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Risk of *Pneumocystis jirovecii* Pneumonia in Patients With HIV in Taiwan: Evidence from a Cross-sectional Study

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Abstract

Background/Aim: Studies have demonstrated that patients with HIV are at a higher risk of *Pneumocystis jirovecii* pneumonia (PJP). Epidemiological knowledge of the risk of PJP among patients with HIV infection is lacking. This study aimed to assess the risk of PJP among patients with HIV.

Patients and Methods: This cross-sectional study was conducted using the National Health Insurance Research Database of Taiwan. The participants were 18,929 patients with new-onset HIV infection from 2002 to 2015. Each patient was matched with four HIV-negative patients for age, sex, insured salary, urbanization status, Charlson Comorbidity Index score, and year of enrollment. The logistic regression with adjustment for relevant variables was performed to analyze the risk of PJP among patients with HIV at the 3-year follow-up. Sensitivity analysis was performed to compare the risk of PJP among different cohorts (patients with chronic kidney disease) and at different follow-up periods (6-month, 1-year, and 2-year follow-up).

Results: Patients with HIV had a higher risk of PJP [adjusted odds ratio (aOR)=199.36; 95% confidence interval (CI)=119.47-332.66] than HIV-negative individuals at the 3-year follow-up. Male patients had a higher risk of PJP

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(aOR=1.62; 95%CI=1.18-2.24) than female patients. Patients with chronic obstructive pulmonary disease (COPD) had a higher risk of PJP (aOR=1.74; 95%CI=1.27-2.39) at the 3-year follow-up.
Conclusion: Patients with HIV had a higher risk of PJP. Male patients had a higher risk of PJP than female patients. The risk of PJP was higher among patients with COPD.

Keywords: *Pneumocystis jirovecii* pneumonia, human immunodeficiency virus, infections, real-world data.

Introduction

The risk of infectious pulmonary complications is higher in patients with human immunodeficiency virus (HIV) (1) because of their immunocompromised state. Immunocompromised individuals are more likely to develop infectious disease, be reinfected, or experience the reactivation of a latent infection (2). Patients with HIV are also susceptible to opportunistic infections, which remain a major cause of morbidity and mortality (3).

Pneumocystis jirovecii pneumonia (PJP) is a significant health concern in patients with HIV. PJP is a severe lung infection caused by the fungus *P. jirovecii* (PJ) (4). It is a potentially life-threatening and opportunistic infection in immunocompromised individuals, particularly patients with HIV (5). Because of the combined use of antiretroviral therapy and routine prophylaxis for PJP, the incidence of PJP has declined among patients with HIV (6). However, PJP continues to be the most common opportunistic infection among patients with acquired immunodeficiency syndrome (AIDS) in many countries (6).

Patients with HIV have a higher risk of PJP than the healthy population. PJP is a cause of morbidity and mortality in patients with HIV; this is a clinical problem that should be addressed. Little is known about the risk of PJP among patients with HIV; therefore, epidemiological studies should assess this risk, especially by using a nationwide database. This study assessed the risk of PJP following HIV infection by using the National Health Insurance Research Database (NHIRD) of Taiwan.

Patients and Methods

Data sources. This study performed secondary data analysis on NHIRD data from 2001 to 2018. The NHIRD data are published by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Taiwan. It includes beneficiaries enrolled in Taiwan's National Health Insurance (NHI) program, NHI enrollment files, and medical service data (diagnoses, prescriptions, and examinations). The NHI program is a compulsory single-payer health care system providing comprehensive health care for >99% of the residents of Taiwan. The diagnoses were coded using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) for data from before 2016 and the Tenth Revision (*ICD-10-CM*) for data from after 2016. The NHIRD is commonly employed for real-world data collection to inform clinical decision-making and health-care policy development (7, 8).

