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ORIGINAL ARTICLE

Risk of stroke following diagnosis with pyogenic liver abscess: a nationwide population-based study

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Abstract
Purpose In the recent years, the mortality rates attributed to pyogenic liver abscess (PLA) have decreased substantially on account of advancements in antibiotics and surgical techniques. It is thus important to better understand the risks associated with the increased number of survivors. This population-based study was designed to estimate the risk of stroke during a 1 year period following diagnosis with PLA, compared to individuals who did not suffer from PLA.
Methods Data were obtained from the Taiwan National Health Insurance Research Database. A total of 9,977 patients receiving ambulatory with a diagnosis of PLA were included, together with 49,885 non-PLA patients as our comparison group. Each individual was followed for 1 year, with check-ups at 30 days, 90 days, and 1 year post diagnosis to identify the subsequent occurrence of stroke. Cox proportional hazards regressions were performed for the analysis.
Results During the 1 year follow-up period, 475 (4.76%) strokes occurred among the PLA patients and 1,713 (3.43%) patients in the non-PLA comparison cohort. The diagnosis of PLA was independently associated with 1.99 (95% confidence interval (CI) 1.68–2.34), 1.72 (95% CI 1.52–1.97), and 1.43 (95% CI 1.28–1.59) times greater risks of stroke during the 30 days, 90 days, and 1 year follow-up periods, respectively, after adjusting for urbanization level, geographic region, monthly income, hypertension, diabetes, coronary heart diseases, renal diseases, heart failure, hyperlipidemia, atrial fibrillation, obesity, and alcohol abuse/alcohol-dependence syndrome.
Conclusions We suggest a need for more intensive medical monitoring following PLA infection, especially during the first few months. However, data regarding smoking were unavailable in our dataset and may have biased our findings.

Keywords Pyogenic liver abscess · Stroke · Epidemiology

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Introduction

Pyogenic liver abscess (PLA) is a potentially fatal disease that requires prompt diagnosis and treatment. Pyogenic abscesses account for three-quarters of all the liver abscesses that occur in industrialized countries [1], with one out of every 4,500–7,000 hospital admissions being due to a liver abscess [2, 3]. Before 1980s, the most commonly isolated organism from liver abscesses was *Escherichia coli*, but recently in Taiwan, there has been a shift to *Klebsiella pneumonia* as being the primary causative agent [4]. Some researchers have speculated that this same etiologic shift is currently occurring in the USA [5], as *K. pneumonia* has more recently been found to be the primary causative agent in the USA as well [6]. In addition to this etiologic shift, advancements in antibiotics and surgical techniques have greatly improved mortality rates over the past two decades [7].

Although the treatment of PLA continues to evolve and is currently a topic of controversy among medical practitioners [8], as of now, surgical treatment is reported to yield the best chances of survival with mortality rates ~11.24%. This statistic can be compared with rates that were as high as 69%, as reported by Malik et al. [9], among patients suffering from PLA from 1928 to 1937, and 24% in a study conducted more recently on patients in the USA between 1966 and 1978 [10]. On account of the decreased mortality rates and increased number of PLA survivors, clinicians need to be more aware of the comorbidities related to having suffered from PLA.

One of the most debilitating and life-threatening diseases of the modern world is stroke [11]. It has previously been demonstrated that heightened inflammatory responses originating from conditions of the liver increase a patient's risk of stroke [12]. To the best of the researchers' knowledge, no study to date has sought to evaluate the relationship between infection with PLA and subsequent stroke. This nationwide population-based study was designed to estimate the risk of stroke during a 1 year follow-up period after an ambulatory care visit or hospitalization for PLA, compared to individuals who were not diagnosed with PLA during the same period.

Methods

Database

The data for analysis were sourced from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD was derived from the system of Taiwan National Health Insurance (NHI) program and maintained by the Taiwan National Health Research Institute. Each year, the National Health Research Institute collects data from the NHI program and classifies them into the NHIRD. In 2008, 22.89 million of the country's 22.96 million people (amounting to 99.7% of the island's population) were covered by the NHI program. More than 300 studies have been published in peer-reviewed journals based on the NHIRD.

