Risk Factors for *Pneumocystis jiroveci* Pneumonia in Glomerulonephritis Patients Receiving Immunosuppressants

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Abstract

Objective *Pneumocystis jiroveci* pneumonia (*PJP*) infection is a rare but lethal complication in immunocompromised hosts. However, risk factors for *PJP* infection in glomerulonephritis (GN) patients receiving immunosuppressants are unknown.

Methods From August 2009 to July 2010, we encountered a cluster occurrence of *PJP* infection in our renal biopsy patients. Seven of 73 GN patients under immunosuppressant agents developed *PJP* infection, which were diagnosed by the Giemsa and Gomori's methenamine silver stains of the bronchoalveolar lavage specimen.

Results The average time of *PJP* onset was 2.4 months after immunosuppressant initiation. We found that the immunosuppressant regimens were equal between patients with and without the development of *PJP* infection regarding the daily dose per body weight, treatment duration, and accumulative dose per body weight. Logistic regression analysis indicated that high serum creatinine, low hemoglobin, and low absolute lymphocyte count at immunosuppressant initiation, and high chronicity indices of kidney pathology were predictors of *PJP* infection. In addition, patients with *PJP* infection had persistently worse renal function, more severe anemia, and more severe lymphocytopenia as compared to those without.

Conclusion Prophylactic therapy for *P. jiroveci* and immunosuppressant dose reduction should be considered in GN patients with high chronicity of their kidney diseases and/or persistent lymphocytopenia.

Key words: *Pneumocystis jiroveci* pneumonia, glomerulonephritis, immunosuppressants, chronic kidney disease

(Intern Med 51: 2869-2875, 2012)

(DOI: 10.2169/internalmedicine.51.6774)

Introduction

Immunocompromised patients are at risk for *Pneumocystis jiroveci* pneumonia (*PJP*) infection. Previous studies have identified several risk factors in such patients, including patients infected with human immunodeficiency virus, cancer patients receiving chemotherapy, patients with connective tissue diseases, and transplant recipients (1-9). However, to date *PJP* risk factors in patients with glomerular kidney diseases other than Wegener's granulomatosis have not been investigated.

Pneumocystis jiroveci is a ubiquitous fungal pathogen throughout the world. It is unknown whether *P. jiroveci*

colonization leads to the development of *PJP*, and current data are insufficient to justify routine *PJP* screening in immunocompromised individuals (10, 11). Therefore, it is crucial to identify risk factors for *PJP* infection in non-HIV patients receiving immunosuppressant therapy, not only to prevent *PJP* diseases but also to avoid unnecessary drug toxicity. Previous studies have shown that renal transplant recipients with poor renal function, graft rejection, mycophenolate mofetil use, and persistent lymphocytopenia are at risk for *PJP* infections (7-9). However, the immunosuppressant regimens are different between glomerulonephritis (GN) patients and renal transplant recipients. Nearly all renal transplant recipients received life-long immunosuppressants with recommended drug level targets (12), whereas the immunosup-

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Received for publication October 20, 2011; Accepted for publication February 13, 2012

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Figure 1. Flow diagram for the study.

pressant dosage and treatment duration in GN patients are considerably varied. Therefore, *PJP* risk factors of GN patients deserve investigation.

We encountered a cluster occurrence of *PJP* infection in our GN patients. All of them were receiving immunosuppressant therapy at onset of *PJP* infection. The aim of this study was to determine the risk factors among the patients in this group in order to determine who might be indicated for *PJP* chemoprophylaxis. Therefore, we compared *PJP* patients with patients who did not acquire *PJP* infection under immunosuppressant therapy.

Materials and Methods

Study protocol and subjects

From August 2009 to July 2010, there were 130 patients who underwent percutaneous kidney needle biopsy at the Taipei Veterans General Hospital, a tertiary-care referral hospital. They were not on immunosuppressant therapy prior to renal biopsy except for renal transplant recipients. As shown in Fig. 1, we excluded renal transplant recipients ($n=13$), patients who were followed up for less than 6 months ($n=14$), and patients who were not indicated for immunosuppressant therapy ($n=30$). Eventually, a total of 73 patients were enrolled. *PJP* chemoprophylaxis was not given to these patients. During this period, we encountered a cluster occurrence of *PJP* infection among our renal biopsy patients ($n=7$). All of these 7 patients were receiving immunosuppressant therapy at the onset of *PJP* infection.

