Does pyogenic liver abscess increase the risk of delayed-onset primary liver cancer?
Evidence from a nationwide cohort study

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\textbf{Abstract}

Delayed-onset primary liver cancer (PLC) including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) in patients with pyogenic liver abscess (PLA) is not common. The relationship between PLA and delayed-onset PLC is unclear. We investigated the association in a nationwide cohort study.

From Taiwan National Health Insurance claims data, a cohort of 17,531 patients with PLA was generated after excluding patients with a history of cancer (n = 2034) and those diagnosed with PLC (n = 572) and other cancers (n = 627) within 1 year of a diagnosis of PLA. An age-, sex-, index year-, and diabetes mellitus (DM)-matched control cohort of 70,124 persons without PLA was selected from the same dataset. Both cohorts were followed up until the end of 2011. The risk of PLC was estimated for both cohorts.

The incidence of PLC was nearly 2-fold greater in the PLA group than in the control cohort (29.3 per 10,000 person-years vs. 16.2 per 10,000 person-years). The incidences of HCC and ICC were 1.5- (22.1 per 10,000 person-years vs. 15.0 per 10,000 person-years) and 11-fold greater (6.73 per 10,000 person-years vs. 0.62 per 10,000 person-years), respectively, in the PLA group than in the control cohort. The PLA cohort also had high risks of PLC (adjusted hazard ratio [aHR] = 1.15; 95% confidence interval [CI] = 1.05–1.23), HCC (aHR = 1.34; 95% CI = 1.15–1.57), and ICC (aHR = 6.94; 95% CI = 4.23–11.57).

In conclusion, in this nationwide cohort study, PLA increased the risk of delayed-onset PLC.

\textbf{Abbreviations:} aHR = adjusted hazard ratio, CI = confidence interval, DM = diabetes mellitus, HCC = hepatocellular carcinoma, HR = hazard ratio, ICC = intrahepatic cholangiocarcinoma, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIP = National Health Insurance Program, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PLA = pyogenic liver abscess, PLC = primary liver cancer.

\textbf{Keywords:} biliary tract cancer, hepatoma, infection, pyogenic liver abscess, risk factor
1. Introduction

Pyogenic liver abscess (PLA), a type of liver abscess caused by bacteria, is not an uncommon infectious and life-threatening disease with a high mortality rate of approximately 5% to 6%. Klebsiella pneumoniae (K pneumoniae) and Escherichia coli (E coli) were the most common microorganisms among patients with PLA. A high annual incidence of 17.6 per 100,000 people is noted in Taiwan. In the Denmark, the incidence of PLA increased from 0.6 to 1.8 per 100,000 for men and from 0.8 to 1.2 per 100,000 for women between 1977 and 2002. The major comorbidities of PLA are diabetes mellitus, intra-abdominal infection, and pancreatic and biliary tract diseases including cholangitis, cholecystitis, diverticulitis, appendicitis, and peptic ulcer.

The main infection routes of PLA are hematologic entry from the portal systemic organs because of mucosal defects or disease that compromises barrier function and ascending infection from the pancreaticobiliary system. Some studies illustrated that gastrointestinal premalignant or malignant lesions are associated with PLA. Primary liver cancer (PLC) including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) can initially present with PLA or arise within 1 year of a diagnosis of PLA were reported by a large-scale cohort study and some case series reports. The associated risk of PLC was unclear after 1 year in patients with PLA (we defined delayed-onset PLC as that diagnosed >1 year after a diagnosis of PLA) because of the relative small sample size and scarcity of reports.

At present, no large-scale population-based study has been conducted to evaluate the association between PLA and delayed-onset PLC including HCC and ICC. The aim of this study was to estimate the risk of delayed-onset PLC in patients with PLA using a nationwide population-based database in Taiwan.

