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ORIGINAL ARTICLE

Association between chronic pancreatitis and pyogenic liver abscess: a nationwide population study

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ABSTRACT

Background: The relationship between chronic pancreatitis (CP) and subsequent pyogenic liver abscess (PLA) is not well understood.

Methods: We investigated the risk of PLA in patients with CP using inpatient claims data from the Taiwan National Health Insurance Program for the period 2000–2010. We identified 17,810 patients with chronic pancreatitis (CP group) and 71,240 patients without CP (non-CP group). Both cohorts were followed until a diagnosis of PLA, until they were censored from the study because of loss to follow-up, death, or termination of insurance, or until the study cut-off date of 31 December 2011. Incidence and risk factors for development of PLA, and the effects of comorbidities, were assessed.

Results: The incidence of PLA in the CP group was 12.9 times that in the non-CP group (38.3 vs. 2.89 events per 1000 person-years; 95% confidence interval [CI], 10.5–15.8). After adjusting for age, sex, and the comorbidities of hypertension, diabetes, hyperlipidemia, cerebral vascular accident, cirrhosis, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, cancer, alcoholism, other diseases of the pancreas, cholecystitis, and cholelithiasis and other disorders of the biliary tract and endoscopic insertion of stent (tube) into the bile duct, the risk of PLA remained higher among CP patients than among the comparison cohort (adjusted hazard ratio, 6.40; 95% CI, 4.83–8.49). CP patients with five or more comorbidities had a significantly higher risk of PLA (adjusted hazard ratio, 24.9; 95% CI, 18.3–33.8).

Conclusion: CP was associated with increased risk of subsequent PLA. The risk of PLA was higher in patients with five or more comorbidities.

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Chronic pancreatitis; cohort; diabetes mellitus; pyogenic liver abscess

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disorder characterized by irreversible morphologic and functional change of the pancreas. Chronic changes include fibrosis of the parenchyma, calcifications, cysts, and development of pancreatic stones. These changes lead to loss of exocrine and endocrine functions, which can result in impaired digestion and diabetes mellitus.

Patients with CP have higher incidences of comorbidities than do people without CP[1]. Complications include pseudocyst[2,3], biliary obstruction[4], splenic vein thrombosis[5], and diabetes mellitus[6]. The most common and well established cause of CP is alcoholism[7], which is also a risk factor for development of complications in patients with liver abscess[8]. Infection of the liver parenchyma, leading to liver abscess, is a severe and often fatal complication.

Pyogenic liver abscess (PLA) is most prevalent in Western countries. Because of patient debilitation and persistence of the underlying cause, mortality approaches 15%[9]. PLA has multiple causes. It is more frequent among elderly adults with hepatobiliary tract diseases and intra-abdominal infections, including cholecystitis, suppurative cholangitis, suppurative pylephlebitis, diverticulitis, and peritonitis[10]. Moreover, patients with PLA are susceptible to subsequent infections, especially those with PLA caused by *Klebsiella pneumonia*, which can lead to extra hepatic infections such as endophthalmitis, pneumonia, pulmonary abscess, empyema, splenic abscess, and psoas abscess[11]. Treatment of PLA often requires percutaneous or surgical drainage in addition to antibiotics treatment. Patients without drainage are likely to receive prolonged antibiotics treatment for months. It is thus important to identify patients at risk for liver abscess.

The annual incidence of PLA in Taiwan increased from 10.83 per 100,000 person-years in 2000 to 15.45 per 100,000 person-years in 2011[12]. Previous studies identified some of the risk factors for PLA, including end-stage renal disease[13], splenectomy[14], inflammatory bowel disease[15], and zolpidem use[16]. However, little is known of the relationship between chronic pancreatitis and liver abscess.

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A prospective study of patients who underwent pancreaticojejunostomy reported spontaneous abscess formation in the pancreas and liver during follow-up for chronic pancreatitis. However, the pathogenesis of spontaneous abscess formation is not well understood[17]. Recent studies found that liver abscess caused by *K pneumonia* was strongly associated with diabetes. Indeed, during the past two decades, *K pneumonia* has surpassed *Escherichia coli* (*E coli*) as the predominant isolate from patients with PLA[18]. Compared with euglycemic individuals, patients with uncontrolled glycemia tend to have higher rates of cryptogenic liver abscess, gas-forming liver abscess, and metastatic infection[19]. Previous studies suggest that loss of endocrine function, as in diabetes mellitus, and change in pancreato-biliary structure are important in the development of PLA.

