

## Short Communication

# Epidemiologic Trends and Clinical Features of *Pneumocystis jirovecii* Pneumonia in Non-HIV Patients in a Tertiary-Care Hospital in Korea over a 15-Year-Period

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**SUMMARY:** Subsequent to the increasing use of immunosuppressant therapy, *Pneumocystis jirovecii* pneumonia (PcP) has emerged as a life-threatening condition in human immunodeficiency virus (HIV)-negative patients. We investigated changes in epidemiological and clinical characteristics among PcP cases with and without HIV infections. Data of 424 patients diagnosed with PcP in a 2,700-bed Korean tertiary care hospital between February 2003 and April 2017 were retrospectively analyzed. The study included patients with compatible clinical findings in whom PcP was confirmed via direct immunofluorescence assay. The annual average number of cases increased from 12.2 (initial 5-year period) to 42.2 (recent 5-year period). In HIV-negative patients, hematologic malignancy (34.8%) and solid organ transplantation (32.9%) were the most frequent major underlying conditions, and immunosuppressive therapies including corticosteroids (342/362, 94.5%) and chemotherapy (122/362, 33.7%) were significantly associated with PcP infection ( $p < 0.001$  for both). The incidence of PcP has continued to increase among non-HIV-infected immunocompromised patients in recent years.

*Pneumocystis jirovecii* pneumonia (PcP) is a life-threatening opportunistic infection in immunocompromised patients due to the human immunodeficiency virus (HIV) (1,2). Although the incidence of PcP has rapidly declined among HIV-infected patients following the development of highly active antiretroviral therapy treatment and trimethoprim-sulfamethoxazole (TMP-SMX) anti-PcP prophylaxis since the 1990s (3), PcP remains an important cause of HIV-associated complications (4). For HIV patients, primary prophylaxis is indicated if the CD4<sup>+</sup> cell count in peripheral blood is below 200 cells/ $\mu$ L (3,5). Currently, the number of patients with PcP without HIV infection has been rapidly increasing because of the increased use of intensive chemotherapy or immunosuppressive drugs, including high-dose corticosteroids or immunomodulatory monoclonal antibodies administered to patients (6).

Although several studies have documented this general trend, the issues related to the clinical manifestation and outcomes of PcP in patients with and without HIV remain undetermined. In this context, we became interested in the epidemiologic changes among PcP cases with and without HIV infections at our institution during a 15-year period. In this study, we compared the characteristics of each patient group, including basic demographics and clinical features.

Additionally, we aimed to provide data regarding the underlying diseases or conditions associated with PcP in patients without HIV.

We retrospectively reviewed the medical records of 424 patients with and without HIV confirmed between February 2003 and April 2017 at Asan Medical Center, a 2,700-bed tertiary care hospital located in Seoul, Korea. The diagnosis was based on polymerase chain reaction detection of the gene encoding mitochondrial large ribosomal subunit (*mtLSU*) rRNA and a direct immunofluorescence assay using the monoclonal antibody clone 2G2 (Light Diagnostics™ *Pneumocystis carinii* DFA Kit; Millipore, Billerica, MA, USA) or an immunocytochemistry assay using the monoclonal antibody clone 3F6 (DAKO Corp., Carpinteria, CA, USA) in bronchoalveolar lavage fluid from patients with compatible symptoms (dyspnea, cough, sputum, and fever) and radiologic findings. This work was approved by the Research Ethics Committee at Asan Medical Center. As this was a retrospective study without intervention or the need to collect additional clinical specimens, the Institutional Review Board waived the requirement for informed consent.

In HIV-negative patients, underlying conditions were classified according to the Korean Standard Classification of Disease and Cause of Death (7). We defined mortality due to PcP as any death occurring up to one month after the diagnosis of PcP for HIV-negative patients, given the diversity of underlying diseases and severity in this cohort, and as any death up to 3 months after the diagnosis of PcP for HIV-positive patients. The underlying diseases for HIV-negative patients with PcP were stratified by frequency. Long-term corticosteroid treatment was defined as a course of therapy longer than one month.

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## Epidemiologic Trends of PcP Infection without HIV

