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The risk of pyogenic liver abscess and endoscopic sphincterotomy: A population-based cohort study

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Abstract.

Objectives: To evaluate the risk pyogenic liver abscess (PLA) in patients receiving endoscopic sphincterotomy (ES).

Setting: A population-based cohort study using data from Taiwans' National Health Insurance Research Database was conducted. Patients aged 20 or older who had undergone an ES were considered as the ES cohort. The dates for the first hospitalization of the ES patients were defined as the index dates.

Participants: patients in the ES and non-ES cohorts were selected by 1:1 matching ratio based on a propensity score. A total of 8174 sex-, age-, and index year-matched (1:1) pairs of patients receiving ES and 8174 patients without ES served as controls. Cox proportional hazards regression was employed to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between PLA and ES.

Results: The overall incidence of PLA was significantly higher in the ES cohort than in the non-ES cohort (4.20 vs 0.94, respectively, per 1000 person-year) with the adjusted HR (aHR) = 4.50 (95% CI = 3.38-6.58) A stratified analysis during the follow-up years revealed that when the ES cohort was compared with the non-ES cohort, they displayed a higher risk of PLA during the first follow-up year (aHR = 4.35, 95% CI = 2.26-8.39) which continued significantly over the next 4–5 years of follow-up.

Conclusions: Patients receiving ES are associated with having a higher risk of PLA.

Article summary

- Endoscopic sphincterotomy is a procedure which eliminates the anatomic barrier of the biliary tract and intestine, and is considered to be a well-established, standard procedure for treating

choledocholithiasis. There is not study have direct link the risk of pyogenic liver abscess in patients receiving an Endoscopic sphincterotomy.

- Patients receiving endoscopic sphincterotomy are associated with having a higher risk of pyogenic liver abscess. The availability of these two large cohorts and follow-up conducted in pyogenic liver abscess risk after patients receiving endoscopic sphincterotomy.
- We used the code for only endoscopic sphincterotomy, and the details of underlying diseases, which included mostly biliary, and pancreatic diseases are not clearly defined in the database.

Introduction

Endoscopic sphincterotomy (ES) is the most commonly used therapy for treatment of common bile duct stones, and is today considered to be a well-established standard of treatment for pancreato-biliary diseases. (1-3) Standard ES involves the application of electrocautery to create an incision through the musculature of the biliary portion of the sphincter of Oddi and its use is considered as a safe, therapeutic procedure. (4, 5)

Depending on the time frame after an ES, the complications resulting from an ES are both short-term and long term. The percentage of short term complications is estimated to be approximately 10 percent, where procedural related bleeding, perforation, pancreatitis, and cardiopulmonary distress are considered as the short-term complications.(5) Long-term complications following an ES include stone recurrence, papillary stenosis, and cholangitis, any of which may which occur in approximately 6 to 24 percent of patients. (6-10)

Pyogenic liver abscesses (PLA) are the most common type of human visceral abscess. The mechanism may be due to either the leakage of bowel contents or microbes which subsequently spread to the liver via the portal circulation, or in the setting of a biliary infection. Risk factors for PLA include diabetes mellitus, underlying hepatobiliary or pancreatic disease, end-stage renal disease and the possible need for a liver transplant. (11-13) Additionally, geographic and host associations should also be considered, such as Klebsiella pneumoniae which has been experienced in East Asia.(14)

Regarding the long-term follow-up after ES, most previous studies displayed recurrent biliary stones, cholangitis, stenosis and malignancy. (7-10, 15-17)

ES creates a communication of bowel contents to both the biliary system, and liver. Thus, it is reasonable to consider that PLA is associated with ES. Up until now, there has been a lack of data associating the risk of PLA with ES.

To illuminate the risk of PLA and ES, we conducted a population-based, cohort study to analyze the risk of PLA among patients receiving an ES.

Materials and Methods

Data Source

This was a longitudinal, cohort study using the National Health Institute Research Database (NHIRD) of the National Health Insurance (NHI) program in Taiwan. The NHI program began in 1995, and 99% of the 23.74 million Taiwan residents became covered (18). The details of the NHI program and the NHIRD have been well documented in previous studies (16, 19). Diseases were coded in the NHIRD according to the 2001 International Classification of Diseases, Ninth revision, Clinical Modification

(ICD-9-CM). This study was approved by the Institutional Review Board (IRB) of China Medical University and Hospital in Taiwan (CMUH104-REC2-115).

Sampled Participants

Patients aged 20 or older years who had undergone an ES (ICD-9-OP 51.84) were considered as the ES cohort. The dates for the first hospitalization of the ES patients were defined as the index dates. We excluded patients younger than 20 years, along with those having a history of PLA (ICD-9-CM code 572.0) before the index date, any PLA diagnosed within 1 year after the index date, a history of amoebic liver abscess (ICD-9-CM code 006.3), and/or those lacking information on their age and sex. The non-ES cohort was identified during the same period occurring from the years 2000-2010, with exclusion criteria similar to the ES cohort. Patients in the ES and non-ES cohorts were selected by a 1:1 matching ratio based on a propensity score (20). The propensity score was calculated using a logistic regression to estimate the probability of the disease assignment, based on the baseline variables, including year of ES diagnosis, age, gender, and comorbidities of congestive heart failure (ICD-9-CM code 428), biliary stone (ICD-9-CM code 574), cancer (ICD-9-CM codes 140-208), hypertension (ICD-9-CM codes 401-405), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), hyperlipidemia (ICD-9-CM code 272), alcoholic liver damage (ICD-9-CM code 571.0, 571.1, and 571.3), cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6), cholangitis (ICD-9-CM code 576.1), cholecystitis (ICD-9-CM code 575), pancreatic diseases (ICD-9-CM code 577), chronic kidney disease (ICD-9-CM codes 580-589), appendicitis (ICD-9-CM codes 540-543), inflammatory bowel disease (ICD-9-CM codes 555, 556), and diverticulosis (ICD-9-CM codes 562).

Follow-up and Outcome

All of the patients were monitored up until either a diagnosis of PLA was made, they were censored for withdrawal from the NHI program, their death, or December 31, 2011, whichever occurred first.

Statistical analysis

Distributions in demographic variables, including age, gender, and comorbidities were compared between the ES and non-ES cohorts. The baseline characteristics of the ES and non-ES cohorts were compared using standardized mean differences (21). A value of standardized mean differences equaled .1 or less, which indicates there was a negligible difference in means between ES and non-ES cohorts. Incidence density rates of PLA by gender, age, and comorbidity were calculated in both cohorts. We assessed the cumulative incidence of PLA by using the Kaplan-Meier method in both the ES and non- ES cohorts, with significance based on the log-rank test. Univariable and multivariable Cox proportional hazard regressions were performed to measure the overall, gender-, age-, comorbidity-, follow-up years- risk of developing PLA. Hazard ratios (HRs) and 95% confidence intervals (CIs) were also estimated in the Cox model. The multivariate models were simultaneously adjusted for age, sex, and the comorbidities of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive pulmonary disease, hyperlipidemia, alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis. The entire matching procedure and all statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). A two-tailed $P < .05$ was considered significant.

Results

Characteristics of patients

Our study cohort consisted of 8,174 patients with ES and 8,174 patients without ES. The mean age (±SD) of the ES and non-ES cohorts was 66.9 ± 15.0 and 68.5 ± 14.6 years, respectively (Table 1). Most patients were men (53.1%). The major comorbidities were biliary stone (65.1% vs. 69.7%), and hypertension (39.0% vs. 43.5%) in these study cohorts, followed by pancreatic diseases (17.2% vs.