CP is associated with pathological changes of the biliary tract and development of diabetes mellitus. This retrospective cohort study investigated whether the risk of developing PLA was higher among CP patients.

Methods

Data source

The universal National Health Insurance (NHI) program in Taiwan integrated all public insurance systems into a single-payer program in 1995 and now provides coverage to 99% of the country's 23.74 million residents[20]. The National Health Research Institutes (NHRI) receives insurance claims data. This data is then compiled and presented in the National Health Insurance Research Database (NHIRD), which is made available for administrative use and research. To ensure confidentiality, all personal identification numbers are encrypted before release of the database to the public. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115). The IRB also specifically waived the consent requirement. International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to identify patient diagnoses.

Sampled participants

Patients with a new diagnosis of CP (ICD-9-CM code 577.1) were identified from inpatient claims during 2000–2010. Patients with a history of PLA (ICD-9-CM code 572.0) or missing information for age or sex were excluded. The remaining 17,810 patients with CP were included in the CP cohort. The date of admission for an initial CP diagnosis was set as the index date for subsequent estimation of duration of follow-up. For each CP patient, four control patients were randomly selected from the entire insured population without CP and were frequency matched with the CP patients by age (by 5 year age span), sex, and index year. The index date for control patients was a randomly selected month and day from the same index year as that of the matched CP cases. The above-mentioned exclusion criteria were also applied to non-CP controls. Ultimately, 17,810 patients with CP and 71,240 non-CP patients were included in the analysis. Both cohorts were followed until a diagnosis of PLA, until they were censored from the study because of loss to follow-up, death, or termination of insurance, or until the study cut-off date of 31 December 2011 was reached.

Comorbidities

The comorbidities of each patient at baseline were ascertained, namely hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), cerebral vascular accident (CVA) (ICD-9-CM codes 430–438), cirrhosis (ICD-9-CM code 571), heart failure (ICD-9 code 428), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, 496), chronic kidney disease (CKD) (ICD-9-CM codes 580–589), cancer (ICD-9-CM codes 140–208), alcoholism (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3, V11.3), other diseases of the pancreas (ICD-9-CM codes 557, 577.0, 557.2, 557.8, 557.9), cholecystitis (ICD-9-CM code 575), cholelithiasis and other disorders of the biliary tract (ICD-9-CM codes 574, 576) and endoscopic insertion of stent (tube) into the bile duct (ICD-9-CM procedure 5187).

Statistical analysis

The chi-square test was used to analyze differences in the distributions of demographic factors and comorbidities between the cohorts with and without CP. The mean ages and mean follow-up periods of the cohorts were determined and compared using Student's *t*-test. Incidence densities of PLA by demographic status and comorbidity were calculated. Univariable and multivariable Cox proportional hazards regression were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of PLA. The multivariable model was adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, CVA, cirrhosis, heart failure, COPD, CKD, cancer, alcoholism, other diseases of the pancreas, cholecystitis, cholelithiasis and other disorders of the biliary tract, and endoscopic insertion of stent (tube) into the bile duct. Further data analysis evaluated the joint effect of CP and PLA-associated risk factors on PLA. For further data analysis, we assessed the effects of CP-related treatment (including pancreatic cyst drainage, endoscopic treatment of pancreas, surgery) on the risk for PLA (including PLA with aspiration and drainage or PLA with surgical removal) compared with the non-CP cohort. We used SAS software (version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA) for all statistical analyses, and the results were considered significant when two-tailed *p*-values were less than 0.05.

Results

Table 1 shows the demographic characteristics and comorbidities of the two cohorts; 62.9% of subjects were younger than 49 years and 82.6% were male. The mean ages of the CP and non-CP cohorts were 48.6 ± 15.2 and 48.2 ± 15.4 years, respectively. Compared with the non-CP cohort, the CP

Table 1. Demographics and comorbidities of chronic pancreatitis patients and controls.

