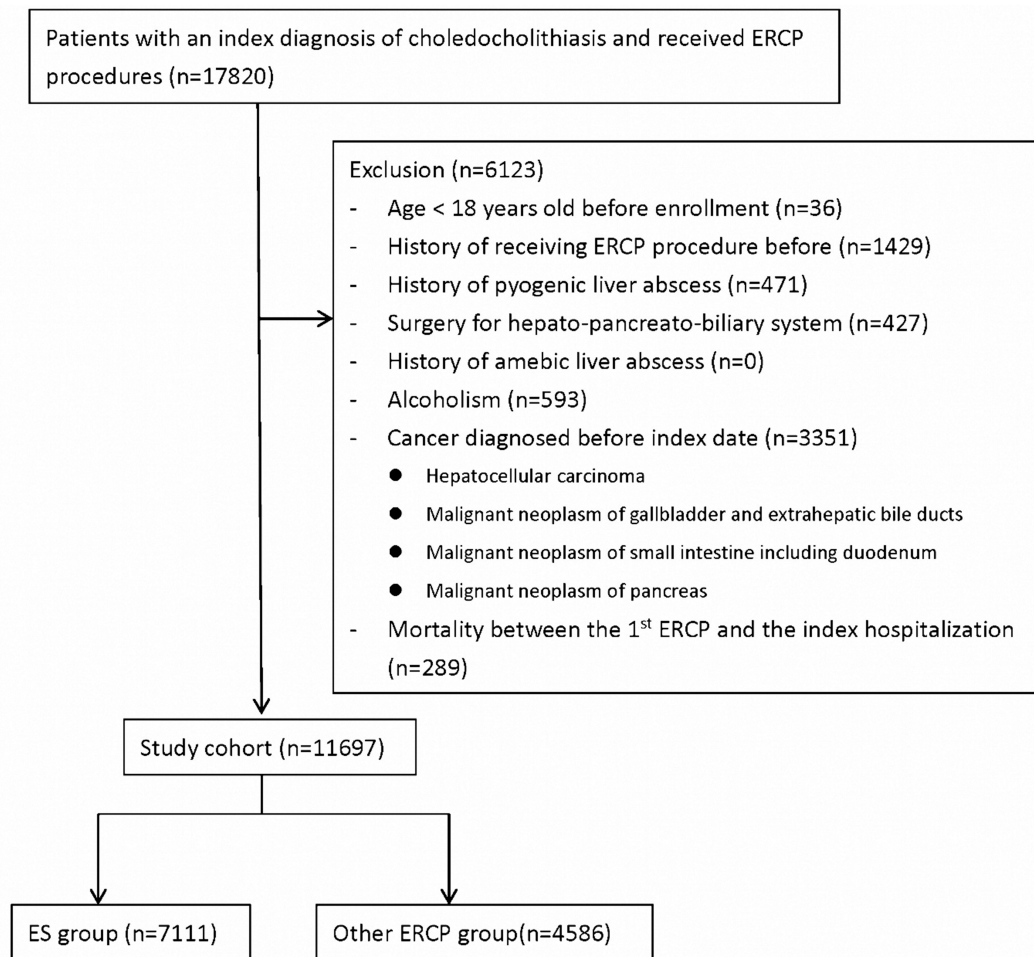


Figure 1 Schematic flowchart of the study design.

Abbreviations: ERCP, endoscopic retrograde cholangio-pancreatography; ES, endoscopic sphincterotomy.

abscess, death, or end of following time on December 31, 2018, whichever came first. Besides, the complications related to liver abscess such as endophthalmitis, brain abscess, intra-spinal abscess, brain meningitis, lung abscess, osteomyelitis and prostate abscess were also collected for analysis. The complication of liver abscess was defined as occurrence of infectious events in the same hospitalization.

The secondary outcomes included the occurrence of acute pancreatitis, cholangitis, recurrence of common bile duct stones <180 days or ≥ 180 days and in-hospital mortality rates.

Confounder Assessment

As shown in [Supplementary Table S1](#), patient's underlying comorbidities were identified based on ≥ 1 claim of inpatients or ≥ 1 claims of outpatients in 1 year prior to the index hospitalization, which included liver cirrhosis,

chronic kidney disease (CKD), diabetes mellitus (DM), disorders of lipid, coronary artery disease (CAD), and hypertensive cardiovascular disease (HCVD).