18.9%), cholangitis (15.5% vs. 9.70%) and hyperlipidemia (9.69% vs. 12.9%). The average follow-up duration was 4.33 ± 2.71 years for the ES cohort and 4.30 ± 2.60 years for the non-ES cohort, respectively. Figure 1 shows that the cumulative incidence of PLA was higher in the ES cohort than that in the non-ES cohort by 3.33% at the end of the follow-up period (log-rank test P < 0.001).

Incidence and adjusted hazard ratio of PLA after ES

The overall incidence of PLA was significantly higher in the ES cohort than in the non-ES cohort (4.20 vs 0.94, respectively, per 1000 person-year) with the adjusted HR (aHR) = 4.50 (95% CI = 3.38-6.58) (Table 2). The ES cohort to the non-ES cohort aHR of PLA was significant for each status (including gender, age group, and those with or without comorbidity).

Trend of PLA risk by stratified follow-up years

A stratified analysis of the follow-up years revealed that the ES cohort when compared with the non-ES cohort, had higher risk of PLA during the first follow-up year (aHR = 4.35, 95% CI = 2.26-8.39) and remained significantly so during 4–5 years of follow-up (aHR = 4.59, 95% CI = 1.72-12.2). The risk of PLA remained even beyond 5 years of follow-up (aHR =12.1, 95% CI = 2.80-52.2) (Table 3).

Risk of Pyogenic liver abscess by Endoscopic sphincterotomy and Cholangitis

Table 4 outlines the interaction effects of ES and cholangitis towards the risk of PLA. Relative to the non-ES cohort without cholangitis, the ES patients with cholangitis were at a much higher risk of PLA (aHR=6.64, 95% CI=3.82-11.5), when compared to patients with only cholangitis (aHR=3.77, 95% CI=1.69-8.41) or with only ES (aHR=5.48, 95% CI=3.56-8.44) (Table 4, the P-value of interaction=0.03).

Discussion

The association between PLA and ES is demonstrated by our results, which show that patients receiving ES have higher incidence rates of PLA than those in the control group (4.02 vs. 0.94 cases per 1000 person-years, p < 0.001). The adjusted HR for PLA was found to be 4.50 (95% CI 3.08–6.58)

for patients receiving EST, after adjusting for age, sex, and any possible comorbidities. The risk becomes even more significant when the follow-up years exceed 5 (adjust HR12.1, 95% CI 2.80- 52.2). Thus, PLA would be considered as one of the events which is associated with EST during long-term follow-up. ES experience is also considered to be one of the risks of PLA.

There is no clearly set time for the duration of follow-up when discussing the long-term complications of ES. A hospital-based study regarding endoscopic retreatment for biliary stones after ES is defined to be 5 years, and then a follow-up choledochal conditions due to increased risk of complications is suggested. (22) According to our results, PLA risk was determined to occur within 1 year after ES, and could be found to be increasing even more than that during the 5 year span. Thus, PLA risk would be need to be carefully monitored throughout follow-up. Risk of PLA was found to be more significant in non-comorbridity and young aged patients. We could explain that elderly patients and those experiencing co-morbidity carry a higher risk of PLA.

After decades of development, ES is still considered to be the requisite standard of care, and therefore has become the most commonly used procedure for the endoscopic treatment of biliay diseases, including choledocholithiasis. ES is applied to cut the biliary sphincter in order to eliminate the principal anatomic barrier impeding stone passage, and facilitate biliary manipulation. Upon reviewing available literature, long-term choledochal complications after ES include recurrent cholangitis, choledocholithiasis, biliary stenosis and cholecystitis. (6-10, 17) After ES, the anatomic barrier of the hepato-biliary system and intestine is removed, resulting in the communication causing an ascending migration of the bowel contents. The ascending movement would not be limited to strictly the biliary system only. Intrahepatic biliary system and even in hepatic cananliculi would be involved. Patients experiencing ES would remain under the risk of PLA.

PLA has become a worldwide health problem that is not limited to only Taiwan. When focusing on the risks of PLA, diabetes, end-stage renal disease, hepatobiliary diseases, pancreatic diseases, and the need for a liver transplant are all considered risk factors. (11-13, 23-25) Biliary disease is also considered as a risk of PLA, but there is lack of mention to ES. (26) Based on our results, patients receiving ES would also be considered to be a risk of PLA.

In the study, we first defined the association between ES and PLA, and recognized ES as a definite risk factor for PLA. There are however several limitations for the present study. First, we used the code for only ES, and any underlying diseases, which included mostly biliary, and pancreatic diseases. However, we did adjust both biliary and pancreatic disease, as shown in table 1. Second, the follow-up duration is around 4.3 years, with the longest set at about 7 years, due to the limitations of the database. We would expect to see a more significant PLA risk appearing under a longer follow-up period.

Our results demonstrate a significant risk of PLA during follow-up periods for patients receiving ES. Further investigations including bacterial culture, details of biliary systems and the analysis of clinical data, would be valuable studies that could be performed under a hospital-based inquiry.

Contributor ship statement

Author contributions: Conception and design: Yen-Chun Peng, Cheng-Li Lin, Fung-Chang Sung; Administrative support: Yen-Chun Peng; Collection and assembly of data: Yen-Chun Peng, Cheng-Li Lin, Fung-Chang Sung; Data analysis and interpretation: Yen-Chun Peng, Cheng-Li Lin, Fung-Chang Sung; Manuscript writing and revision: All authors; Final approval of manuscript: All authors.

competing interests

The authors declare no competing interests

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Data sharing statement

The Ministry of Health and Welfare must approved our application to access this data.

Any researcher interested in accessing this dataset can submit an application form to

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the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

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Figure Legends

Figure 1. Kaplan-Meir method determined the cumulative incidence of pyogenic liver abscess compared between endoscopic sphincterotomy cohorts and comparisons without endoscopic sphincterotomy.

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Table 1. Comparisons in demographic characteristics and comorbidities between patients with and without endoscopic sphincterotomy

	Endoscopic sphincterotomy				
	No (n=8174)		Yes (n=8174)		Standard difference
	n	%	n	%	
Age, mean(SD)†	68.5	14.6	66.9	15.0	0.11
Gender					
Women	3734	45.7	38232	46.9	0.02
Men	4440	54.3	4342	53.1	0.02
Comorbidity					
Congestive heart failure	564	6.90	491	6.01	0.04
Biliary stone	5695	69.7	5319	65.1	0.10

Cancer	687	8.40	580	7.10	0.06
Hypertension	3556	43.5	3186	39.0	0.09
Chronic obstructive lung disease	855	10.5	714	8.74	0.06
Hyperlipidemia	1052	12.9	792	9.69	0.10
Alcoholic liver damage	296	3.62	191	2.34	0.08
Cirrhosis	561	6.86	455	5.57	0.05
Cholangitis	793	9.70	1264	15.5	0.18
Cholecystitis	663	8.11	602	7.36	0.03
Pancreatic diseases	1544	18.9	1407	17.2	0.04
Chronic kidney disease	795	9.73	657	8.04	0.06
Appendicitis	167	2.04	152	1.86	0.01
Inflammatory bowel disease	34	0.42	20	0.24	0.03
Diverticulosis	215	2.63	206	2.52	0.01

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Table 2. Incidence and adjusted hazard ratio of Pyogenic liver abscess stratified by sex, age and comorbidity compared patients with and without endoscopic sphincterotomy