Ethics statement. This study was conducted in accordance with the Declaration of Helsinki. Data used in the analysis were released by the Health and Welfare Data Science Center (HWDC) using scrambled random identification numbers for insured patients to protect the privacy of beneficiaries. The data were anonymous, and the HWDC deidentified insured patients to protect their privacy. The requirement for informed consent was waived. The study was approved as a completely ethical review by the Institutional Review Board of Chung Shan Medical University Hospital, Taiwan (No. CS2-20013).

Study participants. Patients with new-onset HIV (ICD-9-CM 042-044) between 2002 and 2015 were enrolled. Patients

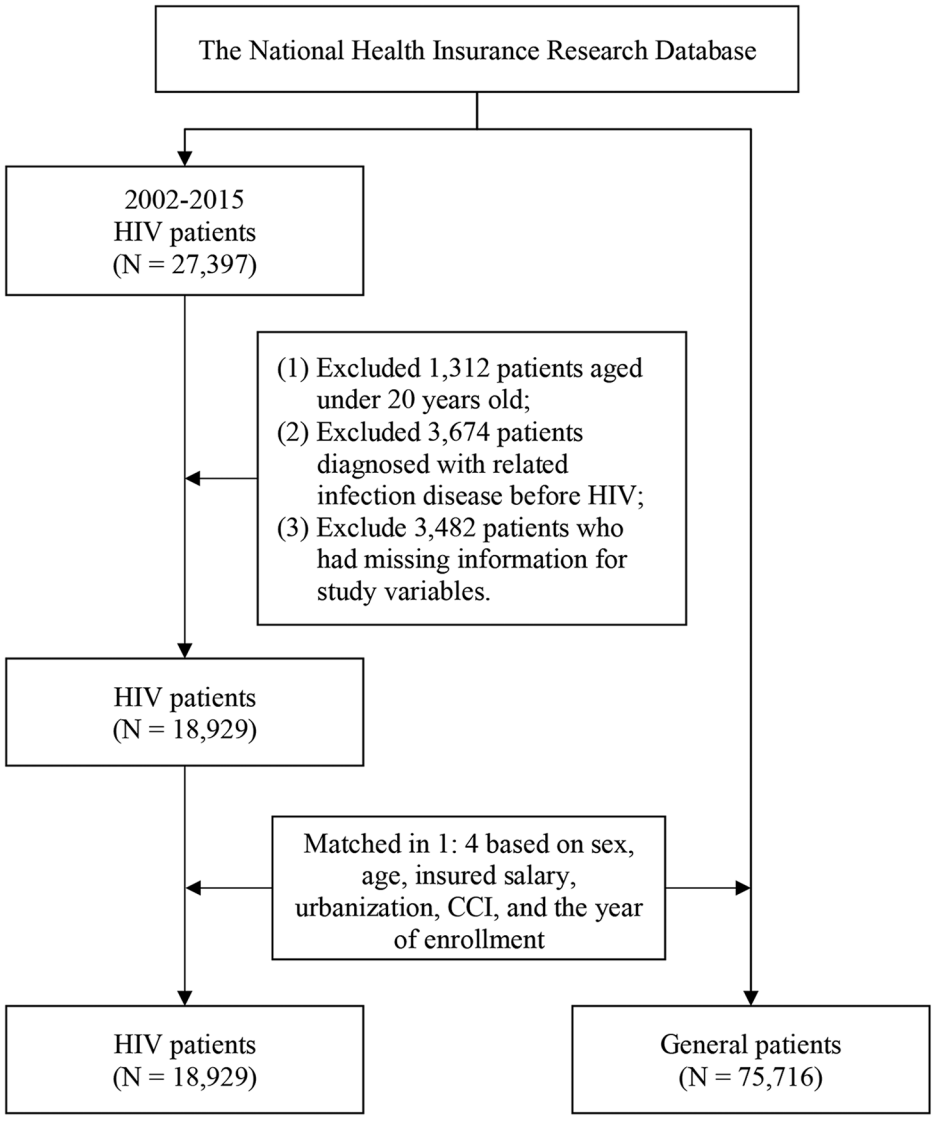

Figure 1. *Flowchart of the study subject selection process.*

who were aged under 20 years, were diagnosed as having any related infectious disease before HIV infection (PJP, cytomegalovirus disease, or herpes simplex virus infection), and had missing information regarding the study variables were excluded. Propensity score matching (PSM) was used to obtain 1:4 matches for each patient. PSM is a statistical matching technique used to prevent confounding caused by unbalanced covariates in nonexperimental settings. The PS is the probability calculated using the logistic regression model. This score is a unit assigned to patients with HIV. The scores can be used to reduce or eliminate selection bias in observational studies by considering the characteristics of patients with and without HIV. The characteristics selected for matching in this study were sex, age, insured salary, urbanization status, Charlson Comorbidity Index (CCI) score, and year of enrollment in the study. A total of 94,645 participants were included from 2002 to 2015; 18,929 were patients with HIV, and 75,716 were from the

Table I. *The baseline characteristics of study subjects.*

	Total		General patients		HIV patients		*p*-Value
Variables	N	%	N	%	N	%	