As the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempted from full review by the Taipei Medical University Institutional Review Board.

Study population

A study group and a comparison group were utilized to examine the relationship between PLA and the subsequent risk of stroke. The study group was selected by first identifying the 14,343 patients who had visited outpatient care centers or were hospitalized with a principal diagnosis of PLA (ICD-9-CM code 572.0) between 1 January 2006 and 31 December 2008. Their first visit for PLA between 1 January 2006 and 31 December 2008 was assigned as their index date. To increase the potential of only including newly onset cases, we excluded the patients who had received a PLA diagnosis before their index date ($n = 1{,}154$). We also excluded patients <40 years of age ($n = 1{,}329$) because stroke was a rare occurrence in this age group. We also excluded all the patients who had ever received a diagnosis of any type of stroke (ICD-9-CM codes 430–438) before their index dates ($n = 1{,}883$). However, because the NHI was initiated in 1995, patients who had received a diagnosis of stroke before 1996 but had not been diagnosed with a subsequent stroke would have been included. We also ensured that none of the selected PLA patients had also received a diagnosis of amoebic liver abscess (ICD-9-CM code 006.3). In total, 9,977 patients with PLA were included in the study group.

The Longitudinal Health Insurance Database 2000 (LHID2000) was utilized to select a comparison group. To help scholars conduct research, the Taiwan National Health Research Institute created the LHID2000. The LHID2000 is a database that includes all the original claim data of 1,000,000 individuals who were randomly sampled from the NHIRD 2000 Registry for Beneficiaries. The LHID2000 enables researchers to trace the medical service utilizations of 1,000,000 enrollees since the initiation of the NHI program in 1995. A ratio of 1:5 was used to randomly extract 49,885 comparison patients from LHID2000, matched with the study group based on age group (40–49, 50–59, 60–69, 70–79, and >79 years), sex, diabetes, and the year of index date. On account of diabetes being a major risk factor for both PLA and stroke, we matched the distribution of diabetes in PLA cases with comparison patients. The first ambulatory care visit occurring in the index year was designed as the index date. All the selected comparison patients were assured to have not ever received a diagnosis of PLA since the initiation of the Taiwan NHI program. All the selected comparison subjects were likewise ensured to have never suffered a stroke between the initiation of NHI and their index date.

In total, this study comprised 59,862 subjects. Each subject was individually tracked for a 1 year period beginning with their index date, and those who received a diagnosis of stroke were identified (ICD-9-CM codes 430–438).

Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform all the statistical analyses included in this study. We used χ^2 tests to explore the differences in the distributions of urbanization level, geographic region (northern, central, eastern, and southern Taiwan), monthly income (0, NT\$1–15,840, NT15,841–25,000, $\geq$ NT25,001), as well as the medical comorbidities (including hypertension, coronary heart diseases, renal diseases, heart failure, hyperlipidemia, atrial fibrillation, obesity, and alcohol abuse/alcohol-dependence syndrome) between patients diagnosed with PLA and those who did not receive such a diagnosis. We only included these comorbidities if they occurred in an inpatient setting or if they appeared in two or more ambulatory care claims coded within 1 year previous to the index date. A Kaplan–Meier survival analysis and a log-rank test were further used to examine the differences in the risk of stroke between patients with and without PLA. Stratified cox proportional hazards regressions (stratified on age, sex, and diabetes) were also utilized to compute the 3, 6, and 12 month stroke-free survival rates after adjusting for the above mentioned variables. Further analyses stratified by age group and sex were performed to evaluate the association between PLA and stroke during the 1 year follow-up period. Hazard ratios (HRs) and 95% confidence intervals (CIs) were also presented. This study considered a value of $p < 0.05$ as statistically significant.

Results

The mean age for the 59,862 sampled subjects was 62.8 (±12.4) years. Table 1 shows the distributions of demographic characteristics and medical comorbidities according to the presence/absence of PLA after matching for age and sex. We found that patients with PLA had a higher prevalence of renal diseases (10.8 vs. 5.2%, $p < 0.001$) and heart failure (7.6 vs. 6.5%, $p < 0.001$). However, patients with PLA had a lower prevalence of hyperlipidemia (29.4 vs. 31.9%, $p < 0.001$) when compared with patients without PLA. There were no significant differences in the prevalence of hypertension, coronary heart diseases, atrial fibrillation, or obesity between patients with and without PLA. Demographically, there was neither any significant difference in monthly income and geographic region between patients with and without PLA. Patients with PLA were more likely to reside in less urbanized communities ($p < 0.001$) than patients without PLA.

