Journal of Microbiology, Immunology and Infection (2011) 44, 274–281

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

# Mortality predictors of *Pneumocystis jirovecii* pneumonia in human immunodeficiency virus-infected patients at presentation: Experience in a tertiary care hospital of northern Taiwan

**Hsiao-Wei Wang [a], Cheng-Chih Lin [a], Chen-Feng Kuo [a], Chang-Pan Liu [a,b], Chun-Ming Lee [a,b,c,*]**

[a] *Division of Infectious Disease, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Mackay Medicine, Nursing and Management College, Taipei, Taiwan*
[c] *Taipei Medical University, Taipei, Taiwan*

Received 20 April 2010; received in revised form 25 June 2010; accepted 12 August 2010

**KEYWORDS**
Acquired immunodeficiency syndromes;
Highly active antiretroviral therapy;
Human immunodeficiency virus;
Mortality;
*Pneumocystis jirovecii* pneumonia

*Background: Pneumocystis jirovecii* pneumonia (PJP) remains the leading cause of opportunistic infections and deaths among human immunodeficiency virus (HIV)-infected patients. We would like to identify the predictors of mortality of these patients at initial presentation, and assist clinicians to aware the patients in risk of mortality earlier.
*Methods:* From 1997 to 2009, adults with HIV infection and a discharge diagnosis of PJP at Mackay Memorial Hospital were included in this retrospective study. Patients' demographic data and laboratory data were analyzed by reviewing the medical records.
*Results:* Eighty-five patients were included in this study. The overall mortality rate was 37.7%. Univariate analysis revealed several host factors significantly related to mortality, including age, systolic blood pressure, diastolic blood pressure, partial pressure of oxygen in arterial blood ($PaO_2$), percentage of lymphocyte, percentage of CD4 lymphocyte, CD4 counts, serum total protein, serum albumin, and blood urea nitrogen. Multivariate analysis identified three independent predictors associated with mortality, i.e. systolic blood pressure $\leq$110 mmHg [adjusted odds ratio (AOR) 3.88; 95% confidence interval (CI) 1.17–12.83; $p = 0.03$], $PaO_2$ at room air $\leq$60 mmHg (AOR 4.97; 95% CI 1.34–18.23; $p = 0.01$), and lymphocytes $\leq$10% (AOR 8.19; 95% CI 1.48–45.36; $p = 0.02$). With these predictors, we can stratify patients into three groups with increasing risks for mortality, $\leq$one predictor (mortality rate 14%), any two predictors (47%), and three predictors (75%).

* Corresponding author. Division of Infectious Disease, Department of Medicine, Mackay Memorial Hospital, No. 92, Section 2, Chungshan North Rd, Taipei, Taiwan.
*E-mail address:* idwang6366@gmail.com (C.-M. Lee).

1684-1182/$36 Copyright © 2011, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.
doi:10.1016/j.jmii.2010.08.006

*Conclusions:* HIV-infected patients with PJP can be clinically stratified by three prognostic variables identified by multivariate analysis. Early recognition of patients in higher risk can assist clinicians to prevent rapid deterioration and seek for better outcomes.
Copyright © 2011, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.

## Introduction

*Pneumocystis jirovecii* pneumonia (PJP) (previously known as *Pneumocystis carinii*), is a common opportunistic infection for hospitalization of patients with acquired immunodeficiency syndromes (AIDS), and is often life threatening.[1–4] The mortality rate for human immunodeficiency virus (HIV)-infected patient with PJP ranged from 11 to 53% in recent studies.[1,5–9] Because of high-mortality rate, experts take effort to determine events affecting mortality earlier for providing better care and outcomes in hospital.

Several factors associated with mortality from HIV-infected PJP patients have been identified previously, including age of the patient,[3,6,10] poor oxygenation at admission to hospital [based on partial pressure of oxygen in the arteries ($PaO_2$) at room air or alveolar-arterial $O_2$ (A-a $O_2$) gradient],[1,3,10] septic shock requiring vasopressor use,[11,12] low-hemoglobin level,[3] low-total leukocyte count,[12] low-serum albumin level,[1,9,10,13] higher total bilirubin level,[10] need for mechanical ventilation support,[6,9,11,13] development of pneumothorax,[6,9] wasting,[1] higher acute physiology and chronic health evaluation II score,[12] number of acute respiratory failure causes,[11] recent injection drug use,[10] pulmonary Kaposi sarcoma,[3] and acute kidney injury requiring renal replacement therapy.[12] Among these factors, some could not be quantitated precisely, such as wasting, vasopressor use, or severity of pneumothorax; some would be too complicated to be required, such as acute physiology and chronic health evaluation II score, renal replacement therapy, or pulmonary Kaposi sarcoma. Because of these limitations, clinicians need a simple tool for stratifying HIV-infected patients with PJP by risk for mortality at illness presentation.

