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Increased risk of pneumonia following pyogenic liver abscess: a nationwide population-based study

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SUMMARY

Objective: This nationwide study aimed to estimate the risk of pneumonia during a 90-day period following diagnosis with pyogenic liver abscess (PLA) compared to individuals who did not suffer PLA.
Methods: We investigated the incidence of pneumonia during the 90 days after diagnosis of PLA among 12 868 patients who received medical services for this condition, and compared it to that of 64 340 controls who received medical services for other medical conditions.
Results: We found that the incidence rates of pneumonia were 9.59 and 1.87 per 10 000 person-days in patients with and without PLA, respectively. Stratified Cox proportional hazard regressions found that the hazard ratio for pneumonia among patients with PLA was 5.28 times higher than that of patients without PLA after adjusting for potential confounding factors. We further found *Klebsiella pneumoniae* to be the causative organism in 84.9% of the cases, but in only 11.7% of the comparison group.
Conclusions: Our study suggests an increased risk of pneumonia among individuals who have suffered a PLA.

1. Introduction

Pyogenic liver abscess (PLA) is a potentially fatal disease. It currently accounts for three-quarters of all liver abscesses occurring in industrialized countries,[1] with one out of every 4500–7000 hospital admissions being due to a liver abscess.[2,3] Prior to the 1980s, the most commonly isolated organism from liver abscesses was *Escherichia coli*, but in Taiwan there has been a shift to *Klebsiella pneumoniae*, which is now highly endemic and the major cause of community-acquired pyogenic infections.[4–7] Some researchers are now suggesting that this same etiologic shift is occurring in the USA,[8] with *K. pneumoniae* recently being found to be the primary causative agent there as well.[9] In addition to this etiologic shift, other factors affecting the prognosis of PLA include advancements in antibiotics and surgical techniques, which have greatly reduced mortality rates over the last two decades.[10]

Although the treatment of PLA continues to evolve and is currently a topic of controversy among medical practitioners,[11] surgical advancements have recently yielded mortality rates around 11.24%.[12] This can be compared with rates that were as high as 69% among PLA patients afflicted between 1928 and 1937,[12] and 24% in a study conducted more recently on patients in the USA between 1966 and 1978.[13] 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 a PLA.

PLA patients often have high rates of bacteremia and subsequent metastatic complications, and even higher rates of both when afflicted by *K. pneumoniae* as the causative agent.[4,14] Therefore, it is possible that many future survivors of PLA will suffer from bacterial infections subsequent to their original PLA infections. Based on these elements, we hypothesize that patients with PLA will have a subsequent higher incidence of pneumonia than individuals without PLA.[5,6,15,16]

Thus, on account of the possible association between PLA and cases of pneumonia characterized by high rates of early mortality, this study set out to estimate the risk of pneumonia within 90 days following a diagnosis of PLA compared to patients without PLA, utilizing a nationwide population-based dataset in Taiwan.

2. Methods

2.1. Database

The data for the analyses performed in this study were retrieved from Taiwan's National Health Insurance Research Database

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(NHIRD). The NHIRD is derived from the Taiwan National Health Insurance (NHI) program and is maintained by the National Health Research Institute, Taipei, Taiwan. The NHIRD includes the registration files and original claims data for the reimbursements of 22.89 million of the country's 22.96 million inhabitants as of 2008.

2.2. Study population

We used a study cohort and a comparison cohort to examine the relationship between pneumonia and PLA. For the study cohort, we retrieved 14 343 patients from the NHIRD who visited outpatient care centers or were hospitalized with a principal diagnosis of PLA (International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) code 572.0) between January 1, 2006 and December 31, 2008. In Taiwan, if a physician suspects PLA the patient first undergoes sonography or a computed tomography scan. If an abscess is visualized and it is of sufficient size, it is aspirated with a needle and drained. A pus culture is conducted in every case to determine the etiology and the results must be coded in the administrative database to receive reimbursement for the test. If the abscess is too small to be aspirated, a blood culture is performed instead. The patient's first visit for PLA during this study period was assigned as the index date. We first excluded patients who had been diagnosed with PLA prior to their index date (n = 1154) in order to include only new onset patients. Then we excluded patients aged <18 years (n = 148) in order to include only an adult population. We also excluded patients who had received a diagnosis of pneumonia within 6 months prior to their index date (n = 173). Ultimately, there were 12 868 patients with PLA in the study cohort.

In this study, we used the NHIRD to select a comparison cohort. A total of 64 340 subjects were randomly extracted from the NHIRD, at a ratio of 1:5, matched with the study cohort on age, sex, and the year of index date (2006–2008). The date of first medical services occurring in the index year was assigned as the index date. We also ensured that none of the selected comparison cohort had a history of PLA since the initiation of the Taiwan NHI program. In addition, we ensured that all the selected comparison subjects had not been diagnosed with pneumonia during the 6 months preceding their index date.

