Impact of Pneumocystis Pneumonia on Non-HIV Immunocompromised Patient Outcomes

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Research article

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Abstract

Backgrounds

Pneumocystis pneumonia (PCP) remains an important cause of morbidity and mortality in non-HIV immunocompromised patients especially solid organ transplant（SOT）recipients. There is a lack of data on the effects of PCP on the outcomes of them.

Method

We retrospectively analyzed the clinical data of 34 non-HIV immunocompromised patients who were diagnosed with PJP by metagenomic next-generation sequencing(mNGS) combined with clinical symptoms and CT imaging changes admitted to our hospital from October 2018 to December 2020. We use univariable analysis and multi-logistic regression analysis to screen the main risk factors that affect the prognosis.

Results

A total of 65 patients found *Pneumocystis jiroveci* through mNGS from the BALF. Among them 34 non-HIV immunocompromised patients who were diagnosed with PCP were included. The mortality rate was 41.2%. Among them, 19 were kidney recipients, 1 liver recipient, 5 cases of connective tissue disease，4 cases of blood system diseases, 5 cases of others (including tumors and skin diseases). The ICU occupancy rate was 85.3%. The univariable analysis between the two groups found that the main risk factors affecting the outcome included age, body mass index (BMI), albumin (ALB), SOFA score on the first day of entering the ICU, the interval time between symptom onset and the start of TMP/SMX treatment, and invasive mechanical ventilation. However, patients who accepted early combination seems to get better outcome.

Conclusion

Old age, low BMI, hypoalbuminemia, mechanical ventilation, and delayed treatment may be associated with a worse outcome. Early diagnosis and treatment are key factors to improve the outcome of PCP. We should actively correct the malnutrition condition, and give early combination of TMP/SMX and echinocandin therapy may improve the prognosis.

Background

Pneumocystis pneumonia (PCP) is a common opportunistic infection with high mortality in immunocompromised patients, especially non-HIV patients. The mortality of PCP in HIV positive patients has decreased significantly nowadays, instead of increasing in non-HIV patients, most of them were kidney transplant recipients[1−3]. PCP can be insidious and sometimes without specific symptoms at the initial time, but can cause fatal respiratory failure. Because the *Pneumocystis jirovecii* cannot be reliably grown in vitro, the limitations of *Pneumocystis jirovecii* testing tools like microscopical examinations or

Gomori's methenamine silver staining which suffer from low sensitivity[4]. Besides that, the real-time PCR is not conducted in most hospital,which might not be so suitable for immunocompromised patients and delay the treatment. Metagenomic next-generation sequencing (mNGS) of pathogen nucleic has emerged as an important approach for no hypothesis of potential infectious etiologies[5]. Previous studies have found that mNGS has greatly improved the early diagnosis rate of PCP[6–7]，which means the diagnosis of PCP is no longer a challenge, but the prognosis of non-HIV PCP patients varies greatly. There are few studies on PCP in non-HIV patients, and the conclusions of the studies are also inconsistent[8–12]. Our research mainly analyzed the clinical data of 34 non-HIV immunocompromised PCP patients by to describe the clinical characteristics and the prognostic factors of them, in order to find the risk factors, give early intervention, and improve the survival rate.

Methods

Study design and subjects

The mNGS test was performed on clinically suspected PCP patients，and the remaining specimens were sent to microbiological laboratory for Giemsa stain，we didn't conduct PCR for *Pneumocystis jirovecii*. A total of 65 non-HIV immunocompromised patients were found to have *Pneumocystis jirovecii* in the BALF or Blood through mNGS testing. Among them, 34 patients were diagnosed as PCP based on the clinical features，imaging findings and the comprehensive judgment from two senior clinicians in Sichuan Provincial People's Hospital from October 2018 to December 2020.

The clinical data of 34 patients were collected, including: ① demographic data, gender, age, BMI, primary disease; ② clinical symptoms; ③ laboratory test: white blood cell count (WBC), hemoglobin (Hgb), lymphocyte count (L), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), albumin (ALB), lactate dehydrogenase (LDH), creatinine(Cr), $CD4^+/CD8^+$，lymphocyte count, 1-3-β-D-glucan, oxygenation index, Cytokines, SOFA score, mNGS results, mechanical ventilation time, ICU stay, survival time, outcome; ④imaging characteristics, whether co-infected with cytomegalovirus (CMV), bacterial or fungi; ⑤ Treatment plan: starting treatment time, the antibiotic regimen.

