


Cholecystectomy Reduces Recurrent Pancreatitis and Improves Survival After Endoscopic Sphincterotomy

Shih-Hao Young^{1,2} · Yen-Ling Peng^{1,2} · Xi-Hsuan Lin^{1,2} · Yung-Tai Chen^{1,3} ·
Jiing-Chyuan Luo^{1,2,4}  · Yen-Po Wang^{1,4} · Ming-Chih Hou^{1,2,4} · Fa-Yauh Lee^{1,2}

Received: 17 July 2016 / Accepted: 17 September 2016 / Published online: 27 October 2016
© 2016 The Society for Surgery of the Alimentary Tract

Abstract

Background The aim of this study was to assess whether cholecystectomy can decrease the recurrent pancreatitis in the elderly patients who received endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST) and successful clearance of bile duct (BD) stones after gallstone-related acute pancreatitis.

Methods We analyzed data from National Health Insurance Research Database of Taiwan. Elderly patients (age ≥ 70 years old) who had gallstone-related acute pancreatitis and underwent successful EST with BD stones clearance were eligible for enrollment. This nationwide, population-based, propensity score (PS)-matched cohort study involved two cohorts: (1) patients who underwent cholecystectomy after ERCP with BD stone clearance as study group and (2) those who adopted wait-and-see strategy (without cholecystectomy) after ERCP with BD stone clearance as control group. The primary and secondary endpoints were recurrent acute pancreatitis and all-cause mortality, respectively.

Results During the study period, a total of 670 elderly patients (male 291, female 379) with a mean age of 79.1 was enrolled for analysis after PS matching. The incidence rate of recurrent acute pancreatitis was 12.39 per 1000 person-years in the cholecystectomy cohort and 23.94 per 1000 person-years in the PS-matched control cohort. The risk of recurrent acute pancreatitis was significantly lower in the cholecystectomy cohort (HR, 0.56; 95 % confidence interval [CI], 0.34–0.91; $P = 0.021$). The HR for all-cause mortality among the cholecystectomy cohort was 0.75 (95 % CI, 0.59–0.95; $P = 0.016$) compared with the control cohort.

Conclusions Cholecystectomy decreased the subsequent recurrent acute pancreatitis and the all-cause mortality in elderly patients with EST and clearance of BD stones after gallstone-related acute pancreatitis.

Yung-Tai Chen and Jiing-Chyuan Luo contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s11605-016-3284-y) contains supplementary material.

✉ Yung-Tai Chen
ytchen0117@gmail.com

✉ Jiing-Chyuan Luo
jcluo@vghtpe.gov.tw

¹ Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan

² Department of Medicine, Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, 201, Shih-Pai Road, Section 2, Taipei 11217, Taiwan

³ Department of Medicine, Taipei City Hospital Heping Fuyou Branch, 33, Zhonghua Road, Section 2, Taipei, Taiwan

⁴ Endoscopic Center for Diagnosis and Therapy, Taipei Veterans General Hospital, Taipei, Taiwan

Keywords Acute pancreatitis · Cholecystectomy · Endoscopic retrograde cholangiopancreatography · Endoscopic sphincterotomy · Gallstones

Background

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) are suggested for the treatment of bile duct (BD) stones.^{1,2} Prophylactic cholecystectomy is recommended after endoscopic clearance of BD stones to reduce subsequent biliary-related events, such as cholangitis and cholecystitis in previous randomized controlled trials (RCTs).^{3–5} However, whether prophylactic cholecystectomy after endoscopic clearance of BD stones decreases the incidence of subsequent recurrent pancreatitis and all-cause mortality remains uncertain in RCTs.^{3–5} Only a

cohort study showed that higher rate of pancreatitis occurred in patients with deferred cholecystectomy than patients with prophylactic cholecystectomy after ERCP with EST with BD stone removal.⁶ Elderly patients often had more underlying comorbidities and had a higher operation risk evening receiving laparoscopic cholecystectomy due to their underlying comorbidities. The study aimed to assess whether prophylactic cholecystectomy can lower the incidence of subsequent acute pancreatitis and the all-cause mortality in the elderly patients who received endoscopic clearance of BD stones after gallstone-related pancreatitis.