Total	94,645	100.00	75,716	80.00	18,929	20.00	
Sex[1]							0.929
Female	8,914	9.42	7,128	9.41	1,786	9.44	
Male	85,731	90.58	68,588	90.59	17,143	90.56	
Age (year)[1]							1.000
≤24	19,127	20.21	15,293	20.20	3,834	20.25	
25-29	22,980	24.28	18,384	24.28	4,596	24.28	
30-34	18,762	19.82	15,008	19.82	3,754	19.83	
35-39	12,483	13.19	9,988	13.19	2,495	13.18	
≥40	21,293	22.50	17,043	22.51	4,250	22.45	
Mean±SD	33.72±14.85		33.84±15.72		33.24±10.63		
Insured salary (NTD)[1]							0.973
≤19,200	50,504	53.36	40,389	53.34	10,115	53.44	
19,201-26,400	21,374	22.58	17,107	22.59	4,267	22.54	
≥26,401	22,767	24.06	18,220	24.06	4,547	24.02	
Urbanization[1]							0.999
Level 1	30,840	32.58	24,668	32.58	6,172	32.61	
Level 2	28,437	30.05	22,741	30.03	5,696	30.09	
Level 3	16,451	17.38	13,160	17.38	3,291	17.39	
Level 4	11,330	11.97	9,064	11.97	2,266	11.97	
Level 5	1,716	1.81	1,383	1.83	333	1.76	
Level 6	2,865	3.03	2,292	3.03	573	3.03	
Level 7	3,006	3.18	2,408	3.18	598	3.16	
CCI score[1]							0.920
0	65,297	68.99	52,236	68.99	13,061	69.00	
1	17,957	18.97	14,353	18.96	3,604	19.04	
≥2	11,391	12.04	9,127	12.05	2,264	11.96	
Enrolled year[1]							
2002	5,295	5.59	4,236	5.59	1,059	5.59	
2003	4,315	4.56	3,452	4.56	863	4.56	
2004	5,355	5.66	4,284	5.66	1,071	5.66	
2005	6,325	6.68	5,060	6.68	1,265	6.68	
2006	12,965	13.70	10,372	13.70	2,593	13.70	
2007	8,490	8.97	6,792	8.97	1,698	8.97	
2008	6,340	6.70	5,072	6.70	1,268	6.70	
2009	5,685	6.01	4,548	6.01	1,137	6.01	
2010	6,010	6.35	4,808	6.35	1,202	6.35	
2011	6,445	6.81	5,156	6.81	1,289	6.81	
2012	6,430	6.79	5,144	6.79	1,286	6.79	
2013	6,900	7.29	5,520	7.29	1,380	7.29	
2014	6,780	7.16	5,424	7.16	1,356	7.16	
2015	7,310	7.72	5,848	7.72	1,462	7.72	
Comorbidities							
HTN							<0.001
No	87,907	92.88	69,771	92.15	18,136	95.81	
Yes	6,738	7.12	5,945	7.85	793	4.19	
DM							<0.001
No	90,909	96.05	72,450	95.69	18,459	97.52	
Yes	3,736	3.95	3,266	4.31	470	2.48	
HPL							<0.001
No	90,595	95.72	72,064	95.18	18,531	97.90	
Yes	4,050	4.28	3,652	4.82	398	2.10	

