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Pyogenic Liver Abscess is Associated With Increased Risk of Acute Kidney Injury

A Nationwide Population-Based Cohort Study

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Abstract: The aim of this large population-based cohort study was to determine whether pyogenic liver abscess (PLA) is associated with the risk of acute kidney injury (AKI).

A total of 31,815 patients aged 20 years or older diagnosed with PLA for the first time during hospitalization between 2000 and 2011 were included in a PLA cohort, and 127,620 age- and sex-matched patients without PLA were included in a non-PLA cohort. The incidence and the risk of the first attack of AKI at the end of 2011 were measured. Cox proportional hazard regression models were used to analyze the risk of AKI.

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In mean follow-up periods of 4.36 and 4.94 years for the PLA and non-PLA cohorts, respectively, the overall incidence of AKI was 1.51-fold greater in the PLA cohort than in the non-PLA cohort (9.25 vs 6.11 events per 1000 person-years; 95% confidence intervals [CIs] = 1.42–1.61). After we controlled for potential confounding factors, the adjusted hazard ratio (aHR) of AKI was 1.36 (95% CIs = 1.27–1.46) for the PLA cohort compared with the non-PLA cohort. Moreover, among patients without comorbidities, the risk of AKI remained higher in the PLA cohort compared with the non-PLA cohort (aHR: 1.91, 95% CIs = 1.59–2.29).

This study suggests that PLA associates with an increased risk of AKI. Clinicians should be aware of the potential risk of AKI after diagnosis of PLA.

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Abbreviations: aHR = adjusted hazard ratio, AKI = acute kidney injury, CAD = coronary artery disease, CHF = congestive heart failure, CIs = confidence intervals, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ESRD = end-stage renal disease, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, NHIRD = National Health Insurance Research Database, PLA = pyogenic liver abscess.

INTRODUCTION

Pyogenic liver abscess (PLA) is a global public health problem and a critical infectious disease with severe morbidity and mortality.^{1,2} The overall incidence rates of PLA in Canada, Denmark, and the United States range from 1.1 to 3.6 per 100,000 population,^{2–4} and the incidence rate of PLA in Taiwan, 17.6 per 100,000 population,⁵ is higher than that in Western countries. In addition, the epidemiology has changed dramatically in recent years, with the annual increases in incidence being 5.6% and 6.4% in the United States and Taiwan, respectively. The overall mortality rates of PLA remain high, ranging from 2.5% to 19%,^{2–4,6,7} and the mortality rate in Taiwan is approximately 8.3%.⁸ Recently, PLA has been associated with an increased risk of malignancy,^{9–11} subsequent infections,^{12–15} acute pancreatitis,¹⁶ and stroke.¹⁷ However, the relationship between PLA and the risk of acute kidney injury (AKI) remains unclear.

AKI is a common clinical problem, imposing health care costs and increasing morbidity and mortality.^{18–21} According to epidemiologic reports, AKI develops in 3% to 5% of community residents per year,²² and an estimated 36% of all patients with AKI are admitted to intensive care units.^{23,24} The incidence of AKI is rising according to observational studies.^{18,22,25} The etiologies of AKI in critically ill patients are often complex and multifactorial. Among these patients, sepsis has consistently been determined to be the most common factor contributing to AKI.^{18,20,26} Only few small studies have examined AKI in

patients with PLA,^{27,28} focusing on clinical findings during short hospitalizations. The epidemiology and long-term outcome of subsequent AKI in patients with PLA remain unknown, and no large population-based study has evaluated the association between PLA and the risk of AKI.

Therefore, this large population-based cohort study investigated whether PLA is associated with a risk of AKI. We used the Taiwan National Health Insurance Research Database (NHIRD) for statistical analysis to compare the risk of AKI between patients with and those without a first hospitalization for PLA between 2000 and 2011. We hypothesized that PLA correlates with an increased risk of subsequent AKI.

MATERIALS AND METHODS

Data Source

The data for this nationwide population-based retrospective cohort study were retrieved from the NHIRD. The National Health Insurance (NHI) program was initiated by the Taiwan government in 1995 to provide comprehensive health care to all residents (<http://nhird.nhri.org.tw/en/Background.html>). The NHIRD has been released to researchers in an electronically encrypted form since 1999. The NHIRD contains medical information including records on outpatient visits, emergency department visits, hospital admission, drug prescriptions, sex, date of birth, and diagnoses coded in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). For this cohort study, we used a subset of the NHIRD containing inpatients claims files and a registry of beneficiaries.