Therefore, we performed a retrospective study of HIV-infected adult patients with diagnosis of PJP in a tertiary care center of northern Taiwan more than 13-year period. We collected clinical and laboratory data from these patients at or soon after their admission, and our goals were to measure the mortality rate in our study group; to compare differences between mortality and survival subgroups; to identify objectively independent predictors of mortality; and to develop a predicting rule that could stratify patients by the risk for mortality.

## Methods

Patients who were discharged with diagnosis of HIV-related diseases between 1 January 1997 and 31 December 2009 at Mackey Memorial Hospital, a 2,100-bed tertiary care center in northern Taiwan, were reviewed in this study. We conducted a computerized search of hospital records by the International Classification of Diseases, 9$^{th}$ revision (ICD-9) codes, and 304 adult patients with 440 admissions were screened because of diagnosis of HIV infection. Their medical records were carefully reviewed. Readmission at more than 2 weeks after discharge was considered as another admission. A definitive PJP was diagnosed by identification of *Pneumocystis* cystic or trophic forms on microscopic examination of Giemsa-stained induced sputum or bronchoalveolar lavage (BAL) specimens. Presumptive diagnosis was dependent on a history of recent onset (within the past 3 months) of dyspnea on exertion or nonproductive cough, image studies [including high-resolution computed tomography (HRCT) scan] with typical findings such as diffuse pattern of ground-glass opacity, and no evidence of a bacterial pneumonia or concurrent opportunistic infections.

## Data collection

The patients' medical records were retrospectively reviewed. Clinical data abstraction included: demographic characteristics; medical history; HIV and non—HIV-related comorbid conditions; cigarette, alcohol, and drug use history; preadmission use of antiretroviral and prophylactic medications; CD4 counts, CD8 counts, and plasma HIV viral load titer within 1 month of admission; and initial vital signs, arterial blood gas, and the initial laboratory data at presentation.

Highly active antiretroviral therapy (HAART) was defined as use of at least three antiretroviral agents from at least two classes among the following: protease inhibitors, nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors. We defined patients as receiving HAART if the medication was prescribed for more than 30 days before admission. Mortality was defined as death in the hospital or discharged at critical condition. Prior pulmonary diseases were defined as a history of physician-diagnosed nonmalignant lung diseases, such as pulmonary tuberculosis, chronic bronchitis/emphysema, or asthma. Recent injection drug use was defined as injection during the 6 months before admission.

## Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS Inc., Chicago, IL, USA). Results are reported as numbers and percentages. Continuous variables were analyzed by means, standard deviations (SDs), medians, and ranges. Independent sample *t* test was used to check the association between clinical characteristics and mortality. A $p$ value of $<0.05$ was considered statistically significant, and two-tailed test was adopted for all probabilities. Univariate and multivariate analyses were performed using logistic regression with mortality as the dependent variable. Predictors with nonnormal distribution were dichotomized

using cut-off points based on either median or clinically relevant values. We considered all predictors with $p$ value $<0.05$ in univariate analysis for inclusion in the multivariate model.

## Results

Forty-five patients were diagnosed as definitive PJP by positive sputum/BAL cytology. Among patients with a definitive diagnosis, two patients were excluded because of concurrent opportunistic infections, and two patients with evidences of pulmonary bacterial infection. Among the other 203 patients, 76 with pulmonary bacterial infection, 55 patients without HRCT scan, 10 with positive sputum acid-fast stains, 3 with presumed pulmonary cytomegalovirus (CMV) infections, and one with pulmonary Kaposi's sarcoma, were excluded. Overall, HRCT scans of 58 patients were reviewed by a radiologist, and 12 patients were excluded for absence of typical radiological evidence on HRCT scans. Therefore, only 44 patients were considered as presumptive cases of PJP. Clinical information of 41 and 44 patients with definitive and presumptive cases of PJP, respectively, were abstracted from their medical records.

## Demographic data

In this retrospective study, 85 HIV-infected patients diagnosed with *P jirovecii* pneumonia were enrolled, and the clinical characteristics are shown in Table 1. The mean age (±standard deviation) at the time of diagnosis was 37.64 ± 10.15 years (range, 23–76 years), and the majority was men (96.5%). Thirty-four patients (40%) had history of tobacco use. While the main risk factor for HIV infection was being a man who has sex with other men (58 patients, 68.2%), injection drug use was not so common (5 patients, 5.9%). HIV was newly diagnosed during evaluation for PJP in 66 patients (77.6%). While high risk of opportunistic infection exposures, only three patients (3.5%) were taking HAART and four patients (4.7%) were taking PJP prophylaxis before admission (Table 1). Four patients had previously received HAART, but had discontinued it more than 6 months before presentation.