Table I. *Continued*

Table I. *Continued*

Variables	Total		General patients		HIV patients		*p*-Value
	N	%	N	%	N	%	
Hepatitis B							0.005
No	93,318	98.60	74,695	98.65	18,623	98.38	
Yes	1,327	1.40	1,021	1.35	306	1.62	
Hepatitis C							<0.001
No	94,077	99.40	75,431	99.62	18,646	98.50	
Yes	568	0.60	285	0.38	283	1.50	
IBD							<0.001
No	94,313	99.65	75,522	99.74	18,791	99.27	
Yes	332	0.35	194	0.26	138	0.73	
CKD							0.943
No	94,208	99.54	75,367	99.54	18,841	99.54	
Yes	437	0.46	349	0.46	88	0.46	
COPD							0.002
No	92,249	97.47	73,859	97.55	18,390	97.15	
Yes	2,396	2.53	1,857	2.45	539	2.85	
Hematological malignancies							<0.001
No	94,482	99.83	75,615	99.87	18,867	99.67	
Yes	163	0.17	101	0.13	62	0.33	
TMP-SMX use							<0.001
No	93,613	98.91	74,982	99.03	18,631	98.43	
Yes	1,032	1.09	734	0.97	298	1.57	

[1]Variables for propensity score matching. HIV: Human immunodeficiency virus; CCI: Charlson comorbidity index; HTN: hypertension; DM: diabetes mellitus; HPL: hyperlipidemia; IBD: inflammatory bowel disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; TMP-SMX: trimethoprim–sulfamethoxazole.

general population (HIV negative). The participant selection process is presented in Figure 1.

Study design. A 3-year follow-up period was used to assess the risk of PJP among patients with HIV. PJP was defined as *ICD-9-CM* code 136.3 or *ICD-10-CM* code B59. The control variables were sex, age, insured salary, urbanization status, CCI score, comorbidities, and trimethoprimsulfamethoxazole (TMP-SMX) medication use. Comorbidities were identified using outpatient department visits and hospital admission records for the 2 years before enrollment in the study. The comorbidities were hypertension (HTN) (*ICD-9-CM* 401-405), diabetes mellitus (DM; *ICD-9-CM* 250), hyperlipidemia (*ICD-9-CM* 272.0-272.4), hepatitis B (*ICD-9-CM* 070.2-070.3), hepatitis C (*ICD-9-CM* 070.70, 070.4-070.5), inflammatory bowel disease (IBD; *ICD-9-CM* 555-556), chronic kidney disease (CKD; *ICD-9-CM* 585), chronic obstructive pulmonary disease (COPD; *ICD-9-CM* 490-492, 494-496), and hematological malignancies (*ICD-9-CM* 200-209). TMP-SMX medication use was defined using the Anatomical Therapeutic Chemical (ATC) code J01EE01.

Statistical analyses. Statistical analysis was conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). The chi-squared test was used to evaluate the distribution of baseline characteristics among the participants. The risk of PJP among patients with HIV was assessed using multiple logistic regression analysis with adjustment for relevant variables. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Sensitivity analysis was performed to assess the risk of PJP among patients with HIV at different follow-up periods (6-month, 1-year, and 2-years).

Table II. *The risk of incident Pneumocystis jirovecii pneumonia among HIV patients in the 3-year follow-up.*

