The outcome predictors and therapeutic strategy of pneumocystis pneumonia in North China: a double-center retrospective study

Wei Hua
Capital Medical University
Yang Yang
Capital Medical University
Zheng Zhang
the Infectious Disease Hospital in Herbin
Wei Zhang
Capital Medical University
Jing Zeng
Capital Medical University
Caiping Guo
Capital Medical University
Yulin Zhang (zhangyulin1968@126.com)
Capital Medical University https://orcid.org/0000-0003-2354-7458

Research article

Keywords: outcome predictor, pneumocystis jirovecii, pneumocystis pneumonia, treatment, trimethoprim-sulfamethozole

Posted Date: April 17th, 2019

DOI: https://doi.org/10.21203/rs.2.9235/v1

Abstract

Background: Pneumocystis pneumonia (PCP) is common in HIV/AIDS patients with advanced immunosuppression. Trimethoprim/sulfamethoxazole (TMP/SMX) is recommended as the first-line anti-pneumocystis agent as soon as PCP is suspected based on its typical feature. However, the clinical characteristic and therapeutic strategy of Chinese PCP were not well-known. Methods: We retrospectively investigated 473 HIV associated PCPs in North China from double centers, Beijing You An Hospital during 2010 to 2017 and the Infectious Disease Hospital in Harbin during 2015 to 2017. HIV associated PCP were diagnosed as the guideline recommended by CDC, NIH and HIV Medicine Association of IDSA. Demographic and clinic data were collected and statistically analysed as the parameter distribution feature. Results: Among 473 HIV associated PCPs, we found that men were over-represented in PCP due to the high incidence of HIV infection among male homosexuality, and over one-third of them were aware of their HIV infection ago but did not maintain effective antiretroviral therapy. A history of smoking and multi-organism infection or system infection were common among them. In the multivariate analysis, we found lactate dehydrogenase (LDH) (OR 1.020, 95% CI 1.006-1.033, P=0.005), alveolar-arterial O2 difference ([A-a] DO2) and neutrophils counts (OR 1.051, 95% CI 1.005-1.099, P=0.030) were unfavourable predictors and CD4 cell counts (OR 0.900, 95% CI 0.813-0.996, P=0.041) were favourable predictor of PCP outcome. Trimethoprim/sulfamethozole (TMP/SMZ) but not TMP/SMX was used to anti-pneumocystis therapy in these patients with a low side-effect incidence which mainly forcused on epispasis, fever, liver injury and myelosuppression. Caspofungin was the only alternative medicine for those presented poor efficacy or could not tolerate the side-effects of TMP-SMZ and near 30 percent of moderate/severe PCP received glucocorticoid treatment. Conclusion: The present data suggest that high levels of serum-LDH, [A-a] DO2 and neutrophils counts and low CD4 cell counts predict poor outcome of PCP. TMP/SMZ can cure most PCPs with a low side-effect incidence and caspofungin is an effective alternation. A larger prospective study is needed to obtain better estimates of PCP in China.

Background

Pneumocystis pneumonia (PCP), mainly caused by *pneumocystis jirovecii*, is a common opportunistic infection in HIV/AIDS patients and non-HIV/AIDS patients with advanced immunosuppression [1, 2]. It is estimated that nearly 500,000 cases of PCP occur annually in the world [3]. PCP remains a frequent AIDS-defining disease in the developed countries, but the epidemiologic data from the developing countries with high burden of HIV/AIDS are limited [4]. The diagnosis of *pneumocystis* infection usually meet the difficulty that this fungal pathogen cannot be cultured and invasive bronchoalveolar lavage (BAL) is necessary to improve positive diagnosis [5]. So most PCP cases were a presumptive diagnosis and accompanied by empiric anti-*Pneumocystis* therapy. Trimethoprim/sulfamethoxazole (TMP/SMX) is recommended as first-line anti-PCP and prophylaxis regimen, but high incidence of intolerable side effects and putative sulfonamide drug resistance, and fewer alternative regimens are emerging concern [4]. In China, HIV/AIDS is a high risk factor which contributes over 70 percent of PCP cases, far exceeding organ transplantation, malignancy or hypoimmunity. The mortality of PCP patients was 14.61% even if

anti-*pneumocystis* therapy [6]. The only anti-*pneumocystis* sulfonamide is trimethoprim/sulfamethozole (TMP/SMZ) but not TMP/SMX in China. There is still a certain gap between China and developed countries in the diagnosis and treatment of HIV associated PCP. Further, HIV/AIDS is managed and admitted to the special hospitals for infectious diseases in China which cannot compare with general hospitals in both medical equipment and technology. There is also a gap in the technology of diagnosis and treatment of PCP between different regions of this country. Therefore, we selected Beijing You An Hospital, one of the best medical condition in China, and the Infectious Disease Hospital in Harbin with relatively backward medical condition to investigate the clinical feature, therapeutic strategy and outcome of HIV associated PCP in North China, for the purpose of collecting references for draft diagnosis and treatment norms of the disease.