The potential medications influencing the outcomes were collected according to Anatomical Therapeutic Chemical code and are shown in [Supplementary Table S1](#), which included nonsteroidal anti-inflammatory drugs (NSAIDs)/Cyclooxygenase-2 (COX-2) inhibitors, aspirin, clopidogrel, warfarin, dipyridamole, cilostazol, systemic steroids, anti-hypertensives (diuretics, beta blocking agents, calcium channel blockers and angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB)), ursodeoxycholic acid, statin (atorvastatin, fluvastatin, pitavastatin, rosuvastatin and simvastatin), and other Lipid lowering drugs (clofibrate, bezafibrate, gemfibrozil, fenofibrate, nicotinic acid, ezetimibe, bile acid sequestrants, nicotinic acid and derivatives and other lipid modifying agents).

Interventional procedures or diseases that occurred during the follow-up period possibly influencing the outcomes were also collected for further analysis, which included endoscopic retrograde biliary drainage (ERBD), endoscopic papillary balloon dilation (EPBD), surgery for hepato-pancreato-biliary system, cholecystectomy and hepatobiliary malignancy (HCC, malignant neoplasm of gallbladder and extrahepatic bile ducts, malignant neoplasm of small intestine including the duodenum and malignant neoplasm of the pancreas).

Statistical Analysis

The categorical data were presented as frequencies and percentages and analyzed by using Pearson's Chi-square or Fisher's exact 2-tailed tests. The continuous data were presented as means±standard deviation (SD) and analyzed using the *t*-test, where appropriate.

For accurate assessment of the competing risks on the impact of PLA, we applied a cause-specific approach of the Cox proportional hazard model to estimate the relative hazard ratio of outcome events between comparison groups. The regression model was made after adjustment of host factors, clinical conditions, and medication usage. Kaplan-Meier method with the Log rank test was used to compare cumulative incidence between comparison groups. Two-tailed *p*-values <0.05 were considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute's Inc., Cary, NC).

Results

Patient Characteristics

Demographic data for the two groups are shown in Table 1. The gender was similar between the two groups. Patients with ES procedure were significantly older than those with other ERCP (64.70±16.28 vs 63.87±15.22, *p*=0.0051). As for comorbidities, the ES group had higher prevalence of DM (24.82% vs 23.11%, *p*=0.0352), disorders of lipid metabolism (16.07% vs 14.13%, *p*=0.0044), and HCVD (43.96% vs 37.07%, *p*<0.0001), whereas the other ERCP group had higher rates of liver cirrhosis (6.21% vs 4.12%, *p*<0.0001). As for baseline medications, the ES group had significantly higher prescription of NSAID/COX-2 inhibitors (46.44% vs 38.01%, *p*<0.0001), aspirin

(10.87% vs 8.55%, *p*<0.0001), clopidogrel (3.68% vs 2.99%, *p*=0.0426), beta blocking agents (11.03% vs 9.59%, *p*=0.0136), calcium channel blockers (15.19% vs 12.8%, *p*=0.0003), and statin (9.58% vs 8.16%, *p*=0.0088) than those of the other ERCP group.

Outcomes

The outcomes are shown in Table 2. There was no significant difference with respect to the occurrence of liver abscess (ES [143, 2.01%] versus other ERCP [77, 1.68%], *p*=0.1970) between the two groups in the 18 years follow-up. There was no significant difference between the two groups about complications of liver abscess including bacterial meningitis and lung abscess.

Notably, the ES group had significantly lower incidence of acute pancreatitis (3.80% vs 5.56%, *p*<0.0001), cholangitis (18.14% vs 21.26%, *p*<0.0001), and recurrent CBD stones <180 days (12.60% vs 15.05%, *p*=0.0002) than those of the other ERCP group. The in-hospital mortality rate was similar between the two groups. Interestingly, we also sought the results of microbial cultures from blood or pus. The predominant pathogens were *Klebsiella pneumoniae* (ES [26.3%] vs other ERCP [17.8%]) and *Escherichia coli* (ES [19.8%] vs other ERCP [20.7%]).