Variables	*Pneumocystis jirovecii* pneumonia							
	No		Yes		*p*-Value	Adjusted model		
	N	%	N	%		OR	95%CI	*p*-Value
Total	93,892	99.20	753	0.80				
Patients					<0.001			
General patients	75,701	99.98	15	0.02		1		
HIV patients	18,191	96.10	738	3.90		199.36	119.47-332.66	<0.001
Sex					<0.001			
Female	8,884	99.66	30	0.34		1		
Male	85,008	99.16	723	0.84		2.85	1.96-4.14	<0.001
Age (year)					<0.001			
≤24	19,022	99.45	105	0.55		1		
25-29	22,796	99.20	184	0.80		1.48	1.16-1.89	0.002
30-34	18,601	99.14	161	0.86		1.56	1.21-2.02	<0.001
35-39	12,375	99.13	108	0.87		1.50	1.14-1.98	0.004
≥40	21,098	99.08	195	0.92		1.33	1.03-1.73	0.031
Mean±SD	33.71±14.88		34.54±10.63					
Insured salary (NTD)					0.474			
≤19,200	50,111	99.22	393	0.78		1		
19,201-26,400	21,190	99.14	184	0.86		1.13	0.94-1.36	0.179
≥26,401	22,591	99.23	176	0.77		0.91	0.75-1.10	0.316
Urbanization					0.527			
Level 1	30,584	99.17	256	0.83		1		
Level 2	28,228	99.27	209	0.73		0.89	0.74-1.08	0.230
Level 3	16,314	99.17	137	0.83		1.03	0.83-1.28	0.764
Level 4	11,240	99.21	90	0.79		0.93	0.73-1.20	0.587
Level 5	1702	99.18	14	0.82		0.88	0.50-1.54	0.653
Level 6	2,848	99.41	17	0.59		0.71	0.43-1.18	0.184
Level 7	2,976	99.00	30	1.00		1.26	0.85-1.86	0.261
CCI score					<0.001			
0	64,888	99.37	409	0.63		1		
1	17,783	99.03	174	0.97		1.53	1.27-1.85	<0.001
≥2	11,221	98.51	170	1.49		2.49	2.01-3.10	<0.001
Comorbidities								
HTN					0.005			
No	87,188	99.18	719	0.82		1		
Yes	6,704	99.50	34	0.50		0.72	0.49-1.07	0.106
DM					0.484			
No	90,182	99.20	727	0.80		1		
Yes	3,710	99.30	26	0.70		0.84	0.54-1.33	0.462
HPL					0.017			
No	89,861	99.19	734	0.81		1		
Yes	4,031	99.53	19	0.47		0.94	0.56-1.56	0.804
Hepatitis B					0.447			
No	92,578	99.21	740	0.79		1		
Yes	1,314	99.02	13	0.98		0.72	0.41-1.28	0.265
Hepatitis C					0.009			
No	93,334	99.21	743	0.79		1		
Yes	558	98.24	10	1.76		0.65	0.34-1.25	0.196
IBD					<0.001			
No	93,568	99.21	745	0.79		1		
Yes	324	97.59	8	2.41		1.29	0.63-2.67	0.487

Table II. *Continued*

Table II. *Continued*

Variables	*Pneumocystis jirovecii* pneumonia							
	No		Yes		*p*-Value	Adjusted model		
	N	%	N	%		OR	95%CI	*p*-Value
CKD					0.797			
No	93,458	99.20	750	0.80		1		
Yes	434	99.31	3	0.69		0.61	0.19-1.99	0.410
COPD					<0.001			
No	91,548	99.24	701	0.76		1		
Yes	2,344	97.83	52	2.17		1.62	1.18-2.24	0.003
Hematological malignancies					0.017			
No	93,733	99.21	749	0.79		1		
Yes	159	97.55	4	2.45		0.77	0.27-2.17	0.618
TMP-SMX use					<0.001			
No	92,905	99.24	708	0.76		1		
Yes	987	95.64	45	4.36		3.75	2.65-5.31	<0.001

HIV: Human immunodeficiency virus; CCI: Charlson comorbidity index; HTN: hypertension; DM: diabetes mellitus; HPL: hyperlipidemia; IBD: inflammatory bowel disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval; TMP-SMX: trimethoprim–sulfamethoxazole.

Furthermore, we also compared with patients with CKD to assess the risk of PJP among different patients. Statistical significance was defined as $p<0.05$.