Methods

Data Sources

This study was based on data from the National Health Insurance Research Database (NHIRD) released by the National Health Research Institute (NHRI) of Taiwan. Taiwan started the NHI program in 1995 providing comprehensive health care for all its inhabitants. Enrollment in the NHI program is mandatory. The total population of Taiwan is around 23.3 million by the end of 2014, and there are presently more than 23 million enrollees, representing approximately 99 % of Taiwan's population.⁷ The NHI program offers integrated medical care, including outpatient, inpatient, emergency, dental, and drug prescriptions. The NHIRD includes the entire registry and claims data from the NHI system, ranging from demographic data to detailed orders including ambulatory and inpatient care. The NHIRD is managed and publicly released by the NHRI and contains registration files and original reimbursement claims data for all enrollees in Taiwan. These features make the NHIRD one of the largest and most complete nationwide health care service datasets in the world.^{8–10} The diagnostic codes of the patients in the NHIRD are in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and are established by board-certified physicians in their corresponding specialties. The diagnostic accuracy for the major diseases in the NHIRD has been well validated.¹¹ All the information that might potentially identify any individual patient was encrypted before the database releasing. Subjects' informed consent was waived. The confidentiality of the database was in accordance with the data regulations of the Bureau of NHI and the NHRI, Taiwan. The NHRI guarded the privacy of all beneficiaries and provided health insurance data to researchers.

Patients

Patients who were 70 and older than 70 years old and who were hospitalized after January 1, 2000 with diagnosis of

gallstone-related pancreatitis (ICD-9-CM codes 577.0 plus 574, 574.0, 574.1x, 574.2x, 574.6x–574.9x) and underwent successful endoscopic clearance of BD stones were eligible for the study. Within 3 months after ERCP with EST and stone clearance, patients who underwent cholecystectomy were considered as study group and those who adopted wait-and-see strategy without cholecystectomy were considered as control group. To avoid immortal time bias, the index date was defined the date of 91 days after ERCP with EST and stone clearance. The patients with primary and secondary malignancy (ICD-9-CM codes 14x.xx–19x.xx, 200.xx–208.91, 230.xx–239.9); benign neoplasm of liver, bile duct, and pancreas (211.5, 211.6); disorders related to gallbladder, bile duct, and pancreas (574.xx–577.9); alcoholism (291.xx, 303.xx, 305.xx); chronic pancreatitis (577.1); hypercalcemia (227.1, 252.0, 252.9, 275.4x); and hypertriglyceridemia (272.1, 272.2, 272.3) before index date were excluded.

We examined the baseline sociodemographic characteristics of the cohort, including age, sex, monthly income, urbanization level, outpatient visits in the past 1 year, Charlson comorbidity index (CCI) score, and other underlying comorbidities.^{12,13} Urbanization levels in Taiwan are divided into four strata according to the Taiwan NHRI, in which level 1 is referred to as the “most urbanized” and level 4 as the “least urbanized.” Though original CCI score was designed to predict the 1-year mortality rate for the different underlying comorbid conditions,¹² it was widely used to determine overall systemic health, with each score increase reflecting a stepwise increase in cumulative mortality, and was used to match two study groups with different underlying disease in retrospective cohort studies to decrease selection bias.^{13,14} The comorbidities included coronary artery disease (CAD) [ICD-9-CM codes 410.xx–414.xx], ischemic stroke [ICD-9-CM codes 433.xx–434.xx], diabetes mellitus (DM) [ICD-9-CM code 250.xx], myocardial infarction (MI) [ICD-9-CM code 410.xx], hypertension [ICD-9-CM codes 401.xx–405.xx], heart failure [ICD-9-CM code 428.00], arrhythmia [ICD-9-CM code 427.xx], peripheral vascular disease [ICD-9-CM code 443.xx], valvular heart disease (VHD) [ICD-9-CM codes 393.xx–398.xx], uncomplicated and complicated peptic ulcer disease (PUD) [ICD-9-CM code 533.xx], chronic kidney disease (CKD) [ICD-9-CM codes 585, 586, 588.8, 588.9, 250.4, 274.1, 403.x1, 404.x2, 404.x3, 440.1], dyslipidemia [ICD-9-CM code 272.x], chronic liver disease including cirrhosis [ICD-9-CM codes 571.0, 571.1, 571.2, 571.3, 571.4, 571.4x, 571.5, 571.6, 571.8, 571.9], autoimmune disease [ICD-9-CM code 279.4], and obesity [ICD-9-CM codes 278, 278.0, 278.00].