Ethics Statement

The NHIRD ensures the encryption of patient information and only provides researchers with nameless numbers associated with required data. As a result, informed consent form of the patients is not necessary in the current study. Moreover, this study has been approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115) to exempt from requiring informed consent to access the NHIRD.

Study Patients

Patients aged 20 years or older who were diagnosed with PLA (ICD-9-CM code 572.0) during hospitalization for the first time between 2000 and 2011 were included in a PLA cohort. The initial date of discharge with a diagnosis of PLA was defined as the index date. Patients with a history of chronic kidney disease (CKD) (ICD-9-CM codes 580–589) or end-stage renal disease (ESRD) (ICD-9-CM code 585), those aged <20 years, and those with incomplete medical information, were excluded. NHI beneficiaries aged 20 years and older without PLA were randomly selected for inclusion in a comparison cohort and frequency matched with the patients in the PLA cohort at a 4:1 ratio according to age (in 5-year bands), sex, and year of the index date, and the same exclusion criteria were applied. The study cohorts comprised 31,815 PLA cases and 127,620 non-PLA controls. All patients were followed from the index date to the occurrence of AKI (ICD-9-CM code 584), withdrawal from the insurance program, or December 31, 2011.

Outcome Measurement

All study patients were followed up until they received their first diagnosis of PLA during hospitalization. The follow-

up period began from the index date and ended on the date of AKI diagnosis, withdrawal from the NHI program, or the end of 2011. Cumulative incidence, overall incidence, and the effects of PLA on the risk of AKI will be analyzed.

Comorbidities

We considered comorbidities as confounding factors. The baseline comorbidities were diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, and 496), congestive heart failure (CHF) (ICD-9-CM code 428), coronary artery disease (CAD) (ICD-9-CM codes 410–414), stroke (ICD-9-CM codes 30–438), alcoholism (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3, and V11.3), biliary stone (ICD-9-CM code 574), hepatobiliary malignancy (ICD-9-CM codes 155–156), and cirrhosis (ICD-9-CM code 571).

Statistical Analysis

Differences in demographic characteristics, namely age group, sex, and comorbidities, between patients with and those without PLA were examined using the χ^2 test, and differences in the mean age and mean follow-up period were computed using the Student *t* test. We used the Kaplan-Meier method to plot AKI cumulative incidence curves for the PLA and non-PLA cohorts. The overall and age-, sex-, comorbidity-, and follow-up time-specific incidence densities of AKI (per 1000 person-years) were estimated. Univariate and multivariate Cox proportional hazard regression models were used for estimating hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the effects of PLA on the risk of AKI and mortality from AKI between patients with and without PLA. The multivariate models were simultaneously adjusted for age, sex, and comorbidities, namely hypertension, hyperlipidemia, COPD, CHF, stroke, alcoholism, biliary stone, hepatobiliary malignancy, and cirrhosis. SAS 9.2 software (SAS Institute, Cary, NC) was used for data management and statistical analysis. A 2-sided *P* value <0.05 indicated statistical significance.

RESULTS

Baseline Characteristics of the Study Population

We identified 31,815 PLA patients and 127,620-matched non-PLA controls with similar age and sex distributions (Table 1). The mean (\pm standard deviation) ages of the PLA and non-PLA cohorts were 60.3 (\pm 14.8) and 60.0 (\pm 15.0) years, respectively, with 40.0% of the patients being aged \geq 65 years. Men were outnumbered by women (62.5% vs 37.5%). The mean follow-up periods were 4.36 \pm 3.40 years for the PLA cohort and 4.94 \pm 3.31 years for the non-PLA cohort. The principal diseases in non-PLA patients included diabetes (39.5%), hypertension (25.1%), CAD (10.0%), stroke (9.95%), hyperlipidemia (7.71%), cirrhosis (6.73%), whereas the principal diseases in PLA patients included diabetes (39.5%), hypertension (29.9%), biliary stone (22.9%), cirrhosis (16.9%), and CAD (9.84%). The proportions of all comorbidities except diabetes and CAD were higher in the patients with PLA than in those in the non-PLA cohort (all *P* < 0.001).