Validation Analysis

After enrollment, a total of 220 patients were diagnosed as liver abscess. We then decrypted to connect the electronic medical records. After further chart reviewing, 100% (220/220) of them had the right diagnosis of liver abscess and received ERCP exams. We randomly selected the non-liver abscess ICD code in the same period of hospitalization of study groups, and there were negative diagnoses of liver abscess in these 220 cases.

Independent Association Factors of Development of Liver Abscess During Follow-Up Period

As shown in Figure 2A, patients receiving ES procedure had significantly higher cumulative incidence of liver abscess than that of other ERCP groups during the first 15-year follow-up (5-year cumulative incidence 2.4% vs 1.7%; 10-year cumulative incidence 3.9% vs 3.2%; 15-year cumulative incidence

Table 1 Patient's Characteristics Prior to the Index Hospitalization between the Two Groups

	ES Group (n=7,111)	Other ERCP (n=4,586)	p-value
Age at the index date, years	64.70±16.28	63.87±15.22	0.0051
Sex , n (%)			0.1015
Male	3,658 (51.44)	2,288 (49.89)	
Female	3,453 (48.56)	2,298 (50.11)	
Covariate , n (%)			
Liver cirrhosis	293 (4.12)	285 (6.21)	<0.0001
Chronic kidney disease	1,124 (15.81)	698 (15.22)	0.3933
Diabetes mellitus	1,765 (24.82)	1,060 (23.11)	0.0352
Disorders of lipid metabolism	1,143 (16.07)	648 (14.13)	0.0044
CAD	611 (8.59)	388 (8.46)	0.8034
HCVD	3,126 (43.96)	1,700 (37.07)	<0.0001
Baseline Medication			
NSAID/COX-2 inhibitors	3,302 (46.44)	1,743 (38.01)	<0.0001
Aspirin	773 (10.87)	392 (8.55)	<0.0001
Clopidogrel	262 (3.68)	137 (2.99)	0.0426
Warfarin	51 (0.72)	44 (0.96)	0.1541
Dipyridamole	67 (0.94)	30 (0.65)	0.0935
Cilostazol	68 (0.96)	31 (0.68)	0.1062
Systemic steroids	322 (4.53)	184 (4.01)	0.1805
Anti-hypertensives			
Anti-hypertensives	127 (1.79)	70 (1.53)	0.2868
Diuretics	657 (9.24)	415 (9.05)	0.7282
Beta blocking agents	784 (11.03)	440 (9.59)	0.0136
Calcium channel blockers	1,080 (15.19)	587 (12.8)	0.0003
ACEI/ARB	1,119 (15.74)	669 (14.59)	0.0920
Ursodeoxycholic acid	362 (5.09)	324 (7.06)	<0.0001
Statin	681 (9.58)	374 (8.16)	0.0088
Other Lipid lowering drugs	199 (2.8)	105 (2.29)	0.0912
Concomitant covariate (during follow-up)			
ERBD	399 (5.61)	324 (7.06)	0.0014
EPBD	385 (5.41)	278 (6.06)	0.1391
Surgery for hepato-pancreato-biliary system	691 (9.72)	612 (13.34)	<0.0001
Cholecystectomy	1,072 (15.08)	545 (11.88)	<0.0001
Hepatobiliary malignancy	403 (5.67)	378 (8.24)	<0.0001

Notes: Continuous data are presented as mean±SD; Number of event are presented as n (%).

Abbreviations: CAD, coronary artery disease; HCVD, hypertensive cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; ACEI, angiotensin- converting enzyme inhibitors; ARB, angiotensin receptor blockers; ERBD, endoscopic retrograde biliary drainage; EPBD, endoscopic papillary balloon dilation.

7.0% vs 3.8%, log-rank $p=0.0177$) after competing risk analysis.