A propensity score (PS)-matching analysis was performed with a ratio of 1:1 in the study and control group to reduce selection bias. The covariates in the propensity score model were listed in Supplementary Table 1. For each subjects in study and control groups, we calculated a PS for the

probability of receiving cholecystectomy. We matched one subject in study groups with each subject in control group according to propensity score (calipers of width equal to 0.1 SD of the logit of the propensity score) based on nearest neighbor matching without replacement.

Endpoints

The primary endpoint was recurrent pancreatitis (ICD-9-CM code 577.0) as the major diagnosis during hospitalization between January 1, 2000 and December 31, 2012. The secondary endpoint is the all-cause mortality.

Statistical Analysis

Descriptive statistics was used to describe the baseline characteristics of the study cohorts. These characteristics were compared between groups by using Pearson χ^2 tests for categorical variables and independent *t* tests for continuous variables, respectively. Standardized mean difference was used to compare the characteristics between groups after PS matching. PSs for the likelihood of cholecystectomy were calculated by multivariate logistic regression, conditional on baseline covariates (Supplementary Table 1). The cumulative incidence of recurrent pancreatitis and the all-cause mortality were calculated by using the Kaplan–Meier method and compared between groups by using the log-rank test. Cox regression models with a conditional approach and stratification were used to calculate hazard ratios (HRs) and 95 % confidence intervals (CIs) for the occurrence of recurrent pancreatitis and all-cause mortality between cohorts in each group.¹⁵ The competing risk regression was also calculated based on the model by Fine and Gray.¹⁵ Data linkage, processing, and analysis were conducted with the SQL Server 2012 (Microsoft Corporation, Redmond, WA). We used SAS version 9.3 (SAS Institute, Cary, NC) to calculate PSs and used STATA statistical software (version 13.0; StataCorp, College Station, TX) to perform other statistical analyses. The designated level of statistical significance was $P < 0.05$.

Results

Patients' Characteristics

During the study period, a total of 1185 elderly patients with gallstone-related pancreatitis were eligible for analysis. Among these patients, 352 underwent cholecystectomy (study group) and 833 receive deferred cholecystectomy (control group). The demographic data of the study and control groups are shown in Table 1. Patients in the study group were significantly younger than those in the control group (78.5 vs. 81.1 years old). The gender, monthly income, times of

outpatient visit in the past 1 year, and urbanization of the patients have no significant difference between the study and control groups. Compared to the control group, the study group had a lower Charlson comorbidity index score and had a lower proportion of comorbidities including ischemic stroke, DM, hypertension, and chronic liver disease. After PS matching including the parameters of patient number, mean age, sex, monthly income, urbanization level, outpatient visits in the past 1 year, Charlson comorbidity index score, and all the comorbidities, 335 study population and 335 controls were included for PS-matching analysis (Table 1, right column).

Risks of Recurrent Acute Pancreatitis and the All-Cause Mortality

During the follow-up period, 130 patients developed recurrent acute pancreatitis and 509 died before the end of the study. The incidence rates of recurrent acute pancreatitis were 11.47 per 1000 person-years in the cholecystectomy cohort and 28.10 per 1000 person-years in the control cohort. The risk of recurrent acute pancreatitis was significantly lower in the cholecystectomy cohort than in the control cohort (HR, 0.48, 95 % confidence interval [CI], 0.31–0.75; $P = 0.001$; Table 2). The HR for all-cause mortality among the cholecystectomy cohort was 0.66 (95 % CI, 0.54–0.80; $P < 0.001$) compared with the control cohort. Multivariate Cox regression analysis showed that the risk of recurrent acute pancreatitis and all-cause mortality was significantly lower in the cholecystectomy cohort than in the control cohort (HR, 0.46 and 0.75, respectively, P all < 0.05 ; Table 2).

Similar to the results of multivariate Cox regression analysis without PS matching, the risk of recurrent acute pancreatitis was significantly lower in the cholecystectomy cohort than in the PS-matched control cohort after PS matching (HR, 0.56; 95 % CI, 0.34–0.91; $P = 0.021$, Table 2). The HR for all-cause mortality among the cholecystectomy cohort was 0.75 (95 % CI, 0.59–0.95; $P = 0.016$) compared with the PS-matched control cohort.