The incidence of stroke within the 3, 6, and 12 month follow-up periods after the index date are presented in Table 2. When compared with patients without PLA, log-rank tests revealed that patients with PLA had significantly higher incidence rates of stroke within the 3 month (2.15 vs. 1.10%), 6 month (3.20 vs. 1.91%), and 12 month (4.76 vs. 3.43%) periods following the index date (all $p < 0.001$).

Table 2 displays the HRs for stroke within the 3, 6, and 12 month follow-up periods after the index date. After adjusting for urbanization level, geographic region, monthly income, hypertension, coronary heart diseases, renal diseases, heart failure, hyperlipidemia, atrial fibrillation, obesity, and alcohol abuse/alcohol-dependence syndrome, a stratified cox proportional hazards regression (stratified on age, sex, and diabetes) revealed that when compared with patients without PLA, the HR for stroke for patients with PLA was 1.99 (95% CI 1.68–2.34, $p < 0.001$) times higher within the 3 month period, 1.72 (95% CI 1.52–1.97, $p < 0.001$) times higher within the 6 month period, and 1.43 (95% CI 1.28–1.59, $p < 0.001$) times higher within the 12 month period.

Table 3 shows the HRs for stroke by stroke type. The adjusted HR of ischemic stroke, hemorrhage stroke, and unspecified stroke for patients with PLA was found to be 1.33 (95% CI 1.14–1.53, $p < 0.001$), 1.46 (95% CI 1.09–1.98, $p < 0.001$), and 1.51 (95% CI 1.26–1.82, $p < 0.001$), respectively, when compared with patients without PLA.

Table 4 presents the details of the crude and adjusted HRs for stroke by sex. Among men, the hazard of stroke during the 1 year follow-up period was 1.34 times greater (95% CI 1.18–1.56, $p < 0.001$) for patients with PLA than for patients without PLA. Among women, the HR for stroke for patients with PLA was 1.54 (95% CI 1.31–1.82, $p < 0.001$) greater than patients without PLA.

Table 5 includes a further analysis stratified by age group. The younger cohort, which included individuals less than 50 years of age, had the greatest risk of subsequent stroke. The adjusted HR for stroke associated with PLA was 2.52 for patients aged 40–49 years (95% CI 1.45–4.27), 1.56 for those aged 50–59 years (95% CI 1.21–2.04), 1.31 for those aged 60–69 years (95% CI 1.09–1.69), 1.40 for those aged 70–79 years (95% CI 1.18–1.718), and 1.28 for patients >79 years (95% CI 1.01–1.61).

Discussion

To the best of our knowledge, this is the first study to demonstrate that PLA infection is a potential risk factor for subsequent stroke. This finding may have only now been realized on account of the etiological shift among PLA patients with *K. pneumonia* now being an increasing common global causative pathogen. In a study conducted on PLA patients between 1990 and 1996 in a veteran hospital in Taiwan, 87.9% of the PLA cases were found to

Table 1 Distributions of demographic characteristics and comorbid medical disorders for patients in Taiwan with PLA and comparison patients, 2006–2008 ($n = 59{,}862$)

