RESEARCH ARTICLE

Pyogenic Liver Abscess as a Warning Sign for Primary Liver Cancer: A Nationwide Population-based Study

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Abstract

Background: There have been no large-scale population-based studies to estimate the subsequent risk of primary liver cancer (PLC) among patients with pyogenic liver abscess (PLA). This study aimed to provide relevant data. Materials and Methods: The Taiwan Longitudinal Health Insurance Database for the years 2000 and 2005 was used. The PLA group were adult inpatients who were newly diagnosed with PLA from 2000 to 2008. The control group was randomly selected and matched with the PLA group in terms of age, sex, and date in which medical treatment was sought other than for PLA. Results: There were 1,987 patients each in the PLA and control groups. In total, 56 had PLC, 48 (2.4%, 601.5 per 100,000 person-years) from the PLA group, and 8 from the control group. After adjusting for potential covariates, the hazard ratio of PLC for the PLA group was 3.4 times that of the control group (95% confidence interval = 1.6-7.3, p <0.001). The PLC risk for the PLA group was significantly higher within the first year after PLA diagnosis (hazard ratio: 35.4) as compared with the control group and became insignificant (hazard ratio: 2.0, 95% confidence interval = 0.8-4.9) more than one year after PLA diagnosis. Conclusions: Patients with PLA have a higher rate of PLC than matched controls, especially within the first year after the diagnosis of PLA, suggesting PLA is a warning sign for PLC.

Keywords: Liver abscess - liver neoplasms - cohort studies - risk

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Introduction

Primary liver cancer (PLC), including hepatocellular carcinoma and intrahepatic cholangiocarcinoma, were the fifth most common cancers worldwide (Jemal et al., 2011). Taiwan is one of the most endemic countries with an age-adjusted annual incidence of 36.82 per 100,000 persons, and a mortality rate of 27.12 per 100,000 persons in 2008 (Taiwan Cancer Registry, 2012). The fatality of PLC is extremely high despite some progress having been made in combined modality treatment (Montomoli et al., 2011; El-Serag HB et al., 2011). Hence, identifying patients at higher risk for PLC is critical to improve the treatment outcome.

Pyogenic liver abscess (PLA), as the result of bacterial infection with subsequent inflammatory reaction and pus formation of the liver parenchyma, is endemic in Taiwan. The annual incidence of PLA has increased steadily in Taiwan from 11.15 per 100,000 individuals in 1996 to 17.59 per 100,000 individuals in 2004 (Tsai et al., 2008). PLA has been regarded as the initial manifestation of hepatobiliary neoplasms in several reports with a range of 3 to 10 cases (Okuda et al., 1991; Yeh et al., 1998; Chong et al., 2009; Huang et al., 2009; Li et al., 2012). Lin et al. reported 2.15% of patients with underlying hepatocellular carcinoma (HCC) presented with PLA as the initial manifestation (Lin et al., 2011). They arbitrarily defined patients with PLA as the initial manifestation of underlying HCC when the diagnosis date of HCC was within 60 days of diagnosis of PLA, which might lead to misclassification bias regarding HCC status (Copeland et al., 1977). In addition, lack of a matched non-PLA control group in Lin's study is a drawback.

The high incidences of both PLA and PLC in Taiwan provide a unique opportunity to examine the association between these two diseases. Hence, in this study, we used a nationwide population-based cohort in Taiwan to estimate the incidence of PLC after the diagnosis of PLA and to explore the risks of PLC by including a non-PLA control group. Data is further stratified by time after the diagnosis of PLA to explore the role of PLA on PLC.

