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CLINICAL—LIVER

Increased Incidence of Gastrointestinal Cancers Among Patients With Pyogenic Liver Abscess: A Population-Based Cohort Study

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BACKGROUND & AIMS: The relationship between pyogenic liver abscess (PLA) and gastrointestinal (GI) cancer was first reported more than 20 years ago, yet little is known about this connection. We evaluated this association in a population-based, retrospective, cohort study. **METHODS:** Using Taiwan National Health Insurance claims data, we collected data on a cohort of 14,690 patients with PLA diagnosed from 2000 to 2007. A reference cohort of 58,760 persons without PLA (controls) was selected from the same database, frequency matched by age, sex, and index year. Both cohorts were followed up until the end of 2009, and incidences of GI cancer were calculated. **RESULTS:** The incidence of GI cancer was 4.30-fold higher among patients with PLA compared with controls (10.8 vs 2.51/1000 person-years). Site-specific analysis showed that the highest incidence of colorectal cancer was among patients with PLA and diabetes mellitus, followed by patients with PLA without diabetes and controls with diabetes (9.58, 5.76, and 1.49/10,000 person-years, respectively). The PLA cohort also had a high risk of small intestine cancer (adjusted hazard ratio [aHR], 12.7; 95% confidence interval [CI], 5.79–27.7) and biliary tract cancer (aHR, 9.56; 95% CI, 6.68–13.7). Their risk of pancreatic cancer (aHR, 2.51; 95% CI, 1.68–3.76) was also significant. However, patients with PLA did not have an increased risk of gastric cancer compared with controls. **CONCLUSIONS:** In a population-based study, we found that the incidence of GI cancer is increased more than 4-fold among patients with PLA compared with controls. PLA might therefore be an indicator of GI cancer. Patients with PLA had the highest incidence of colorectal cancer, followed by cancers of the biliary tract, pancreas, and small intestine.

Keywords: Colon Cancer; Pancreas; Risk Factor; Infection.

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Pyogenic liver abscess (PLA) is a critical infectious disease with high rates of morbidity and mortality.[1] In Taiwan, the annual incidence of PLA has increased steadily from 11.2/100,000 population in 1996 to 17.6/100,000 population in 2004.[2] In Western countries, the annual incidence rates are lower, with 1.0/100,000 population in Denmark[3] and 2.3/100,000 population in Canada.[4] Associated comorbidities include diabetes mellitus (DM),[1,5] pancreaticobiliary tract diseases, and intra-abdominal infections such as cholecystitis, suppurative cholangitis, peritonitis, appendicitis, suppurative pylephlebitis, and diverticulitis.[6–8] Cases without pancreaticobiliary tract disease, intra-abdominal infection, or other obvious etiologies are called cryptogenic PLA.[8–10]

The major mechanisms leading to PLA include ascending infection from the biliary and pancreatic ducts and hematologic spread from organs of the portal system caused by gastrointestinal (GI) lesions (including neoplasms) with mucosal defects or a compromised mucosal barrier. *Klebsiella pneumoniae* is the most common infectious pathogen in patients with DM who have PLA.[11,12] Several studies have found that PLA is associated with an increased risk of biliary tract and pancreatic cancers, although the magnitude of risk is uncertain.[4,8,11,13] The relationship between colorectal cancer and colonic tubulovillous adenoma and PLA is uncertain.[8,14–20] The stomach and small intestine are also organs of the portal system and could be associated with risk.[21]

To date, no large-scale population-based study has been conducted to elucidate the relationship between PLA and subsequent risk of GI cancers. Our primary aim was to determine if patients with PLA have an increased risk of GI

*Authors share co-first authorship. §Authors share co-senior authorship.

Abbreviations used in this paper: aHR, adjusted hazard ratio; CI, confidence interval; DM, diabetes mellitus; GI, gastrointestinal; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PLA, pyogenic liver abscess.

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cancers relative to population-based controls without PLA using a nationwide population-based database in Taiwan.

Patients and Methods

Data Sources

This study used reimbursement claims data from the Taiwan National Health Insurance Program, which is a universal insurance system reformed in 1996 by the Taiwan Department of Health to provide health care to almost 99% of the 23 million people in Taiwan.[22] The claims data were updated annually in the National Health Insurance Research Database by the National Health Research Institutes, with insured identifications scrambled for public access. The scrambled identifications were used to link files to retrieve information on insured demographic data, medical services for both outpatient and inpatient care, and expenditures from 1996 to 2009. Diagnoses were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Population

Using the inpatient claims data file, patients 18 years of age or older with PLA (ICD-9-CM 572.0) that was newly diagnosed in 2000 to 2007 were identified as the PLA cohort (Figure 1). The diagnosis date of PLA served as the index date. For each patient with PLA, 4 reference subjects without PLA were randomly selected for the non-PLA cohort (controls), frequency matched by sex, age, history of DM, and index year of the patient with PLA. Subjects with a history of cancer of any kind (ICD-9-CM 140–239 identified from the catastrophic illness registry) before the index date were excluded. The claims data for both cohorts were assessed from the index date to December 31, 2009 (end of the study), until the time of diagnosis of GI cancer, or until the patient was censored for withdrawal from insurance or lost to follow-up. Figure 1 shows the flow chart for selecting the study cohorts.