Variables	Patients with PLA (n = 9,977)		Comparison patients (n = 49,885)		p value
	Total no.	Column (%)	Total no.	Column (%)	
Sex					1.000
Male	6,041	60.6	30,205	60.6	
Female	3,936	39.4	19,680	39.4	
Age (years)					1.000
40–49	1,685	16.9	8,425	16.9	
50–59	2,840	28.5	14,200	28.5	
60–69	2,315	23.2	11,575	23.2	
70–79	2,110	21.2	10,550	21.2	
>79	1,027	10.3	5,135	10.3	
Hypertension	4,887	49.0	23,971	48.1	0.089
Diabetes	3,999	40.1	19,995	40.1	1.000
Hyperlipidemia	2,929	29.4	15,901	31.9	<0.001
Renal disease	1,080	10.8	2,592	5.2	<0.001
Coronary heart disease	1,994	20.0	10,006	20.1	0.870
Heart failure	758	7.6	3,249	6.5	<0.001
Atrial fibrillation	157	1.6	748	1.5	0.579
Obesity	77	0.8	379	0.8	0.900
Alcohol abuse/alcohol-dependence syndrome	90	0.9	159	0.3	<0.001
Monthly income					0.143
NT$0–15,840	4,545	45.6	22,398	44.9	
NT$15,841–25,000	3,531	35.4	17,560	35.2	
≥NT$25,001	1,901	19.0	9,927	19.9	
Geographic region					0.285
Northern	4,277	42.9	20,952	42.0	
Central	2,367	23.7	11,923	23.9	
Southern	3,058	30.7	15,514	31.1	
Eastern	275	2.7	1,496	3.0	
Urbanization level					<0.001
1 (most urbanized)	2,765	27.7	14,885	29.8	
2	2,628	26.3	14,156	28.4	
3	1,576	15.8	7,967	16.0	
4	1,586	15.9	7,071	14.2	
5 (least urbanized)	1,422	14.3	5,806	11.6	

have liver abscesses caused by *K. pneumonia* alone, and the rest to have cases caused by mixed flora [13]. Thus, it can be assumed that a very high proportion of PLA cases in Taiwan could more accurately be diagnosed as Klebsiella liver abscesses (KLA).

As it has been previously documented that inflammatory responses originating from the liver, at least in the case of non-alcoholic fatty liver disease (NAFLD), increase the risk of stroke [12]; it is possible that inflammation may be at play in the increased risk of stroke following PLA infection, especially in the light of the possible increased inflammatory response owing to the etiological shift to *K. pneumonia* as the causative agent.

The increased risk of stroke arising from an increased inflammatory response accompanying the etiologic shift to *K. pneumonia* as the primary causative agent in PLA infections may proceed through an increased risk of bacteremia and metastatic complications. In a study conducted on all the KLA cases in the USA, it was found that 83% had concurrent bacteremia and 28% had metastatic complications [4]. In a study conducted in the USA on records taken from 1994 to 2005 among 8,286 PLA patients, the

Table 2 Hazard ratios for stroke among the sample patients during the 1 year follow-up period starting from the index date (n = 59,862)

Presence of stroke	Total sample		Patients with PLA		Comparison patients	
	No.	%	No.	%	No.	%
30 days follow-up period						
Yes	762	1.27	215	2.15	547	1.10
Crude HR[a] (95% CI)	–		2.01*** (1.71–2.36)		1.00	
Adjusted HR[b] (95% CI)	–		1.99*** (1.68–2.34)		1.00	
90 days follow-up period						
Yes	1,274	2.13	319	3.20	955	1.91
Crude HR[a] (95% CI)			1.71*** (1.51–1.95)		1.00	
Adjusted HR[b] (95% CI)			1.72*** (1.52–1.97)		1.00	
1 year follow-up period						
Yes	2,188	3.66	475	4.76	1,713	3.43
Crude HR[a] (95% CI)			1.43*** (1.28–1.58)		1.00	
Adjusted HR[b] (95% CI)			1.43*** (1.28–1.59)		1.00	

*** $p < 0.001$

[a] Hazard ratio was calculated by the stratified cox regression model (stratified on age, sex, and diabetes)

[b] Adjustments are made for patients' geographic location, urbanization level, monthly income, hypertension, coronary heart disease, heart failure, atrial fibrillation, hyperlipidemia, obesity, and alcohol abuse/alcohol-dependence syndrome

Table 3 Hazard ratios for stroke among the sample patients during the 1 year follow-up period starting from the index date (n = 59,862)