2. Materials and methods

2.1. Data source

Taiwan National Health Insurance (Taiwan NHI) is a nationwide, single-payer health insurance program that is compulsory for all citizens. Taiwan NHI was established in 1995, and 99% of Taiwan's 23 million citizens were covered in 1998. The Taiwanese government ordered the National Health Research Institutes (NHRI) to construct and manage the National Health Insurance Research Database (NHIRD). The NHIRD handles all of the claims data of Taiwan NHI, including the registry for beneficiaries, ambulatory and inpatient care, prescription records, and other medical services. The NHRI renews the database annually. To protect the confidentiality of the insured subjects, the NHRI removed the original identification number and published the database with an encoded identification number to link each medical service file. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMU104-REC2-115).

The disease diagnosis record system in the NHIRD is categorized according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The cancer history of each patient was collected from a catastrophic illness patient registry, a subcomponent of the NHIRD. PLA- and PLC-associated comorbidity data were collected from inpatient files.

2.2. Study population

We designed a retrospective population-based cohort study to investigate the association between PLA and PLC risk. Figure 1 presents a schematic of the study population selection protocol. The PLA cohort consisted of patients who were newly diagnosed with PLC (ICD-9-CM 572.0) between 2000 and 2008, and the initial date of the PLA diagnosis was set as the index date. The control cohort consisted of individuals with no PLA diagnosis record in the NHIRD, and these individuals were matched by age (per 5 years), sex, and history of DM history (ICD-9-CM 250) with the PLA cohort. The index date of the control cohort was randomly assigned to match that of the matched case. The study cohort was followed up at 1 year after the index date. We excluded subjects younger than 18 years and those with a history of cancer (ICD-9-CM 140-208) before follow-up. The major event of interest in the study was the occurrence of newly diagnosed PLC (ICD-9-CM 155), which could be classified into 3 subtypes: HCC (ICD-9-CM 155.0), ICC (155.1), and others. Follow-up was terminated when an individual withdrew insurance or PLC developed, or on December 31, 2011, whichever occurred first.

We considered PLC-associated comorbidities as confounding factors in this study. PLC-associated comorbidities arising before the index date included hepatitis B virus (HBV) infection (ICD-9-CM 070.2 and 070.3), hepatitis C virus (HCV) infection (ICD-9-CM 070.41, 070.44, 070.51, and 070.34), unspecified chronic hepatitis (ICD-9-CM 070.9, 571.4, 571.8, 571.9), alcoholic liver disease (571.0-571.3), liver cirrhosis (ICD-9-CM 571.5 and 571.6), cholelithiasis (ICD-9-CM 574), cholecystitis (ICD-9-CM 575.0 and 575.1), and cholangitis (ICD-9-CM 576.1).

We also investigated the microorganisms identified concurrently with PLC in patients with PLA. The microorganisms included Staphylococcus (ICD-9-CM 038.0 and 041.0X), E coli (ICD-9-CM 038.42 and 041.4), Streptococcus (ICD-9-CM 038.0 and 041.0X), Pneumococcus (ICD-9-CM 038.1X and 041.1X), K pneumoniae (ICD-9-CM 041.3), Proteus (ICD-9-CM 041.6), Gram-negative bacteria (ICD-9-CM 038.40, 038.49, and 041.85), and other/unspecified bacteria (ICD-9-CM 038.8, 038.9, and 041).

2.3. Statistical analysis

The mean and standard deviation (SD) for age as well as the number and percentage for sex and PLC-associated comorbidities of the study cohort were showed. To assess differences in distribution between the PLA and control cohorts, we used the t test for age and the χ² test for category variables. The incidence density of PLC was calculated as the number of PLC events divided by the total sum of the follow-up years for each study cohort and presented as the rate per 10,000 person-years. We used the Kaplan-Meier method to estimate the cumulative incidence curves and tested the difference of the curves using the log rank test. Univariate and multivariate Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of PLC. We also estimated the association between an increasing frequency of PLA diagnosis and PLC risk and tested the trend for increasing PLC risk with the frequency of PLA diagnosis as a continuous variable using a Cox proportional hazard regression model. Finally, we performed a stratified analysis to estimate the effect of PLA on PLC risk for different demographics and comorbidities.

All data management and analyses were performed using SAS software (version 9.4 for Windows; SAS Institute, Inc., Cary,
The cumulative incidence curves were also drawn using SAS software. The level of statistical significance was 2-sided and set at 0.05.