Materials and Methods

Taiwan National Health Insurance Research Dataset

The primary data source of this study was retrieved

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from the "Longitudinal health Insurance Database (LHID)" released by the Taiwan National Health Research Institute (NHRI). The National Health Insurance (NHI) program has been implemented since 1995 to provide affordable health care for all residents in Taiwan. There are currently 23.72 million enrollees covered by the program, representing over 99% of the island's population. For research purposes, the NHIRD releases sets of sampling files, called the Longitudinal Health Insurance Database (LHID) for year 2000 and 2005. The National Health Research Institute randomly sampled 1,000,000 beneficiaries in the selected year from the entire population of NHI beneficiaries. All registration and claims data for these 1,000,000 beneficiaries from 1996 to 2008 were included in each LHID. There is no significant difference in gender between LHID and the original NHIRD (National Health Insurance Research Database, 2012). In this cohort dataset, original identification number of each patient has been scrambled to protect patient privacy. Obtaining informed consent from each individual was not required because of the de-identified data. This study was approved by the Institutional Review Board at Chang Gung Memorial Hospital (CGMH) (100-4376B).

Study design

A hybrid study of cohort with comparative group was used. Both the 2000 and 2005 longitudinal cohorts were used for this study to obtain patients with PLA (PLA group) and without PLA (control group). The PLA group were adult (age≥18) patients who were hospitalized due to a new diagnosis of PLA (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM], code 572.0) between 2000 and 2008. The diagnosis of PLA was based on evidence of imaging studies and antibiotics treatment during admission. The index date was defined as the date of the first hospitalization for PLA. The control group was randomly selected from the remaining patients in the database, which matched the PLA group in terms of sex, year of birth, and the index date when patients sought treatment for diseases other than PLA. The ratio of the PLA group and the control group was 1:1. Subjects were followed until December, 2008. We excluded patients diagnosed with PLC before the index date of PLA for both the PLA group (n=93) and the control group (n=752).

Measurements

Other than demographic variables, documented risk factors for PLC, including hepatitis B virus infection (ICD-9-CM codes 070.2, 070.3, and V02.61), hepatitis C virus infection (070.41, 070.44, 070.51, 070.54 and V02.62), alcoholic liver disease (571.0 and 571.3), liver cirrhosis (571.5, 571.2, and 571.6), non-alcoholic fatty liver disease (571.8 and 571.9), cholelithiasis (574), cholangitis (576.1), diabetes mellitus (250 and V58.67) were retrieved. The outcome variable is PLC (ICD-9-CM codes 155.0 and 155.1). All the data regarding the diagnosis of PLC were verified with the catastrophic illness certificates provided in NHIRD. The approval of the status of catastrophic illness is subject to review by the Bureau of NHI.

Statistical analysis

Descriptive statistics, such as mean, standard deviation (SD), frequency and percentage were used to summarize characteristics of the sample. Chi-square test and independent t-test were used to compare the data between the two study groups, where appropriate. The incidence rates of PLC were computed using the Kaplan-Meier method. The univariate Log-rank test and the multivariate Cox hazard model were used to examine the effect of PLA on PLC. Stratification of the data by different time intervals after diagnosis of PLA was made to examine the role of PLA on PLC. The significance level is 0.05. All statistical analyses were performed using SAS (version 9.1, SAS Institute, Cary, NC).

Results

Characteristics of the patients

From 2000 to 2008, 1,987 PLA cases and 1,987 matched controls were obtained. The mean age was 60.2 years (SD, 14.8 years) and 63.8% were male. The PLA group had a significantly higher rate of liver cirrhosis, hepatitis B infection, hepatitis C infection, chronic liver disease, nonalcoholic fatty liver disease, cholelithiasis, cholangitis and diabetes mellitus than the control group (Table 1).

Incidence of primary liver cancer

PLC occurred in 56 patients (1.4%), including 48 (2.4%) in the PLA group and 8 (0.4%) in the control group. 50% of PLC occurred within one month after the diagnosis of PLA, and 73% of PLC occurred within one year after the diagnosis of PLA. The incidence rate of PLC was higher in the PLA group than in the control group (601.5 vs. 93.3 per 100,000 person-years) (Table 2).