The result of association factors for liver abscess is shown in Table 3, patients who underwent ES procedure were at higher risk of liver abscess than those of the other ERCP group (adjusted hazard ratio [aHR] =1.49; 95% CI=1.12–1.98, $p=0.0058$). Female gender

(aHR=0.74; 95% CI=0.57–0.97, $p=0.0298$) was a protective factor against liver abscess. Besides, aging (aHR=1.02; 95% CI= 1.00–1.03, $p=0.0048$), endoscopic retrograde biliary drainage (ERBD) procedure (aHR=1.66; 95% CI=1.08–2.54, $p=0.0196$), surgery for hepato-pancreato-biliary system (aHR=1.60; 95% CI=1.13–2.28, $p=0.0080$), and development of

Table 2 Outcomes

	ES Group (n=7,111)	Other ERCP (n=4,586)	p-value
Primary outcome, n (%)			
- Liver abscess	143 (2.01)	77 (1.68)	0.1970
Complications of liver abscess, n (%)			
- Endophthalmitis	0 (0)	0 (0)	
- Brain abscess	0 (0)	0 (0)	
- Intra-spinal abscess	0 (0)	0 (0)	
- Bacterial meningitis	2 (0.03)	0 (0)	0.2560
- Lung abscess	1 (0.01)	0 (0)	0.4219
- Osteomyelitis	0 (0)	0 (0)	
- Abscess of the prostate	0 (0)	0 (0)	
Secondary outcome, n (%)			
- Acute pancreatitis	270 (3.80)	255 (5.56)	<0.0001
- Cholangitis	1,290 (18.14)	975 (21.26)	<0.0001
- Recurrent CBD stones <180 days	896 (12.60)	690 (15.05)	0.0002
- Recurrent CBD stones ≥180 days	1,028 (14.46)	699 (15.24)	0.2423
- In-hospital mortality	316 (4.44)	198 (3.80)	0.7448

Notes: Number of event are presented as n (%).

hepatobiliary malignancy (aHR=2.91; 95% CI=2.07–4.08, $p<0.0001$) were significant association factors for development of liver abscess.

Independent Association Factors of Occurrence of Acute Pancreatitis, Cholangitis, or Recurrent Bile Duct Stones ≥180 Days during Follow-Up Period

There was a significantly lower incidence of acute pancreatitis observed in the ES group with ES procedure than that of the other ERCP group (Figure 2B, log-rank $p=0.0002$). As shown in Table 4, patients receiving ES procedure had lower risk of acute pancreatitis than that of the other ERCP group (aHR=0.72, 95% CI=0.60–0.85, $p=0.0002$). Aging (aHR=0.99; 95% CI: 0.99–1.00, $p=0.0111$) was a protective factor

against acute pancreatitis. There was no significant difference with respect to underlying comorbidities between the two groups.

There was significantly lower incidence of cholangitis observed in the ES group than in the other ERCP group (Figure 2C, log-rank $p=0.0102$). On multivariate analysis, as shown in Table 5, patients receiving ES procedure (aHR=0.91, 95% CI=0.84–0.99, $p=0.0259$) and female gender (aHR=0.82, 95% CI=0.75–0.89, $p<0.0001$) were protective factors against cholangitis. Aging (aHR=1.01 95% CI=1.00–1.01, $p=0.0001$) was an association factor for occurrence of cholangitis. Patients with liver cirrhosis (aHR=1.34; 95% CI=1.13–1.58, $p=0.0007$) and DM (aHR=1.14, 95% CI= 1.02–1.26, $p=0.0172$) were at higher association rate for cholangitis. The prescription of systemic steroids (aHR=1.36; 95% CI=1.12–1.64, $p=0.0016$) and ursodeoxycholic acid (aHR=1.27; 95% CI=1.08–1.49, $p=0.0036$) were association factors for cholangitis.

The result of association factors for occurrence of recurrent CBD stones is shown in Table 6 and Figure 2D. Aging (aHR=1.02; 95% CI=1.01–1.02, $p<0.0001$), liver cirrhosis (aHR=1.33, 95% CI= 1.10–1.62, $p=0.0033$), chronic kidney disease (aHR=1.18; 95% CI=1.02–1.37, $p=0.0256$) and the prescription of ursodeoxycholic acid (aHR=1.32; 95% CI=1.09–1.58, $p=0.0037$) were association factors for recurrence of CBD stone ≥180 days after index ERCP treatment.