Incidence and Risk of AKI in the PLA Cohorts

The cumulative incidence of AKI in the PLA cohort was higher than that in the non-PLA cohort by 4.10% (both log-rank, *P* < 0.001) at the end of follow-up (during hospitalization

TABLE 1. Demographic Characteristics and Comorbidities in PLA and Non-PLA Cohorts

Variable	Pyogenic Liver Abscess		P
	No N = 127,260	Yes N = 31,815	
Age, y			0.99
≤49	31,484 (24.7)	7871 (24.7)	
50–64	44,868 (35.3)	11,217 (35.3)	
≥65	50,908 (40.0)	12,727 (40.0)	
Mean±SD [†]	60.0 (15.0)	60.3 (14.8)	0.01
Sex			0.99
Female	47,688 (37.5)	11,922 (37.5)	
Male	79,572 (62.5)	19,893 (62.5)	
Comorbidity			
Diabetes	50,320 (39.5)	12,580 (39.5)	0.99
Hypertension	31,990 (25.1)	9514 (29.9)	<0.001
Hyperlipidemia	9815 (7.71)	2189 (6.88)	<0.001
COPD	6387 (5.02)	2089 (6.57)	<0.001
CHF	3798 (2.98)	1117 (3.51)	<0.001
CAD	12,769 (10.0)	3130 (9.84)	0.30
Stroke	12,662 (9.95)	2834 (8.91)	<0.001
Alcoholism	1183 (0.93)	553 (1.74)	<0.001
Biliary stone	4918 (3.86)	7276 (22.9)	<0.001
Hepatobiliary malignancy	710 (0.56)	2094 (6.58)	<0.001
Cirrhosis	8559 (6.73)	5375 (16.9)	<0.001

CAD=coronary artery disease, CHF=congestive heart failure, COPD=chronic obstructive pulmonary disease, PLA=pyogenic liver abscess.

[†]χ² test: t test.

between 2000 and 2011), as shown in Figure 1. Overall, the incidence rates of AKI in the PLA and non-PLA cohorts were 9.25 and 6.11 per 1000 person-years, respectively (Table 2). After adjustment for age, sex, and comorbidities, the overall risk of AKI in patients with PLA was higher than that in the non-PLA cohort (adjusted HR [aHR] = 1.36, 95% CI = 1.27–1.46). The incidence of AKI increased with age. Compared with patients aged ≤49 years, the risk of AKI development was 1.65-fold higher in those aged 50 to 64 years (95% CIs = 1.49–1.83) and 3.90-fold higher in those aged 65 years and older (95% CIs = 3.55–4.30). In addition, patients with diabetes, hypertension, COPD, CHF, stroke, alcoholism, hepatobiliary malignancy, and cirrhosis had a higher risk of AKI than that of patients without comorbidities.

The overall incidence and risk of AKI were compared between the PLA and non-PLA cohorts stratified using multivariate Cox model according to several variables, namely age, sex, comorbidity status, and follow-up period (Table 3). We found that patients with PLA have higher risk of AKI compared with those without PLA. The risk decreased over time, but persisted throughout the follow-up period. The risk of AKI in all patients with PLA, except those with a follow-up period >5 years, was higher than that of the non-PLA cohort. The risk was the highest during the first year of follow-up (aHR = 2.32, 95% CIs = 2.04–2.65). Moreover, among patients without comorbidities, the risk of AKI remained higher in the PLA cohort compared with the non-PLA cohort (aHR = 1.91, 95% CIs = 1.59–2.29). As for the mortality, AKI patients with PLA