PJP infection was diagnosed by bronchoalveolar lavage (BAL) performed by expert chest physicians. The BAL specimens were sent for analysis with Giemsa and Gomori's methenamine silver stains. The demographic features and clinical parameters, including age, gender, diabetes mellitus,

pathological diagnosis of kidney diseases, serum biochemical data, and urine protein/creatinine ratio were recorded. Serum and urine laboratory data were obtained at 3 separate time points, including the time point of immunosuppressant agent initiation, one month later, and at *PJP* onset (for *PJP* patients)/3 months after immunosuppressant initiation (for patients without *PJP*). Estimated glomerular filtration rate (eGFR) was calculated by the Cockcroft-Gault formula. Absolute neutrophil count (ANC) was calculated by total white blood cell (WBC) count multiplied by neutrophil percentage. Absolute lymphocyte count (ALC) was calculated by total WBC count multiplied by lymphocyte percentage. Urine protein/creatinine ratio (PCR) was calculated from urine protein (mg/dL) divided by urine creatinine (Cr) (mg/dL).

Kidney pathology of each patient was examined by two pathologists who were specialists in kidney diseases. Percentages of glomerulosclerosis, including global and segmental, were calculated from the number of sclerosed glomeruli divided by the number of total glomeruli within the specimen. Percentages of interstitial fibrosis and tubular atrophy refer to the proportion of renal parenchymal involvement.

Immunosuppressant regimens

Immunosuppressant regimens of patients consisted of oral corticosteroids, intravenous corticosteroid pulse therapy, cyclophosphamide, cyclosporine A, mycophenolate mofetil, and azathioprine. Due to the retrospective nature of our study, the choice and dosage of immunosuppressants were at the discretion of each attending nephrologist. The daily dose, treatment duration, and accumulative dose of each immunosuppressant agents were collected. Daily dose per body weight was calculated from total accumulative dose divided by the total treatment duration and body weight. Accumulative dose per body weight was calculated from the total accumulative dose divided by body weight.

Statistical analysis

Chi-square analysis or Fisher's exact test was used for comparison of categorical variables as appropriate. Continuous variables were compared by the Student's *t*-test. Values of the continuous variables are presented as mean and standard deviation, unless otherwise specified. Logistic regression analysis was used to determine the significance of variables in predicting a short-term outcome, *PJP* infection. SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. All probabilities were two-tailed and a *p* value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of study subjects

Table 1 shows the baseline characteristics of the 73 pa-

Table 1. Demographic Data between *PJP* Patients (n = 7) and Controls (n = 66)

	All	<i>PJP</i>	no <i>PJP</i>	p value
Patient number (n)	73	7	66	
Male gender (%)	53.4	71.4	51.5	0.438
Age at IS initiation (year)	46.6 ± 19.6	55.3 ± 19.1	45.7 ± 19.5	0.219
Diabetes mellitus (%)	16.4	28.6	15.2	0.323
Pathological diagnosis of kidney diseases				
Membranous glomerulonephritis (%)	19.2	14.3	19.7	1.000
Minimal change disease (%)	17.8	0.0	19.7	<0.001*
Focal segmental glomerulosclerosis (%)	19.2	28.6	18.2	0.514
IgA nephropathy (%)	17.8	42.9	15.2	0.102
Lupus nephritis (%)	15.1	0.0	16.7	0.585
Pauci-immune glomerulonephritis (%)	8.2	14.3	7.6	0.466
Fibrillary glomerulonephritis (%)	2.7	0.0	3.0	1.000
Pathological findings of kidney biopsy				
Global glomerulosclerosis (%)	22.8 ± 25.4	44.0 ± 24.6	20.5 ± 24.6	0.019*
Segmental glomerulosclerosis (%)	13.4 ± 18.0	17.3 ± 17.6	13.0 ± 18.1	0.552
Interstitial fibrosis (%)	13.5 ± 14.9	30.7 ± 11.3	11.6 ± 14.0	0.001*
Tubular atrophy (%)	13.3 ± 15.2	34.3 ± 13.0	11.0 ± 13.6	<0.001*
Laboratory data at IS initiation				
Albumin (mg/dL)	3.0 ± 0.8	3.2 ± 0.3	3.0 ± 0.9	0.286
BUN (mg/dL)	34.9 ± 21.6	51.3 ± 11.7	33.1 ± 21.8	0.005*
Cr (mg/dL)	2.7 ± 2.2	4.5 ± 1.7	2.5 ± 2.2	0.022*
eGFR (C-G) (mL/min)	58.5 ± 48.1	14.9 ± 4.2	63.1 ± 48.4	<0.001*
Hb (g/dL)	11.6 ± 2.3	9.3 ± 1.6	11.8 ± 2.2	0.005*
ANC (per cumm)	5,494.9 ± 2,140.6	6,174.6 ± 1,523.7	5,419.4 ± 2,194.8	0.380
ALC (per cumm)	1,673.3 ± 844.7	1,046.4 ± 523.0	1,738.2 ± 846.2	0.039*
Urine PCR (mg/mg)	6.4 ± 5.5	5.7 ± 3.2	6.5 ± 5.7	0.610