	Endoscopic sphincterotomy							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR[†] (95 % CI)	Adjusted HR[&] (95 % CI)
All	33	35113	0.94	149	35454	4.20	4.50(3.08, 6.56)***	4.50(3.08, 6.58)***
Gender								
Women	12	16394	0.73	67	16970	3.95	5.42(2.93, 10.0)***	5.41(2.92, 10.0)***
Men	21	18719	1.12	82	18483	4.44	3.97(2.46, 6.42)***	4.02(2.48, 6.53)***
Age								
<49	4	4928	0.81	23	5558	4.14	5.16(1.79, 14.9)**	7.30(2.42, 22.0)***
50-64	10	7762	1.29	38	8620	4.41	3.47(1.73, 6.96)***	3.30(1.63, 6.69)***
65+	19	22423	0.85	88	21276	4.14	4.90(2.99, 8.05)***	4.80(2.91, 7.90)***
Comorbidity								
No	2	4721	0.42	14	1715	8.16	20.4(4.60, 90.2)***	19.9(4.46, 88.6)***
Yes	31	30392	1.02	135	33738	4.00	3.95(2.67, 5.83)***	3.90(2.64, 5.78)***

Rate[#], incidence rate, per 1000 person-years

Crude HR[†], relative hazard ratio

Adjusted HR[&], adjusted hazard ratio, adjusted for age, sex, and comorbidity of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive lung disease, hyperlipidemia,

alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis.

*p<0.05, **p<0.01,***p<0.001

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Table 3 Trends of Pyogenic liver abscess risks by stratified follow-up years

Follow-up time, years	Endoscopic sphincterotomy							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
≤1	11	15458	0.71	52	15319	3.39	4.81(2.51, 9.23)***	4.35(2.26, 8.39)***
2-3	15	9931	1.51	52	9785	5.31	3.54(1.99, 6.28)***	3.64(2.04, 6.50)***
4-5	5	5512	0.91	22	5692	3.87	4.27(1.62, 11.3)**	4.59(1.72, 12.2)**
>5	2	4213	0.47	23	4658	4.94	10.4(2.45, 44.0)**	12.1(2.80, 52.2)***

Rate[#], incidence rate, per 1000 person-years

Crude HR[†], relative hazard ratio

Adjusted HR[&], adjusted hazard ratio, adjusted for age, sex, and comorbidity of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive lung disease, hyperlipidemia, alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis.

*p<0.05, **p<0.01,***p<0.001

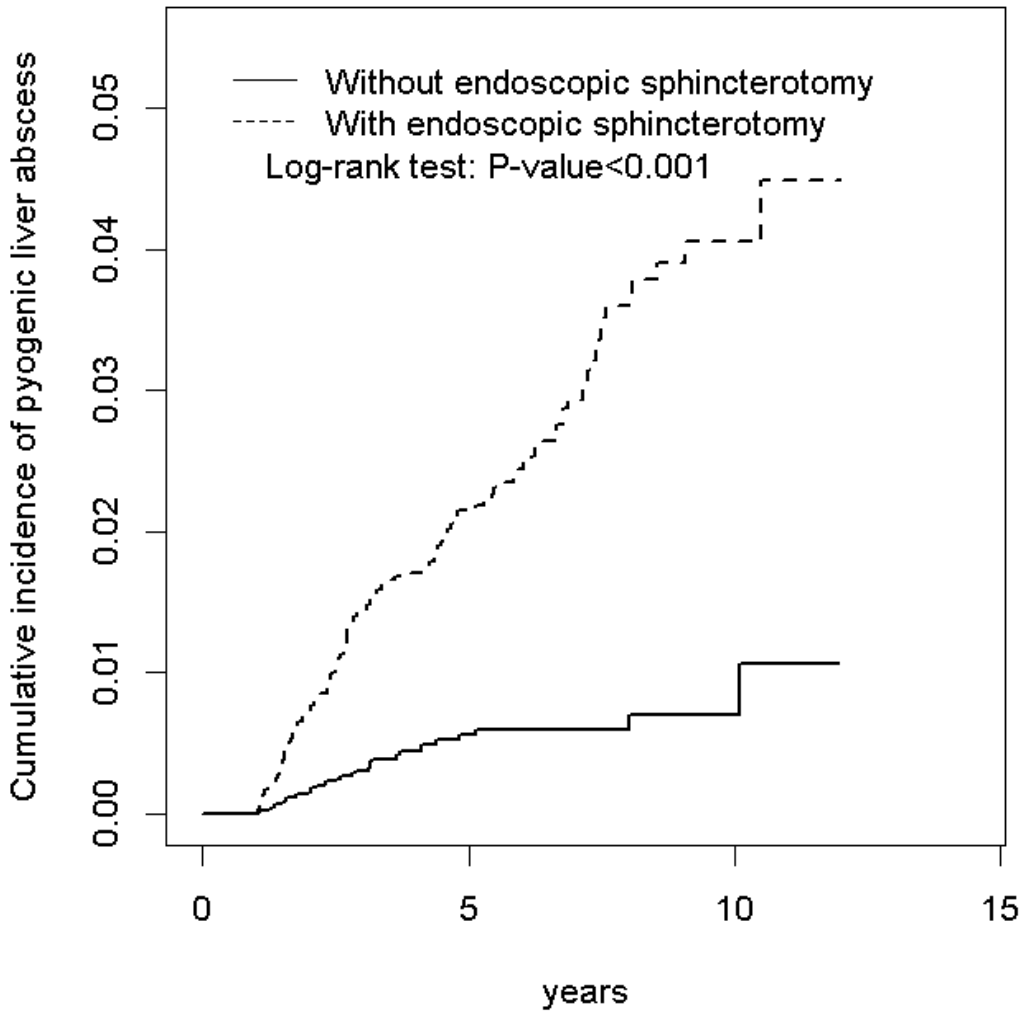
Table 4. Cox Proportional Hazard Regression Analysis for the risk of pyogenic liver abscess by endoscopic sphincterotomy and Cholangitis

Variables		Event	Rate[#]	Adjusted HR[†] (95% CI)	p-value[#]
Endoscopic sphincterotomy	Cholangitis				0.03
No	No	25	0.78	1(Reference)	
No	Yes	8	2.72	3.77(1.69, 8.41)**	
Yes	No	122	4.02	5.48(3.56, 8.44)***	
Yes	Yes	27	5.32	6.64(3.82, 11.5)***	

Rate[#], per 1,000 person-year;

[†] Model was adjusted for age, sex and other comorbidities. *p<0.05, **p<0.01, ***p<0.001

[#]p-value for interaction


Without endoscopic sphincterotomy
With endoscopic sphincterotomy
Log-rank test: P-value<0.001
Cumulative incidence of pyogenic liver abscess
0.00
0.01
0.02
0.03
0.04
0.05
0
5
10
15
years

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Abstract.

Objectives: To evaluate the risk pyogenic liver abscess (PLA) in patients receiving endoscopic sphincterotomy (ES).

Setting: A population-based cohort study using data from Taiwans' National Health Insurance Research Database was conducted. Patients aged 20 or older who had undergone an ES were considered as the ES cohort. The dates for the first hospitalization of the ES patients were defined as the index dates.

Participants: patients in the ES and non-ES cohorts were selected by 1:1 matching ratio based on a propensity score. A total of 8174 sex-, age-, and index year-matched (1:1) pairs of patients receiving ES and 8174 patients without ES served as controls. Cox proportional hazards regression was employed to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between PLA and ES.

Results: The overall incidence of PLA was significantly higher in the ES cohort than in the non-ES cohort (4.20 vs 0.94, respectively, per 1000 person-year) with the adjusted HR (aHR) = 4.50 (95% CI = 3.38-6.58) A stratified analysis during the follow-up years revealed that when the ES cohort was compared with the non-ES cohort, they displayed a higher risk of PLA during the first follow-up year (aHR = 4.35, 95% CI = 2.26-8.39) which continued significantly over the next 4–5 years of follow-up.