	Chronic pancreatitis		*p*-value
	Yes ($N = 17,810$) *N* (%)	No ($N = 71,240$) *N* (%)	
Age, years			.99
20–34	12,472 (17.5)	3118 (17.5)	
35–49	32,356 (45.4)	8089 (45.4)	
50–64	14,300 (20.1)	3575 (20.1)	
>64	12,112 (17.0)	3028 (17.0)	
Mean (SD)[a]	48.6 (15.2)	48.2 (15.4)	.004
Sex			.99
Female	3101 (17.4)	12,404 (17.4)	
Male	14,709 (82.6)	58,836 (82.6)	
Comorbidities			
Hypertension	4754 (26.7)	4656 (6.54)	<.001
Diabetes	5824 (32.7)	2642 (3.71)	<.001
Hyperlipidemia	4451 (25.0)	1424 (2.00)	<.001
CVA	1207 (6.78)	2095 (2.94)	<.001
Cirrhosis	8496 (47.7)	1854 (2.60)	<.001
Heart failure	624 (3.50)	676 (0.95)	<.001
COPD	1093 (6.14)	1144 (1.61)	<.001
CKD	1789 (10.0)	924 (1.30)	<.001
Cancer	607 (3.41)	1245 (1.75)	<.001
Alcoholism	5179 (29.1)	272 (0.38)	<.001
Other diseases of the pancreas	9996 (56.1)	370 (0.52)	<.001
Cholecystitis	1595 (8.96)	317 (0.44)	<.001
Cholelithiasis and other disorders of the biliary tract	3125 (17.6)	1116 (1.57)	<.001
Endoscopic insertion of stent (tube) into the bile duct[b]	267 (1.50)	5 (0.01)	<.001

The chi-square test was used to analyze categorical data.
[a]The *t*-test was used to analyze continuous data.
[b]Fisher's exact test was used for small sample sizes.
CVA: cerebral vascular disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

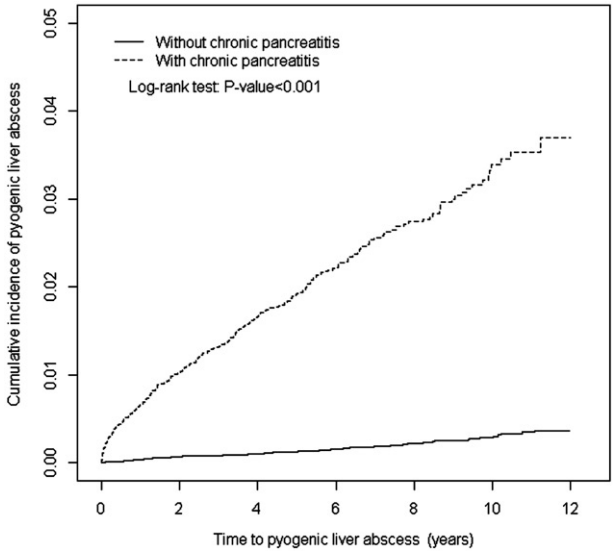

Figure 1. Cumulative incidence of pyogenic liver abscess in patients with and without chronic pancreatitis.

cohort had significantly higher prevalence of all comorbidities at baseline ($p < .001$ for all). The mean duration of follow-up was shorter in the CP cohort than in the non-CP cohort (4.83 vs. 6.03 years, $p < .001$). Kaplan–Meier analysis showed that the cumulative incidence of PLA was 3.26% higher in the CP cohort than in the non-CP cohort (log-rank test, $p < .001$) (Figure 1).

PLA was diagnosed in 330 CP patients, an incidence of 38.3 per 10,000 person-years, and in 124 non-CP patients, an incidence of 2.89 per 10,000 person-years (crude HR, 12.9; 95% CI, 10.5–15.8) (Table 2). After adjusting for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, CVA, cirrhosis, heart failure, COPD, CKD, cancer, alcoholism, other diseases of the pancreas, cholecystitis, cholelithiasis and other disorders of the biliary tract and endoscopic insertion of stent (tube) into the bile duct, the risk of PLA was higher in CP patients than in the comparison cohort (adjusted HR [aHR], 6.40; 95% CI, 4.83–8.49). The overall incidence and risk of PLA were compared in the CP cohort and comparison cohort in relation to several covariates, including sex, age, and presence or absence of comorbidities. PLA risk was higher in CP patients than in the non-CP cohort in all subgroup analyses.