3. Results

The PLA and control cohorts consisted of 17,531 and 70,124 people, respectively (Table 1). Because the cohorts were matched for age, sex, and history of DM, the mean age (58 years), sex distribution (male: 62.6%), and history of DM (34.5%) were similar between the cohorts. The frequencies of comorbidities were greater in the PLA cohort than in the control cohort (P < .0001).

The incidence of PLC was 29.32 per 10,000 person-years in the PLA cohort and 16.19 per 10,000 person-years in the control cohort (Table 2). Figure 2 presents the PLC cumulative incidence curves for the 2 cohorts. The incidence curve for the PLA cohort was significantly larger than that for the control cohort (P < .0001). The incidences of HCC and ICC in the PLA cohort were nearly 1.4- and 10-fold higher, respectively, than those in the control cohort. The incidence of the other subtypes of PLC was not different between the cohorts. After adjusting for age, sex, and all comorbidities, PLA was significantly associated
with an increased risk of PLC (adjusted HR \( \text{aHR} \) = 1.56; 95% CI = 1.35–1.81). Compared with the control cohort, the PLA cohort had a 1.34- and 6.94-fold greater risk of HCC (aHR = 1.34; 95% CI = 1.15–1.57) and ICC (aHR = 6.94; 95% CI = 4.23–11.38), respectively.

Table 3 illustrates the association between an increasing frequency of PLA diagnosis and PLC risk. The incidence of PLC was 16.19 per 10,000 person-years for the control cohort, versus 26.44, 38.54, and 83.56 per 10,000 person-years for <2, 2 to 3, ≥4 diagnoses of PLA, respectively. After adjusting for age, sex, and all comorbidities, compared with the control cohort, patients with <2, 2 to 3, and ≥4 PLA diagnoses had a 1.45- (95% CI = 1.23–1.70), 1.92- (95% CI = 1.49–2.48), and 3.65-fold (95% CI = 1.86–7.13) increased risk of PLC, respectively. The risk of PLC was significantly increased with an increased frequency of PLA diagnosis (\( P \) for trend < .0001).

Table 4 presents the age-, sex-, and comorbidity-specific stratified analyses. Relative to the control cohort, PLA was significantly associated with an increased risk of PLC in patients aged 40 to 59 years and ≥65 years. The PLA cohort had a significantly higher risk of PLC than the control cohort for both males and females. The results also revealed that PLA was only significantly associated with an increased risk of PLC in the study population in the absence of each comorbidity.
In total, 81.6% of patients with PLA and PLC had positive microorganism test results during the observation period (Table 5). *K pneumoniae* was the major microorganism in patients with HCC (25.5%), and *E coli* was the main microorganism in patients with ICC (34.8%).

### 4. Discussion

This large-scale, nationwide cohort study is the first to reveal the significantly higher risk of delayed-onset PLC (aHR = 1.56; 95% CI = 1.35–1.81) in patients with PLA, including HCC (aHR = 1.34; 95% CI = 1.14–1.57) and ICC (aHR = 6.94; 95% CI = 14.23–11.38). The incidence of delayed-onset PLC was increased in both sexes in the PLA cohort compared with the control cohort. The risk of delayed-onset PLC was significantly higher in patients with repeated hospitalization because of PLA than in patients with a single PLA-related hospitalization and the controls. *E coli* and *K pneumoniae* were the most common microorganisms detected in patients with PLA and delayed-onset PLC. *K pneumoniae* was the major microorganism in patients