Conclusions: Patients receiving ES are associated with having a higher risk of PLA.

Article summary

- Endoscopic sphincterotomy is a procedure which eliminates the anatomic barrier of the biliary tract and intestine, and is considered to be a well-established, standard procedure for treating choledocholithiasis. There is no study have direct link the risk of pyogenic liver abscess in patients receiving an Endoscopic sphincterotomy.

- Patients receiving endoscopic sphincterotomy are associated with having a higher risk of pyogenic liver abscess. The availability of these two large cohorts and follow-up conducted in pyogenic liver abscess risk after patients receiving endoscopic sphincterotomy.
- We used the code for only endoscopic sphincterotomy, and the details of underlying diseases, which included mostly biliary, and pancreatic diseases are not clearly defined in the database.

Introduction

Endoscopic sphincterotomy (ES) is the most commonly used therapy for treatment of common bile duct stones, and is today considered to be a well-established standard of treatment for pancreato-biliary diseases. (1-3) Standard ES involves the application of electrocautery to create an incision through the musculature of the biliary portion of the sphincter of Oddi and its use is considered as a safe, therapeutic procedure. (4, 5)

Depending on the time frame after an ES, the complications resulting from an ES are both short-term and long term. The percentage of short term complications is estimated to be approximately 10 percent, where procedural related bleeding, perforation, pancreatitis, and cardiopulmonary distress are considered as the short-term complications.(5) Long-term complications following an ES include stone recurrence, papillary stenosis, and cholangitis, any of which may which occur in approximately 6 to 24 percent of patients. (6-10)

Pyogenic liver abscesses (PLA) are the most common type of human visceral abscess. The mechanism may be due to either the leakage of bowel contents or microbes which subsequently spread to the liver via the portal circulation, or in the setting of a biliary infection.

Risk factors for PLA include diabetes mellitus, underlying hepatobiliary or pancreatic disease, end-stage renal disease and the possible need for a liver transplant. (11-13) Additionally, geographic and host associations should also be considered, such as Klebsiella pneumoniae which has been experienced in East Asia.(14)

Regarding the long-term follow-up after ES, most previous studies displayed recurrent biliary stones, cholangitis, stenosis and malignancy. (7-10, 15-17)

ES creates a communication of bowel contents to both the biliary system, and liver. Thus, it is reasonable to consider that PLA is associated with ES. Up until now, there has been a lack of data associating the risk of PLA with ES.

To illuminate the risk of PLA and ES, we conducted a population-based, cohort study to analyze the risk of PLA among patients receiving an ES.

Materials and Methods

Data Source

This was a longitudinal, cohort study using the National Health Institute Research Database (NHIRD) of the National Health Insurance (NHI) program in Taiwan. The NHI program began in 1995, and 99% of the 23.74 million Taiwan residents became covered (18). The details of the NHI program and the NHIRD have been well documented in previous studies (16, 19). Diseases were coded in the NHIRD according to the 2001 International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM). This study was approved by the Institutional Review Board (IRB) of China Medical University and Hospital in Taiwan (CMUH104-REC2-115).

Sampled Participants

Patients aged 20 or older years who had undergone an ES (ICD-9-OP 51.84) were considered as the ES cohort. The dates for the first hospitalization of the ES patients were defined as the index dates. We excluded patients younger than 20 years, along with those having a history of PLA (ICD-9-CM code 572.0) before the index date, any PLA diagnosed within 1 year after the index date, a history of amoebic liver abscess (ICD-9-CM code 006.3), and/or those lacking information on their age and sex. The non-ES cohort was identified during the same period occurring from the years 2000-2010, with exclusion criteria similar to the ES cohort. Patients in the ES and non-ES cohorts were selected by a 1:1 matching ratio based on a propensity score (20). The propensity score was calculated using a logistic regression to estimate the probability of the disease assignment, based on the baseline variables, including year of ES diagnosis, age, gender, and comorbidities of congestive heart failure (ICD-9-CM code 428), biliary stone (ICD-9-CM code 574), cancer (ICD-9-CM codes 140-208), hypertension (ICD-9-CM codes 401-405), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), hyperlipidemia (ICD-9-CM code 272), alcoholic liver damage (ICD-9-CM code 571.0, 571.1, and 571.3), cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6), cholangitis (ICD-9-CM code 576.1), cholecystitis (ICD-9-CM code 575), pancreatic diseases (ICD-9-CM code 577), chronic kidney disease (ICD-9-CM codes 580-589), appendicitis (ICD-9-CM codes 540-543), inflammatory bowel disease (ICD-9-CM codes 555, 556), and diverticulosis (ICD-9-CM codes 562).

Follow-up and Outcome

All of the patients were monitored up until either a diagnosis of PLA was made, they were censored for withdrawal from the NHI program, their death, or December 31, 2011, whichever occurred first.

Statistical analysis

Distributions in demographic variables, including age, gender, and comorbidities were compared between the ES and non-ES cohorts. The baseline characteristics of the ES and non-ES cohorts were compared using standardized mean differences (21). A value of standardized mean differences equaled .1 or less, which indicates there was a negligible difference in means between ES and non-ES cohorts. Incidence density rates of PLA by gender, age, and comorbidity were calculated in both cohorts. We assessed the cumulative incidence of PLA by using the Kaplan-Meier method in both the ES and non- ES cohorts, with significance based on the log-rank test. Univariable and multivariable Cox proportional hazard regressions were performed to measure the overall, gender-, age-, comorbidity-, follow-up years- risk of developing PLA. Hazard ratios (HRs) and 95% confidence intervals (CIs) were also estimated in the Cox model. The multivariate models were simultaneously adjusted for age, sex, and the comorbidities of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive pulmonary disease, hyperlipidemia, alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis. The entire matching procedure and all statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). A two-tailed $P < .05$ was considered significant.

Results

Characteristics of patients

Our study cohort consisted of 8,174 patients with ES and 8,174 patients without ES. The mean age (±SD) of the ES and non-ES cohorts was 66.9 ± 15.0 and 68.5 ± 14.6 years, respectively (Table 1). Most patients were men (53.1%). The major comorbidities were biliary stone (65.1% vs. 69.7%), and hypertension (39.0% vs. 43.5%) in these study cohorts, followed by pancreatic diseases (17.2% vs. 18.9%), cholangitis (15.5% vs. 9.70%) and hyperlipidemia (9.69% vs. 12.9%). The average follow-up duration was 4.33 ± 2.71 years for

the ES cohort and 4.30 ± 2.60 years for the non-ES cohort, respectively. Figure 1 shows that the cumulative incidence of PLA was higher in the ES cohort than that in the non-ES cohort by 3.33% at the end of the follow-up period (log-rank test P < 0.001).

Incidence and adjusted hazard ratio of PLA after ES

The overall incidence of PLA was significantly higher in the ES cohort than in the non-ES cohort (4.20 vs 0.94, respectively, per 1000 person-year) with the adjusted HR (aHR) = 4.50 (95% CI = 3.38-6.58) (Table 2). The ES cohort to the non-ES cohort aHR of PLA was significant for each status (including gender, age group, and those with or without comorbidity).

Trend of PLA risk by stratified follow-up years

A stratified analysis of the follow-up years revealed that the ES cohort when compared with the non-ES cohort, had higher risk of PLA during the first follow-up year (aHR = 4.35, 95% CI = 2.26-8.39) and remained significantly so during 4–5 years of follow-up (aHR = 4.59, 95% CI = 1.72-12.2). The risk of PLA remained even beyond 5 years of follow-up (aHR =12.1, 95% CI = 2.80-52.2) (Table 3).