Results

Table I presents the baseline characteristics of the participants. Only 9.42% of the participants were women. The participants' average age was 33.72±14.85 years. The average age of the patients with HIV was 33.24±10.63 years, and that of the HIV-negative participants was 33.84±15.72 years. The matched variables (sex, age, insured salary, urbanization status, and CCI score) were similar between groups ($p>0.05$). Of the patients with HIV, 4.19% had HTN, 2.48% had DM, 2.85% had COPD, and 1.57% had received TMP-SMX medication ($p<0.001$).

The average age of the patients with PJP was 34.54±10.63 years (Table II). A total of 738 patients with HIV (3.90%) developed PJP ($p<0.001$). The incidence of PJP was higher among patients with hepatitis C, IBD, COPD, and hematological malignancies than among those without comorbidities ($p<0.001$). The incidence of PJP was higher among patients receiving TMP-SMX medication ($p<0.001$). After adjustment for control variables, the incidence of PJP was higher among patients with HIV than among HIV-negative individuals at the 3-year follow-up (aOR=199.36; 95%CI=119.47-332.66). Male patients had a higher risk of PJP than female patients (aOR=2.85; 95%CI=1.96-4.14). In terms of comorbidities, patients with COPD had a higher risk of PJP than those without comorbidities (aOR=1.62; 95%CI=1.18-2.24). Patients receiving TMP-SMX medication also had a higher risk of PJP (aOR=3.75; 95%CI=2.65-5.31).

Table III presents the risk of PJP at each follow-up and in each cohort (patients with HIV and patients with CKD). The risk of PJP was higher among patients with HIV than among HIV-negative individuals, with the aORs being 895.32 (95%CI=223.43-3,596.95), 1,024.99 (95%CI= 255.39-4,109.87), and 362.59 (95%CI=172.10-763.90) at the 6-month, 1-year, and 2-year follow-ups, respectively. Patients with HIV had a higher risk of PJP than patients with CKD at the 6-month (aOR=259.24; 95%CI=189.46-354.70), 1-year (aOR=187.39; 95%CI=145.39-241.53), 2-year (aOR= 133.70; 95%CI=109.73-162.90), and 3-year (aOR=117.12; 95%CI=98.78-138.85) follow-ups.

Table III. *Sensitivity analysis at different follow-up periods and with different cohorts.*

	Pneumocystis jirovecii pneumonia		
Variables	Adjusted OR	95%CI	*p*-Value
Compared with general patients			
Six-months follow-up	895.32	223.43-3,596.95	<0.001
One-year follow-up	1024.99	255.39-4,109.87	<0.001
Two-year follow-up	362.59	172.10-763.90	<0.001
Compared with CKD cohort			
Six-months follow-up	259.24	189.46-354.70	<0.001
One-year follow-up	187.39	145.39-241.53	<0.001
Two-year follow-up	133.70	109.73-162.90	<0.001
Three-year follow-up	117.12	98.78-138.85	<0.001

OR: Odds ratio; CI: confidence interval.

Discussion

To the best of our knowledge, large-scale epidemiological studies have assessed the risk of PJP among patients with HIV in Taiwan. In this nationwide population-based retrospective cohort study, we discovered that patients with HIV had a higher risk of developing PJP over the 6-month, 1-year, 2-year, and 3-year study periods, with the highest risk being noted over two years. We also observed that male patients had a higher risk of PJP than female patients. In addition, patients with HIV with COPD had a higher risk of PJP than those without comorbidities. Patients with HIV had a higher risk of PJP than patients with CKD.

HIV infection, even without AIDS, predisposes patients to several infectious and noninfectious pulmonary complications (9, 10). Pneumonia is a common complication in patients with HIV (11). PJP is currently recognized as a major cause of pneumonia among patients with HIV (12). PJP is one of the most frequent AIDS-defining illnesses (2) and a life-threatening opportunistic infection in patients with HIV (13), being second only to esophageal candidiasis (14). The clinical characteristics of PJP differ considerably between patients with HIV and HIV-negative individuals (10, 15-17). HIV-negative individuals with PJP tend to have a more progressive course, higher mortality (5), and more severe clinical course (18). In most cases of PJP in patients with HIV, respiratory failure develops gradually, and bronchoalveolar lavage fluid contains a large number of microorganisms (15). In patients with HIV, the most common features of PJP are gradually progressive dyspnea, fever, nonproductive cough (19), and chest discomfort that worsens within days to weeks (20).