Values are expressed as mean ± SD or percent unless otherwise listed. Abbreviations: *PJP*: *Pneumocystis jiroveci* pneumonia, IS: immunosuppressants, BUN: blood urea nitrogen, Cr: creatinine, eGFR (C-G): estimated glomerular filtration rate by Cockcroft-Gault formula, Hb: hemoglobin, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, PCR: protein/creatinine ratio. *p < 0.05.

tients. At enrollment, the mean age was 47 years, 53% of patients were male, and 16% of patients had diabetes mellitus. A total of 14 patients (19%) were diagnosed membranous nephropathy, 13 patients (18%) were minimal change disease, 14 patients (19%) were focal segmental glomerulosclerosis, 13 patients (18%) were IgA nephropathy, 11 patients (15%) were lupus nephritis, 6 patients (8%) were pauci-immune glomerulonephritis, and 2 patients (3%) were fibrillary glomerulonephritis.

Fig. 2 shows the differences between laboratory data at 3 different time points, including at immunosuppressant initiation, 1 month after immunosuppressant initiation, and at *PJP* onset (for *PJP* patients)/3 months after immunosuppressant initiation (for patients without *PJP*), respectively. Compared to patients without *PJP* infection, those who developed *PJP* infection had a significantly higher blood urea nitrogen (BUN), higher serum Cr, lower eGFR, lower hemoglobin (Hb), and lower ALC at these 3 time points.

Pathological findings of the kidney biopsy

We compared the kidney pathological findings between patients with and without *PJP* infection. We found that patients who developed *PJP* infection possessed a significantly higher chronicity of their kidney pathology at the time of immunosuppressant initiation, including global glomerulosclerosis (p=0.019), interstitial fibrosis (p=0.001), and tubular atrophy (p<0.001). Segmental glomerulosclerosis percentage in kidney pathology did not differ between the 2 groups of patients (p=0.552). This is compatible with the

findings that *PJP* patients had persistently lower eGFR, which were 14.9±4.2 (range, 8.2 to 20.3), 16.5±7.3 (range 10.3 to 30.9), and 15.3±5.5 (range 10.3 to 26.6) mL/min at immunosuppressant initiation, one month later, and at *PJP* onset, respectively.

First 3-month immunosuppressant regimens

The mean follow-up time after immunosuppressant initiation was 11.7±4.8 months, during which 7 patients were infected with *PJP*. We found that patients developed *PJP* infection after an average period of 2.4±0.5 months of immunosuppressant therapy (range, 1.8 to 3.2 months). Therefore, we compared the immunosuppressant dose in the first 3 months between patients with and without *PJP* infection. Table 2 shows that there was no difference in immunosuppressants between these 2 groups of patients, including daily dose per body weight, treatment duration, and accumulative dose per body weight, except for the daily dose of oral corticosteroids per body weight. Patients who developed *PJP* infection received a significantly higher average dose of oral corticosteroids (0.63±0.24 mg/kg/day) in the first 3 months than those without *PJP* infection (0.45±0.25 mg/kg/day) (p=0.048).