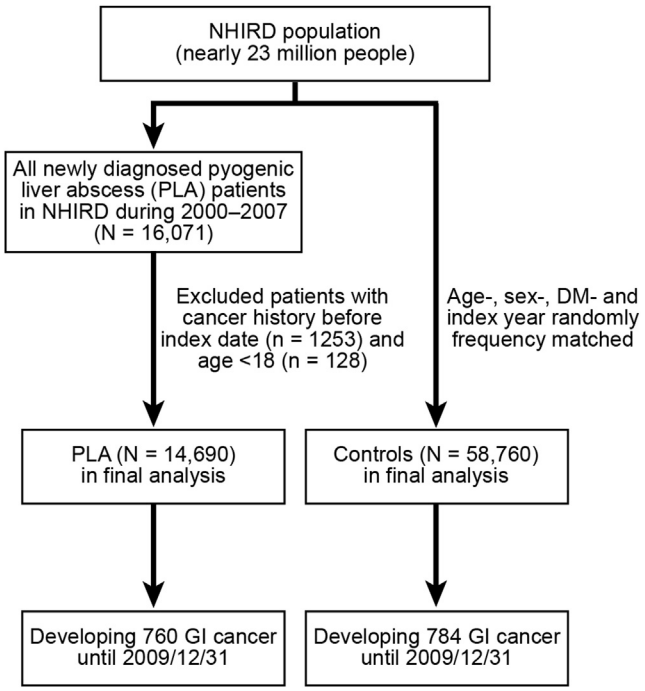

Figure 1. Flow chart of patient selection. NHIRD, National Health Insurance Research Database.

Criteria and Definitions

GI cancers, including stomach cancer (ICD-9-CM 151), small intestine cancer (including duodenal cancer, ICD-9-CM 152), colorectal cancer (ICD-9-CM 153 and 154), biliary tract cancer (ICD-9-CM 156), and pancreatic cancer (ICD-9-CM 157), were identified. Pancreaticobiliary diseases were considered confounding factors associated with the development of GI cancers in the study population. Baseline comorbidities of DM (ICD-9-CM 250), gallstones (ICD-9-CM 574), cholecystitis (ICD-9-CM 575.0, 575.1, 575.11, and 575.12), cholangitis (ICD-9-CM 576.1), or pancreatitis (ICD-9-CM 577.0 and 577.1) were also identified.

Concurrent microorganisms such as *Streptococcus* (ICD-9-CM 038.0 and 041.0X), *Staphylococcus* (ICD-9-CM 038.0 and 041.0X), *Pneumococcus* (ICD-9-CM 038.1X and 041.1X), *Escherichia coli* (ICD-9-CM 038.42 and 041.4), *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 041.81) were identified.

Statistical Analysis

In this study, the cohorts were first compared by risk factors, including age, sex, and pancreaticobiliary diseases. The incidence rates by demographic and baseline comorbidities were estimated and compared. Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of GI cancers by demographic status and comorbidities.

Further data analyses measured the incidence of GI cancer for patients with PLA and the control cohort with and without DM. The HRs and 95% CIs of GI cancers for patients with PLA were assessed and compared with those of controls. The incidence of GI cancer by duration of follow-up (<2, 2–4, and >4 years) was also measured, and the diagnostic examination results for *K pneumoniae* and other microorganisms were also reported. The Kaplan–Meier method was used to estimate the GI cancer–free proportion for the PLA cohort with and without DM and the control cohort.

Data management and analysis were performed using SAS 9.1 software (SAS Institute, Cary, NC). The survival curves were depicted using R software and tested using the log-rank test. Statistically significance was set a 2-tailed P value of $<.05$.

Results

There were 14,690 patients in the PLA cohort and 58,760 patients in the control cohort, and the distributions by age, sex, and prevalence of DM (41.0%) were similar (Table 1). There were more men than women (63.0% vs. 37.0%). Pancreaticobiliary diseases were more prevalent in the PLA group than in the control group ($P < .0001$).

The incidence of GI cancer was more than 4-fold higher in the PLA group than in the control group (10.8 vs. 2.51 per 1000 person-years) (Table 2). The risk of GI cancer was higher in women than in men with PLA compared with the control group (adjusted hazard ratio [aHR], 5.67 vs. 4.04). The incidence of GI