Criteria for outcome: Recovered group: Clinical symptoms and laboratory tests improved when discharge, and chest CT lesions absorbed better than before. Death group: Patients with worsening clinical symptoms after PCP treatment, deterioration of laboratory or radiological examination results or died in hospital, or extremely low blood oxygen saturation even after using an invasive mechanical ventilator, gave up treatment which eventually lead to clinical death[13].

Diagnostic criteria of PCP: ①Solid organ transplantation or hematopoietic stem cell transplantation, blood system diseases, rheumatic immune system diseases, tumors, skin system diseases and other non-HIV immunocompromised hosts; ② Subacute onset, progressive breathing difficulty, accompanied by symptoms such as fever, dry cough, dyspnea, and fatigue, with or without positive lung signs; ③ High-resolution chest CT showed typical diffuse network nodes of both lungs starting from the hilum nodal

interstitial infiltration, mainly diffuse ground glass opacity, occasionally with patches, consolidation; ▯ Blood specimens or BALF can find *Pneumocystis jirovecii* from mNGS [14-15].

Statistical method

Statistical analysis was performed on SPSS20.0. Quantitative data conforming to the normal distribution are represented by mean ± standard deviation (x± s), and quantitative data not conforming to the normal distribution are described by the median and interquartile range (P25, P75). The independent-sample t test was used for the data that conformed to the normal distribution, and the rank sum test was used for the data that did not conform to the normal distribution. The qualitative data is expressed by frequency, using the x^2 test method. When the frequency is too small (T<1), the Fisher exact test method was used. The risk factors that affect the prognosis obtained in the univariable analysis were further analyzed by multi-logistic regression analysis. Stata 12.0 was used for Kaplan-Meier survival estimates.

Results

Demographic data and baseline characteristics

There were 34 PCP patients, among them 22 were males (64.7%), 12 females▯35.3%▯, and mortality was 41.2%. 17 cases (50%) required invasive mechanical ventilation, 5 cases in the recovered group, and 12 cases in the death group. Among the 34 patients, a total of 29 patients (85.3%) admitted to the ICU, 15 of them recovered and 14 died (*P*=0.063). The age of the death group (59.2±16.2 years) was significantly higher than that of the recovered group (46.6±11.1 years), and the BMI (18.1±2.6kg/m^2) was significantly lower than the recovered group (21.02±3.1 kg/m^2), there was a statistical difference between the two groups (*P*<0.05). Of the 34 patients, 19 were patients after kidney transplantation. The average time of PJP infection was 5 months after surgery, the longest one was 7 years post-transplant. Seven patients experienced delayed graft function (DGF) after transplantation, and there was no statistical difference between the two groups. The immunosuppressive regimen after kidney transplantation was mainly based on tacrolimus (16 cases in total), combined with Mycophenolate Mofetil▯MMF▯and glucocorticoid, and cyclosporine was chosen when tacrolimus intolerance (3 cases). The median reads of mNGS reads in BALF of 34 patients was 2534, ranging from 10-239032. Of the 34 patients, 14 (41.2%) co-infected with bacteria, and 23 (67.6%) co-infected with CMV, and 5 (14.7%) had fungal pneumonia, there was no statistical difference between the recovered group and the dead group in co-infection. There were no statistical differences in admission to ICU, primary disease, clinical symptoms, whether they were combined with shock at admission, the reads detected by mNGS in BALF, and whether they were co-infected with bacterial, viral and fungal infections (Table 1).

Laboratory examination, Chest imaging characteristics and therapeutic options

Laboratory examination found that the CRP, PCT, LDH on the 7th day, SOFA score on the first day of ICU admission, and the rate of invasive mechanical ventilation in the death group was significantly higher than that of the improvement group, and the lymphocyte count and ALB were lower than the recovered

group. Among the 34 patients, 28 patients underwent Giemsa stain, and only 1 case (2.9%) was positive. The positive rate of the 1-3-β-D-glucan was 70.5% (24/34). Among them, 13 cases were tested for human cytokines, mainly presented with elevated IL-6 and IL-10. Univariable analysis found that ALB, SOFA score on the first day of ICU admission, time from onset to TMP/SMX treatment, and invasive mechanical ventilation may be related to the death outcome.（see Table 2 ）