Discussions

Previously, the issue about late complication after ES focused on cholangitis, recurrent bile duct stone, cholecystitis, and cholangiocarcinoma.^{8,16–18} After ES, the barrier between hepatobiliary system and duodenum was broken, and hence promoted duodenal-biliary reflux.^{13,14,19} The following reflux of enteric fluid inside the bile duct might facilitate bacterial colonization, cholangitis, or even liver abscess. The risk of liver abscess after ES should also be considered but lacks attention. Besides, the risk of PLA after ES was demonstrated than that of other ERCP group (aHR=1.49; 95% CI=1.12–1.98, $p=0.0058$). The risk was even increased during the follow-up period (5-year cumulative incidence: 2.4%, and 10-year cumulative incidence: 3.9%; 15-year cumulative incidence: 7.0% vs 3.8%). Besides, aging, male gender, surgery for hepato-pancreato-biliary

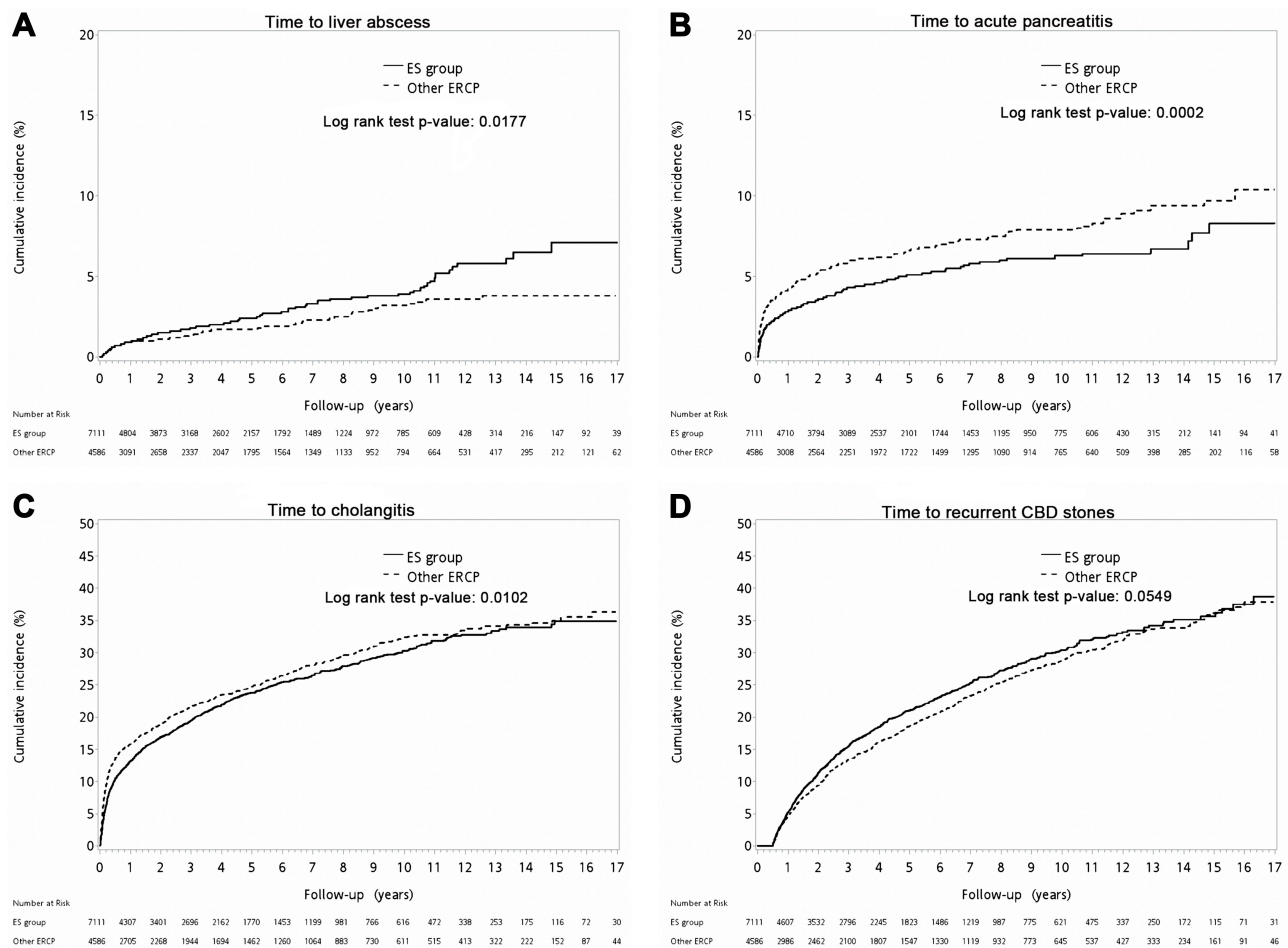


Figure 2 Cumulative incidence between groups: (A) liver abscess; (B) acute pancreatitis; (C) cholangitis; (D) recurrent CBD stones \geq 180 days.

system and development of hepatobiliary malignancy were significant association factors of PLA. There were few cases reporting the development of liver abscess after ES before. Tanaka et al mentioned five of 419 patients who underwent ES developed PLA with an average follow-up period of more than 10 years.¹⁷ Yasuda et al¹⁸ reported that two of 144 patients after ES had PLA during the follow-up period. Recently, Peng et al²⁰ conducted a population-based cohort study from the National Health Institute Research Database (NHIRD) in Taiwan and reported higher risk of PLA among patients receiving ES compared to the general population after 1:1 propensity score matching (4.20 vs 0.94, respectively, per 1,000 person-year). Although the sample size was big, the lack of detail analysis weakened the power of the result. In this current study, we performed a strict selection of cohort and analyzed the data under the consideration of covariate factors including medications and comorbidities.