Risk of Pyogenic liver abscess by Endoscopic sphincterotomy and Cholangitis

Table 4 outlines the interaction effects of ES and cholangitis towards the risk of PLA. Relative to the non-ES cohort without cholangitis, the ES patients with cholangitis were at a much higher risk of PLA (aHR=6.64, 95% CI=3.82-11.5), when compared to patients with only cholangitis (aHR=3.77, 95% CI=1.69-8.41) or with only ES (aHR=5.48, 95% CI=3.56-8.44) (Table 4, the P-value of interaction=0.03).

Discussion

The association between PLA and ES is demonstrated by our results, which show that patients receiving ES have higher incidence rates of PLA than those in the control group (4.02 vs. 0.94 cases per 1000 person-years, p < 0.001). The adjusted HR for PLA was found to be

4.50 (95% CI 3.08–6.58) for patients receiving EST, after adjusting for age, sex, and any possible comorbidities. The risk becomes even more significant when the follow-up years exceed 5 (adjust HR12.1, 95% CI 2.80- 52.2). Thus, PLA would be considered as one of the events which is associated with EST during long-term follow-up. ES experience is also considered to be one of the risks of PLA.

There is no clearly set time for the duration of follow-up when discussing the long-term complications of ES. A hospital-based study regarding endoscopic retreatment for biliary stones after ES is defined to be 5 years, and then a follow-up choledochal conditions due to increased risk of complications is suggested. (22) According to our results, PLA risk was determined to occur ~~within~~ 1 year after ES, and could be found to be increasing even more than that during the 5 year span. Thus, PLA risk would be need to be carefully monitored throughout follow-up. Risk of PLA was found to be more significant in non-comorbridity and young aged patients. We could explain that elderly patients and those experiencing co-morbidity carry a higher risk of PLA.

After decades of development, ES is still considered to be the requisite standard of care, and therefore has become the most commonly used procedure for the endoscopic treatment of biliay diseases, including choledocholithiasis. ES is applied to cut the biliary sphincter in order to eliminate the principal anatomic barrier impeding stone passage, and facilitate biliary manipulation. Upon reviewing available literature, long-term choledochal complications after ES include recurrent cholangitis, choledocholithiasis, biliary stenosis and cholecystitis. (6-10, 17) After ES, the anatomic barrier of the hepato-biliary system and intestine is removed, resulting in the communication causing an ascending migration of the bowel contents. The ascending movement would not be limited to strictly the biliary system only. Intrahepatic biliary system and even in hepatic cananliculi would be involved. Patients experiencing ES would remain under the risk of PLA.

There seemed to be no large survey for PLA after ES except for case reports.(23, 24) Taneka et al report about 5 PLA in 419 ES patients in a long-term follow up for ES study. (25) Interestingly, a smaller study about PLA demonstrated that patients with ES is good prognostic factor associated resolution within 6 weeks.(26) Based on the communicating with intestine, risk of PLA were also found in patients receiving pancreatitcoduodenostomy, and hepatojejunostomy. (27, 28)

PLA has become a worldwide health problem that is not limited to only Taiwan. When focusing on the risks of PLA, diabetes, end-stage renal disease, hepatobiliary diseases, pancreatic diseases, and the need for a liver transplant are all considered risk factors. (11-13, 29-31) Biliary disease is also considered as a risk of PLA, but there is lack of mention to ES. (32) Based on our results, patients receiving ES would also be considered to be a risk of PLA.

In the study, we first defined the association between ES and PLA, and recognized ES as a definite risk factor for PLA. There are however several limitations for the present study. First, we used the code for only ES, and any underlying diseases, which included mostly biliary, and pancreatic diseases. However, we did adjust both biliary and pancreatic disease, as shown in table 1. Second, the follow-up duration is around 4.3 years, with the longest set at about 7 years, due to the limitations of the database. We would expect to see a more significant PLA risk appearing under a longer follow-up period.

Our results demonstrate a significant risk of PLA during follow-up periods for patients receiving ES. Further investigations including bacterial culture, details of biliary systems and the analysis of clinical data, would be valuable studies that could be performed under a hospital-based inquiry.

Contributor ship statement

Author contributions: Conception and design: Yen-Chun Peng, Cheng-Li Lin, Fung-Chang Sung; Administrative support: Yen-Chung Peng; Collection and assembly of data: Yen-Chun Peng, Cheng-Li Lin, Fung-Chang Sung; Data analysis and interpretation: Yen-Chung Peng, Cheng-Li Lin, Fung-Chang Sung; Manuscript writing and revision: all authors; Final approval of manuscript: all authors.

competing interests

The authors declare no competing interests

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Data sharing statement

The Ministry of Health and Welfare must approved our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of

MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

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Figure Legends

Figure 1. Kaplan-Meir method determined the cumulative incidence of pyogenic liver abscess compared between endoscopic sphincterotomy cohorts and comparisons without endoscopic sphincterotomy.

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Table 1. Comparisons in demographic characteristics and comorbidities between patients with and without endoscopic sphincterotomy

	Endoscopic sphincterotomy				
	No (n=8174)		Yes (n=8174)		Standard difference
	n	%	n	%	

Age, mean(SD)†	68.5	14.6	66.9	15.0	0.11
Gender					
Women	3734	45.7	3832	46.9	0.02
Men	4440	54.3	4342	53.1	0.02
Comorbidity					
Congestive heart failure	564	6.90	491	6.01	0.04
Biliary stone	5695	69.7	5319	65.1	0.10
Cancer	687	8.40	580	7.10	0.06
Hypertension	3556	43.5	3186	39.0	0.09
Chronic obstructive lung disease	855	10.5	714	8.74	0.06
Hyperlipidemia	1052	12.9	792	9.69	0.10
Alcoholic liver damage	296	3.62	191	2.34	0.08
Cirrhosis	561	6.86	455	5.57	0.05
Cholangitis	793	9.70	1264	15.5	0.18
Cholecystitis	663	8.11	602	7.36	0.03
Pancreatic diseases	1544	18.9	1407	17.2	0.04
Chronic kidney disease	795	9.73	657	8.04	0.06
Appendicitis	167	2.04	152	1.86	0.01

Inflammatory bowel disease	34	0.42	20	0.24	0.03
Diverticulosis	215	2.63	206	2.52	0.01

Table 2. Incidence and adjusted hazard ratio of Pyogenic liver abscess stratified by sex, age and comorbidity compared patients with and without endoscopic sphincterotomy

	Endoscopic sphincterotomy							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR[†] (95 % CI)	Adjusted HR[&] (95 % CI)
All	33	35113	0.94	149	35454	4.20	4.50(3.08, 6.56)***	4.50(3.08, 6.58)***
Gender								
Women	12	16394	0.73	67	16970	3.95	5.42(2.93, 10.0)***	5.41(2.92, 10.0)***
Men	21	18719	1.12	82	18483	4.44	3.97(2.46, 6.42)***	4.02(2.48, 6.53)***
Age								
<49	4	4928	0.81	23	5558	4.14	5.16(1.79, 14.9)**	7.30(2.42, 22.0)***
50-64	10	7762	1.29	38	8620	4.41	3.47(1.73, 6.96)***	3.30(1.63, 6.69)***
65+	19	22423	0.85	88	21276	4.14	4.90(2.99, 8.05)***	4.80(2.91, 7.90)***
Comorbidity								
No	2	4721	0.42	14	1715	8.16	20.4(4.60, 90.2)***	19.9(4.46, 88.6)***
Yes	31	30392	1.02	135	33738	4.00	3.95(2.67, 5.83)***	3.90(2.64, 5.78)***

Rate[#], incidence rate, per 1000 person-years

Crude HR[†], relative hazard ratio

Adjusted HR[&], adjusted hazard ratio, adjusted for age, sex, and comorbidity of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive lung disease, hyperlipidemia,

alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis.