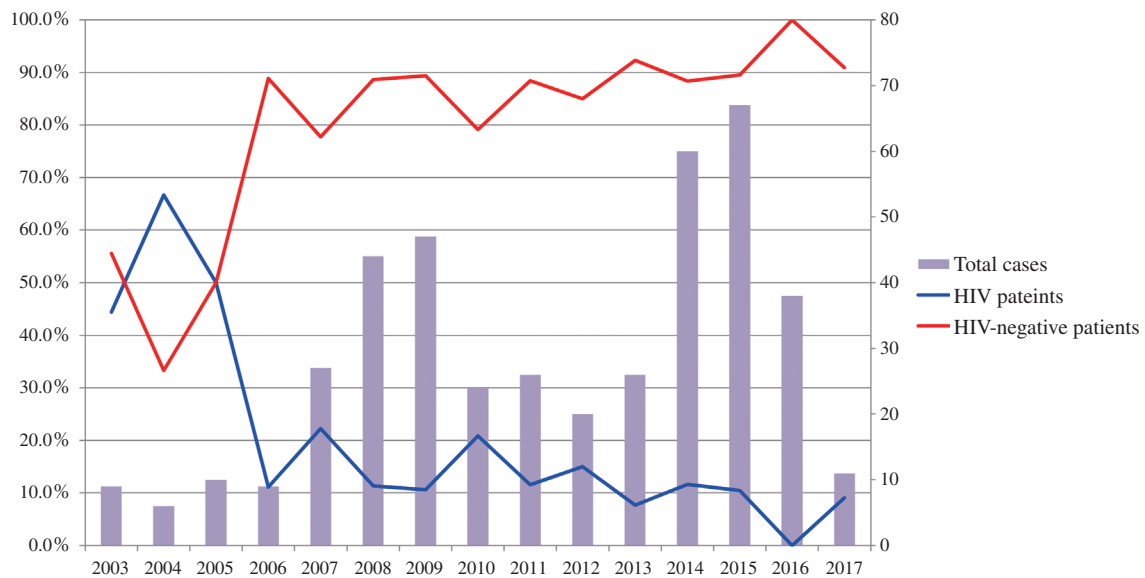


Fig. 1. (Color online) The annual numbers of PcP cases admitted per year and the proportions of HIV-positive and HIV-negative patients.

Table 1. Comparison of the demographics, underlying diseases, and clinical characteristics of HIV-negative and HIV-positive patients with *Pneumocystis pneumonia* (PcP)

Characteristics	HIV-negative PcP (n = 362)	HIV-positive PcP (n = 62)	p-value
Age, yr	51.0 ± 16.5	41.6 ± 13.2	< 0.001
Sex			
Male	211 (58.3%)	58 (93.5%)	< 0.001
Female	151 (41.7%)	4 (6.5%)	
Previous steroid treatment	342 (94.5%)	49 (79.0%)	< 0.001
Prophylaxis before diagnosis	94 (26.0%)	28 (45.2%)	0.002
Chemotherapy	122 (33.7%)	0 (0.0%)	< 0.001
Radiological findings	301 (83.1%)	59 (95.2%)	0.015
Laboratory findings			
Hemoglobin, g/L	9.8 ± 1.9	11.1 ± 1.9	< 0.001
WBC, /μL	8142.1 ± 7036.3	5695.2 ± 3319.2	0.008
ANC, /μL	6408.3 ± 4526.2 (n = 342)	4048.5 ± 2894.3 (n = 48)	< 0.001
ALC, /μL	788.5 ± 922.0	746.3 ± 541.5	0.727
Total protein, g/dL	5.4 ± 0.8 (n = 361)	6.7 ± 1.0 (n = 61)	< 0.001
Albumin, g/dL	2.6 ± 0.6 (n = 361)	2.6 ± 0.6 (n = 61)	0.907
LDH, IU/L	525.9 ± 446.6 (n = 305)	463.3 ± 208.0 (n = 50)	0.331
CRP, mg/dL	12.1 ± 39.7 (n = 354)	7.6 ± 8.0 (n = 54)	0.411
CD4, /μL	303.4 ± 524.3 (n = 190)	45.5 ± 58.5 (n = 46)	< 0.001
CD4/CD8	1.3 ± 1.6 (n = 187)	0.2 ± 0.1 (n = 3)	0.010
Mortality	118 (32.6%)	11 (17.7%)	0.019

Values are shown as means ± standard deviations or numbers (%). HIV, human immunodeficiency virus; IDL, interstitial lung disease; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; CRP, C-reactive protein; LDH, lactate dehydrogenase.

For statistical analysis, categorical variables were analyzed using the chi-square test or Fisher's exact test and continuous variables were analyzed using Student's *t*-test or the Mann-Whitney U test as appropriate. All tests were two-tailed, and a *p* value < 0.05 was considered to be statistically significant. All analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

The annual numbers of PcP cases admitted per year and the proportions of HIV-positive and HIV-negative patients are illustrated in Fig. 1. During the initial 5-year period of the present study (2003–2007), the average annual incidence of PcP was 12.2 cases; by contrast, this incidence increased to an average of 42.2 PcP cases per year during the most recent 5-year period (2012–2016) (Fig.1). Among all PcP cases, the ratio

of patients with and without HIV was 1:2.1 during the initial 5-year period but increased to 1:10.9 during the most recent 5-year period. The total number of cases of PcP increased during the study period, but no difference in seasonal frequency was observed (data not shown).