The cumulative incidence of recurrent acute pancreatitis and the all-cause mortality in patients with cholecystectomy and the PS-matched control cohort were illustrated in Figs. 1 and 2, respectively.

Discussion

This nationwide population-based cohort study revealed that cholecystectomy decreased the subsequent acute pancreatitis and the all-cause mortality in elderly patients receiving ERCP and EST with successful clearance of BD stones after gallstone acute pancreatitis when compared with that of PS-matched control.

Table 1 Baseline characteristics of patients with gallbladder stone^a

Characteristics	Before propensity score-matching			Propensity score-matched		
	Cholecystectomy	Non-cholecystectomy	<i>P</i> value	Cholecystectomy	Non-cholecystectomy	StD ^b
Patient (no.)	352	833		335	335	
Mean age (SD), year	78.5 (7.4)	81.1 (6.8)	<0.001	79.0 (6.7)	79.2 (7.5)	−0.020
Male	155 (44.0)	410 (49.2)	0.102	149 (44.5)	142 (42.4)	0.042
Monthly income, NT\$			0.286			
Dependent	128 (36.4)	295 (35.4)		123 (36.7)	134 (40.0)	−0.067
<19,100	92 (26.1)	246 (29.5)		90 (26.9)	85 (25.4)	0.034
19,100–41,999	128 (36.4)	289 (34.7)		120 (35.8)	115 (34.3)	0.031
≥42,000	4 (1.1)	3 (0.4)		2 (0.6)	1 (0.3)	0.045
Urbanization			0.397			
Level 1	153 (43.5)	392 (47.1)		145 (43.3)	149 (44.5)	−0.024
Level 2	156 (44.3)	344 (41.3)		148 (44.2)	149 (44.5)	−0.006
Level 3	33 (9.4)	83 (10.0)		33 (9.9)	30 (9.0)	0.031
Level 4 (rural area)	10 (2.8)	14 (1.7)		9 (2.7)	7 (2.1)	0.039
Outpatient visits, in the past 1 year			0.703			
0–5 visits	2 (0.6)	9 (1.1)		2 (0.6)	1 (0.3)	0.045
6–10 visits	18 (5.1)	52 (6.2)		17 (5.1)	14 (4.2)	0.043
11–15 visits	26 (7.4)	65 (7.8)		25 (7.5)	25 (7.5)	0.000
>15 visits	306 (86.9)	707 (84.9)		291 (86.9)	295 (88.1)	−0.036
Charlson comorbidity index score (SD)	7.7 (2.7)	8.6 (2.9)	<0.001	7.8 (2.7)	7.8 (2.6)	0.003
Comorbidities						
Coronary artery disease	182 (51.7)	455 (54.6)	0.357	175 (52.2)	187 (55.8)	−0.072
Cerebrovascular disease	110 (31.3)	356 (42.7)	<0.001	107 (31.9)	105 (31.9)	0.013
Diabetes mellitus	124 (35.2)	347 (41.7)	0.039	119 (35.5)	115 (34.3)	0.025
Myocardial infarction	20 (5.7)	52 (6.2)	0.712	19 (5.7)	22 (6.6)	−0.037
Hypertension	258 (73.3)	657 (78.9)	0.037	249 (74.3)	249 (74.3)	0.000
Heart failure	69 (19.6)	196 (23.5)	0.138	67 (20.0)	73 (21.8)	−0.044
Peripheral vascular disease	17 (4.8)	59 (7.1)	0.148	17 (5.1)	19 (5.7)	−0.026
Peptic ulcer disease	198 (56.3)	491 (58.9)	0.390	191 (57.0)	184 (54.9)	0.042
Chronic kidney disease	62 (17.6)	179 (21.5)	0.130	61 (18.2)	57 (17.0)	0.031
Chronic liver disease	74 (21.0)	246 (29.5)	0.003	74 (22.1)	69 (20.6)	0.036
Arrhythmia	115 (32.7)	306 (36.7)	0.182	111 (33.1)	120 (35.8)	−0.056
Dyslipidemia	126 (35.8)	278 (33.4)	0.422	120 (35.8)	119 (35.5)	0.006
Valvular heart disease	37 (10.5)	116 (13.9)	0.109	37 (11.0)	42 (12.5)	−0.046
Obesity	3 (0.9)	4 (0.5)	0.445	2 (0.6)	2 (0.6)	0.000
Autoimmune disease	12 (3.4)	31 (3.7)	0.793	12 (3.6)	11 (3.3)	0.016
Propensity score (SD)	0.36 (0.13)	0.27 (0.12)	<0.001	0.34 (0.12)	0.34 (0.12)	0.003