The immune system plays a complex role in the progression of PJ infection (21). The adhesion of PJ triggers the host immune response, which can cause severe and potentially life-threatening lung injury in immunocompromised patients. In patients with PJP, the immune response involves complex interactions between CD4+ T-cells, CD8+ T-cells, neutrophils, alveolar macrophages, and soluble mediators that can facilitate the clearance of infection (22). A low CD4 count is associated with a higher risk of opportunistic infections. Findings suggest that PJP typically manifests as an opportunistic infection in patients with HIV, especially those with a CD4+ T-cells count of fewer than 100-200 cells/μl (23). The CD4+ T-cells count decreases in patients with HIV, resulting in the inability of the host to eradicate PJ and thereby contributing to inflammatory lung damage (4).

We observed that patients with HIV had a higher risk of PJP than did the general population. Patients with HIV were at a higher risk of developing PJP over the 6-month, 1-year, 2-year, and 3-year study periods, with the highest

risk being noted over 2 years (aOR=362). PJP remains a leading cause of opportunistic infections among patients with HIV, with HIV-associated PJP being reported at varying rates worldwide (23-25). PJP is also a leading cause of disease among patients with AIDS (26); it has a high prevalence among these patients (27). Several studies have reported that approximately 23%-31% of PJP cases occur in patients newly diagnosed with HIV infection at the time of PJP presentation (28-30). Patients with HIV are more prone to PJP recurrence than HIV-negative individuals. PJP is one of the most common opportunistic infections, with considerable morbidity and mortality (31), especially in patients with HIV with associated opportunistic infections (2).

These differences in clinical features of PJP may be attributable to the differences in the innate and adaptive immune responses of the host (4). The incidence of PJP has decreased with the extensive use of chemoprophylaxis and the early use of antiretroviral therapy in patients with HIV (32). However, the mortality associated with PJP remains high (23). The mortality of PJP ranges from 10% to 20% in HIV-infected adults and from 30% to 60% in HIV-negative adults (15, 16, 33).

TMP-SMX has been the standard first-line agent for the prophylaxis and treatment of PJP (34). However, drug resistance to TMP-SMX is considered an emerging concern (23). Widespread and long-term prophylaxis with TMP-SMX in patients with PJP has led to the development of sulfa drug resistance (35). However, with a decrease in susceptibility, PJ strains do not always become fully resistant to these medications (36, 37). In patients with HIV, the CD4 count in peripheral blood samples serves as a sensitive biomarker to determine the risk of pneumocystosis (2). This has led to the recommendation that treatment with TMP-SMX should be initiated in any HIV-infected patient with PJP whose peripheral CD4 count has declined below 200 cells/μl (38, 39). Primary prophylaxis may be discontinued once immune reconstitution is documented, with CD4 counts greater than 200 cells/mm^3 being noted for at least 3 months following antiretroviral therapy (40).

We discovered that patients with HIV with COPD had a higher risk of PJP (aOR=1.74). COPD is a particular concern in patients with HIV. It is more prevalent in patients with HIV than in the general population and leads to increased morbidity and mortality in patients with HIV (41). HIV infection significantly increases the prevalence of COPD (42, 43). The pathogen *Pneumocystis* has been associated with the development of HIV-associated COPD in animal and human studies (44). Persistent *Pneumocystis* colonization and acute pneumonia are associated with permanent obstructive lung damage (45). In patients with HIV, PJP can lead to permanent airway obstruction. A high prevalence of PJ colonization and emphysema has been observed in patients with HIV (46). In addition, patients with HIV with COPD exhibit a more rapidly progressive decline in pulmonary function than HIV-negative individuals (47). An increase in oxidative stress and inflammation has been proposed to be a mechanism linking HIV and COPD (44, 48).