Also, we included the covariate factors such as ERBD, EPBD, surgery for hepato-pancreato-biliary system, cholecystectomy and development of hepatobiliary malignancy during the follow-up period, which would highly influence the risk of PLA. More importantly, we made a validation analysis to ensure the enrolled cohort was correct. This emphasized the result that ES was an independent risk factor associated with PLA after competing risk analysis. We should carefully monitor the risk of PLA among patients receiving ES.

Apart from this, we found that the risk of acute pancreatitis was significantly lower among patients receiving ES than that of the other ERCP group (aHR=0.72; 95% CI=0.60–0.85, $p=0.0002$). We assumed the reason was related to the facilitation of small recurrent common bile duct stones clearance after ES for cutting the ampullary sphincter and bile duct sphincter. The bottom line is that the risk of biliary pancreatitis is decreased. Current practice guidelines also recommend

Table 3 Factors Associated with Liver Abscess

Variable	Adjusted HR	95% CI	p-value
ES group vs Other ERCP	1.49	1.12–1.98	0.0058
Age	1.02	1.00–1.03	0.0048
Sex (female versus male)	0.74	0.57–0.97	0.0298
Covariate			
Liver cirrhosis	0.95	0.54–1.68	0.8557
Chronic kidney disease	1.04	0.68–1.59	0.8698
Diabetes mellitus	1.29	0.93–1.78	0.1292
Disorders of lipid metabolism	0.94	0.58–1.53	0.8155
CAD	0.66	0.37–1.16	0.1467
HCVD	1.02	0.73–1.42	0.9207
Baseline Medication			
NSAID/COX-2 inhibitors	0.95	0.72–1.25	0.7079
Aspirin	0.94	0.55–1.61	0.8328
Clopidogrel	1.92	0.97–3.78	0.0603
Warfarin	0.69	0.09–5.08	0.7176
Dipyridamole	0.92	0.22–3.84	0.9052
Cilostazol	2.35	0.83–6.67	0.1071
Systemic steroids	0.75	0.35–1.61	0.4577
Anti-hypertensives			
Anti-hypertensives	1.60	0.63–4.05	0.3234
Diuretics	1.09	0.64–1.85	0.7610
Beta blocking agents	0.58	0.33–1.05	0.0706
Calcium channel blockers	0.89	0.55–1.45	0.6442
ACEI/ARB	1.01	0.61–1.65	0.9823
Ursodeoxycholic acid	1.35	0.81–2.22	0.2484
Statin	0.79	0.41–1.50	0.4674
Other Lipid lowering drugs	1.44	0.64–3.25	0.3846
Concomitant covariate			
ERBD	1.66	1.08–2.54	0.0196
EPBD	0.61	0.35–1.04	0.0694
Surgery for hepato-pancreato-biliary system	1.60	1.13–2.28	0.0080
Cholecystectomy	0.83	0.56–1.23	0.3483
Hepatobiliary malignancy	2.91	2.07–4.08	<0.0001

Abbreviations: CAD, coronary artery disease; HCVD, hypertensive cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ERBD, endoscopic retrograde biliary drainage; EPBD, endoscopic papillary balloon dilation.