Risk factors for *PJP* infection

As shown in Table 3, logistic regression analysis indicated that *PJP* predictors in GN patients were higher BUN, higher serum Cr, lower Hb, and lower ALC at immunosuppressant initiation, and higher chronicity indices of kidney pathology

Figure 2. Comparisons of serum creatinine (A), hemoglobin (B), and absolute lymphocyte count (C) at the time points of immunosuppressant initiation, 1 month later, and at PJP onset (for PJP patients)/3 months after immunosuppressant initiation (for patients without PJP) between patients with and without PJP infection. Data ranges are expressed as mean $\pm$ SE. PJP, *Pneumocystis jiroveci* pneumonia.

(global glomerulosclerosis, interstitial fibrosis, and tubular atrophy). In addition, we included the daily dose of oral corticosteroids per body weight in logistic regression analysis, which showed a borderline significance in predicting PJP infection ($p=0.059$).

Clinical outcomes

All PJP patients developed respiratory failure requiring endotracheal tube intubation and mechanical ventilation, and all of them were treated at the intensive care unit aggressively. Standard PJP treatment protocol, including intravenous trimethoprim-sulfamethoxazole (TMP-SMX) and corticosteroids, were initiated in a timely fashion, even before

the BAL examination when suspicious clinically. Concomitant broad spectrum antibiotics and/or continuous venovenous hemofiltration were applied if indicated. Unfortunately, six of 7 PJP patients died 3.4 ± 0.3 months after immunosuppressant initiation. The only surviving patient developed end-stage renal disease requiring long-term dialysis therapy. Our PJP patients presented with a very high mortality rate and had a very poor prognosis despite aggressive therapies.

Among patients without PJP development ($n=66$), six patients were hospitalized due to infectious diseases other than PJP within 3 months after immunosuppressant initiation, including 2 atypical pneumonia (time from immunosuppressant initiation to infectious hospitalization, 0.6 and 2.6 months, respectively), 1 cytomegalovirus pneumonia (2.6 months), 1 herpes zoster virus infection at the first trigeminal nerve dermatome (1.9 months), 1 pulmonary tuberculosis (2.1 months), and 1 methicillin-resistant *Staphylococcus aureus* (MRSA) necrotizing fasciitis which complicated with sepsis and death (2.4 months). During the 3-month follow-up after immunosuppressant initiation, only 1 out of these 66 patients died (at 2.6 months; MRSA necrotizing fasciitis with sepsis).

Discussion

The findings of this study indicated that GN patients with worse renal function, more severe anemia, more severe lymphocytopenia, and more chronicity of their kidney pathology were at risk for PJP infection, whereas old age, underlying diabetes, and dosage of immunosuppressants were similar between patients with and without PJP development. Heavy dose of immunosuppressants might not necessarily lead to PJP infection since some patients who did not develop PJP infection simultaneously received a combination of 4 types of immunosuppressant agents. Previous studies have shown that immunosuppressant regimens containing mycophenolate mofetil are risk factor for PJP infection in renal transplant recipients (7, 8). However, we did not find such a relationship in our GN patients, probably due to the short-term use of mycophenolate mofetil (mean duration in PJP patients, 1.9 months).

We also found that patients who developed PJP infection presented with persistently higher serum Cr, lower Hb, and lower ALC at the time points of 1 month and 3 months after immunosuppressant initiation. This implies that these patients possess a higher chronicity of their glomerular kidney diseases. A unique feature of the present study is that all patients received renal biopsy. Therefore, we analyzed their kidney pathological findings, which demonstrated that PJP patients had significantly higher percentages of global glomerulosclerosis, interstitial fibrosis, and tubular atrophy at the time of immunosuppressant initiation as compared to those without PJP. This was compatible with the findings that these PJP patients were in a late stage of chronic kidney disease (CKD), as evidenced by the persistently low

Table 2. Comparisons of the First 3-month Immunosuppressant Regimens between Patients with and without *PJP* Infection