Compared with CP patients with no comorbidities, CP patients with five or more comorbidities had a significantly higher risk of PLA (aHR, 24.9; 95% CI, 18.3–33.8). The risks were lower but still significant for those with four comorbidities (aHR, 20.2; 95% CI, 14.6–27.8), three comorbidities (aHR, 17.2; 95% CI, 12.6–23.4), and one or two comorbidities (aHR, 11.8; 95% CI, 8.78–15.7) (Table 3). Furthermore, CP patients with endoscopic treatment of the pancreas exhibited a significantly higher risk of PLA than that of CP patients without endoscopic treatment of the pancreas (aHR = 2.63, 95% CI, 1.60–4.30) (Table 4). Similar results were observed for CP patients with endoscopic treatment of the pancreas having a higher risk of developing PLA with aspiration and drainage than CP patients without endoscopic treatment of the pancreas (aHR, 2.14, 95% CI, 1.09–4.19). There were 969 patients who had received surgical intervention for CP. Of those, 498 patients (51.4%) received the Whipple operation and 426 patients (44.0%) received partial resection of the pancreas.

Table 2. Incidence and adjusted hazard ratio for pyogenic liver abscess among chronic pancreatitis patients, in relation to sex, age, and comorbidity status.

Variables	Chronic pancreatitis						Versus control	
	Yes			No				
	Events	Person-years	Rate[a]	Events	Person-years	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
All	330	860,687	38.3	124	429,349	2.89	12.9 (10.5, 15.8)***	6.40 (4.83, 8.49)***
Sex								
Female	37	14,864	24.9	30	73,899	4.06	5.79 (3.57, 9.37)***	3.34 (1.77, 6.30)***
Male	293	71,223	41.1	94	355,450	2.64	15.2 (12.1, 19.2)***	7.45 (5.43, 10.2)***
Age, years								
≤34	43	17,405	24.7	8	78,292	1.02	24.4 (11.5, 51.9)***	9.46 (3.34, 26.8)***
35–49	154	41,007	37.6	38	202,176	1.88	19.8 (13.9, 28.3)***	9.35 (5.71, 15.3)***
50–64	76	16,233	46.8	34	85,525	3.98	11.1 (7.42, 16.7)***	5.85 (3.39, 10.1)***
>64	57	11,441	49.8	44	63,355	6.94	6.57 (4.43, 9.75)***	3.94 (2.38, 6.52)***
Comorbidity[d]								
No	23	11,741	19.6	90	383,032	2.35	8.30 (5.25, 13.1)***	7.98 (5.05, 12.6)***
Yes	307	74,346	41.3	34	46,316	7.34	5.66 (3.97, 8.07)***	6.77 (4.68, 9.80)***

[a]Incidence rate per 10,000 person-years.
[b]Relative hazard ratio.
[c]Hazard ratio adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, CVA, cirrhosis, heart failure, COPD, CKD, cancer, alcoholism, other diseases of the pancreas, cholecystitis, and cholelithiasis and other disorders of the biliary tract, and endoscopic insertion of stent (tube) into the bile duct.
[d]The comorbidity group comprised patients with any of the following comorbidities: hypertension, diabetes, hyperlipidemia, CVA, cirrhosis, heart failure, COPD, CKD, cancer, alcoholism, other diseases of the pancreas, cholecystitis, and cholelithiasis and other disorders of the biliary tract, and endoscopic insertion of stent (tube) into the bile duct.
***$p < .001$
CVA: cerebral vascular disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

Table 3. Risk of pyogenic liver abscess in relation to number of comorbidities in patients with and without chronic pancreatitis (CP).

Variable	*N*	No. of Events	Rate[a]	Adjusted HR[b]	95% CI
No CP	61,497	90	2.35	1	(Reference)
CP only	2047	23	19.6	8.26	(5.22, 13.1)***
CP with 1 or 2 comorbidities	6271	91	28.8	11.8	(8.78, 15.7)***
CP with 3 comorbidities	3680	74	41.8	17.2	(12.6, 23.4)***
CP with 4 comorbidities	2837	64	49.6	20.2	(14.6, 27.8)***
CP with ≥5 comorbidities	2975	78	64.4	24.9	(18.3, 33.8)***

[a]Rate per 10,000 person-years.
[b]Multivariable analysis adjusted for age and sex.
***$p < 0.001$

Forty-five patients (4.64%) received total pancreatectomy. CP patients with surgery exhibited a significantly higher risk of PLA than that of CP patients without surgery (aHR, 2.06; 95% CI, 1.46–2.90).