## Clinical and laboratory data

Only 24 of 85 patients had a body temperature greater than 38°C at presentation. Despite the hematocrit and leukocyte counts were mostly within normal range, lymphopenia was common (69 of 85, 81.2%) at the time of admission. The mean total lymphocyte counts were 600 ± 455 cells/μL. Patients were severely immunosuppressed at presentation, whereas the mean CD4 cell counts were 26.24 ± 34.8 cells/μL. Malnutrition status was considered at admission with the mean serum total protein level 6.35 ± 0.98 mg/dL and serum albumin level 2.65 ± 0.55 g/dL (Table 1).

## Predictors of mortality

The overall mortality was 37.7% (32 of 85 patients). The independent sample $t$ test results of all variables at presentation showed that there were several variables had a significant difference ($p < 0.05$) in the mortality and survival group. The variables include age, prior pulmonary diseases, systolic blood pressure (SBP), diastolic blood pressure, partial pressure of oxygen in arterial blood, percentage of lymphocyte, percentage of CD4 lymphocyte, CD4 counts, serum total protein, serum albumin, and blood urea nitrogen (Table 2).

Univariate analyses to determine clinical variables associated with mortality found that age more than 40 years [odds ratio (OR) 4.33, 95% confidence interval (CI) 1.66–11.31, $p = 0.003$], SBP less than 110 mmHg (OR 5.91, 95% CI 2.24–15.56, $p < 0.001$), diastolic blood pressure less than 60 mmHg (OR 3.34, 95% CI 1.26–8.92, $p = 0.02$), $PaO_2$ at room air less than 60 mmHg (OR 5.63, 95% CI 1.62–18.74, $p = 0.001$), percentage of lymphocytes less than 10% (OR 3.08, 95% CI 1.08–7.81, $p = 0.04$), CD4 counts less than 50 cells/μL (OR 4.96, 95% CI 1.04–23.73, $p = 0.04$), serum total protein level less than 6 g/dL (OR 3.78, 95% CI 1.29–9.85, $p = 0.01$), serum albumin level less than 3 g/dL (OR 3.40, 95% CI 1.03–11.26, $p = 0.04$), and serum blood urea nitrogen level more than 10 mg/dL (OR 3.35, 95% CI 1.33–8.48, $p = 0.01$) predicted increased mortality. Other variables such as prior pulmonary diseases, newly diagnosed HIV infection or not, hematocrit percentage, HIV viral RNA levels, serum total bilirubin level, and serum creatinine level were not associated with mortality (Table 3).

Multivariate analysis using forward stepwise regression was performed and demonstrated three independent predictors that were associated with mortality (Table 3), which included SBP ≤110 mmHg [adjusted odds ratio (AOR) 3.88; 95% CI 1.17–12.83; $p = 0.03$], $PaO_2$ at room air ≤60 mmHg (AOR 4.97; 95% CI 1.34–18.23; $p = 0.01$), and lymphocytes ≤10% (AOR 8.19; 95% CI 1.48–45.36; $p = 0.02$).

## Discussion

*P jirovecii* is a ubiquitous organism that is classified as a fungus, but that also shares biologic characteristics with protozoa.[4] PJP is a major cause of morbidity and mortality among immunocompromised persons, and it remains a leading opportunistic infection in HIV-infected patients.[2,14–16] Approximately 90% of PJP cases occurred among patients with CD4 counts <200 cells/μL. Other factors associated with risks for PJP included CD4 cell percentage <14%, previous episodes of PJP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA.[4,17,18]

In this single-center retrospective study of HIV-infected patients with confirmed or presumptive PJP, 85 patients were enrolled. In previous reports, the mortality of HIV-infected patients with PJP before the widespread use of primary PJP prophylaxis and HAART was up to 70–80%, and decreased to 11.3–53% in the HAART era.[1,5–9,19] Our study presented the overall mortality of 37.7%, which was corresponding to previous reports.

The mean age of our patients was 37.64 ± 10.15 years, and the majority was male (96.5%). The major risk factor of HIV infection was men having sex with men (58 of 85 patients, 68.2%). All these characteristics were similar to