A comparison of the basic demographics, clinical history, and laboratory findings between HIV-positive and HIV-negative patients is shown in Table 1. From February 2003 to April 2017, 424 patients with PcP were identified. Among them, 362 patients (85.4%) were HIV-negative and 62 patients (14.6%) were HIV-positive. HIV-negative patients with PcP had a mean age of 51.0 years and no predominance of either sex, whereas HIV-positive patients had a mean age of 41.6 years and were predominantly male. In most HIV-negative patients, the use of immunosuppressive therapies such as corticosteroids (342/362, 94.5%) and a history of chemotherapy (123/362, 34.0%) were associated with PcP infection. HIV-positive patients were significantly more likely to have received prophylaxis before a diagnosis of PcP than HIV-negative patients ( $p = 0.002$ ). The difference in the rate of PcP infection-related mortality between HIV-negative (118/362, 32.6%) and HIV-positive (11/62, 17.7%) patients was statistically significant ( $p = 0.019$ ).

The distribution of underlying diseases at the time of PcP diagnosis in HIV-negative patients is shown in Table 2. Among the 362 HIV-negative patients with

PcP, hematological malignancy was the most frequent underlying condition (34.8%), followed by solid organ transplantation (32.9%), inflammatory and autoimmune diseases (14.6%), and various organ tumors (11.6%). Among the hematologic malignancies, lymphoma and leukemia were the most frequent (19.9% and 13.0%, respectively). The majority of the solid organ transplantations (19.1%) were kidney transplantation. The death rates according to underlying diseases ranged from 21.6% for solid organ transplantation to 51.1% for inflammatory and autoimmune diseases.

Our retrospective study of 424 confirmed cases of PcP yielded several important findings. First, the number of cases of PcP has increased among HIV-negative patients but decreased among HIV-positive patients during the last 15 years; however, PcP remains a significant problem in both HIV-positive and HIV-negative patients. Second, although the clinical outcome of PcP was more unfavorable in HIV-negative patients than in HIV-positive patients, only 26.0% of HIV-negative patients received prophylaxis. Third, our data show that HIV-negative patients harbor a diverse spectrum of underlying diseases of which hematological malignancy (including lymphoma and leukemia) is the most frequent.

PcP remains an unresolved opportunistic fungal infection in HIV-positive as well as HIV-negative patients who are severely immunocompromised as a consequence of the increased use of immunosuppressive drugs (8). Since the 2000s, several studies indicated an increase in the number of patients with PcP without HIV, but only a few studies conducted in France and China have compared the clinical features in HIV-positive and HIV-negative patients with PcP infection (9–11). Those studies emphasized the importance of primary prophylaxis for at-risk patients without HIV infection considering the high mortality rates, which ranged from 30% up to 60%, yet only 3.7% to 5.8% of the patients received prophylaxis (12,13). Comparatively, the PcP-related mortality rate and the PcP prophylaxis rate in HIV-negative patients based on our data were 32.6% and 26.0%, respectively. Both the previous and our studies showed that the mortality rate of HIV-negative patients with PcP was significantly higher, suggesting that early identification of patients at risk is necessary to implement prophylaxis before disease progression.

In conclusion, this study provides the current trend of PcP incidence and significant differences in clinical aspects between HIV-negative and HIV-positive patients with PcP. Our data indicate that immunocompromised patients at risk of PcP infection might need early identification and appropriate prophylaxis in a timely manner.

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**Conflict of interest** None to declare.

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Table 2. Underlying diseases at the time of *Pneumocystis jirovecii* pneumonia diagnosis in HIV-negative patients ( $n = 362$ )

Hematologic malignancies	126 (34.8%)
Lymphoma	72 (19.9%)
Leukemia	47 (13.0%)
Myeloma	2 (0.6%)
Hodgkin's lymphoma	1 (0.3%)
Myelodysplastic syndromes	4 (1.1%)
Transplant	119 (32.9%)
Kidney	69 (19.1%)
Liver	30 (8.3%)
Heart	8 (2.2%)
Pancreas	12 (3.3%)
Inflammatory and autoimmune disorders	53 (14.6%)
Interstitial lung disease	22 (6.1%)
Ulcerative colitis	6 (1.7%)
Dermatomyositis	6 (1.7%)
Systemic lupus erythematosus	5 (1.4%)
Behçet diseases	2 (0.6%)
Autoimmune hepatitis	2 (0.6%)
Rheumatoid polyarthritis	1 (0.3%)
Sarcoidosis	1 (0.3%)
Wegener's granulomatosis	1 (0.3%)
Sjögren's syndrome	1 (0.3%)
Solid tumor	42 (11.6%)
Others <sup>1)</sup>	22 (6.1%)

<sup>1)</sup>: End-stage renal disease, alcoholic liver cirrhosis, Sézary disease, asthma, Stevens-Johnson syndrome, pulmonary embolism, Takayasu's arteritis, Still's disease, immune thrombocytopenic purpura, acute kidney injury, and drug addiction.

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