SD standard deviation, StD standardized difference, NT\$ new Taiwan dollars

^a All data were described as number (%), except mean age and propensity score

^b Imbalance defined as absolute value greater than 0.151

Though RCTs showed that prophylactic cholecystectomy after endoscopic clearance of BD stones reduced subsequent biliary events including cholangitis and cholecystitis,^{3–5} there were few cases of acute gallstone-related pancreatitis in these studies for evaluating whether prophylactic cholecystectomy also decreased the incidence of subsequent acute pancreatitis and all-cause mortality. Only a cohort study showed higher

recurrence of acute pancreatitis in patients with deferred cholecystectomy than patients with prophylactic cholecystectomy after ERCP with EST and BD stone removal (30.0 vs. 4.8 %).⁶ In our study, patients with deferred cholecystectomy were significantly older, sicker, and had a higher mortality rate during follow-up than patients with cholecystectomy. After matching by PS to diminish the selection bias or adjusting

Table 2 Incidence and risk of hospitalization for acute pancreatitis and all-cause of mortality among patients with acute pancreatitis and gallbladder stone

	No. of event	Person-years	Incidence rate ^a	Crude		Adjusted ^b		Competing risk ^c	
				Hazard ratio (95 % CI)	<i>P</i> value	Hazard ratio (95 % CI)	<i>P</i> value	Hazard ratio (95 % CI)	<i>P</i> value
Before propensity score-matching									
Recurrent acute pancreatitis									
Cholecystectomy cohort	25	2180	11.47	0.48 (0.31–0.75)	0.001	0.46 (0.30–0.73)	0.001	0.48 (0.31–0.76)	0.002
Non-cholecystectomy cohort	105	3736	28.10	Reference		Reference		Reference	
All-cause mortality									
Cholecystectomy cohort	133	2274	58.49	0.66 (0.54–0.80)	<0.001	0.75 (0.61–0.92)	0.006	–	
Non-cholecystectomy cohort	376	4180	89.95	Reference		Reference			
After propensity score-matching									
Recurrent acute pancreatitis									
Cholecystectomy cohort	25	2018	12.39	0.56 (0.34–0.91)	0.021	–		0.58 (0.36–0.96)	0.034
Non-cholecystectomy cohort	41	1713	23.94	Reference				Reference	
All-cause mortality									
Cholecystectomy cohort	130	2112	61.56	0.75 (0.59–0.95)	0.016	–		–	
Non-cholecystectomy cohort	157	1917	91.91	Reference					

CI confidence interval

^a Per 10³ person-years

^b Adjusted for propensity score

^c All-cause mortality was calculated as a competing risk in this model

potential confounding factors by Cox regression analysis, our retrospective cohort showed that patients with deferred cholecystectomy had a significantly higher rate of subsequent acute pancreatitis and the all-cause mortality in elderly patients (age ≥ 70 years old) receiving ERCP with successful clearance of BD stones after gallstone-related acute pancreatitis.

The role and the timing of ERCP in acute gallstone pancreatitis remain controversial in the past.^{16–20} A meta-analysis

data revealed that early ERCP in patients with predicted mild and severe acute biliary pancreatitis without acute cholangitis did not lead to a significant reduction in the risk of overall complications and mortality.²¹ Another recent meta-analysis showed that in patients with acute gallstone pancreatitis, there is no evidence that early routine ERCP significantly affects mortality and local or systemic complications of pancreatitis, regardless of predicted severity.²² There is general consensus

Fig. 1 Kaplan–Meier estimates of cumulative hazard of subsequent acute pancreatitis categorized by cholecystectomy and the matched controls ($P = 0.019$ between the two groups by the log-rank test)