**Table 1** Characteristics of 85 HIV-infected patients with *Pneumocystis* pneumonia at illness presentation at Mackay Memorial Hospital, 1997–2009

| Characteristics | All cases (%)[a] | Definitive cases (%) |
|---|---|---|
| | $n = 85$ | $n = 41$ |
| Sociodemographic | | |
| Mean age, yr | 37.64 ± 10.15 | 38.37 ± 9.48 |
| Male gender | 82 (96.5) | 40 (97.6) |
| History of tobacco use | 34 (40) | 13 (31.7) |
| Medical history | | |
| HIV risk factor | | |
| MSM/bisexual males | 58 (68.2) | 32 (78.1) |
| History of injection drug use | 5 (5.9) | 2 (4.8) |
| Heterosexual | 22 (25.9) | 7 (18.1) |
| New diagnosis of HIV | 66 (77.6) | 28 (68.3) |
| Prior pulmonary diseases | 6 (7.1) | 4 (9.8) |
| HAART before admission | 3 (3.5) | 2 (4.8) |
| PJP prophylaxis | 4 (4.7) | 3 (7.3) |
| Vital signs | | |
| Mean temperature, °C | 37.38 ± 1.06 | 37.39 ± 0.95 |
| Mean systolic blood pressure, mmHg | 113.04 ± 15.27 | 113.93 ± 15.17 |
| Mean diastolic blood pressure, mmHg | 67.76 ± 11.01 | 66.73 ± 11.03 |
| Mean $PaO_2$ at room air, mmHg ($n = 71$) | 71.13 ± 19.67 | 68.55 ± 17.77 |
| Mean respiratory rare, breaths/min | 24.12 ± 4.50 | 23.95 ± 3.45 |
| Laboratory data, mean values | | |
| Hematocrit, % | 34.41 ± 5.01 | 34.34 ± 4.78 |
| Leukocyte counts, cells/μL | 7,660 ± 4,223 | 8,291 ± 4,879 |
| Total lymphocyte count, cells/μL ($n = 83$) | 600 ± 455 | 608 ± 438 |
| CD4 cell count, cells/μL ($n = 82$) | 26.24 ± 34.80 | 22.30 ± 23.71 |
| HIV viral load, copies/mL ($n = 69$) | 433,349 ± 372,957 | 394,937 ± 370,886 |
| Total protein, g/dL ($n = 82$) | 6.35 ± 0.98 | 6.22 ± 1.08 |
| Albumin, g/dL ($n = 84$) | 2.65 ± 0.55 | 2.59 ± 0.58 |
| Total bilirubin, mg/dL ($n = 82$) | 0.53 ± 0.33 | 0.55 ± 0.30 |
| GOT, IU/L | 54.73 ± 72.11 | 62.93 ± 96.23 |
| GPT, IU/L | 31.74 ± 35.99 | 34.37 ± 46.06 |
| BUN, mg/dL | 11.62 ± 7.23 | 11.42 ± 5.68 |
| Creatinine, mg/dL | 0.89 ± 0.29 | 0.87 ± 0.20 |
| Sodium, mEq/L | 136.84 ± 3.44 | 136.20 ± 3.44 |
| Potassium, mEq/L | 4.21 ± 0.53 | 4.24 ± 0.52 |

[a] Values are shown as *n* (%) or mean (standard deviation).

BUN = blood urea nitrogen; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; MSM = man who has sex with other men; $PaO_2$ = partial pressure of oxygen in arterial blood; PJP = *Pneumocystis jirovecii* pneumonia.

the distribution of HIV-infected patients in Taiwan in the same period.[20,21] However, the injecting drug users (IDUs) account for five of our patients (5.9%), which was remarkable less than the general distribution (21.5%–32.0%).[20,21] The most important risk factor for Taiwanese IDUs was needle sharing, followed by the sharing of heroin diluents. In our study, the lower IDUs rate compared with general distribution may contribute to two-thirds of Taiwan's IDUs living in central and southern parts.[22]

In our study, most patients were newly diagnosed of HIV infection during evaluation for PJP (66 of 85 patients, 77.6%), which result in small proportion of PJP prophylaxis and HAART (4.7% and 3.5%, respectively) at admission. Poor compliance was observed in four patients who discontinued HAART more than 6 months. In previous studies, HIV was newly diagnosed on PJP patients between 23 and 69%.[3,5,6,10,11] The higher rate of newly diagnosed HIV infection in our study may result from many signs of persistent denial and discrimination in Taiwan.[22] However, lack of recognition may lead to delayed diagnosis, delayed treatment, and higher mortality.[23,24]

Based on the multivariate analysis results, we identified three independent predictors, which were associated with mortality, including SBP ≤110 mmHg, $PaO_2$ at room air