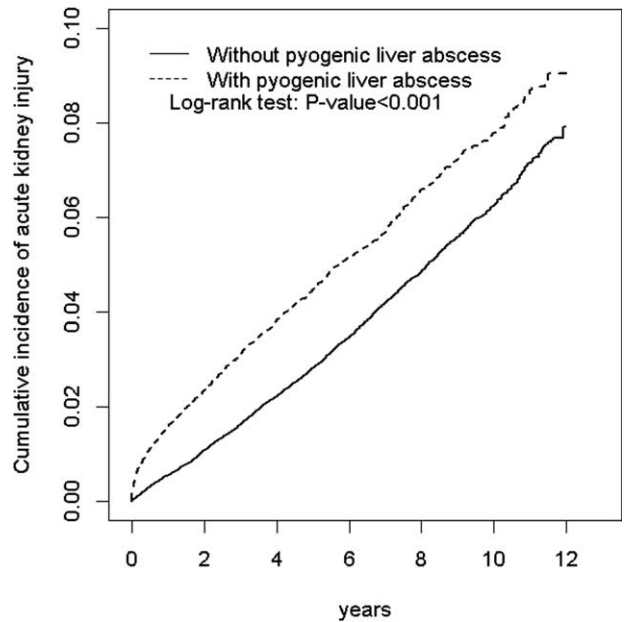


FIGURE 1. Comparison of the cumulative incidence of AKI between patients with (dashed line) and those without (solid line) PLA. AKI = acute kidney injury, PLA = pyogenic liver abscess.

were not significantly higher mortality risk compared with those without PLA (aHR = 1.07, 95% CIs = 0.98–1.18) (Supplemental Table 1, <http://links.lww.com/MD/A653>).

DISCUSSION

The results of this nationwide population-based retrospective cohort study suggest that hospitalized patients diagnosed with PLA have a higher risk of AKI than those without PLA. The overall incidence of AKI was 1.51-fold greater in the PLA cohort than in the non-PLA cohort (Table 2). Moreover, among patients without comorbidities, the risk of AKI remained higher in the PLA cohort compared with the non-PLA cohort (aHR = 1.91, 95% CIs = 1.59–2.29). In particular, the incidence of AKI increased with age, and the risk of AKI in the patients with PLA was the highest during the first year of follow-up (Table 3) and remained substantially higher than that of the patients without PLA during a mean follow-up period of 4 years. These results indicate that PLA is associated with an increased risk of AKI in hospitalized patients.

The mechanism of AKI development in patients with PLA remains unclear. PLA can cause severe infection or sepsis, an established risk factor for the development of AKI. The incidence of AKI increased significantly from sepsis (24%), severe sepsis (39%), to septic shock (89%),²⁹ suggesting that hemodynamic shock with a reduction of renal blood flow is the major risk factor for AKI during hospitalization. Therefore, hemodynamic alterations that result in ischemia reperfusion injury are considered a major cause of AKI in patients with PLA. Moreover, sepsis-induced AKI can also occur in the context of normal or even increased renal blood flow.^{30,31} Meanwhile, recent studies have determined that the pathogenesis of sepsis-induced AKI can involve inflammation, the immune response, intraglomerular hemodynamics, and perturbation of microvascular flow at both peritubular and glomerular levels in the

TABLE 2. Incidence Rates and Hazard Ratios of AKI and AKI-Associated Risk Factors

Variable	Event	PY	Rate [#]	Crude HR (95% CIs)	Adjusted HR ^{&} (95% CIs)
Pyogenic liver abscess					
No	3841	628,241	6.11	1.00	1.00
Yes	1282	138,603	9.25	1.51 (1.42, 1.61) ^{***}	1.36 (1.27, 1.46) ^{***}
Age, y					
≤49	538	218,024	2.47	1.00	1.00
50–64	1366	280,077	4.88	2.00 (1.81, 2.21) ^{***}	1.65 (1.49, 1.83) ^{***}
≥65	3219	268,744	12.0	4.96 (4.52, 5.43) ^{***}	3.90 (3.55, 4.30) ^{***}
Sex					
Female	1939	291,266	6.66	1.00	1.00
Male	3184	475,579	6.70	1.01 (0.95, 1.06)	–
Comorbidity					
Diabetes					
No	1936	483,781	4.00	1.00	1.00
Yes	3187	283,064	11.3	2.83 (2.68, 3.00) ^{***}	2.19 (2.06, 2.33) ^{***}
Hypertension					
No	2900	602,433	4.81	1.00	1.00
Yes	2223	164,412	13.5	2.85 (2.70, 3.01) ^{***}	1.31 (1.23, 1.40) ^{***}
Hyperlipidemia					
No	4577	715,384	6.40	1.00	1.00
Yes	546	51,461	10.6	1.67 (1.52, 1.82) ^{***}	0.97 (0.89, 1.07)
COPD					
No	4596	735,391	6.25	1.00	1.00
Yes	527	31,454	16.8	2.69 (2.46, 2.95) ^{***}	1.29 (1.17, 1.42) ^{***}
CHF					
No	4731	750,514	6.30	1.00	1.00
Yes	392	16,330	24.0	3.84 (3.46, 4.26) ^{***}	1.81 (1.62, 2.01) ^{***}
Stroke					
No	4154	706,679	5.88	1.00	1.00
Yes	969	60,165	16.1	2.77 (2.58, 2.97) ^{***}	1.38 (1.28, 1.49) ^{***}
Alcoholism					
No	5028	760,084	6.62	1.00	1.00
Yes	95	6761	14.1	2.14 (1.75, 2.62) ^{***}	2.15 (1.74, 2.65) ^{***}
Biliary stone					
No	4533	716,665	6.33	1.00	1.00
Yes	590	50,179	11.8	1.86 (1.71, 2.03) ^{***}	1.09 (1.00, 1.20)
Hepatobiliary malignancy					
No	4922	762,031	6.46	1.00	1.00
Yes	201	4813	41.8	6.35 (5.51, 7.32) ^{***}	3.81 (3.27, 4.43) ^{***}
Cirrhosis					
No	4301	709,174	6.06	1.00	1.00
Yes	822	57,670	14.3	2.35 (2.18, 2.53) ^{***}	1.49 (1.37, 1.61) ^{***}