### Table 4

**Age-, sex-, and comorbidity-stratified analysis of the risk of PLC in the control and PLA cohorts.**

| Comorbidity | Control cohort | PLA cohort | Adjusted HR (95% CI) |
|-------------|----------------|------------|---------------------|
| Age, y      | Event Rate    | Event Rate |                      |
| <45         | 33 (4.12)     | 14 (7.14)  | 1.62 (0.86–3.05)     |
| 45–64       | 325 (16.81)   | 142 (30.39)| 1.46 (1.18–1.80)     |
| ≥65         | 291 (22.83)   | 127 (42.07)| 1.64 (1.32–2.04)     |
| Sex         |                |            |                     |
| Female      | 165 (10.98)   | 105 (29.19)| 2.12 (1.64–2.76)     |
| Male        | 484 (19.31)   | 178 (29.4) | 1.38 (1.15–1.64)     |
| DM          | No            | 315 (11.79)| 177 (27.31)          |
|             | Yes           | 334 (25.00)| 33.42               |
| HBV         | No            | 610 (15.29)| 268 (28.02)          |
|             | Yes           | 39 (202.13)| 15 (172.12)         |
| HCV         | No            | 605 (15.15)| 267 (27.83)          |
|             | Yes           | 44 (283.16)| 16 (270.24)         |
| UCH         | No            | 605 (15.49)| 261 (26.62)          |
|             | Yes           | 44 (42.44) | 22 (41.36)          |
| ALD         | No            | 634 (15.91)| 274 (28.82)          |
|             | Yes           | 15 (66.00) | 9 (61.40)           |
| Liver cirrhosis | No       | 579 (14.52)| 241 (25.44)         |
|             | Yes           | 70 (330.98)| 42 (234.40)         |
| Cholelithiasis | No        | 613 (15.64)| 222 (25.70)         |
|             | Yes           | 36 (40.75) | 61 (60.11)         |
| Cholecystitis | No           | 640 (16.02)| 270 (28.64)         |
|             | Yes           | 9 (63.13)  | 13 (57.33)          |
| Cholangitis  | No            | 644 (16.12)| 247 (26.86)         |
|             | Yes           | 5 (36.80)  | 36 (79.02)          |

Model adjusted for age, sex, DM, HBV, HCV, UCH, ALD, liver cirrhosis, choledolithiasis, cholecystitis, and cholangitis. ALD = alcoholic liver disease, CI = confidence interval, DM = diabetes mellitus, HBV = hepatitis B virus infection, HCV = hepatitis C virus infection, HR = hazard ratio, PLA = pyogenic liver abscess, UCH = unspecified chronic hepatitis.

In total, 81.6% of patients with PLA and PLC had positive microorganism test results during the observation period (Table 5). *K pneumoniae* was the major microorganism in patients with HCC (25.5%), and *E coli* was the main microorganism in patients with ICC (34.8%).

### Table 5

**Microorganisms detected concurrently with PLC in patients with PLA (N = 283).**

| Type of PLC | Positive, n (%) | Negative, n (%) | Total, n |
|-------------|-----------------|-----------------|----------|
| All         | 124 (81.6)      | 50 (18.4)       | 174      |
| *K pneumoniae* | 32 (21.1)     | 30 (25.0)       | 62       |
| *E coli*    | 36 (23.7)       | 28 (21.7)       | 64       |
| Others      | 28 (25.0)       | 28 (25.0)       | 56       |
| Overall     | 84 (82.4)       | 16 (17.6)       | 100      |
| HCC         | 37 (80.4)       | 10 (19.6)       | 47       |
| ICC         | 3 (75.0)        | 1 (25.0)        | 4        |

* E coli = Escherichia coli, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, *K pneumoniae* = Klebsiella pneumonia, PLA = pyogenic liver abscess, PLC = primary liver cancer.
with HCC, whereas \textit{E. coli} was the most common microorganism in patients with ICC. HCC and ICC are the 2 most common PLCs, representing 90% and 8%, respectively, of all PLCs.\cite{20} HCC is the fifth most common cancer\cite{21} and the second leading cause of cancer-related death globally.\cite{22,23} Meanwhile, 10% of cholangiocarcinomas are ICC.\cite{23} ICC is highly prevalent in Asian (1.3 per 100,000) and Hispanic people (1.2 per 100,000),\cite{24} and its incidence and associated mortality are increasing in several Western countries.\cite{25,26} The dominant risk factors of HCC are cirrhosis, chronic hepatitis B, chronic hepatitis C, alcoholic consumption, obesity, and diabetes\cite{27} and the major risks of ICC are similar as those of HCC\cite{28} and include hepatolithiasis.\cite{29}