**Table 2** Independent sample *t* test analysis of characteristics associated with mortality in 85 HIV-infected patients with *Pneumocystis jirovecii* pneumonia

| Characteristics | All cases | | | Definitive cases | | |
|---|---|---|---|---|---|---|
| | Died ($n = 32$) | Survived ($n = 53$) | *p* | Died ($n = 18$) | Survived ($n = 23$) | *p* |
| Sociodemographic | | | | | | |
| Mean age | 41.44 | 35.34 | 0.02 | 40.11 | 37.00 | 0.32 |
| Male | 31 | 51 | 0.88 | 17 | 23 | 0.25 |
| MSM/bisexual males | 20 | 38 | 0.34 | 13 | 19 | 0.43 |
| Recent illicit or injection drug use | 1 | 4 | 0.40 | 1 | 1 | 0.85 |
| Tobacco use | 10 | 24 | 0.20 | 6 | 7 | 0.84 |
| Medical history | | | | | | |
| New diagnosis of HIV | 24 | 42 | 0.65 | 15 | 13 | 0.07 |
| Prior pulmonary diseases | 5 | 1 | 0.02 | 3 | 1 | 0.19 |
| HAART before admission | 2 | 1 | 0.29 | 1 | 1 | 0.85 |
| PJP prophylaxis | 2 | 2 | 0.60 | 1 | 2 | 0.70 |
| Vital signs, mean values | | | | | | |
| Temperature, °C | 37.55 | 37.28 | 0.31 | 37.63 | 37.20 | 0.15 |
| SBP, mmHg | 105.63 | 117.51 | 0.001 | 103.78 | 121.87 | <0.001 |
| DBP, mmHg | 63.69 | 70.23 | 0.007 | 61.67 | 70.70 | 0.008 |
| Respiratory rare, breaths/min | 24.94 | 23.62 | 0.19 | 24.44 | 23.57 | 0.44 |
| $PaO_2$ at room air, mmHg ($n = 71$) | 59.90 | 77.61 | 0.001 | 59.42 | 75.20 | 0.005 |
| Laboratory data, mean values | | | | | | |
| Hematocrit, % | 33.98 | 34.67 | 0.54 | 34.10 | 34.53 | 0.78 |
| Leukocyte count, cells/μL | 8,794 | 6,975 | 0.05 | 9,508 | 6,556 | 0.05 |
| Percentage of lymphocyte, % | 6.19 | 11.08 | 0.003 | 4.50 | 12.18 | <0.001 |
| Lymphocyte count, cells/μL | 497.22 | 664.27 | 0.09 | 438.20 | 741.58 | 0.03 |
| Percentage of CD4 T cell, % | 3.25 | 4.89 | 0.06 | 1.98 | 3.90 | 0.007 |
| CD4 T-cell count, cells/μL | 14.52 | 33.36 | 0.004 | 11.87 | 30.47 | 0.01 |
| Percentage of CD8 T cell, % | 53.58 | 52.60 | 0.75 | 51.48 | 55.62 | 0.31 |
| CD8 T-cell count, cells/μL | 280.76 | 365.13 | 0.21 | 237.92 | 441.70 | 0.05 |
| Platelet count, cells/μL | 248,296 | 259,957 | 0.70 | 287,333 | 294,150 | 0.87 |
| Viral load, copies/mL | 366,704 | 462,506 | 0.33 | 305,902 | 441,391 | 0.27 |
| Glucose, mg/dL | 113.34 | 103.77 | 0.19 | 117.67 | 107.09 | 0.41 |
| Total protein, g/dL | 5.90 | 6.63 | 0.001 | 5.58 | 6.73 | <0.001 |
| Albumin, g/dL | 2.43 | 2.79 | 0.003 | 2.27 | 2.84 | 0.001 |
| Total bilirubin, mg/dL | 0.58 | 0.50 | 0.31 | 0.58 | 0.53 | 0.58 |
| GOT, IU/L | 76.63 | 41.51 | 0.08 | 91.89 | 40.26 | 0.09 |
| GPT, IU/L | 42.91 | 25.00 | 0.07 | 49.00 | 22.91 | 0.07 |
| Total cholesterol, mg/dL | 133.69 | 130.67 | 0.70 | 129.50 | 131.87 | 0.86 |
| BUN, mg/dL | 14.53 | 9.87 | 0.01 | 13.22 | 10.00 | 0.08 |
| Creatinine, mg/dL | 0.96 | 0.85 | 0.13 | 0.91 | 0.84 | 0.30 |
| Sodium, mEq/L | 136.69 | 136.92 | 0.76 | 136.06 | 136.30 | 0.82 |
| Potassium, mEq/L | 4.15 | 4.25 | 0.37 | 4.13 | 4.33 | 0.23 |

BUN = blood urea nitrogen; DBP = diastolic blood pressure; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; MSM = man who has sex with other men; $PaO_2$ = partial pressure of oxygen in arterial blood; PJP = *Pneumocystis jirovecii* pneumonia; SBP = systolic blood pressure.