*p<0.05, **p<0.01,***p<0.001

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Table 3 Trends of Pyogenic liver abscess risks by stratified follow-up years

Follow-up time, years	Endoscopic sphincterotomy							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
1-2	11	15458	0.71	52	15319	3.39	4.81(2.51, 9.23)***	4.35(2.26, 8.39)***
2-3	15	9931	1.51	52	9785	5.31	3.54(1.99, 6.28)***	3.64(2.04, 6.50)***
4-5	5	5512	0.91	22	5692	3.87	4.27(1.62, 11.3)**	4.59(1.72, 12.2)**
>5	2	4213	0.47	23	4658	4.94	10.4(2.45, 44.0)**	12.1(2.80, 52.2)***

Rate[#], incidence rate, per 1000 person-years

Crude HR[†], relative hazard ratio

Adjusted HR[&], adjusted hazard ratio, adjusted for age, sex, and comorbidity of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive lung disease, hyperlipidemia, alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis.

*p<0.05, **p<0.01,***p<0.001

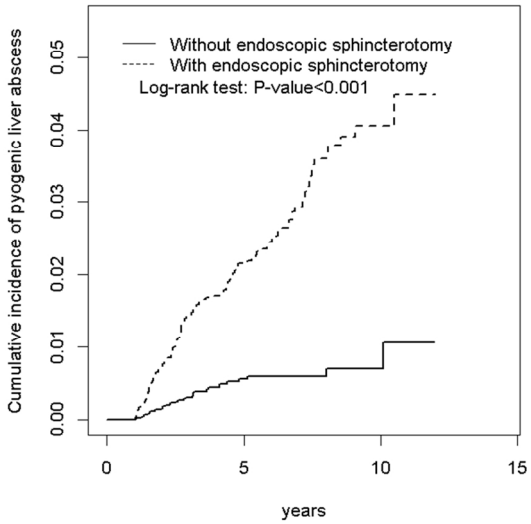
Table 4. Cox Proportional Hazard Regression Analysis for the risk of pyogenic liver abscess by endoscopic sphincterotomy and Cholangitis

Variables		Event	Person-years	Rate[#]	Adjusted HR[†] (95% CI)	p-value[#]
Endoscopic sphincterotomy	Cholangitis					0.03
No	No	25	32177	0.78	1(Reference)	
No	Yes	8	2936	2.72	3.77(1.69, 8.41)**	
Yes	No	122	30378	4.02	5.48(3.56, 8.44)***	
Yes	Yes	27	5076	5.32	6.64(3.82, 11.5)***	

Rate[#], per 1,000 person-year;

[†] Model was adjusted for age, sex and other comorbidities. *p<0.05, **p<0.01, ***p<0.001

[#]p-value for interaction



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The risk of pyogenic liver abscess and endoscopic sphincterotomy: A population-based cohort study

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Abstract.

Objectives: To evaluate the risk pyogenic liver abscess (PLA) in patients receiving endoscopic sphincterotomy (ES).

Setting: A population-based cohort study using data from Taiwans' National Health Insurance Research Database was conducted. Patients aged 20 or older who had undergone an ES were considered as the ES cohort. The dates for the first hospitalization of the ES patients were defined as the index dates.

Participants: patients in the ES and non-ES cohorts were selected by 1:1 matching ratio based on a propensity score. A total of 8174 sex-, age-, and index year-matched (1:1) pairs of patients receiving ES and 8174 patients without ES served as controls. Cox proportional hazards regression was employed to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between PLA and ES.

Results: The overall incidence of PLA was significantly higher in the ES cohort than in the non-ES cohort (4.20 vs 0.94, respectively, per 1000 person-year) with the adjusted HR (aHR) = 4.50 (95% CI = 3.38-6.58) A stratified analysis during the follow-up years revealed that when the ES cohort was compared with the non-ES cohort, they displayed a higher risk of PLA during the first follow-up year (aHR = 4.35, 95% CI = 2.26-8.39) which continued significantly over the next 4–5 years of follow-up.

Conclusions: Patients receiving ES are associated with having a higher risk of PLA.

Article summary

- Endoscopic sphincterotomy is a procedure which eliminates the anatomic barrier of the biliary tract and intestine, and is considered to be a well-established, standard procedure for treating choledocholithiasis. There is no study have direct link the risk of pyogenic liver abscess in patients receiving an Endoscopic sphincterotomy.

- Patients receiving endoscopic sphincterotomy are associated with having a higher risk of pyogenic liver abscess. The availability of these two large cohorts and follow-up conducted in pyogenic liver abscess risk after patients receiving endoscopic sphincterotomy.
- We used the code for only endoscopic sphincterotomy, and the details of underlying diseases, which included mostly biliary, and pancreatic diseases are not clearly defined in the database.

Introduction

Endoscopic sphincterotomy (ES) is the most commonly used therapy for treatment of common bile duct stones, and is today considered to be a well-established standard of treatment for pancreato-biliary diseases. (1-3) Standard ES involves the application of electrocautery to create an incision through the musculature of the biliary portion of the sphincter of Oddi and its use is considered as a safe, therapeutic procedure. (4, 5)

Depending on the time frame after an ES, the complications resulting from an ES are both short-term and long term. The percentage of short term complications is estimated to be approximately 10 percent, where procedural related bleeding, perforation, pancreatitis, and cardiopulmonary distress are considered as the short-term complications.(5) Long-term complications following an ES include stone recurrence, papillary stenosis, and cholangitis, any of which may which occur in approximately 6 to 24 percent of patients. (6-10)

Pyogenic liver abscesses (PLA) are the most common type of human visceral abscess. The mechanism may be due to either the leakage of bowel contents or microbes which subsequently spread to the liver via the portal circulation, or in the setting of a biliary infection.

Risk factors for PLA include diabetes mellitus, underlying hepatobiliary or pancreatic disease, end-stage renal disease and the possible need for a liver transplant. (11-13) Additionally, geographic and host associations should also be considered, such as Klebsiella pneumoniae which has been experienced in East Asia.(14)

Regarding the long-term follow-up after ES, most previous studies displayed recurrent biliary stones, cholangitis, stenosis and malignancy. (7-10, 15-17)

ES creates a communication of bowel contents to both the biliary system, and liver. Thus, it is reasonable to consider that PLA is associated with ES. Up until now, there has been a lack of data associating the risk of PLA with ES.

To illuminate the risk of PLA and ES, we conducted a population-based, cohort study to analyze the risk of PLA among patients receiving an ES.

Materials and Methods

Data Source

This was a longitudinal, cohort study using the National Health Institute Research Database (NHIRD) of the National Health Insurance (NHI) program in Taiwan. The NHI program began in 1995, and 99% of the 23.74 million Taiwan residents became covered (18). The details of the NHI program and the NHIRD have been well documented in previous studies (16, 19). Diseases were coded in the NHIRD according to the 2001 International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM). This study was approved by the Institutional Review Board (IRB) of China Medical University and Hospital in Taiwan (CMUH104-REC2-115).