	<i>PJP</i>	no <i>PJP</i>	p value
Patient number (n)	7	66	
Maximal concomitant oral IS drug number	2.0 ± 0.6	1.8 ± 0.7	0.522
Corticosteroids, oral (n; %)	7; 100	62; 93.9	1.000
Daily dose/BW (mg/kg/day)	0.632 ± 0.244	0.448 ± 0.251	0.048*
Duration (month)	2.2 ± 0.6	2.7 ± 0.5	0.249
Accumulative dose (mg/kg)	44.2 ± 27.6	37.0 ± 22.0	0.315
Corticosteroids, parenteral pulse therapy (n; %)	5; 71.4	26; 39.4	0.127
Daily dose/BW (mg/kg/day)	9.323 ± 5.875	10.404 ± 4.391	0.277
Duration (month)	0.6 ± 1.1	0.2 ± 0.1	0.330
Accumulative dose (mg/kg)	56.2 ± 36.1	47.5 ± 37.8	0.115
Cyclophosphamide (n; %)	3; 42.9	24; 36.4	0.705
Daily dose/BW (mg/kg/day)	0.861 ± 0.173	1.014 ± 0.337	0.998
Duration (month)	1.6 ± 0.9	1.7 ± 0.9	0.797
Accumulative dose (mg/kg)	39.9 ± 14.6	55.0 ± 42.4	0.839
Cyclosporine A (n; %)	2; 28.6	10; 15.2	0.323
Daily dose/BW (mg/kg/day)	1.826 ± 1.325	2.437 ± 0.934	0.689
Duration (month)	1.7 ± 1.8	2.3 ± 2.5	0.769
Accumulative dose (mg/kg)	130.1 ± 167.6	200.8 ± 332.3	0.904
Mycophenolate mofetil (n; %)	2; 28.6	19; 28.8	1.000
Daily dose/BW (mg/kg/day)	18.375 ± 0.597	13.239 ± 3.905	0.587
Duration (month)	1.9 ± 1.6	1.6 ± 1.0	0.828
Accumulative dose (mg/kg)	1,005.3 ± 863.4	621.6 ± 434.2	0.488
Azathioprine (n; %)	1; 14.3	10; 15.2	1.000
Daily dose/BW (mg/kg/day)	0.947	1.324 ± 0.482	0.743
Duration (month)	1.6	3.5 ± 3.4	0.665
Accumulative dose (mg/kg)	46.4	155.2 ± 210.5	0.647

Values are expressed as mean ± SD or percent unless otherwise listed. Abbreviations: *PJP*: *Pneumocystis jiroveci* pneumonia, IS: immunosuppressants, BW: body weight. *p < 0.05.

Table 3. Logistic Regression Analysis of *PJP* Risk Factors

Factor	OR	95% CI		p value
		Lower	Upper	
Male gender (%)	2.353	0.426	13.002	0.327
Age at IS initiation (10 year)	1.289	0.856	1.940	0.224
Diabetes mellitus (%)	2.240	0.381	13.184	0.373
Chronicity indices in kidney pathology				
Global glomerulosclerosis (every 10% increment)	1.347	1.026	1.770	0.032*
Focal glomerulosclerosis (every 10% increment)	1.129	0.759	1.679	0.548
Interstitial fibrosis (every 10% increment)	2.012	1.230	3.291	0.005*
Tubular atrophy (every 10% increment)	2.411	1.391	4.179	0.002*
Laboratory data at IS initiation				
Albumin (mg/dL)	1.283	0.501	3.282	0.603
BUN (mg/dL)	1.037	1.001	1.076	0.047*
Cr (mg/dL)	1.419	1.026	1.963	0.034*
eGFR (C-G) (mL/min)	0.916	0.825	1.018	0.103
Hb (g/dl)	0.545	0.338	0.878	0.013*
ANC (1000 per cumm)	1.162	0.832	1.623	0.378
ALC (1000 per cumm)	0.150	0.024	0.944	0.043*
Urine PCR (mg/mg)	0.974	0.833	1.138	0.738
Maximal concomitant oral IS drug number	1.412	0.497	4.013	0.517
Oral corticosteroids, daily dose/BW (mg/day/kg)	14.492	0.900	233.357	0.059

Values are expressed as mean ± SD or percent unless otherwise listed. Abbreviations: *PJP*: *Pneumocystis jiroveci* pneumonia, OR: odds ratio, CI: confidence interval, IS: immunosuppressants, BUN: blood urea nitrogen, Cr: creatinine, eGFR (C-G): estimated glomerular filtration rate by Cockcroft-Gault formula, Hb: hemoglobin, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, PCR: protein/creatinine ratio, BW: body weight. *p < 0.05.

eGFR. Therefore, chemoprophylaxis for *PJP* should be considered in such patients.