AKI = acute kidney injury, CI = confidence intervals, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = person-years. *** $P < 0.001$.

[#] Rate: incidence rate, per 1000 person-years. Crude HR: relative hazard ratio.

[&] Adjusted HR: multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, CHF, stroke, alcoholism, biliary stone, hepatobiliary malignancy, and cirrhosis.

absence of hypoperfusion and ischemia.^{32,33} These studies have demonstrated that sepsis may affect kidney cells by the generation of inflammatory mediators, such as cytokines. Finally, 73% to 87.9% of all PLA patients were infected by *Klebsiella pneumoniae* alone in Taiwan,^{12,34} and PLA patients infected with *K. pneumoniae* were more prone to experiencing extrahepatic complications and metastasis than those with other types of PLA.^{12,35} PLA-associated extrahepatic metastasis could exacerbate kidney injury caused by sepsis.

In this cohort study, the incidence of AKI in the PLA cohort was approximately 1.51-fold greater than that in the non-PLA cohort (9.25 vs 6.11 events per 1000 person-years; 95% CIs = 1.42–1.61). Although several large studies have reported incidence rates of AKI ranging from 11% to 51% in patients with sepsis,^{20,29,36,37} only few small population studies have reported AKI incidence rates of 32.6% (15/46) and 33.9% (137/404) in patients with PLA.^{27,28} Yun et al²⁸ reported that patients in a PLA group with underlying CKD had a high incidence of

TABLE 3. Incidence of AKI by Age, Sex, Comorbidity, and Follow-Up Period and Hazard Ratios for Patients With PLA Compared With Those Without PLA Estimated Using a Cox Model

Variables	Pyogenic Liver Abscess						Crude HR 95% CI	Adjusted HR ^{&} (95% CI)
	No		Yes		Rate [#]	Event		
	Event	PY	Event	PY			Rate [#]	
Age, y								
≤ 49	370	176,475	2.10	168	41,549	4.04	1.93 (1.61, 2.31) ^{***}	1.73 (1.43, 2.09) ^{***}
50–64	1003	229,248	4.38	363	50,828	7.14	1.63 (1.45, 1.84) ^{***}	1.41 (1.25, 1.60) ^{***}
≥65	2468	222,518	11.1	751	46,226	16.3	1.46 (1.35, 1.59) ^{***}	1.27 (1.16, 1.39) ^{***}
Sex								
Female	1458	238,680	6.11	481	52,586	9.15	1.50 (1.35, 1.66) ^{***}	1.34 (1.20, 1.50) ^{***}
Male	2383	389,561	6.12	801	86,017	9.31	1.52 (1.40, 1.64) ^{***}	1.37 (1.26, 1.50) ^{***}
Comorbidity								
No	822	345,775	2.38	137	40,678	3.37	1.42 (1.19, 1.70) ^{***}	1.91 (1.59, 2.29) ^{***}
Yes	3019	282,467	10.7	1145	97,925	11.7	1.09 (1.02, 1.17) [*]	1.13 (1.06, 1.21) ^{***}
Follow-up period, y								
≤1	659	119,088	5.53	458	27,822	16.5	2.95 (2.62, 3.32) ^{***}	2.32 (2.04, 2.65) ^{***}
2–4	1505	268,872	5.690	458	59,305	7.72	1.38 (1.24, 1.53) ^{***}	1.28 (1.14, 1.43) ^{***}
≥5	1677	240,282	6.98	366	51,476	7.11	1.02 (0.91, 1.14)	1.00 (0.89, 1.13)

AKI = acute kidney injury, CI = confidence intervals, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PLA = pyogenic liver abscess, PY = person-years. ^{*}*P* < 0.05; ^{***}*P* < 0.001.