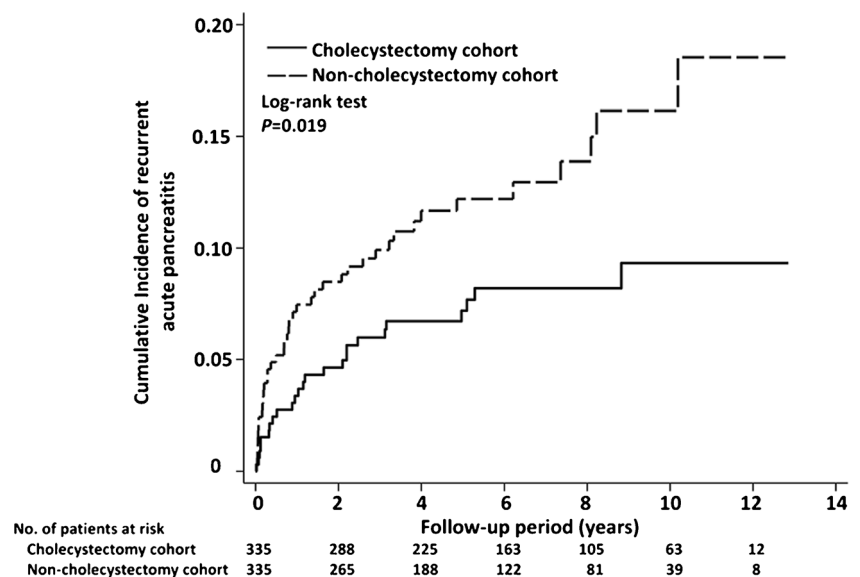
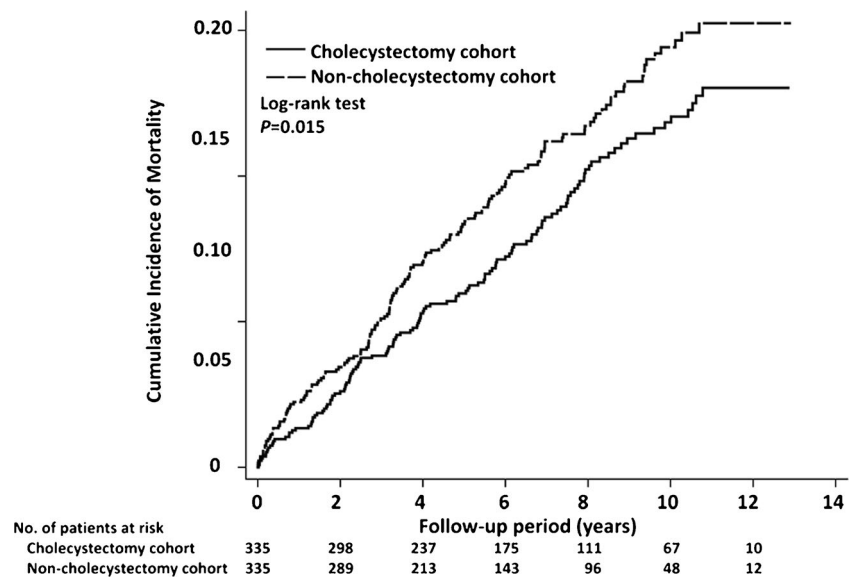


Fig. 2 Kaplan–Meier estimates of cumulative hazard of all-cause mortality categorized by cholecystectomy and the matched controls ($P = 0.015$ between the two groups by the log-rank test)



that (1) early ERCP is not indicated in patients with mild gallstone pancreatitis and (2) concomitant cholangitis or biliary obstruction is an indication for urgent ERCP.^{22,23} In our study, we did not evaluate the role and the timing of ERCP in acute gallstone pancreatitis. We just evaluated whether cholecystectomy or not can decrease the recurrent pancreatitis and all-cause mortality in the elderly patients who had BD stones and received ERCP with EST and successful clearance of BD stones after gallstone acute pancreatitis.

Though prophylactic cholecystectomy was recommended to patients whose gallbladder (GB) remained in situ after EST and BD stone clearance in patients with previous pancreatitis in a previous study,⁶ the study only enrolled patients in North America. As we know, the prevalence of pigmented BD stones was higher in East Asian countries than in Western countries.²⁴ This nationwide population-based cohort study in Taiwan, located in East Asia, also revealed that cholecystectomy decreased the recurrent acute pancreatitis and the all-cause mortality in patients with EST and successful clearance of BD stones after gallstone-related acute pancreatitis after matching by patients' age, gender, and underlying comorbidities.