≤60 mmHg, and lymphocytes ≤10%. The SBP reflected the presence of underlying medical comorbidities and general severity of illness, the $PaO_2$ level represented respiratory condition from PJP, and the percentage of lymphocyte was associated with the severity of underlying HIV disease. The mortality ranged from 14% (≤one predictor), 47% (any two predictors) to 75% (all three predictors). We can easily classify patients by their existing predictors, and aware their possible deterioration. Clinical improvement was observed on patients with severe PJP from intensive care unit care without HAART intervention,[6] therefore we can refer patients to intensive care unit earlier if patients were classified as high risk of mortality by this predicting rule. Meanwhile, better HIV control may contribute to decline mortality and suppress diseases progression.[4,25,26]

To our knowledge, there were no previous studies that demonstrate the associations between SBP and the percentage of lymphocyte with increased PJP mortality.

**Table 3** Characteristics associated with mortality in univariate and multivariate analyses in 85 HIV-infected patients with *Pneumocystis jirovecii* pneumonia

| Univariate predictors | Unadjusted odds ratio (95% CI), *p* | |
|---|---|---|
| | All cases ($n = 85$) | Definitive cases ($n = 41$) |
| Aged more than 40 yr | 4.33 (1.66–11.31), 0.003 | — |
| Prior pulmonary diseases | 9.44 (1.05–84.99), 0.05 | — |
| Systolic blood pressure ≤110 mmHg | 5.91 (2.24–15.56), <0.001 | 16.63 (3.54–78.0), 0.003 |
| Diastolic blood pressure ≤60 mmHg | 3.34 (1.26–8.92), 0.02 | 5.94 (1.43–24.66), 0.01 |
| $PaO_2$ at room air ≤60 mmHg | ($n = 71$) | ($n = 35$) |
| | 5.63 (1.62–18.74), 0.001 | 5.79 (1.34–25.07), 0.02 |
| Percentage of lymphocytes ≤10% | 3.08 (1.08–8.72), 0.04 | 7.46 (1.78–31.36), 0.01 |
| Total lymphocyte count ≤500 cells/μL | – | 2.6 (0.72–9.36), 0.04 |
| Percentage of CD4 T cell ≤5% | – | 13.08 (1.48–11.52), 0.02 |
| CD4 T-cell counts ≤50 cells/μL | ($n = 82$) | ($n = 40$) |
| | 4.96 (1.04–23.73), 0.04 | 5.46 (1.24–24.09), 0.03 |
| Serum total protein level ≤6 g/dL | ($n = 82$) | ($n = 40$) |
| | 3.78 (1.29–9.85), 0.01 | 7.37 (1.84–29.55), 0.005 |
| Serum albumin level ≤3 g/dL | ($n = 84$) | ($n = 41$) |
| | 3.40 (1.03–11.26), 0.04 | 4.88 (1.27–18.65), 0.02 |
| Serum BUN level ≥10 mg/dL | 3.35 (1.33–8.48), 0.01 | – |
| Multivariate predictors (forward stepwise: *R*) | | |
| Systolic blood pressure ≤110 mmHg | 3.88 (1.17–12.83), 0.03 | 15.63 (1.90–25.37), 0.01 |
| $PaO_2$ at room air ≤60 mmHg | 4.97 (1.34–18.23), 0.01 | — |
| Percentage of lymphocytes ≤10% | 8.19 (1.48–45.36), 0.02 | 10.99 (1.19–17.82), 0.04 |

BUN = blood urea nitrogen; CI = confidence interval; HIV = human immunodeficiency virus; $PaO_2$ = partial pressure of oxygen in arterial blood.

There were studies that reported septic shock with vasopressor use as a mortality predictor on HIV-infected PJP patients, which would be a late phenomenon of sepsis, leading organ failure and mortality.[11,12] Use of SBP alone as a predictor could recognize the risk factor earlier and avoid further deterioration. There were reports identified lower total leukocyte counts and CD4 T-cell counts at admission as predictors of HIV disease progression, and increase mortality on HIV-infected patients with PJP.[12,27] However, the percentage of lymphocyte is far more meaningful than total leukocyte count to determine the severity of underlying HIV disease. Therefore our predictors not only detect the risk of mortality earlier than other predicting models, but also reflect the real severity of respiratory condition and immune status.

Despite PJP remains the leading opportunistic infection in HIV-infected patients and causes nonspecific pulmonary symptoms and hypoxia,[2,4] bacterial pneumonia, pulmonary TB, and CMV pneumonitis are common and their manifestations may by atypical.[4,28] In developing world such as India, reports showed the most common opportunistic infection in HIV-infected patients was pulmonary TB, followed by bacterial pneumonia and CMV infection.[29–31] In Taiwan, Tang et al.[32] studied 15 AIDS patients with autopsy, in which six patients diagnosed premortem with PJP, but only one confirmed by postmortem pathological findings, and six of eight patients diagnosed as CMV infection at postmortem examination did not have premortem presumption. The substantial discrepancies between premortem clinical diagnosis and autopsy findings are worth attention, especially CMV infection. Collins et al. mentioned that in patients with AIDS and CMV pneumonia, CT scanning will show diffuse pattern of ground-glass opacity, dense consolidation, bronchial wall thickening or bronchiectasis, and interstitial reticulation without air-space disease, and the presence of an isolated ground-glass infiltrate without additional findings in patients with AIDS is highly suggestive of PJP.[33]