The mean length of hospital stay due to PLA was similar in the CP cohort and in the non-CP cohort (19.1 vs. 19.5 years, $p = .86$) (Table 5). The overall incidence density of deaths was slightly higher in the CP cohort than in the non-CP cohort (8.60 vs. 4.52 per 100 person-years) among patients with pyogenic liver abscess, with an aHR of 2.18 (95% CI, 1.19–4.00).

Discussion

This is the first study to identify an association between CP and the risk of PLA. Analysis of NHIRD inpatient claims data identified 330 patients with PLA out of 17,810 patients hospitalized with CP during an 11 year period. PLA risk was higher for patients with CP than for those without CP. Incidence of deaths was higher in CP with PLA than non-CP with PLA.

Among the causes of liver abscess, biliary tract disease is reported to be the most frequent (15.5–37%), followed by portal pyemia (11–15%); the rate of hematogenous origin is reported to be 6% to 13.5%[21]. Bile duct stricture is a common complication in patients with advanced chronic pancreatitis and has a variable clinical presentation: from an incidental finding to overt jaundice and cholangitis. The incidence of common bile duct stricture in chronic pancreatitis varies widely in relation to the definition used, diagnostic vigor, and the demographics of the studied population. Reported incidence varies from 3% to 46%[22]. Of 330 CP patients with PLA in the present study, 130 (39.39%) patients received aspiration and drainage and only 23 patients received surgical aspiration. CP patients who received endoscopic treatment for pancreas or surgical intervention were more likely to have PLA. The structural change of the biliary tract due to CP per se or either endoscopic intervention or surgery were correlated with the development of PLA. These findings partially explain the high risk of liver abscess in patients with CP.

Other than structural changes of the biliary tract, other factors including endocrine loss due to CP should also be addressed. Immunocompromised individuals, such as those with diabetes mellitus or malignancy, are reported to be at risk for PLA[23]. Diabetes secondary to pancreatic disease is commonly referred to as pancreatogenic diabetes or type 3c diabetes mellitus. It is a clinically relevant condition and has a prevalence of 5% to 10% among all persons with diabetes in Western populations. Chronic pancreatitis appears to be the underlying disease in nearly 80% of all type 3c diabetes mellitus cases[24]. It increases the risk of PLA in patients hospitalized with CP.

Alcohol consumption is also associated with chronic pancreatitis, and liver cirrhosis and alcoholism are significant risk factors for PLA[25]. Alcoholism can result in hepatocellular carcinoma, and chronic pancreatitis and alcoholism frequently cause malnutrition. Hepatocellular carcinoma and

Table 4. Incidences and hazard ratios of pyogenic liver abscess in the chronic pancreatitis (CP) groups stratified by treatment.

Variable	*N*	Event	Person-years	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
PLA						
CP						
Without pancreatic cyst drainage	17,235	310	83,064	37.3	1 (Reference)	1 (Reference)
With pancreatic cyst drainage	575	20	3023	66.2	1.80 (1.15, 2.83)*	1.56 (0.99, 2.46)
CP						
Without endoscopic treatment of pancreas	17,472	313	84,500	37.0	1 (Reference)	1 (Reference)
With endoscopic treatment of pancreas	338	17	1587	107.1	2.86 (1.75, 4.66)***	2.63 (1.60, 4.30)***
CP						
Without surgery	16,841	292	81,621	35.8	1 (Reference)	1 (Reference)
With surgery	969	38	4465	85.1	2.36 (1.68, 3.30)***	2.06 (1.46, 2.90)***
PLA with aspiration and drainage						
CP						
Without pancreatic cyst drainage	17,235	121	83,064	14.6	1 (Reference)	1 (Reference)
With pancreatic cyst drainage	575	9	3023	29.8	1.24 (0.63, 2.45)	1.55 (0.77, 3.12)
CP						
Without endoscopic treatment of pancreas	17,472	120	84,500	14.2	1 (Reference)	1 (Reference)
With endoscopic treatment of pancreas	338	10	1587	63.0	1.83 (0.96, 3.50)	2.14 (1.09, 4.19)*
CP						
Without surgery	16,841	113	81,621	13.8	1 (Reference)	1 (Reference)
With surgery	969	17	4465	38.1	1.15 (0.69, 1.91)	1.23 (0.72, 2.09)
PLA with surgical removal						
CP						
Without pancreatic cyst drainage	17,235	23	83,064	2.77	1 (Reference)	1 (Reference)
With pancreatic cyst drainage	575	0	3023	0.00	—	—
CP						
Without endoscopic treatment of pancreas	17,472	22	84,500	2.60	1 (Reference)	1 (Reference)
With endoscopic treatment of pancreas	338	1	1587	6.30	0.98 (0.13, 7.26)	1.15 (0.15, 9.03)
CP						
Without surgery	16,841	20	81,621	2.45	1 (Reference)	1 (Reference)
With surgery	969	3	4465	6.72	1.10 (0.33, 3.72)	1.19 (0.33, 4.36)