The time from symptom onset to the start of TMP/SMX treatment, and the effect of therapeutic options on the outcome

The treatment plan of 34 PJP patients were reviewed, including the TMP/SMX group alone, the TMP/SMX combined with echinocandin group, and the echinocandin group alone. About the combination group, we divided them into early combination (less than 5 days) and delayed combination (5 days later), no statistical difference was found between the groups (P>0.05). But in the early combination group, the outcome was better than the delayed combination group, which was shown in Table 3. And compared with the recovered group, the initiation time of the TMP/SMX treatment was delayed in the death group (P<0.05) (see Table 4). The average daily dose of TMP/SMX was higher than that of the death group（5.28±2.00g vs 4.15±2.13g）, there was no statistical difference. Besides that, 19 of 34 patients (55.8%) had a TMP/SMX dose lower than the guideline recommended minimum dose (1.44g four times/day).

Multi-factor Logic Analysis

In the univariable analysis, age, BMI, SOFA score on the first day after entering the ICU, ALB, the time from onset to the initiation of TMP/SMX treatment, and whether mechanical ventilation were related with the risk of death, but after multi-logistic regression analysis, we found no independently related factors. And there was statistical difference between early combination and delayed combination（early combination group got a good outcome.

Final outcome: We conducted the follow-up of 20 PCP patients in the recovered group to January 20, 2021. The average follow-up time: 384 days. The average survival time of death group was 21 days (6,56 days). Two patients died in the recovered group after discharge from the hospital, one of them was a patient after stem cell transplantation, he died of repeated PCP one month later after discharge from the hospital. Another one was a pulmonary fibrosis patient who died of severe pneumonia and septic shock one year later.

Discussion

PCP is a common opportunistic infection both in HIV and non-HIV immunocompromised patients. Previous studies have suggested that long-term high-dose glucocorticoid, low lymphocyte counts, males, CMV infection, and older than 65 years of age are risk factors for PCP[16–17]. However, there are few studies on the prognostic factors of PCP in non-HIV immunocompromised patients with inconsistent conclusions. In our study, the PCP mortality was as high as 41.2%, 82.3% (29/34) of the patients admit to

the ICU, 50% patients (17/34) required mechanical ventilation, and the mortality in the ICU was 48.3% (14/29).

In our study, kidney recipients accounted for 55.8%, connective tissue diseases accounted for 14.8%, hematological diseases accounted for 11.7%, and other 14.7%. The mortality of kidney PCP recipients was 31.5%, and the mortality of non-kidney transplant PCP patients was 53.3%. Univariable analysis found that age, BMI, ALB, SOFA score on the first day of ICU admission, delayed initiation of the treatment, and invasive mechanical ventilation may be risk factors for death in PJP patients. This is consistent with the results of a meta-analysis of prognostic factors for death of non-HIV PCP patients conducted by Yao Liu et al, the risk factors associated with increased mortality include old age, women, respiratory failure, high LDH, Hypoproteinemia, bacterial infection, *Aspergillus* co-infection, etc. ($P < 0.05$) [18]. Older age, low BMI, and hypoalbuminemia all reflect the nutritional status of patients, and patients with poor nutritional status often had high risk of death. Malnutrition may cause the immunosuppress in HIV-related immunodeficiency and is an independent factor associated with poor survival[19], which is consistent with the study conducted in children HIV patients [20]. Mouna Hanachi et al. reported a case of anorexia nervosa patient suffered PCP in a malnourished status, and its secondary immune deficiency is related to malnutrition,besides that the degree of immunodeficiency is directly related to the degree of malnutrition[21]. Therefore, for malnourished PCP patients, nutritional support should be strengthened to reduce the persistent state of immunosuppression. Jumpei Akahane et al. retrospectively analyzed 102 cases of non-HIV PJP with a 30-day mortality about 20.5%. Compared with survivors, the serum ALB level significantly lower and the age was older in non-survivors. Multi-logistic regression analysis showed that high nitrogen/ALB ratio is significantly correlated with the 30-day mortality risk at the beginning of treatment[22].