HCC and ICC with PLA as the initial presentation are uncommon, and they are associated with poor outcomes.\cite{14,17,19,20,30} Two major acceptable mechanisms of this presentation are bacterial colonization after spontaneous necrosis in the tumor parenchyma and biliary obstruction with tumor thrombi.\cite{11} Yeh et al.\cite{15} and Okuda et al.\cite{16} reported 5 and 10 cases of PLA, respectively, as the initial manifestation of HCC, with mean survival rates of 2.35 and 3.5 months, respectively. Li et al.\cite{17} described 5 cases of HCCs and 4 cases of ICC presenting with PLA; nevertheless, the survival time ranged from 8 days to 7.5 months in the ICC group. Chong et al.\cite{30} reported 2 cases of HCC and 1 case of ICC that developed as late as 1 year after a diagnosis of PLA (which we defined as delayed-onset PLC). Huang et al.\cite{18} did not identify an increased risk of delayed-onset PLC and revealed as a warning sign for PLC in a related small PLA population. Kao et al.\cite{39} reported that patients with PLA have a standardized incidence ratio of 2.02 (95% CI = 1.08–3.46) for delayed-onset PLC compared to the general population. However, only 13 cases of delayed-onset PLC were reported, which is an insufficient sample size to distinguish HCC from ICC. In addition, no significantly increased risk of delayed-onset PLC was identified in females with PLA, and thus, the relationship between delayed-onset PLC and PLA remains unclear. This study revealed an increased risk of delayed-onset PLC including HCC and ICC in both sexes after a diagnosis of PLA.

We considered the possibility of different mechanisms between delayed-onset PLC in patients with PLA and those with PLA as an initial presentation of PLC. Inflammation can induce malignant changes in cells.\cite{31} In a study of 102 patients with PLA, KC et al.\cite{12} reported ultrasonic evidence of PLA resolution within 2 months after treatment in most patients; however, 8 patients had delay healing with residual abscess after 2 years of follow-up, and 4 patients had calcified lesions after the abscess was resolved. Inflammatory pseudotumors can arise after the onset of PLA,\cite{13,34} and they may be associated with the transformation of PLC.\cite{30} Some literature also revealed an increased risk of lung cancer after pulmonary tuberculosis via a reasonable mechanism of an inflammatory process or scarring.\cite{35,36} This study observed an increased risk of delayed-onset PLC after repeated hospitalization because of PLA.

In patients with PLA, 60% of the detected infectious pathogens are \textit{K. pneumoniae}.\cite{31} This study found that \textit{E. coli} was the most common pathogen in patients with PLA and delayed-onset ICC. This finding was similar with those of Chen et al.\cite{39} and Chuang et al.\cite{38} who found that \textit{E. coli} and PLA were likely to be associated with a biliary tract disease or hepatobiliary malignancy, whereas a previous study identified \textit{K. pneumoniae} as the dominant bacterium in patients with gastrointestinal cancer and PLA.\cite{11}

Our results showed the risk of ICC is much higher than HCC in the PLA group. In our previous study found patient with biliary tract infection have an increased risk of digestive system cancers, particularly biliary tract cancer, with hazard ratio 24.45.\cite{39} Up to 20% of pyogenic liver abscess develop from an infected or inflamed biliary tract.\cite{31} The possible mechanism may be the inflammation of biliary tract epithelium is more intensive than hepatocytes.

The use of a large-scale, representative, nationwide, population-based sample to evaluate the risk of delayed-onset PLC in patients with PLA improved the availability of data and the validity of the findings. The large sample size allowed us to perform a stratified analysis to observe comorbidities in patients with PLA. However, this study has several limitations. First, detailed information associated with the risk of PLC, including data on family history of PLC, smoking, alcohol consumption, coffee consumption, high-fat diet intake, physical activity, and body mass index, were not available. Second, data for microorganism infection may have been incompletely coded, thus compromising the identified risk of PLC in patients with PLA.

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