[a]Incidence rate per 10,000 person-years.
bRelative hazard ratio.
[c]Hazard ratio adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, CVA, cirrhosis, heart failure, COPD, CKD, cancer, alcoholism, other diseases of the pancreas, cholecystitis, and cholelithiasis and other disorders of the biliary tract, and endoscopic insertion of stent (tube) into bile duct.
*$p < .05$
***$p < .001$.
PLA: pyogenic liver abscess; CVA: cerebral vascular disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

Table 5. Hazard ratio of mortality from pyogenic liver abscess between patients with CP and without CP.

	CP		*p*-value
	Yes *n/N*	No *n/N*	
Length of hospital stay due to PLA, mean (SD)	19.1 (20.4)	19.5 (20.7)	.86
Mortality			
Death/pyogenic liver abscess	81/330	17/124	
Rate (per 1,00 person-years)	8.60	4.52	
cHR (95% CI)	1.90 (1.13, 3.21)	1 (Reference)	.02
aHR (95% CI)[a]	2.18 (1.19, 4.00)	1 (Reference)	.01

cHR: crude hazard ratio; aHR: adjusted hazard ratio.
[a]Adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, CVA, cirrhosis, heart failure, COPD, CKD, cancer, alcoholism, other diseases of the pancreas, cholecystitis, and cholelithiasis and other disorders of the biliary tract.
PLA: pyogenic liver abscess; CVA: cerebral vascular disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

malnutrition increase the risk of PLA. Patients with alcoholism who had already developed CP should also be educated for risks of developing PLA.

In the present study, we identified patients by using ICD-9-CM codes and inpatient claims data in the NHIRD but could not review all medical records. Thus, future studies should further investigate the effects of risk factors, as this might reveal the underlying pathophysiological mechanisms.

A strength of our study was that the large sample size was sufficient for meaningful analysis and subgroup analysis. A total of 17,810 patients with a new diagnosis of chronic pancreatitis during an 11 year period were selected from among approximately 23.75 million residents of Taiwan. Patients with CP had a high prevalence of PLA.

However, this study did have limitations, including its retrospective design and the use of ICD-9-CM codes for identifying diseases. In addition, the review of medical records was not comprehensive. Additional patient information on alcohol consumption amount, body mass index, individual pathological, imaging, laboratory data, causative pathogens such as *K pneumonia* or *E coli*, family history contributing to chronic pancreatitis and PLA and even detail of the endoscopic procedures including the size and length of bile stent were not available in the dataset. Medications or services not

covered by NHI were not included in NHIRD. Moreover, the effects of medications including antibiotics that might modify the risk of chronic pancreatitis and PLA were not considered. Finally, only hospitalized patients were included in the analysis.

Conclusion

In conclusion, our findings show that PLA risk was higher among patients hospitalized with CP. CP patients with PLA had higher risks of mortality. The underlying pathophysiological mechanisms remain unclear.

Transparency

Declaration of funding

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Declaration of financial/other relationships

C.-W.T., Y.-T.C., C.-L.L., and J.-A.L. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

CMRO peer reviewer 1 has disclosed that he is a consultant to Pfizer, and has received sponsorship from the company. *CMRO* peer reviewer 2 has no relevant financial or other relationships to disclose.

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