Our study has several strengths. First, the Taiwanese NHIRD is one of the largest databases in the world with comprehensive health care data, and its use allows for a long-term population-based design.^{7–9} Second, a PS-matching analysis was performed to reduce selection bias, and the nationwide retrospective cohort reflected a real-world situation. However, the study findings should be interpreted in the context of several weaknesses. First, this is a retrospective study, not a RCT; some bias indeed existed. Second, the etiology of acute pancreatitis is multifactorial, though we excluded patients with alcoholism, hypercalcemia, hypertriglyceridemia, pancreatobiliary abnormality of stricture, and autoimmune

disease in our exclusion criteria; non-stone-related acute pancreatitis could not be totally excluded. Third, all the diagnoses of gallstone pancreatitis and CBD stones were based on ICD-9-CM codes (577.0 plus 574, 574.0, 574.1x, 574.2x, 574.6x–574.9x). The intervention procedures for BD stones and GB stones such as cholecystectomy and endoscopic sphincterotomy were recorded based on ICD-9-CM procedure codes (51.xx) and claims data of Taiwan National Health Insurance. We ascertained the BD stone clearance in study (cholecystectomy) group by checking the coding of EST, followed by cholecystectomy alone without the coding of choledochostomy, choledocholithotomy, or percutaneous BD drainage before or during cholecystectomy procedure. We ascertained the BD stone clearance in control (without cholecystectomy) group by checking the coding of EST, without the coding of cholecystectomy, choledochostomy, choledocholithotomy, or percutaneous BD drainage within 3 months after EST. It was impossible to have a chart review of study subjects or other confirmatory mechanism to verify the BD clearance after endoscopic sphincterotomy within the database due to the deidentification of study subjects.²⁵ Fourth, to avoid immortal time bias, the index date was defined the date of 91 days after ERCP with EST and stone clearance, not defined the day of the EST and stone clearance. All the events (endpoints) occurring during 1–90 days after ERCP with stone clearance were not included.

Conclusions

This nationwide population-based, PS-matched cohort study revealed that cholecystectomy, but not gallbladders, in situ decreased the subsequent acute pancreatitis and the all-cause

mortality in patients with ERCP and successful clearance of BD stones after gallstone-related acute pancreatitis. Prophylactic cholecystectomy should be recommended in these elder patients.

Authorships Contributions to the conception or design of the work: Shih-Hao Young, Yen-Ling Peng, and Jiing-Chyuan Luo

Acquisition, analysis, or interpretation of data for the work: Shih-Hao Young, Xi-Hsuan Lin, Yung-Tai Chen, Yen-Po Wang, Ming-Chih Hou, and Fa-Yauh Lee.

Drafting the work: Shih-Hao Young, Yen-Ling Peng, Xi-Hsuan Lin, and Jiing-Chyuan Luo.

Revising it critically for important intellectual content: Yen-Po Wang, Yung-Tai Chen, Ming-Chih Hou, and Fa-Yauh Lee.

Final approval of the version to be published: Shih-Hao Young, Xi-Hsuan Lin, Yen-Ling Peng, Jiing-Chyuan Luo, Yung-Tai Chen, Yen-Po Wang, Ming-Chih Hou, and Fa-Yauh Lee.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Shih-Hao Young, Yen-Ling Peng, Xi-Hsuan Lin, Yung-Tai Chen, Jiing-Chyuan Luo, Yen-Po Wang, Ming-Chih Hou, and Fa-Yauh Lee.

Compliance with Ethical Standards

Declaration of Funding Interests This study was funded in part by grants from Taipei Veterans General Hospital (V105C-037 and V104C-019), National Science Council of Taiwan (NSC 101-2314-B-010-012-MY3), and Ministry of Science and Technology of Taiwan (MOST 104-2314-B-010-010-MY3).

Conflict of Interest None of all authors.