ERCP with endoscopic sphincterotomy as an alternative method if cholecystectomy is not feasible for prevention of recurrent gallstone pancreatitis.²¹ As for recurrent choledocholithiasis, we defined its occurrence at least more than 6 months after the index ERCP.²⁰ Although not statistically significant on multivariate analysis, a trend toward higher risk of recurrent CBD stones was observed in the ES group (log-rank, $p=0.0549$, Figure 2D). Aging and liver cirrhosis, with their resultant

Table 4 Factors Associated with Acute Pancreatitis

Variable	Adjusted HR	95% CI	p-value
ES group vs Other ERCP	0.72	0.60–0.85	0.0002
Age	0.99	0.99–1.00	0.0111
Sex (female vs male)	0.96	0.81–1.14	0.6604
Covariate			
Liver cirrhosis	1.08	0.74–1.58	0.6890
Chronic kidney disease	1.28	0.99–1.65	0.0551
Diabetes mellitus	1.02	0.82–1.27	0.8572
Disorders of lipid metabolism	1.17	0.88–1.56	0.2885
CAD	1.02	0.74–1.40	0.9127
HCVD	0.87	0.69–1.09	0.2287
Baseline Medication			
NSAID/COX-2 inhibitors	1.23	1.03–1.46	0.0242
Aspirin	1.25	0.91–1.70	0.1661
Clopidogrel	1.11	0.70–1.75	0.6598
Warfarin	1.24	0.55–2.81	0.6104
Dipyridamole	0.79	0.32–1.94	0.6126
Cilostazol	1.53	0.74–3.17	0.2465
Systemic steroids	0.96	0.63–1.47	0.8668
Anti-hypertensives			
Anti-hypertensives	0.75	0.37–1.55	0.4429
Diuretics	1.16	0.85–1.58	0.3434
Beta blocking agents	1.07	0.79–1.46	0.6466
Calcium channel blockers	0.99	0.74–1.33	0.9715
ACEI/ARB	1.16	0.86–1.57	0.3225
Ursodeoxycholic acid	1.18	0.84–1.64	0.3358
Statin	0.70	0.48–1.01	0.0562
Other Lipid lowering drugs	1.02	0.61–1.71	0.9351

Abbreviations: CAD, coronary artery disease; HCVD, hypertensive cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

delayed biliary emptying and bile stasis were independent association factors for recurrent choledocholithiasis in this study, which was correlated with previous studies.^{13,19} As for cholangitis, liver cirrhosis, DM and aging were association factors in this study. An interesting finding was that the risk of cholangitis was significantly lower in the ES group. Recurrent cholangitis in the absence of retained stones after ES is difficultly defined and the incidence was low in previous studies.^{22–24} As shown in Figure 2C and D, the cumulative incidence between cholangitis and recurrent CBD stones were similar (up to 30% at 10-year follow-up period), which means that the cholangitis was related to retained or recurrent CBD stones after the ERCP procedure. The bottom is that the ES might facilitate clearance of recurrent CBD stones and therefore decrease the incidence of cholangitis.