We observed that male patients with HIV had a higher risk of PJP, which is consistent with a previous finding that the male sex is a risk factor for PJP in patients with HIV with advanced immunodeficiency. A possible reason to explain the influence of sex is the significantly greater decline in CD4 cell counts among men than among women (49).

CKD is associated with immune system impairment (50) and chronic inflammation (51), which can increase the risk of infection (52). Chronic HIV infection is associated with indefinite immune dysfunction (53). We assessed the risk of PJP between patients with HIV and patients with CKD and discovered that patients with HIV had a higher risk of PJP than patients with CKD. Patients with HIV are at an increased risk of renal diseases (54), such as CKD. CKD is a frequent complication of HIV infection, occurring in 3.5%-48.5% of patients with HIV (55). Renal function impairment in patients with CKD can lead to immune system impairment (50). Patients with CKD experience complex immune system impairment, which results in a combination of low-grade chronic inflammation and the inability to induce protective immune responses (51). Because of their impaired innate

and adaptive immune systems, patients with CKD have an increased risk of infection (52, 56, 57). Patients with HIV infection or AIDS are immunodeficient (58). Although combination antiretroviral therapy results in effective viral suppression and prevents HIV transmission, chronic HIV infection results in indefinite inflammation and immune dysfunction (53).

Our study has several strengths. Patients were selected from total population-based nationwide cohorts in Taiwan. The large sample size is thus representative of the entire population and may increase statistical precision. The combination of the NHIRD with multiple data sources could be used as a powerful search engine. The population-based design may also minimize selection bias, which is common in observational studies. Although a prospective population-based cohort study is ideal to assess the risk factors, a retrospective population-based cohort study using insurance data is a suitable alternative.

Study limitations. First, this was not a prospective randomized double-blind study. The severity of PJP analysis could not be accurately determined from the *ICD-9-CM* and *ICD-10-CM* classification codes; thus, severity-based subgroup analysis was not possible. Second, because the NHI database is a population-level data source for generating real-world evidence, it does not include clinical data or culture results. For this reason, we could not analyze certain data, such as CD4+ T-cells or CD8+ T-cells counts, in these patients; these cell counts may play a positive role in the prognosis of PJP (59, 60). Finally, claims data-based analyses were performed in this study. In the claims dataset, some data, such as personal history, clinical manifestations, laboratory test results, and imaging results, were not available. For this reason, the identification of PJP cases was based on the discharge diagnoses and not on any reports of related examinations. However, the regular quality assurance survey of the NHIRD among all medical facilities by the Bureau of National Health Insurance has considerably improved the accuracy of diagnostic codes in the NHIRD (8). Thus, bias attributable to misclassifications was minimized.

Conclusion

This study provides epidemiological data that reveals an increased risk of PJP among patients with HIV. We discovered that patients with HIV were at a higher risk of developing PJP over the 6-month, 1-year, 2-year, and 3-year study periods, with the highest risk being noted over 2 years. This study also identified risk factors for PJP, such as male sex and comorbidities. Male patients had a higher risk of PJP. In addition, patients with COPD had a higher risk of PJP. Patients with HIV also had a higher risk of PJP than patients with CKD.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Conceptualization: Jiun-Yi Wang, Kuang-Hua Huang, Chun-Nan Wu and Chien-Ying Lee; Formal analysis: Shuo-Yan Gau and Tung-Han Tsai; Methodology: Jiun-Yi Wang, Kuang-Hua Huang, Chih-Jaan Tai, Chun-Nan Wu and Chien-Ying Lee; Validation, Chih-Jaan Tai, Chun-Nan Wu and Chien-Ying Lee; Writing – original draft: Jiun-Yi Wang, Kuang-Hua Huang, Chun-Nan Wu and Chien-Ying Lee; Writing – review & editing: Jiun-Yi Wang, Kuang-Hua Huang, Chih-Jaan Tai, Chun-Nan Wu and Chien-Ying Lee.

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