Multi-logistic regression analysis found no independent risk factors associated with death in our research. However, there was a significant difference in the survival time between patients older than 60 years and younger than 60 years. (See Table 5 for the survival curve), which is similar with a study conducted by Benjamin Jean Gaborit and other scholars on the outcome and prognostic factors of non-HIV PJP patients, they found that advanced age may be independent risk factor of progressing to severe PCP, the SOFA score and co-infected with virus are closely related to the 90-day high mortality of the patient, and if the BALF present lymphocyte elevation of alveolar inflammation ((lymphocytes > 10%, neutrophils > 5%, and activation Macrophages), that might be the protective factors[23].

However, in our study, there were no difference on whether there was shock at admission, co-infected with CMV, bacteria or fungi, the average daily dose of TMP/SMX in the first 7 days of treatment, and LDH level on the 7th day. However, the LDH of the death group on day 7 was significantly higher than that of the recovered group. Zaman et al. reported that LDH > 450 U/L can predict *Pneumocystis jirovecii* infection, normal LDH cannot rule out the *Pneumocystis jirovecii* infection, and the progressive increase of LDH level during treatment can predict poor prognosis, but without specificity[24]. A 17 years retrospective study conducted by Julius J Schmidt et al. found that LDH was a predictor of hospital mortality by multi-

logistic regression analysis (adjusted OR 1.17 (95% CI 1.09–1.27), p < 0.0001), the cut-off point of LDH was 495U/L, and the specificity and sensitivity of predicting hospital mortality was 70%[25].

Previous studies have suggested that the combined infection of CMV and *Pneumocystis jirovecii* increased the risk of ARDS and the length of stay in the ICU, but there was no statistical difference in mortality between the two groups, but ARDS was an independent risk factor of death in PCP patients[26]. This is consistent with our research. In this study, 15 patients in the recovered group were simultaneously infected with CMV, and 8 patients in the death group were infected with CMV,there was no statistical difference between the two groups. However, CMV infection may be a risk factor for PCP in kidney transplant patients, because CMV infection may change the recipient's immune response and cause immunocompromise[17]. In our research, we calculated the average daily dose of TMP/SMX and found that there was no statistical difference between the recovered group and the death group. However, 55.8% of patients did not reach the recommended dose, there was a statistical difference in the time from symptom onset to the initiation time of TMP/SMX treatment. The earlier the treatment started, the less likely that to progress to severe cases. An observational study conducted by *Ryoung-Eun Ko* et al. concluded that when the non-HIV PCP patients present hypoxemic respiratory failure, there is no correlation between the time of PCP treatment and the outcome, but age (adjusted OR 1.07, 95% confidence interval 1.01–1.14) and initial treatment failure (adjusted OR 13.03, 95% confidence interval 2.34–72.65) were independently associated with increased mortality[11]. The study by *Julius J Schmidt* et al. found that 40% of patients received TMP/SMX at a lower dose than recommended, and these patients had a higher risk of death (HR 1.80 (95% CI 1.10–3.44), P = 0.02)[25].

The clinical treatment plan of all patients in our study were mainly divided into the single TMP/SMX group, the early combination with echinocandin, delayed combination with echinocandin and single echinocandin group. We found that the P value was equal to 0.07 between the four groups, there was no statistical difference, maybe it was because of the small sample size. However, it can be seen from Table 6 that the early combination group accounted for the highest proportion in the recovered group. The patients who died were mainly distributed in the single TMP/SMX group or delayed combination group. TMP/SMX is the first-line treatment choice of PCP. It is recommended that TMP (trimethoprim) 15-20mg/kg/day, 3–4 times per day, and last about 14–21 days. Or 5mg/kg TMP, 25mg/kg SMX 3–4 times per day, for 21 days[13] .However, the effectiveness of TMP/SMX in the treatment of PCP is limited by its serious adverse drug side effects. The drug side effects and intolerance can cause the initial treatment failure or insufficient dose which may cause bad outcome. In our study, we also calculated the total dose of TMP/SMX in the first 7 days of patients, and found that the total dose in the first 7 days in the improvement group (35.1 ± 16.01g) was higher than that of the death group (29.08 ± 15.01g), but there was no statistical difference between the two groups. As we know, *Pneumocystis jirovecii* is divided into three forms: trophozoites, cysts, and sporozoites. Caspofungin can inhibit the formation of *Pneumocystis jirovecii* cysts, but there are few studies on the safety and effectiveness of combined with TMP/SMX. In a retrospective study of HIV-infected patients with moderate to severe PJP, it was found that compared with TMP/SMX monotherapy, combination of caspofungin and TMP/SMX was an effective and promising