Presence of stroke	Total sample		Patients with PLA		Comparison patients	
	No.	%	No.	%	No.	%
Ischemic stroke						
Yes	1,355	2.3	277	2.8	1,078	2.2
Crude HR[a] (95% CI)	–		1.31*** (1.14–1.50)		1.00	
Adjusted HR[b] (95% CI)	–		1.33*** (1.14–1.53)		1.00	
Hemorrhagic stroke						
Yes	486	0.8	106	1.1	380	0.8
Crude HR[a] (95% CI)			1.41*** (1.06–1.88)		1.00	
Adjusted HR[b] (95% CI)			1.46*** (1.09–1.98)		1.00	
Unspecified						
Yes	347	0.6	92	0.9	255	0.5
Crude HR[a] (95% CI)			1.55*** (1.29–1.86)		1.00	
Adjusted HR[b] (95% CI)			1.51*** (1.26–1.82)		1.00	

*** $p < 0.001$

[a] Hazard ratio was calculated by the stratified cox regression model (stratified on age, sex, and diabetes)

[b] Adjustments are made for patients' geographic location, urbanization level, monthly income, hypertension, coronary heart disease, heart failure, atrial fibrillation, hyperlipidemia, obesity, and alcohol abuse/alcohol-dependence syndrome

most common bacterial sources were streptococcus (29.5%) and *E. coli* (18.1%). Among these cases only 52.1% (95% 50.9–53.3) suffered from bacteremia. Thus, it is possible that KLA cases are more likely to present with bacteremia [14]. As the presence of bacteria in the blood would increase the immune system's inflammatory response, it would also contribute to an inflammatory response-increased risk of stroke.

Another source of further increased inflammation could arise from metastatic complications. In a study conducted in Taiwan on data sourced between 1995 and 2000 on 225 cases of PLA, it was found that PLA infections with *K. pneumonia* as the causative were more likely to have metastatic complications (adjusted OR 5.0, 95% CI 1.1–47) and that cases presenting with bacteremia also had an increased risk for metastatic complications (adjusted OR 5.4, 95% CI 1.4–30).

Table 4 Crude and adjusted hazard ratios for stroke among the sample patients during the 1 year follow-up period starting from the index date stratified by sex ($n = 59{,}862$)

Presence of stroke	Male				Female			
	Patients with PLA ($n = 6{,}041$)		Comparison patients ($n = 30{,}205$)		Patients with PLA ($n = 3{,}936$)		Comparison patients ($n = 19{,}680$)	
	No.	%	No.	%	No.	%	No.	%
90-days follow-up period								
Yes	262	4.34	1,008	3.34	213	5.41	705	3.58
Crude HR[a] (95% CI)	1.35*** (1.17–1.55)		1.00		1.56*** (1.33–1.83)		1.00	
Adjusted HR[b] (95% CI)	1.34*** (1.18–1.56)		1.00		1.54*** (1.31–1.82)		1.00	

***$p < 0.001$

[a] Hazard ratio was calculated by the stratified Cox regression model (stratified on age, sex, and diabetes)

[b] Adjustments are made for patients' geographic location, urbanization level, monthly income, hypertension, coronary heart disease, renal disease, heart failure, atrial fibrillation, hyperlipidemia, obesity, and alcohol abuse/alcohol-dependence syndrome

Table 5 Crude and adjusted hazard ratios for stroke among the sample patients during the one-year follow-up period starting from the index date stratified by age group ($n = 59{,}862$)

Presence of stroke	Age group (years)					
	40–49		50–59		60–69	
	Patients with PLA (n (%))	Comparison (n (%))	Patients with PLA (n (%))	Comparison (n (%))	Patients with PLA (n (%))	Comparison (n (%))
Yes	22 (1.31)	37 (0.44)	81 (2.85)	230 (1.62)	110 (4.75)	414 (3.58)
Crude OR[a] (95% CI)	2.72*** (1.52–4.16)	1.00	1.64*** (1.27–2.12)	1.00	1.44** (1.16–1.79)	1.00
Adjusted OR[b] (95% CI)	2.52*** (1.45–4.27)	1.00	1.56*** (1.21–2.04)	1.00	1.31* (1.09–1.69)	1.00