As a result, we included 77 208 subjects in this study and individually tracked each subject for 90 days beginning with their index date to identify those who were subsequently diagnosed with pneumonia (ICD-9-CM codes 480–483.8, 485–486, and 487.0). In Taiwan, all pneumonia cases are hospitalized, receive a chest radiograph, and undergo microbiological tests to ascertain the causative organism. The first microbiological tests include a culture of the sputum and a Gram stain smear. If the culture is unsuccessful, the blood may be tested as well as the urine for pneumococcal antigen. The results of these tests must also be coded for in the administrative database to receive reimbursement.

2.3. Statistical analysis

We used the SAS statistical package for all statistical analyses. Pearson Chi-square tests were used to examine the distributions of urbanization level, geographic region (northern, central, eastern, and southern Taiwan), and monthly income of both patients with and without PLA. We also performed a Kaplan–Meier survival analysis and log-rank test to detect differences in the risk of

Table 1
Demographic characteristics and comorbid medical disorders of patients in Taiwan with pyogenic liver abscess (PLA) and patients in the comparison cohort (no PLA), 2006–2008 (N = 77 208)

Variable	Patients with PLA (n = 12 868)		Comparison patients (n = 64 340)		p-Value
	Total No.	%	Total No.	%	
Sex					1.00
Male	7875	61.2	39 375	61.2	
Female	4993	38.8	24 965	38.8	
Age, years					1.000
18–39	1173	9.1	5865	9.1	
40–49	1778	13.8	8890	13.8	
50–59	3073	23.9	15 365	23.9	
60–69	2727	21.2	13 635	21.2	
70–79	2676	20.8	13 380	20.8	
>79	1441	11.2	7205	11.2	
Hypertension	6516	50.6	28 265	43.9	<0.001
Diabetes	5057	39.3	13 081	20.3	<0.001
Heart disease[a]	2682	20.8	11 736	18.2	<0.001
Lung disease[b]	1164	9.1	5734	8.9	0.628
Acute/chronic kidney disease	1435	11.2	3685	5.7	<0.001
	Total No.	Column %	Total No.	Column %	
Monthly income, NT$					<0.001
0–15 840	5899	45.8	22 671	35.2	
15 841–25 000	4565	35.5	27 670	43.0	
≥25 001	2404	18.7	13 999	21.8	
Geographic region					<0.001
Northern	5661	44.0	29 934	46.5	
Central	3057	23.8	15 446	24.0	
Southern	3814	29.6	17 274	26.9	
Eastern	336	2.6	1686	2.6	
Urbanization level					<0.001
1 (most urbanized)	3600	28.0	18 768	29.2	
2	3469	26.9	18 129	28.2	
3	2055	16.0	10 658	16.6	
4	2035	15.8	9042	14.0	
5 (least urbanized)	1709	13.3	7743	12.0	

[a] Heart disease: ischemic heart disease, arrhythmias, and heart failure.
[b] Lung disease: chronic obstructive pulmonary disease, asthma, pulmonary emphysema, and pneumoconiosis.

pneumonia between patients with and without PLA. Stratified Cox proportional hazards regressions (stratified on age, sex, and the year of index date) were conducted to calculate the hazard of pneumonia following a diagnosis of PLA. In this study, we also took several medical comorbidities into consideration in the regression model, including hypertension, diabetes, heart disease, lung disease, and acute/chronic kidney disease. These comorbidities were only included if they either occurred in an inpatient setting or appeared in two or more ambulatory care claims coded 6 months before the index date. A p-value of <0.05 was considered statistically significant.

3. Results

The mean age of the total 77 208 sampled subjects was 62.2 (± 15.2) years; 61% were males. We found that *K. pneumoniae* (ICD-9-CM code 041.3) was the causative organism in 73.2% of the patients with PLA in this study. After matching for age and sex, it was found that patients with PLA were more likely than patients without PLA to have the following comorbidities: hypertension ($p < 0.001$), diabetes ($p < 0.001$), heart disease ($p < 0.001$), and acute/chronic kidney disease ($p < 0.001$) (Table 1). There was no significant difference in the prevalence of lung disease between patients with and without PLA ($p = 0.628$). In addition, it was found that patients with PLA had a greater tendency to have no monthly income and to reside in the southern part of Taiwan and in less urbanized communities than patients without PLA (Table 1).