In our study, the confirmation of PJP was mainly from BAL and induced sputum samples, which are frequently used for the investigation of PJP with good sensitivity (50–90% and 90–99%, respectively). Despite open lung biopsy is considered as a gold standard with better sensitivity (95–100%), it is rarely performed in the current clinical practice.[4,14,34] The routine cytological staining techniques (Giemsa, Papanicolaou, and Grocott's methenamine silver nitrate) are used before, but specialized techniques such as immunocytochemistry and polymerase chain reaction are more promising and recommended currently.[2,34,35]

This study had several limitations. First, it was retrospective and from a single center. As not an observational cohort study, some clinically significant differences might not being detected. Different population or different hospitals could be expected to have different results. Second, it included not only patients with laboratory-proven PJP, but also patients with presumptive PJP in the earlier period, which might be diagnosed as other pulmonary opportunistic infection or coinfection eventually.[32] Third, it examined mortality risk factors present at or

soon after hospital admission, which would be days or even weeks before PJP diagnosed. Some patients would not be enrolled to this study if they were too severe to confirm the diagnosis. Next, we did not follow patients after hospital discharge, therefore the predictors of long-term mortality and any impact of HAART on long-term survival remain unknown. Large, prospective studies would be needed to determine the predicting factors of mortality from HIV-infected patient with PJP at presentation.

In summary, the overall mortality from HIV-infected patients with PJP patient at this medical center over the 15-year period of this study was 37.7%. In multivariate analysis, we identified three clinical and laboratory data, including SBP, $PaO_2$, and percentage of lymphocyte, as predictors of mortality from HIV-infected patients with PJP at presentation. These predictors were easily obtained at patient's admission to hospital, and a higher mortality rate was observed when more predictors were present. Although this prediction rule requires further validation in cohorts, it is likely a practical method to stratify patients by risk for in-hospital mortality, and therefore may assist clinicians to take accurate strategies for better care and outcomes of HIV-infected patients with PJP.

## Acknowledgment

The authors would like to thank the staff of the Mackay Memorial Hospital medical records department for the help in locating all patient charts for this study.