Table 1. Demographic Characteristics and Co-Morbid Disorders Between Pyogenic Liver Abscess (PLA) Group and Control Group

	PLA group (n=1987)	Control group (n=1987)	*P*-value
Liver cirrhosis	295 (14.9%)	83 (4.2%)	<0.0001†
Hepatitis B infection	210 (10.6%)	120 (6.0%)	<0.0001†
Hepatitis C infection	107 (5.4%)	57 (2.9%)	<0.0001†
Chronic liver disease	452 (22.8%)	291 (14.7%)	<0.0001†
Non-alcoholic fatty liver disease	381 (19.2%)	177 (8.9%)	<0.0001†
Cholelithiasis	421 (21.2%)	139 (7.0%)	<0.0001†
Cholangitis	190 (9.6%)	18 (0.9%)	<0.0001†
Alcoholic liver disease	99 (5.0%)	38 (1.9%)	<0.0001†
Diabetes mellitus	1130 (56.9%)	700 (35.2%)	<0.0001†
Age (yrs) diagnosis of PLA			
18-49	494 (24.9%)	494 (24.9%)	1.0000†
50-69	900 (45.3%)	900 (45.3%)	
70+	593 (29.8%)	593 (29.8%)	
mean±SD	60.2 ± 14.8	60.4 ± 15.0	0.7726‡
Sex – Male	1268 (63.8%)	1268 (63.8%)	1.0000†

†Chi-square test; ‡independent t test. The control group was matched with the PLA group by sex, age, and the index date (date of first diagnosis of PLA for the PLA group and the same date for those who sought treatment for diseases other than PLA for the control group). PLA, pyogenic liver abscess

Table 2. Incidence Rate (per 100 000 person-years) of Primary Liver Cancer Between the PLA Group and the Control Group

Duration after index date	PLA group		Control group	
	n(%)	Cumulative n(%)	n(%)	Cumulative n(%)
0-<1 month	24(50.0%)	24(50.0%)	0(0.0%)	0(0.0%)
1-<2 month	3(6.3%)	27(56.3%)	0(0.0%)	0(0.0%)
3-<4 month	1(2.1%)	28(58.4%)	1(12.5%)	1(12.5%)
4-<5 month	4(8.3%)	32(66.7%)	0(0.0%)	1(12.5%)
5-<6 month	2(4.2%)	34(70.9%)	0(0.0%)	1(12.5%)
6-<12 month	1(2.1%)	35(73.0%)	0(0.0%)	1(12.5%)
1-<2 year	8(16.7%)	43(89.7%)	2(25.0%)	3(37.5%)
2-<3 year	4(8.3%)	47(98.0%)	3(37.5%)	6(75.0%)
3-<4 year	0(0.0%)	47(98.0%)	1(12.5%)	7(87.5%)
4-<5 year	1(2.1%)	48(100.0%)	1(12.5%)	8(100.0%)
5-8 year	0(0.0%)	48(100.0%)	0(0.0%)	8(100.0%)
Person-years	7980.6		8577.8	
Incidence rate	601.5		93.3	
(95%CI)	(431.3-771.6)		(40.3-183.8)	

The control group was matched with the PLA group by gender, age, and the index date (date of first diagnosis with PLA for the PLA group and the same date for those who sought medical treatment other than PLA for the control group). PLA, pyogenic liver abscess; CI, confidence interval

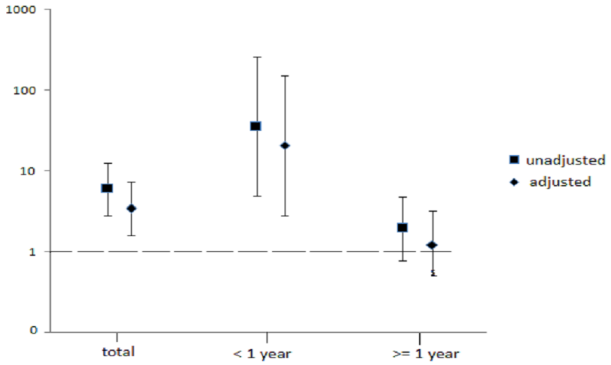

Figure 1. Hazard Ratios of Primary Liver Cancer for Specified Follow-up Intervals. Unadjusted and adjusted hazard ratio of primary liver cancer for patients with pyogenic liver abscess, as compared with the age, sex and index date matched controls. Square symbols represent unadjusted hazard ratio, diamond symbols represent adjusted hazard ratio for cirrhosis, hepatitis B infection, hepatitis C infection and sex