first-line treatment without more adverse events. Patients receiving caspofungin treatment have a better treatment response and lower all-cause hospital mortality. It is recommended that we should start combination with caspofungin as soon as possible[27]. A retrospective cohort study conducted by *Zhang Gensheng* et al. found that caspofungin combined with TMP/SMX was an effective treatment for severe non-HIV PCP patients, especially mechanical ventilated patients, although the samples size was just 14[28],which is consistent with our research. *Fan Jin* et al. found that high initial BDG concentration may be an indicator for predicting the efficacy of caspofungin in non-HIV PCP patients, and even suggest that in non-HIV PCP patients with moderate to severe respiratory failure and whose BDG ≥ 800 pg/ml, caspofungin and TMP/SMX combination should be chosen as initial treatment[29], which was the same with our research that early combination tend to get better prognosis. Besides, other studies have shown that low-dose TMP/SMX combined with caspofungin for kidney transplant recipients can effectively treat PCP and reduce the adverse reactions of TMP/SMX[30].

The guidelines recommend that glucocorticoids can be used to treat moderate to severe HIV-positive PCP patients. However, the use of glucocorticoids in non-HIV PCP patients is still controversial. In this study, glucocorticoids are not used as routine treatments for non-HIV patients, except for liver and kidney transplantation, in whom we suspended all the anti-rejection drugs, and prescribed 40–80 mg methylprednisolone per day as an alternative treatment. Recently, *William Mundo* et al. found that glucocorticoids can significantly reduce the mortality of non-HIV PCP patients[31], although it still remains controversial. Glucocorticoid treatment may increase the risk of Candida and other fungal infections.

The PCP guidelines for SOT recommend routine TMP-SMX prevention for 6–12 months after transplantation. Routine prevention should also be carried out for patients who suffered connective tissue diseases and take 20 mg prednisone for more than 8 weeks. The recommended preventive dose is 0.48-0.96g qd or 0.96g tiw. Due to the adverse effects of TMP-SMX, no patients in our research were routinely prevented before PCP occurred, which is similar to other previous studies[13–14].

According to our research, for patients with poor nutritional status, elderly SOT or oral prednisone 20mg glucocorticoid patients, more education should be strengthened, we should perform targeted prevention, because these patients may have higher mortality and worse prognosis.

This study still has some limitations. First, because PCP is a rare disease, the sample size of the study is small, which may affect the results of multi-logic regression analysis, resulting in false negatives and unable to establish a prognostic model. But recently we included more and more PCP patients than before because the application of mNGS and can screen more PCP patients earlier than before, we are conducting prospective research and looking forward to sharing more research results in the future. Second, as a retrospective study, patients came from different ICU, and there may be differences in diagnosis and treatment which may cause selection bias. Third, because the enrolled patients are immunocompromised patients with different primary diseases, such as stem cell transplantation, kidney transplantation and autoimmune disease itself, whose different immunosuppression status may lead to selection bias.

Conclusion

Non-HIV PCP patients progresses rapidly and with a high mortality rate. Old age, malnutrition, hypoproteinemia, mechanical ventilation, and delayed treatment may be associated with a worse prognosis. Early diagnosis and treatment are key factors to improve the outcome of PCP. We should actively correct the malnutrition condition, and give early combination of TMP/SMX and echinocandin therapy may improve the prognosis.

Declarations

1. The work described has not been submitted elsewhere for publication, in whole or in part, and all the authors listed have approved the manuscript that is enclosed.
2. I have read and have abided by the statement of ethical standards for manuscripts submitted to Journal of Cardiothoracic Surgery.
3. Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images. The ethics committee of our institution approved to publish this case report.Approved by Sichuan Academy of Medical Sciences & Sichuan Procvincial People's Hospital. No:2019.321
4. Conflict-of-interest statement: All authors declare that they have no conflict of interest.
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7. Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory).Contributors RY; SP; YH; FY were responsible for the organization and coordination of the case. Contributors XZ; HH; MCwere responsible for the data collection. XL; TLwere responsible for the data analysis. Contributors XH; LPwere the chief investigators. All authors developed the trial design.All authors contributed to the writing of the final manuscrip.

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Tables

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