The incidence of pneumonia during the 90-day follow-up period for these two cohorts is presented in Table 2. Of the total 77 208 sample, 2193 (2.8%) subjects were diagnosed with pneumonia during the 90-day follow-up period; pneumonia was found in 1109 (8.6%) patients with PLA and 1084 (1.7%) patients without PLA. The incidence rates of pneumonia were 9.59 (95% confidence interval (CI) 9.03–10.15) and 1.87 (95% CI 1.76–1.99) per 10 000 person-days in patients with and without PLA, respectively. We used the log-rank test to test the difference in the 90-day pneumonia-free survival rate between these two cohorts. It was found that patients with PLA had significantly lower 90-day pneumonia-free survival rates than patients without PLA (Chi-square value 2248.8; $p < 0.001$). Figure 1 shows the results of the Kaplan–Meier survival analysis.

The crude hazard ratios (HR) for pneumonia between patients with and without PLA are also displayed in Table 2. A stratified Cox proportional hazards regression (stratified on age and sex) revealed that when compared to patients without PLA, the crude HR for pneumonia among patients with PLA was 5.64 (95% CI 5.17–6.15).

After adjusting for patient monthly income, geographic location, urbanization level, hypertension, diabetes, heart disease, lung disease, and acute/chronic kidney disease, the HR for pneumonia among patients with PLA was 5.28 (95% CI 4.81–5.78) times that of patients without PLA (Table 3). We further analyzed the etiology of pneumonia cases in this investigation and found *K. pneumoniae* to be the causative organism in 84.9% of the cases, but only 11.7% of the comparison cohort.

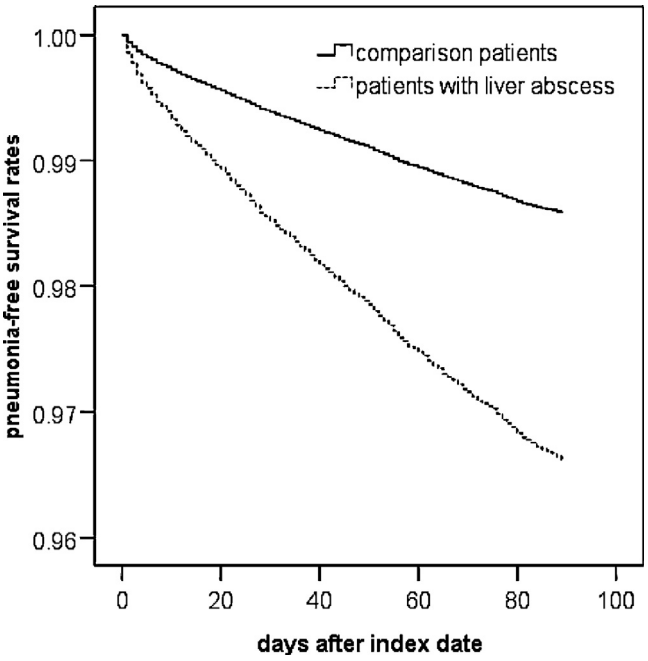

Figure 1. Pneumonia-free survival rates for patients with pyogenic liver abscess and comparison patients in Taiwan.

4. Discussion

To the best of our knowledge, this is the first study to demonstrate that PLA infection is a potential risk factor for subsequent pneumonia. This study found the adjusted HR for pneumonia among patients with PLA to be 5.28 times higher than that of patients without PLA.

One explanation for our results stems from the increasing number of PLA survivors. Studies conducted in the USA show that the mortality rate of PLA cases has dropped from rates as high as 69% in the early 1900s,[12] to 24% in the 1960s and 1970s,[13] and are now, on account of modern surgical techniques, as low as 11.24%.[12] This decreasing trend in mortality rates has yielded far more PLA survivors. As a result the case numbers are now sufficient to provide the statistical power required to conduct large-scale epidemiological studies; there is also an increased need for such studies to better understand this emerging demographic of PLA survivors.

A second explanation for our findings could be related to the etiologic shift among PLA cases. Prior to the 1980s, the most common organism isolated from PLAs was *E. coli*. In Taiwan, however, there has been a shift towards *K. pneumoniae* as the major cause of all community-acquired pyogenic infections.[4–7] In our

Table 2
Crude and adjusted hazard ratios for pneumonia among the sample patients during the 90-day follow-up period starting from the index ambulatory care visit ($N = 77\,208$)

Presence of pneumonia	Total sample		Patients with PLA		Comparison group	
	No.	%	No.	%	No.	%
90-day follow-up period						
Yes	2193	2.8	1109	8.6	1084	1.7
Incidence rate per 10 000 person-days (95% CI)	3.16 (3.03–3.29)		9.59 (9.03–10.15)		1.87 (1.76–1.99)	
Crude HR (95% CI)	–		5.64[a] (5.17–6.15)		1.00	

PLA, pyogenic liver abscess; HR, hazard ratio; CI, confidence interval. Hazard ratio was calculated by stratified Cox regression model (stratified on age, sex, and index date).
[a] Indicates $p < 0.001$.