Sampled Participants

Patients aged 20 or older years who had undergone an ES (ICD-9-OP 51.84) were considered as the ES cohort. The dates for the first hospitalization of the ES patients were defined as the index dates. We excluded patients younger than 20 years, along with those having a history of PLA (ICD-9-CM code 572.0) before the index date, any PLA diagnosed within 1 year after the index date, a history of amoebic liver abscess (ICD-9-CM code 006.3), and/or those lacking information on their age and sex. The non-ES cohort was identified during the same period occurring from the years 2000-2010, with exclusion criteria similar to the ES cohort. Patients in the ES and non-ES cohorts were selected by a 1:1 matching ratio based on a propensity score (20). The propensity score was calculated using a logistic regression to estimate the probability of the disease assignment, based on the baseline variables, including year of ES diagnosis, age, gender, and comorbidities of congestive heart failure (ICD-9-CM code 428), biliary stone (ICD-9-CM code 574), cancer (ICD-9-CM codes 140-208), hypertension (ICD-9-CM codes 401-405), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), hyperlipidemia (ICD-9-CM code 272), alcoholic liver damage (ICD-9-CM code 571.0, 571.1, and 571.3), cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6), cholangitis (ICD-9-CM code 576.1), cholecystitis (ICD-9-CM code 575), pancreatic diseases (ICD-9-CM code 577), chronic kidney disease (ICD-9-CM codes 580-589), appendicitis (ICD-9-CM codes 540-543), inflammatory bowel disease (ICD-9-CM codes 555, 556), and diverticulosis (ICD-9-CM codes 562).

Follow-up and Outcome

All of the patients were monitored up until either a diagnosis of PLA was made, they were censored for withdrawal from the NHI program, their death, or December 31, 2011, whichever occurred first.

Statistical analysis

Distributions in demographic variables, including age, gender, and comorbidities were compared between the ES and non-ES cohorts. The baseline characteristics of the ES and non-ES cohorts were compared using standardized mean differences (21). A value of standardized mean differences equaled .1 or less, which indicates there was a negligible difference in means between ES and non-ES cohorts. Incidence density rates of PLA by gender, age, and comorbidity were calculated in both cohorts. We assessed the cumulative incidence of PLA by using the Kaplan-Meier method in both the ES and non- ES cohorts, with significance based on the log-rank test. Univariable and multivariable Cox proportional hazard regressions were performed to measure the overall, gender-, age-, comorbidity-, follow-up years- risk of developing PLA. Hazard ratios (HRs) and 95% confidence intervals (CIs) were also estimated in the Cox model. The multivariate models were simultaneously adjusted for age, sex, and the comorbidities of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive pulmonary disease, hyperlipidemia, alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis. The entire matching procedure and all statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). A two-tailed $P < .05$ was considered significant.

Results

Characteristics of patients

Our study cohort consisted of 8,174 patients with ES and 8,174 patients without ES. The mean age (±SD) of the ES and non-ES cohorts was 66.9 ± 15.0 and 68.5 ± 14.6 years, respectively (Table 1). Most patients were men (53.1%). The major comorbidities were biliary stone (65.1% vs. 69.7%), and hypertension (39.0% vs. 43.5%) in these study cohorts, followed by pancreatic diseases (17.2% vs. 18.9%), cholangitis (15.5% vs. 9.70%) and hyperlipidemia (9.69% vs. 12.9%). The average follow-up duration was 4.33 ± 2.71 years for

the ES cohort and 4.30 ± 2.60 years for the non-ES cohort, respectively. Figure 1 shows that the cumulative incidence of PLA was higher in the ES cohort than that in the non-ES cohort by 3.33% at the end of the follow-up period (log-rank test P < 0.001).

Incidence and adjusted hazard ratio of PLA after ES

The overall incidence of PLA was significantly higher in the ES cohort than in the non-ES cohort (4.20 vs 0.94, respectively, per 1000 person-year) with the adjusted HR (aHR) = 4.50 (95% CI = 3.38-6.58) (Table 2). The ES cohort to the non-ES cohort aHR of PLA was significant for each status (including gender, age group, and those with or without comorbidity).

Trend of PLA risk by stratified follow-up years

A stratified analysis of the follow-up years revealed that the ES cohort when compared with the non-ES cohort, had higher risk of PLA during the first follow-up year (aHR = 4.35, 95% CI = 2.26-8.39) and remained significantly so during 4–5 years of follow-up (aHR = 4.59, 95% CI = 1.72-12.2). The risk of PLA remained even beyond 5 years of follow-up (aHR =12.1, 95% CI = 2.80-52.2) (Table 3).

Risk of Pyogenic liver abscess by Endoscopic sphincterotomy and Cholangitis

Table 4 outlines the interaction effects of ES and cholangitis towards the risk of PLA. Relative to the non-ES cohort without cholangitis, the ES patients with cholangitis were at a much higher risk of PLA (aHR=6.64, 95% CI=3.82-11.5), when compared to patients with only cholangitis (aHR=3.77, 95% CI=1.69-8.41) or with only ES (aHR=5.48, 95% CI=3.56-8.44) (Table 4, the P-value of interaction=0.03).

Discussion

The association between PLA and ES is demonstrated by our results, which show that patients receiving ES have higher incidence rates of PLA than those in the control group (4.02 vs. 0.94 cases per 1000 person-years, p < 0.001). The adjusted HR for PLA was found to be

4.50 (95% CI 3.08–6.58) for patients receiving EST, after adjusting for age, sex, and any possible comorbidities. The risk becomes even more significant when the follow-up years exceed 5 (adjust HR12.1, 95% CI 2.80- 52.2). Thus, PLA would be considered as one of the events which is associated with EST during long-term follow-up. ES experience is also considered to be one of the risks of PLA.

There is no clearly set time for the duration of follow-up when discussing the long-term complications of ES. A hospital-based study regarding endoscopic retreatment for biliary stones after ES is defined to be 5 years, and then a follow-up choledochal conditions due to increased risk of complications is suggested. (22) According to our results, PLA risk was determined to occur ~~within~~ 1 year after ES, and could be found to be increasing even more than that during the 5 year span. Thus, PLA risk would be need to be carefully monitored throughout follow-up. Risk of PLA was found to be more significant in non-comorbridity and young aged patients. We could explain that elderly patients and those experiencing co-morbidity carry a higher risk of PLA.

After decades of development, ES is still considered to be the requisite standard of care, and therefore has become the most commonly used procedure for the endoscopic treatment of biliay diseases, including choledocholithiasis. ES is applied to cut the biliary sphincter in order to eliminate the principal anatomic barrier impeding stone passage, and facilitate biliary manipulation. Upon reviewing available literature, long-term choledochal complications after ES include recurrent cholangitis, choledocholithiasis, biliary stenosis and cholecystitis. (6-10, 17) After ES, the anatomic barrier of the hepato-biliary system and intestine is removed, resulting in the communication causing an ascending migration of the bowel contents. The ascending movement would not be limited to strictly the biliary system only. Intrahepatic biliary system and even in hepatic cananliculi would be involved. Patients experiencing ES would remain under the risk of PLA.

There seemed to be no large survey for PLA after ES except for case reports.(23, 24) Taneka et al report about 5 PLA in 419 ES patients in a long-term follow up for ES study. (25) Interestingly, a smaller study about PLA demonstrated that patients with ES is good prognostic factor associated resolution within 6 weeks.(26) Based on the communicating with intestine, risk of PLA were also found in patients receiving pancreatitcoduodenostomy, and hepatojejunostomy. (27, 28)

PLA has become a worldwide health problem that is not limited to only Taiwan. When focusing on the risks of PLA, diabetes, end-stage renal disease, hepatobiliary diseases, pancreatic diseases, and the need for a liver transplant are all considered risk factors. (11-13, 29-31) Biliary disease is also considered as a risk of PLA, but there is lack of mention to ES. (32) Based on our results, patients receiving ES would also be considered to be a risk of PLA.