Occurrence of stroke	Age group (years)			
	70–79		>79	
	Patients with PLA (n (%))	Comparison (n (%))	Patients with PLA (n (%))	Comparison (n(%))
Yes	164 (7.77)	641 (6.08)	98 (9.54)	391 (7.61)
Crude OR[a] (95% CI)	1.40*** (1.17–1.67)	1.00	1.26* (1.00–1.59)	1.00
Adjusted OR[a] (95% CI)	1.40*** (1.18–1.71)	1.00	1.28* (1.01–1.61)	1.00

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[a] Hazard ratio was calculated by the stratified Cox regression model (stratified on age, sex, and diabetes)

[b] Adjustments are made for patients' geographic location, urbanization level, monthly income, hypertension, coronary heart disease, renal disease, heart failure, atrial fibrillation, hyperlipidemia, obesity, and obesity, and alcohol abuse/alcohol-dependence syndrome

Such metastatic complications have been found to spread widely throughout the body [15], and by further spreading the infection would also result in an increased inflammatory response which could increase the risk of subsequent stroke.

Although antibiotic treatment may play a role in mechanism underlying subsequent stroke, it is unlikely. In Taiwan, the most commonly prescribed pharmaceuticals are metronidazole and cephalosporins. Metronidazole is relatively inexpensive and often utilized. Although it has been implicated in contributing to blood clotting, and is often administered to PLA patients intravenously on account of the severity of the disease, any clots that would form would be unlikely to migrate to the brain and contribute to ischemic stroke.

Cephalosporins, on the other hand, are associated with hypoprothrombinemia, and could contribute to hemorrhagic stroke [16–18]. But, in this study the risks for both types of strokes following PLA were comparable. Ischemic stroke had a HR of 1.33 (1.14–1.53) and hemorrhagic stroke had a HR of 1.46 (1.09–1.98).

This study was conducted on a predominantly Han Chinese population in Taiwan where *K. pneumonia* was first reported as a causative agent of PLA and where liver abscess is often associated with diabetic or cryptogenic etiology [19–21]. As the shift to *K. pneumonia* as a causative agent is now being mirrored in the West, the results of this study should also be of concern in other countries, such as the USA, which might also suffer the same consequences, including an increased risk of stroke following PLA infection, as a result of the etiological shift arising from a shift in causative bacteria in PLA infections.

The strengths of this study include the use of a longitudinal, population-based dataset. This enabled us to trace all the cases of PLA and stroke during the study period. Moreover, the large sample size afforded the considerable statistical advantage for detecting real differences between the two cohorts.

This study suffered some several potential limitations. First, some clinically relevant patient and lifestyle information, such as smoking status, alcohol consumption and dietary habits, body mass index, and pharmaceutical use, all of which may contribute to these two conditions, was not available through the administrative dataset. Although we did adjust for urbanization level which may reflect lifestyle, as well as both obesity and alcohol abuse/dependence syndrome, the association between PLA and stroke may be partially explained by the residual confounding of the unadjusted factors. Second, although it is strongly supported that the vast majority of PLA cases were caused by *K. pneumonia*, the identification of causative organisms was not included in the population-based dataset and could not be included in this study. Third, the risk of stroke may vary with the severity and form of the inflammatory response arising on account of PLA infection; however, there was no information concerning the type or concentration of inflammatory biomarkers available for this study.

This is the first evidence-based study to suggest an increased risk of stroke among individuals who have suffered from PLA. Future studies are needed to elucidate the mechanisms by which PLA is associated with stroke, and whether through an inflammatory pathway or not, to clarify whether the identity of the causative organism influences the risk of subsequent stroke. As this study was conducted on a population in Taiwan, it offered the statistical power leveraged through a population-based dataset to make significant estimates about the association between PLA and subsequent stroke in a population where the etiology of the disease has already shifted toward *K. pneumonia* as the primary causative organism. As this etiologic shift is just now being mirrored in other parts of the world, including the USA, this study offers other regions just embarking on similar transitions a window into the risk of subsequent stroke associated with what could be considering an emerging infectious disease. As such locations at the forefront of the transition may not have the statistical power to make significant estimates about the associated risks of PLA/KLA, it is the hope of the authors that this study highlights the need for a coordinated and systematic approach to prevent patients with PLA/KLA from subsequent stroke and to optimize outcomes both in Taiwan and overseas.

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Conflict of interest All authors have no conflicts of interest to declare.

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