Table 3
Adjusted hazard ratios for pneumonia during the 90-day follow-up period for patients with pyogenic liver abscess and comparison patients in Taiwan ($N = 77\,208$)

Variables	Pneumonia occurrence		
	HR	95% CI	*p*-Value
Pyogenic liver abscess	5.28	4.81–5.78	<0.001
Hypertension	0.90	0.82–0.99	0.041
Diabetes	1.29	1.17–1.42	<0.001
Heart disease	1.10	0.99–1.23	0.067
Lung disease	2.00	1.78–2.24	<0.001
Acute/chronic kidney disease	1.33	1.16–1.52	<0.001
Monthly income, NT$			
0–15 840 (reference group)	1.00		
15 841–25 000	1.02	0.92–1.13	0.726
≥25 001	0.76	0.65–0.88	<0.001
Geographic region			
Northern (reference group)	1.00		
Central	1.15	1.02–1.30	0.019
Southern	1.02	0.91–1.14	0.781
Eastern	1.35	1.06–1.73	0.016
Urbanization level			
1 (reference group)	1.00		
2	1.16	1.02–1.31	0.021
3	1.05	0.91–1.22	0.517
4	1.07	0.92–1.25	0.380
5	1.20	0.99–1.36	0.073

HR, hazard ratio; CI, confidence interval. Hazard ratios were all derived from the stratified Cox regression model (stratified on age and sex) and adjusted for all other variables.

study, *K. pneumoniae* was the causative organism in 84.9% of post-PLA pneumonia cases, but only 11.7% of pneumonia cases in the control group. Thus, the increased risk of pneumonia observed in this study may very well stem from factors accompanying the etiologic shift to *K. pneumoniae* as the primary causative agent of PLA infections.

This study had two principal strengths. This first was our use of a population-based database which granted us the statistical power to detect differences between the study and comparison cohorts. The second was the availability of the etiology of each diagnosis of PLA and pneumonia. In contrast to most prior studies which have often lacked the etiology of pneumonia, all PLA and pneumonia cases in Taiwan are hospitalized and are required to be tested microbiologically to determine the causative agent.

This study suffered from several limitations. First, the diagnoses of the conditions analyzed in this study were sourced from an administrative database using ICD-9-CM codes. These diagnoses may be less accurate than those collected prospectively according to standardized procedures. For example, it is possible that some PLA patients developed right lower lobe atelectasis, which can be difficult to distinguish clinically from pneumonia. However, all of the pneumonia patients in this study were evaluated microbiologically and had their causative etiology documented. Furthermore, in this study we only utilized discharge diagnoses. This strongly discounts the possibility that atelectasis would have been misdiagnosed as pneumonia.

A second limitation is that some clinically relevant patient and lifestyle information, such as smoking status, alcohol consumption and dietary habits, body mass index, and the use of pharmaceuticals, all of which may have contributed to these two conditions, was not available through the administrative dataset. While 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 pneumonia may be partially explained by the residual confounding of unadjusted factors.

A final limitation is that the PLA patients sourced in this study had a mean hospital stay of 16.6 days (standard deviation 12.2 days), and hospitalization is clearly a risk factor for the development of nosocomial pneumonia. However, we performed a further analysis of our data after excluding PLA subjects whose pneumonia developed as a complication during hospitalization. We found that the HR for pneumonia during the 90-day follow-up period for patients with PLA was 2.71 (95% CI 2.17–3.40) compared to patients without PLA after adjusting for patient monthly income, geographic location, urbanization level, hypertension, diabetes, heart disease, lung disease, and acute/chronic kidney disease. Therefore, although hospitalization appears to have contributed to the associations detected in this study, since after excluding hospitalized pneumonia cases the adjusted HR remained significant, it is also very likely that PLA infection is an independent risk factor for subsequent pneumonia.

In conclusion, this is the first study to suggest an increased risk of pneumonia subsequent to an episode of PLA. Because the vast majority of post-PLA pneumonia cases are caused by *K. pneumoniae*, and because pneumonia caused by this organism has been associated with a more complicated course, our findings can help clinicians to more appropriately risk-stratify patients who present with pneumonia after PLA. Future studies will be needed to better elucidate the mechanisms by which PLA is associated with subsequent pneumonia.

Conflict of interest: All authors have no conflicts or financial interests to declare.

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