In the study, we first defined the association between ES and PLA, and recognized ES as a definite risk factor for PLA. There are however several limitations for the present study. First, we used the code for only ES, and any underlying diseases, which included mostly biliary, and pancreatic diseases. However, we did adjust both biliary and pancreatic disease, as shown in table 1. Second, the follow-up duration is around 4.3 years, with the longest set at about 7 years, due to the limitations of the database. We would expect to see a more significant PLA risk appearing under a longer follow-up period.

Our results demonstrate a significant risk of PLA during follow-up periods for patients receiving ES. Further investigations including bacterial culture, details of biliary systems and the analysis of clinical data, would be valuable studies that could be performed under a hospital-based inquiry.

Contributor ship statement

Author contributions: Conception and design: Yen-Chun Peng, Cheng-Li Lin, Fung-Chang Sung; Administrative support: Yen-Chung Peng; Collection and assembly of data: Yen-Chun Peng, Cheng-Li Lin, Fung-Chang Sung; Data analysis and interpretation: Yen-Chung Peng, Cheng-Li Lin, Fung-Chang Sung; Manuscript writing and revision: all authors; Final approval of manuscript: all authors.

competing interests

The authors declare no competing interests

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Data sharing statement

The Ministry of Health and Welfare must approved our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of

MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

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Figure Legends

Figure 1. Kaplan-Meir method determined the cumulative incidence of pyogenic liver abscess compared between endoscopic sphincterotomy cohorts and comparisons without endoscopic sphincterotomy.

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Table 1. Comparisons in demographic characteristics and comorbidities between patients with and without endoscopic sphincterotomy

	Endoscopic sphincterotomy	Standard

	No (n=8174)		Yes (n=8174)		difference
	n	%	n	%	
Age, mean(SD)†	68.5	14.6	66.9	15.0	0.11
Gender					
Women	3734	45.7	3832	46.9	0.02
Men	4440	54.3	4342	53.1	0.02
Comorbidity					
Congestive heart failure	564	6.90	491	6.01	0.04
Biliary stone	5695	69.7	5319	65.1	0.10
Cancer	687	8.40	580	7.10	0.06
Hypertension	3556	43.5	3186	39.0	0.09
Chronic obstructive lung disease	855	10.5	714	8.74	0.06
Hyperlipidemia	1052	12.9	792	9.69	0.10
Alcoholic liver damage	296	3.62	191	2.34	0.08
Cirrhosis	561	6.86	455	5.57	0.05
Cholangitis	793	9.70	1264	15.5	0.18
Cholecystitis	663	8.11	602	7.36	0.03

Pancreatic diseases	1544	18.9	1407	17.2	0.04
Chronic kidney disease	795	9.73	657	8.04	0.06
Appendicitis	167	2.04	152	1.86	0.01
Inflammatory bowel disease	34	0.42	20	0.24	0.03
Diverticulosis	215	2.63	206	2.52	0.01

Table 2. Incidence and adjusted hazard ratio of Pyogenic liver abscess stratified by sex, age and comorbidity compared patients with and without endoscopic sphincterotomy

	Endoscopic sphincterotomy							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR[†] (95 % CI)	Adjusted HR[&] (95 % CI)
All	33	35113	0.94	149	35454	4.20	4.50(3.08, 6.56)***	4.50(3.08, 6.58)***
Gender								
Women	12	16394	0.73	67	16970	3.95	5.42(2.93, 10.0)***	5.41(2.92, 10.0)***
Men	21	18719	1.12	82	18483	4.44	3.97(2.46, 6.42)***	4.02(2.48, 6.53)***
Age								
<49	4	4928	0.81	23	5558	4.14	5.16(1.79, 14.9)**	7.30(2.42, 22.0)***
50-64	10	7762	1.29	38	8620	4.41	3.47(1.73, 6.96)***	3.30(1.63, 6.69)***
65+	19	22423	0.85	88	21276	4.14	4.90(2.99, 8.05)***	4.80(2.91, 7.90)***
Comorbidity								
No	2	4721	0.42	14	1715	8.16	20.4(4.60, 90.2)***	19.9(4.46, 88.6)***
Yes	31	30392	1.02	135	33738	4.00	3.95(2.67, 5.83)***	3.90(2.64, 5.78)***

Rate[#], incidence rate, per 1000 person-years

Crude HR[†], relative hazard ratio

Adjusted HR[&], adjusted hazard ratio, adjusted for age, sex, and comorbidity of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive lung disease, hyperlipidemia,

alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis.

*p<0.05, **p<0.01,***p<0.001

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Table 3 Trends of Pyogenic liver abscess risks by stratified follow-up years

Follow-up time, years	Endoscopic sphincterotomy							
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
1-2	11	15458	0.71	52	15319	3.39	4.81(2.51, 9.23)***	4.35(2.26, 8.39)***
2-3	15	9931	1.51	52	9785	5.31	3.54(1.99, 6.28)***	3.64(2.04, 6.50)***
4-5	5	5512	0.91	22	5692	3.87	4.27(1.62, 11.3)**	4.59(1.72, 12.2)**
>5	2	4213	0.47	23	4658	4.94	10.4(2.45, 44.0)**	12.1(2.80, 52.2)***

Rate[#], incidence rate, per 1000 person-years

Crude HR[†], relative hazard ratio

Adjusted HR[&], adjusted hazard ratio, adjusted for age, sex, and comorbidity of congestive heart failure, biliary stone, cancer, hypertension, chronic obstructive lung disease, hyperlipidemia, alcoholic liver damage, cirrhosis, cholangitis, cholecystitis, pancreatic diseases, chronic kidney disease, appendicitis, inflammatory bowel disease, and diverticulosis.

*p<0.05, **p<0.01,***p<0.001

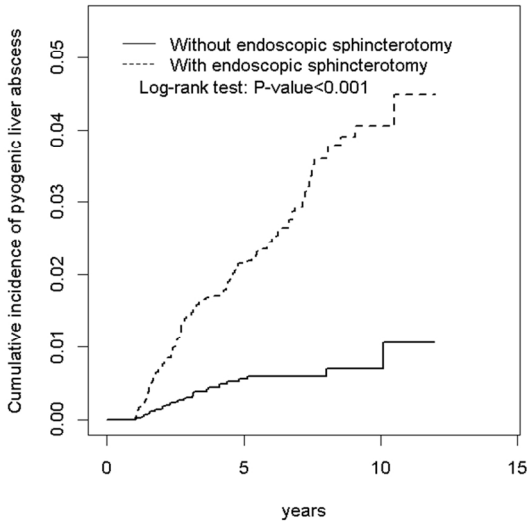
Table 4. Cox Proportional Hazard Regression Analysis for the risk of pyogenic liver abscess by endoscopic sphincterotomy and Cholangitis

Variables		Event	Person-years	Rate[#]	Adjusted HR[†] (95% CI)	p-value[#]
Endoscopic sphincterotomy	Cholangitis					0.03
No	No	25	32177	0.78	1(Reference)	
No	Yes	8	2936	2.72	3.77(1.69, 8.41)**	
Yes	No	122	30378	4.02	5.48(3.56, 8.44)***	
Yes	Yes	27	5076	5.32	6.64(3.82, 11.5)***	

Rate[#], per 1,000 person-year;

[†] Model was adjusted for age, sex and other comorbidities. *p<0.05, **p<0.01, ***p<0.001

[#]p-value for interaction



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4, 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4,5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7,
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	6, 7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7, 8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.