## References

1. Arozullah AM, Yarnold PR, Weinstein RA, Nwadiaro N, McIlraith TB, Chmiel JS, et al. A new preadmission staging system for predicting inpatient mortality from HIV-associated Pneumocystis carinii pneumonia in the early highly active antiretroviral therapy (HAART) era. *Am J Respir Crit Care Med* 2000;**161**(4 Pt 1):1081—6.
2. Huang L, Morris A, Limper AH, Beck JM. An Official ATS Workshop Summary: recent advances and future directions in pneumocystis pneumonia (PCP). *Proc Am Thorac Soc* 2006;**3**: 655—64.
3. Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from Pneumocystis jirovecii pneumonia in HIV-infected patients: 1985-2006. *Clin Infect Dis* 2008;**46**:625—33.
4. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009;**58**(RR-4):1—207 [quiz CE1-4].
5. Hui M, Kwok WT. Pneumocystis carinii pneumonia in Hong Kong: a 10 year retrospective study. *J Med Microbiol* 2006;**55**: 85—8.
6. Miller RF, Allen E, Copas A, Singer M, Edwards SG. Improved survival for HIV infected patients with severe Pneumocystis jirovecii pneumonia is independent of highly active antiretroviral therapy. *Thorax* 2006;**61**:716—21.
7. Tabarsi P, Baghaei P, Karimi S, Alizadeh H, Mansoori SD, Masjedi MR, et al. Pneumocystis pneumonia in patients with human immunodeficiency virus. *Tanaffos* 2007;**6**:26—9.
8. Monnet X, Vidal-Petiot E, Osman D, Hamzaoui O, Durrbach A, Goujard C, et al. Critical care management and outcome of severe Pneumocystis pneumonia in patients with and without HIV infection. *Crit Care* 2008;**12**:R28.
9. Radhi S, Alexander T, Ukwu M, Saleh S, Morris A. Outcome of HIV-associated Pneumocystis pneumonia in hospitalized patients from 2000 through 2003. *BMC Infect Dis* 2008;**8**:118.
10. Fei MW, Kim EJ, Sant CA, Jarlsberg LG, Davis JL, Swartzman A, et al. Predicting mortality from HIV-associated Pneumocystis pneumonia at illness presentation: an observational cohort study. *Thorax* 2009;**64**:1070—6.
11. Barbier F, Coquet I, Legriel S, Pavie J, Darmon M, Mayaux J, et al. Etiologies and outcome of acute respiratory failure in HIV-infected patients. *Intensive Care Med* 2009;**35**(10): 1678—86.
12. Yang ST. Predictors of mortality of newly-diagnosed human-immunodeficiency-infected patients who develop Pneumocystis jirovecii pneumonia-associated acute respiratory failure requiring admission to the intensive care unit. *Chest* 2009;**136**: 130S-b.
13. Powell K, Davis JL, Morris AM, Chi A, Bensley MR, Huang L. Survival for patients with HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. *Chest* 2009;**135**:11—7.
14. Turner D, Schwarz Y, Yust I. Induced sputum for diagnosing Pneumocystis carinii pneumonia in HIV patients: new data, new issues. *Eur Respir J* 2003;**21**:204—8.
15. D'Avignon LC, Schofield CM, Hospenthal DR. Pneumocystis pneumonia. *Semin Respir Crit Care Med* 2008;**29**:132—40.
16. Sun HY, Chen MY, Hsieh SM, Sheng WH, Chang SY, Hsiao CF, et al. Changes in the clinical spectrum of opportunistic illnesses in persons with HIV infection in Taiwan in the era of highly active antiretroviral therapy. *Jpn J Infect Dis* 2006;**59**: 311—6.
17. Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary Pneumocystis carinii pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. *J Infect Dis* 1998;**178**:1126—32.
18. Kaplan JE, Hanson DL, Jones JL, Dworkin MS. Viral load as an independent risk factor for opportunistic infections in HIV-infected adults and adolescents. *AIDS* 2001;**15**:1831—6.
19. Phair J, Munoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of Pneumocystis carinii pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med* 1990;**322**:161—5.
20. Yang CH, Huang YF, Hsiao CF, Yeh YL, Liou HR, Hung CC, et al. Trends of mortality and causes of death among HIV-infected patients in Taiwan, 1984-2005. *HIV Med* 2008;**9**:535—43.
21. HIV/AIDS. In: Centers for Disease Control DoH, R.O.C. (Taiwan), editor. *CDC Annual report 2009*. R.O.C. (Taiwan): Centers for Disease Control, Department of Health; 2009.
22. Chen YM, Kuo SH. HIV-1 in Taiwan. *Lancet* 2007;**369**:623—5.
23. Udwadia ZF, Doshi AV, Bhaduri AS. Pneumocystis carinii pneumonia in HIV infected patients from Mumbai. *J Assoc Physicians India* 2005;**53**:437—40.
24. Delpierre C, Lauwers-Cances V, Pugliese P, Poizot-Martin I, Billaud E, Duvivier C, et al. Characteristics trends, mortality and morbidity in persons newly diagnosed HIV positive during the last decade: the profile of new HIV diagnosed people. *Eur J Public Health* 2008;**18**:345—7.
25. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 2006;**41**:194—200.
26. Barbosa AN, Souza LR. Occurrence of pneumocystis pneumonia in HIV-infected patients and the interference of the highly active antiretroviral therapy. *J Venom Anim Toxins* 2008;**14**: 152—60.

27. Post FA, Wood R, Maartens G. CD4 and total lymphocyte counts as predictors of HIV disease progression. *Q J Med* 1996;**89**: 505—8.
28. Wolff AJ, O'Donnell AE. HIV-related pulmonary infections: a review of the recent literature. *Curr Opin Pulm Med* 2003;**9**: 210—4.
29. Deshmukh SD, Ghaisas MV, Rane SR, Bapat VM. Pneumocystis carinii pneumonia and its association with other opportunistic infections in AIDS—an autopsy report of five cases. *Indian J Pathol Microbiol* 2003;**46**:207—11.
30. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of human immunodeficiency virus disease in southern India. *Clin Infect Dis* 2003; **36**:79—85.
31. Lanjewar DN, Duggal R. Pulmonary pathology in patients with AIDS: an autopsy study from Mumbai. *HIV Med* 2001;**2**: 266—71.
32. Tang HJ, Liu YC, Yen MY, Chen YS, Wann SR, Lin HH, et al. Opportunistic infections in adults with acquired immunodeficiency syndrome: a comparison of clinical and autopsy findings. *J Microbiol Immunol Infect* 2006;**39**:310—5.
33. Collins J, Stern EJ. Ground glass opacity on CT scanning of the chest: what does it mean? *Appl Radiol* 1998;**12**:17—24.
34. Wazir JF, Ansari NA. Pneumocystis carinii infection. Update and review. *Arch Pathol Lab Med* 2004;**128**:1023—7.
35. Krajicek BJ, Limper AH, Thomas Jr CF. Advances in the biology, pathogenesis and identification of Pneumocystis pneumonia. *Curr Opin Pulm Med* 2008;**14**:228—34.