Table 5 Factors Associated with Cholangitis

Variable	Adjusted HR	95% CI	p-value
ES group vs Other ERCP	0.91	0.84–0.99	0.0259
Age	1.01	1.00–1.01	0.0001
Sex (female vs male)	0.82	0.75–0.89	<0.0001
Covariate			
Liver cirrhosis	1.34	1.13–1.58	0.0007
Chronic kidney disease	0.92	0.81–1.05	0.2411
Diabetes mellitus	1.14	1.02–1.26	0.0172
Disorders of lipid metabolism	0.86	0.74–1.00	0.0476
CAD	0.90	0.76–1.06	0.1882
HCVD	0.89	0.80–0.99	0.0385
Baseline Medication			
NSAID/COX-2 inhibitors	0.89	0.82–0.97	0.0077
Aspirin	1.01	0.86–1.19	0.8724
Clopidogrel	1.05	0.83–1.35	0.6703
Warfarin	0.90	0.55–1.48	0.6828
Dipyridamole	1.30	0.88–1.92	0.1850
Cilostazol	1.11	0.71–1.75	0.6405
Systemic steroids	1.36	1.12–1.64	0.0016
Anti-hypertensives			
Anti-hypertensives	1.07	0.77–1.49	0.6695
Diuretics	1.07	0.91–1.25	0.4370
Beta blocking agents	0.87	0.74–1.02	0.0920
Calcium channel blockers	0.99	0.86–1.15	0.9192
ACEI/ARB	1.07	0.91–1.24	0.4142
Ursodeoxycholic acid	1.27	1.08–1.49	0.0036
Statin	0.95	0.78–1.15	0.5723
Other Lipid lowering drugs	0.85	0.63–1.15	0.2987

Abbreviations: CAD, coronary artery disease; HCVD, hypertensive cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

There were some limitations in this study. First, although the laboratory data was available in CGRD, however, the lack of complete laboratory data did not allow us to perform more detailed regression analysis. Since the issue about PLA after ES is late complication and the risk increase by years, it's reasonable to think there is less impact of index laboratory data on the occurrence of PLA after ES. Second, the factors influencing the bile flow such as peri-ampullary diverticulum, biliary stricture, and the size of CBD dilatation were not available in CGRD. Further study should be clarified for identification of their impact on the occurrence of PLA after ES.

In conclusion, this current study showed a significant risk of PLA after patients receiving ES compared with the other ERCP group. We should also carefully monitor the association factors of PLA after ERCP treatment of choledocholithiasis including aging, male gender, surgery for hepato-pancreato-biliary system, and development of hepatobiliary malignancy.

Table 6 Factors Associated with Recurrent Bile Duct Stones ≥ 180 Days

Variable	Adjusted HR	95% CI	p-value
ES group vs Other ERCP	1.09	0.99–1.20	0.0781
Age	1.02	1.01–1.02	<0.0001
Sex (female vs male)	1.01	0.92–1.12	0.7781
Covariate			
Liver cirrhosis	1.33	1.10–1.62	0.0033
Chronic kidney disease	1.18	1.02–1.37	0.0256
Diabetes mellitus	0.97	0.86–1.10	0.6366
Disorders of lipid metabolism	0.82	0.69–0.98	0.0275
CAD	0.85	0.71–1.02	0.0794
HCVD	0.97	0.86–1.10	0.6550
Baseline Medication			
NSAID/COX-2 inhibitors	0.92	0.84–1.02	0.1113
Aspirin	1.03	0.86–1.23	0.7663
Clopidogrel	1.00	0.76–1.32	0.9739
Warfarin	0.84	0.46–1.53	0.5735
Dipyridamole	0.99	0.61–1.58	0.9517
Cilostazol	0.73	0.40–1.34	0.3159
Systemic steroids	1.18	0.94–1.48	0.1626
Anti-hypertensives			
Anti-hypertensives	0.92	0.62–1.36	0.6691
Diuretics	0.99	0.83–1.19	0.9405
Beta blocking agents	0.95	0.79–1.13	0.5612
Calcium channel blockers	1.04	0.88–1.22	0.6522
ACEI/ARB	1.00	0.84–1.18	0.9577
Ursodeoxycholic acid	1.32	1.09–1.58	0.0037
Statin	1.07	0.86–1.32	0.5529
Other Lipid lowering drugs	1.06	0.77–1.45	0.7153

Abbreviations: CAD, coronary artery disease; HCVD, hypertensive cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Data Sharing Statement

No data will be shared except besides what is included in the manuscript.

Ethics Approval and Informed Consent

The study protocol was approved by the Institutional Review Board and the Ethics Committee of Chang Gung Memorial Hospital at Taoyuan in Taiwan (permitted number 201900919B0C601). This study was performed in accordance with relevant guidelines and regulations. The Ethics Committee waived the requirement for informed consent for this study, and the data were analyzed anonymously. This study was performed in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared that they have no conflicts of interest.

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