Risk factors of primary liver cancer

Univariate analysis reveals that liver cirrhosis, hepatitis B infection, hepatitis C infection, chronic liver disease, non-alcoholic fatty liver disease, PLA, and sex was significantly associated with PLC. The unadjusted hazard ratio (HR) of PLC was 6.2 times greater (95% CI, 2.9-13.0; $p < 0.0001$) for patients with PLA than for those without PLA. Cox proportional hazard regression shows that liver cirrhosis, hepatitis B infection, hepatitis C infection, PLA, and sex were independently associated with a higher risk of PLC. The adjusted hazard ratio (HR) of PLC was 3.4 times greater (95% CI, 1.6-7.3; $p = 0.0015$) for patients with PLA than for those without PLA (Table 3). The hazard ratio of PLC stratified by follow-up time after initial PLA diagnosis is shown in Figure 1. The PLC risk for the PLA group was significantly higher within the first year of follow-up after PLA diagnosis (HR: 35.4, 95% CI: 4.9-258.5) as compared with the control group and became insignificant (HR: 2.0, 95% CI: 0.8-4.9) after the first year after PLA diagnosis.

Table 3. Univariate and Mulitivariate Analysis of Primary Liver Cancer Development

	Event/total	Univariate HR (95% CI)	*p*	Multivariate Adjusted HR (95% CI)	*p*
Total	56 /3974(1.4%)				
Liver cirrhosis					
No	16/3596(0.4%)				
Yes	40/ 378(10.6%)	24.3(13.6-43.5)	<0.0001	10.1(5.4-17.0)	<0.0001
Hepatitis B infection					
No	30/3644(0.8%)				
Yes	26/ 330(7.9%)	10.1(6.0-17.1)	<0.0001	3.2(1.8-5.7)	<0.0001
Hepatitis C infection					
No	37/3810(1.0%)				
Yes	19/ 164(11.6%)	12.5(7.2-21.7)	<0.0001	3.5(1.9-6.3)	<0.0001
Chronic liver disease					
No	36/3231(1.1%)				
Yes	20/ 743(2.7%)	2.4(1.4-4.1)	0.0017		
Non-alcoholic fatty liver disease					
No	42/3416(1.2%)				
Yes	14/ 558(2.5%)	2.0(1.1-3.7)	0.0248		
Cholelithiasis					
No	48/3414(1.4%)				
Yes	8/ 560(1.4%)	1.0(0.5-2.2)	0.9256		
Cholangitis					
No	51/3766(1.4%)				
Yes	5/ 208(2.4%)	1.8(0.7-4.5)	0.2119		
Alcoholic liver disease					
No	53/3837(1.4%)				
Yes	3/ 137(2.2%)	1.6(0.5-5.1)	0.4325		
Diabetes mellitus					
No	26/2144(1.2%)				
Yes	30/1830(1.6%)	1.3(0.8-2.3)	0.2740		
Age					
18-49	13/ 988(1.3%)				
50-69	26/1800(1.4%)	1.1(0.6-2.2)	0.6971		
70+	17/1186(1.4%)	1.2(0.6-2.4)	0.7323		
Sex					
Female	9/1438(0.6%)				
Male	47/2536(83.9%)	2.9(1.4-6.0)	0.0031	2.5(1.2-5.1)	0.0132
PLA					
No	8/1987(0.4%)				
Yes	48/1987(2.4%)	6.2(2.9-13.0)	<0.0001	3.4(1.6-7.3)	0.0015

HR, hazard ratio; PLA, pyogenic liver abscess

Discussion

To our knowledge, this is the first large population-based cohort study to estimate the incidence of PLC in patients with PLA. Our results show that the incidence rate of PLC (601.5 per 100,000 person-years) for the PLA group was much higher than that of the control group (93.3 per 100,000 person-years). The PLC risk for the PLA group was significantly higher within the first year after PLA diagnosis (HR: 35.4, 95% CI: 4.9-258.5) as compared with the control group and became insignificant (HR: 2.0, 95% CI: 0.8-4.9) after first year after PLA diagnosis.