References

- Davidson BR, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for common bile duct calculi in patients with gallbladder in situ considered unfit for surgery. *Gut* 1988;29(1):114–20.
- Roy A, McAlister V, Passi RB. Endoscopic retrograde cholangiopancreatography in the management of choledocholithiasis with laparoscopic cholecystectomy. *Can J Surg*. 1993;36(1): 81–4.
- Lau JY, Leow CK, Fung TM, Suen BY, Yu LM, Lai PB, Lam YH, Ng EK, Lau WY, Chung SS, Sung JJ. Cholecystectomy or gallbladder in situ after endoscopic sphincterotomy and bile duct stone removal in Chinese patients. *Gastroenterology* 2006;130(1):96–103.
- Boerma D, Rauws EA, Keulemans YC, Janssen IM, Bolwerk CJ, Timmer R, Boerma EJ, Obertop H, Huibregtse K, Gouma DJ. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile duct stones: a randomised trial. *Lancet* 2002;360(9335):761–5.
- McAlister VC, Davenport E, Renouf E. Cholecystectomy deferral in patients with endoscopic sphincterotomy. *Cochrane Database Syst Rev*. 2007;4: CD006233.
- Archibald JD, Love JR, McAlister VC. The role of prophylactic cholecystectomy versus deferral in the care of patients after endoscopic sphincterotomy. *Can J Surg*. 2007;50(1):19–23.
- Chen YJ, Wu CY, Shen JL, Chen TT, Chang YT. Cancer risk in patients with chronic urticaria: a population-based cohort study. *Arch Dermatol*. 2012;148(1):103–8.
- Luo JC, Leu HB, Huang KW, Huang CC, Hou MC, Lin HC, Lee FY, Lee SD. Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis. *CMAJ* 2011;183(18):E1345–51.
- Luo JC, Leu HB, Hou MC, Huang KW, Lin HC, Lee FY, Chan WL, Lin SJ, Chen JW. Nonpeptic ulcer, nonvariceal gastrointestinal bleeding in hemodialysis patients. *Am J Med*. 2013; 126(3):264. e25–32
- Lin CC, Hu HY, Luo JC, Peng YL, Hou MC, Lin HC, Lee FY. Risk factors of gastrointestinal bleeding in clopidogrel users: a nationwide population-based study. *Aliment Pharmacol Ther*. 2013;38(9): 1119–28.
- Lin CC, Lai MS, Syu CY, Chang SC, Tseng FY. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. *J Formos Med Assoc*. 2005;104(3):157–63.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–83
- Chien SC, Ou SM, Shih CJ, Chao PW, Li SY, Lee YJ, Kuo SC, Wang SJ, Chen TJ, Tarng DC, Chu H, Chen YT. Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in terms of major cardiovascular disease outcomes in elderly patients. *Medicine (Baltimore)*. 2015;94(43):e1751. doi: 10.1097/MD.0000000000001751
- Shih CJ, Wu YL, Lo YH, Kuo SC, Tarng DC, Lin CC, Ou SM, Chen YT. Association of hypoglycemia with incident chronic kidney disease in patients with type 2 diabetes: a nationwide population-based study. *Medicine (Baltimore)*. 2015;94(16):e771. doi: 10.1097/MD.0000000000000771.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Statist Assoc*. 1999;94: 496–509.
- Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988;2(8618):979–83.
- Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med*. 1993;328(4):228–32.
- Folsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeldt W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med*. 1997;336(4):237–42.
- Carl-Locke DL. Biliary pancreatitis. *Can J Gastroenterol*. 2003;17(3):205–8.
- van Santvoort HC, Besselink MG, de Vries AC, Boermeester MA, Fischer K, Bollen TL, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. *Ann Surg*. 2009;250(1):68–75.
- Petrov MS, van Santvoort HC, Besselink MGH, van der Heijden GJM G, van Erpecum KJ, Gooszen HG. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis. A meta-analysis of randomized trials. *Ann Surg*. 2008;247(2):250–7.
- Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev*. 2012;5 CD009779.
- van Geenen EJ, van Santvoort HC, Besselink MG, van der Peet DL, van Erpecum KJ, Fockens P, Mulder CJ, Bruno MJ. Lack of consensus on the role of endoscopic retrograde cholangiography in

- acute biliary pancreatitis in published meta-analyses and guidelines: a systematic review. *Pancreas* 2013;42(5):774–80
24. Chang YR, Jang JY, Kwon W, Park JW, Kang MJ, Ryu JK, Kim YT, Yun YB, Kim SW. Changes in demographic features of gallstone disease: 30 years of surgically treated patients. *Gut Liver* 2013;7(6):719–24.
25. Cheng YL, Hu HY, Lin XH, Luo JC, Peng YL, Hou MC, Lin HC, Lee FY. Use of SSRI, but not SNRI, increased upper and lower gastrointestinal bleeding: a nationwide population-based cohort study in Taiwan. *Medicine (Baltimore)*. 2015;94(46):e2022. doi: [10.1097/MD.0000000000002022](https://doi.org/10.1097/MD.0000000000002022)