[#]Rate: incidence rate, per 1000 person-years. Crude HR: relative hazard ratio

[&]Adjusted HR: multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, CHF, and stroke, alcoholism, biliary stone, hepatobiliary malignancy, and cirrhosis

AKI (11/20) and a significantly higher progression rate during the average admission period of 20.7 days (±12.8). Moreover, Sriramnaveen et al²⁷ reported that 26.6% of patients with PLA received hemodialysis. However, our study excluded patients with history of CKD or ESRD; therefore, the overall incidence of AKI was lower. Nevertheless, the increased risk of AKI persisted for 4 years, enabling clinicians to notice the risk of AKI after diagnosing PLA.

AKI is consistently associated with several comorbidities of PLA. The HR increased to 3.81 in patients with hepatobiliary malignancy, 2.19 in patients with diabetes, 2.15 in patients with alcoholism, 1.81 in patients with CHF, 1.49 in patients with cirrhosis, 1.38 in patients with stroke, 1.31 in patients with hypertension, and 1.29 in patients with COPD, implying that these comorbidities increase the risk of AKI in patients with PLA (Table 2). Hepatobiliary malignancy, diabetes, and alcoholism are the comorbidities most strongly associated with AKI development. Clinicians should treat these comorbidities to potentially reduce the risk and severity of AKI. To further clarify the association between PLA with/without comorbidities and the risk of AKI, we used multivariate model stratified by age, sex, and comorbidities (Table 3). Among patients without comorbidities, we found an approximately 1.91-fold AKI risk was observed in PLA patients compared with patients without PLA. These results illustrate that PLA is uniquely associated with an increased risk of AKI in hospitalized patients independent of these comorbidities.

The NHI is a mandatory health insurance in Taiwan, and all Taiwan residents have access to medical care with characteristics of low co-payments. Therefore, the NHIRD is a reliable and effective database to provide population-based studies with sex- and age-matched groups. Patients who were coded with

AKI and PLA by ICD-9 codes should meet the standard clinical diagnostic criteria consisting of typical clinical symptoms and signs, laboratory data, and radiologic findings. The codings were made by the medical specialists for insurance claims, which were managed by the Bureau of NHI for medical reimbursement purposes. Moreover, several published studies in high-quality journals have proved the accuracy of the diagnosis codes used in this study.^{10,38,39} Therefore, the diagnoses of AKI and PLA are reliable.

Several limitations remain in this study. First, we cannot obtain detailed clinical information regarding clinical presentation or causal pathogens that can enable exploring whether pathogens influence the risk of AKI from the NHIRD. Meanwhile, the NHIRD does not provide laboratory data, such as blood urea nitrogen, creatinine level, and radiologic findings for single or multiple PLA. Second, we have excluded PLA patients with a history of CKD or ESRD in the present study; therefore, the incidence rate of AKI was provided only for patients without any history of CKD or ESRD. Third, clinical information regarding disease course and treatment strategies of AKI, and antibiotics treatment between PLA and non-PLA groups was not obtained. Some kinds of antibiotics may be nephrotoxic and could cause AKI when circulating blood volume is insufficient, which could be a potential confounding factor in this study. Finally, a key limitation of this study was the potential bias resulting from possible unknown confounders in a retrospective observation study although we have made the conscientious study design.

In conclusion, an advantage of this study was the use of a longitudinal nationwide population-based cohort analysis of the risk of AKI among Asian patients with PLA. We demonstrated for the first time that PLA is associated with an increased risk of

subsequent AKI. Comorbidities including diabetes, hypertension, COPD, CHF, stroke, alcoholism, hepatobiliary malignancy, and cirrhosis may increase the risk of AKI. Clinicians should consider the potential risk of AKI after diagnosis of PLA, particularly during the first year.

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