Considering IgA nephropathy with CKD for example, immunosuppressant therapy for such patients remains controversial. A major barrier for physicians to use immunosuppressants is the possible side effects of therapy. Although it

has been reported that there is a “point of no return” (serum Cr of 3 mg/dL) in IgA nephropathy patients with CKD (13), there is also evidence showing successful treatment by immunosuppressants (14, 15). Therefore, once immunosuppressant therapy is chosen rather than conservative treatment in GN patients with high chronicity of kidney pathology, we

suggest *PJP* chemoprophylaxis should be highly considered since these patients are at high risk for *PJP* infection, a rare but potentially life-threatening complication.

The logistic regression analysis showed that for patients with a high chronicity of kidney pathology were at risk for *PJP* infection after immunosuppressant therapy. The present findings are compatible with previous studies showing immune dysfunction in CKD patients. The underlying mechanisms have been proposed to be the result of defective co-stimulatory signaling from antigen presenting cells, less interleukin-2 production of T-lymphocytes, and abnormal interleukin-2 receptor expression of T-lymphocytes in CKD patients (16-20). On the other hand, though the immunosuppressant dosages of the present *PJP* patients were less than those of patients without *PJP*, they were not significantly different. Since some of these drugs are cleared by the kidneys, one possible explanation for our findings might be that impaired renal function and reduced drug clearance led to an increased immunosuppressant effect and the development of *PJP* infection. Therefore, dose reduction of the immunosuppressant agent and careful monitoring of its serum level might decrease *PJP* risk in advanced CKD patients requiring immunosuppressant therapy.

Although the incidence of *PJP* is low, the prognosis of patients who developed *PJP* infection was very poor and generally fatal in patients with connective tissue diseases (6). Furthermore, the mortality rate can be even up to 63.6% in *PJP* patients who developed acute respiratory failure with underlying HIV infection, hematological malignancy, or connective tissue diseases (21). A recent study showed that the mortality rate was 27% in renal transplant recipients with *PJP* infection (eGFR 31 ± 11 mL/min) (8). However, the current *PJP* patients presented with a much higher mortality rate. Possible explanations for this discrepancy included that the underlying kidney pathology was different, and our *PJP* patients had worse renal function (eGFR 14.9 ± 4.2 mL/min).

In the present study, *PJP* infection was confirmed by examining the BAL specimen instead of the induced sputum in order to increase the diagnostic yield. Although conventional PCR might detect asymptomatic colonization (22), the staining method we used is less sensitive than the PCR-based method. Therefore, we cannot completely exclude the possibility of false negative results in the remaining 66 cases. On the other hand, serum β -D-glucan is a reliable diagnostic marker for *PJP* (23-25). Because the sensitivity for *PJP* is very high, serum β -D-glucan can be used as a screening tool for *PJP*, especially for patients who are not suitable for the BAL procedure (23, 24). Nevertheless, some studies did not find its prognostic value in *PJP* patients (26, 27).

The limitations of our study were the small number of *PJP* patients and its retrospective design. However, we demonstrated significant associations between kidney pathological chronicity and persistent lymphocytopenia and the development of *PJP* in GN patients. Since our study only identified risk factors in GN patients receiving immunosuppres-

sants, it requires further longitudinal studies to elucidate the benefits of *PJP* chemoprophylaxis in such high risk patients. Nevertheless, there have been many reports supporting the rationale and effectiveness of *PJP* chemoprophylaxis in high risk patients. After the introduction of *PJP* chemoprophylaxis among HIV-positive individuals in developed countries, the incidence of *PJP* has decreased (28). A meta-analysis of randomized controlled trials has shown that prophylaxis with TMP-SMX significantly reduced *PJP* infections and *PJP*-related mortality in immunocompromised non-human immunodeficiency virus (HIV)-infected solid and non-solid organ recipients at risk for *PJP* (29). Moreover, routine *PJP* chemoprophylaxis was highly recommended in all renal transplant recipients for the first 3-6 months following transplantation (30, 31).

In conclusion, the findings of the present study indicated that GN patients with high chronicity of kidney pathology were at high risk for *PJP* infection. In addition, the prognosis was very poor in our GN patients with *PJP* infections probably because of immune dysfunction and reduced immunosuppressant clearance caused by advanced CKD. We suggest that prophylactic therapy for *P. jiroveci* and immunosuppressant dose reduction should be considered in such patients, especially when persistent lymphocytopenia is present.

The authors state that they have no Conflict of Interest (COI).

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