The overall increased risk of PLC in patients with PLA can be partly explained by the high proportions of risk factors of PLC in the PLA group (Table 1). The short temporal duration between PLA and PLC suggests that PLC masquerades as PLA before its definite diagnosis. The mechanisms that probably explain how PLC manifests as PLA are spontaneous tumor necrosis or biliary obstruction caused by tumor thrombi superimposed with bacterial infection (Yeh et al., 1998).

On the other hand, the link between infection/chronic

inflammation and cancer has been demonstrated by several studies (Lochhead et al., 2007; Matsuzaki et al., 2007; Grivennikov et al., 2010). Chronic infection with hepatitis B virus and hepatitis C virus were considered the dominant risk factors in hepatocellular carcinoma development (Beasley et al., 1981; Tsukuma et al., 1993). Chronic cholangitis and intrahepatic stone disease were strongly associated with intrahepatic cholangiocarcinoma (Su et al., 1997). PLA, as an inflammatory process, damaged hepatic parenchyma tissue and is likely to participate in the development of liver tumorigenesis. However, it takes considerable time in inflammation-mediated carcinogenesis (Coussens et al., 2002). Our findings revealed that PLC risk was significantly higher within the first year of follow-up after PLA diagnosis but not afterward, suggesting that PLA is a warning sign rather than a trigger factor of PLC.

The reasons to differentially diagnose between PLA and PLC are as follows. First, PLC mimicking PLA remains a diagnostic challenge. It is difficult to distinguish between PLA and PLC by specific clinical symptoms, laboratory tests and imaging studies (Shimizu et al., 2011; Li et al., 2012). Yeh et al. suggested male gender, hepatitis B and/or C infection and cirrhosis might provide meaningful clues to underlying liver cancers (Yeh et al., 1998), which was supported by our findings. Furthermore, histopathologic examination should be taken into consideration when physicians raised concern about the possibility of PLC. Second, in the study conducted by Lin et al, patients diagnosed with HCC who initially manifested as PLA had a worse prognosis than those without PLA (Lin et al., 2011). They supposed that management of PLA may lead to delayed diagnosis and that drainage procedures may cause tumor to spread if physicians are not on heightened alert for PLC. In the study by Yeh et al., the prognosis of patients with HCC presented as PLA was poor, with a mean survival of 3.5 months (Yeh et al., 1998). Taken together, it is worth noting that patients with PLA should be intensely monitored to detect PLC as soon as possible.

The strength of our study is the use of a nationwide database as a population-based sample that was highly representative of the Taiwanese population. A large sample size, a long follow-up period, and rich co-morbid disorders allow us to examine the risk of PLA in PLC longitudinally and multivariately. The study has some limitations inherent to administrative data. First, although major risk factors were adjusted, other possible risk variables, such as smoking, alcohol use, and obesity, were not examined (McGlynn et al., 2011). Second, the lack of microbiologic data was an obstacle to investigation of the association between causative pathogens and PLCs. Finally, information regarding the severity and duration of PLA were not reliably available.

In conclusion, patients with PLA were associated with a significantly higher risk of PLC relative to patients without PLA, especially within the first year after the diagnosis of PLA, suggesting that PLA is a warning sign for PLC. Hence, patients with PLA should be intensely monitored to quickly detect PLC. Further studies are needed to clarify the mechanism underlying the relationship between PLA and PLC.

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