Methods

Patients

473 HIV/AIDS patients with PCP infection who were received anti-PCP therapy in Beijing You An Hospital during 2010 to 2017 and the Infectious Disease Hospital in Harbin during 2015 to 2017 were screened in this study. All of them had a fever, cough or dyspnea symptom and were presumptively diagnosed PCP in accordance with the typical diffuse ground glass obstacle (GGO) in chest X-ray scan and a positive HIV screaning test and low CD4 cell counts. They did not confess their HIV infection before but a series of tests confirmed the suspected diagnosis. Demographic and clinical information were obtained from the information network management center in both hospitals. This study was approved by the Ethics Committee of Beijing You An Hospital.

Diagnosis of HIV infection and anti-HIV therapy

Western blotting was used as a definite diagnosis test for HIV infection in the patients with positive serum anti-HIV antibody. HIV RNA load in plasma and CD4 cell counts were regularly monitored in these patients. Most of these patients received first-line antiretroviral therapy (ART) including tenofovir (300mg once per day) or zidovudine (300mg twice per day), lamivudine (300mg once per day) and efavirenz (600mg once per day) or Nevirapine (200mg twice per day), and some of them received second-line ART because of drug resistance in which efavirenz or Nevirapine was substituted by lopinavir/ritonavir (400/100 mg twice per day). Both first-line and second-line ART were freely provided by China government.

Pneumocystis Pneumonia diagnosis and grouping

As the guidelines from CDC, NIH and HIV Medicine Association of IDSA [2], a presumptive diagnosis strategy for PCP included: 1) a definite HIV infection with CD4 counts below 200 cells/mm3, 2) subacute onset of fever, dry cough, progressive dyspnea and chest tight, 3) high breath and heart rate with or without dry rale or Velcro rale, 4) typical diffuse GGO starting from the hilus of the lungs in chest X-ray examination, and 5) hypoxemia without hypercapnia in blood gas analysis. A further definitive diagnosis of PCP included cytopathologic demonstration of organisms with Giemsa or Gram-Weigert stain in

spontaneously expectorated or induced sputum, bronchoalveolar lavage (BAL) fluid, or in tissue. Polymerase chain reaction (PCR) was selected as an rapid method for diagnosing PCP. PCP was divided into mild group (room air arterial oxygen [pO2] ≥70 mm Hg or alveolar-arterial O2 difference [A-a] DO2 <35 mm Hg) and moderate/severe group ([A-a] DO2 ≥35 mm Hg).

Anti-*Pneumocystis* treatment

Once PCP was presumptively diagnosed, 21 days of trimethoprim-sulfamethozole (TMP-SMZ) were rapidly selected as first-line anti-PCP therapy, in which TMP was 15-20 mg/kg/d and SMZ was 75-100 mg/kg/d. Caspofungin was selected as a combined treatment for the severe cases, or alternative medicine for the cases those did not tolerate TMP-SMZ.

Statistical analysis

In univariate analysis, *Mann-Whitney U* test was used to analyse non-normal distribution variables, *Chi-square* test was used for counting variable. Multivariate logistic regression analysis was used to obtain the independent risk factors and *OR* values, and the prognostic model with independent risk factors. The area under the curve (*AUC*), cut-off value, sensitivity and specificity of the prognostic model were analyzed with the receiver operating curve (*ROC*). A statistical significance was defined as a value of $p<0.05$ and PASW statistics 18 software was used in this study.

Results

1. Participants

Among the two recruitment sites, 429 participants were selected from Beijing You An Hospital, the famous infectious disease hospital in the capital of the country, and 44 participants were selected from the Infectious Disease Hospital in Harbin, located in northeast China. Although these participants were only selected from the two sites, they were distributed throughout the country, especially North China (**Fig. 1**). Average age of these subjects was 38.9-year-old, and 95.35 percent of them were men owe to the high HIV infection rate in men. 27.27 percent of subjects had a history of smoking. Over one-third (32.77%) of these patients knew that they had infected HIV before, and 41.29 percent of them had received irregular ART which did not effectively reconstitute host immunity. Most participants were homosexual (30.44%), even if 49.05 percent of them intentionally or unintentionally concealing HIV infection route. Near half of 473 participants accompanied extra-lung organism infection (48.41%), and over two third of them had other organism infection in lung (77.59%). The demographics of two groups were summarized in **Table 1**. There was no difference in demographics between the two groups except for age and former lung diseases.

2. The clinical feature of these patients with *pneumocystis* pneumonia

The consciousness of almost all 473 patients was clear even in severe cases (99.63% in mild group and 99.51% in moderate/severe group). The respiratory rates were fast in these patients (21.59±4.75 breath

per minute in mild group and 23.18±5.82 breath per minute in moderate/severe group) and the respiratory rates of moderate/severe group were faster than that of mild group (p<0.01). Similarly, heart rates were relatively fast (93.07±15.89 beat per minute in mild group and 95.68±16.10 beat per minute in moderate/severe group). Overall, average auxiliary temperature was 37.14°C in mild group and 37.40°C in moderate/severe group and the body temperature of moderate/severe group were higher than that of mild group (p<0.01). Mean blood pressure of these patients was in the normal range (87.38 mmHg in mild group and 86.91 mmHg in moderate/severe group). The median of white blood cell counts was 5.26×109/L in mild group and 6.67×109/L in moderate/severe group, and white blood cell counts of moderate/severe group was more than that of mild group (p<0.01). These patients had mild anemias and the average hemoglobin were 118.15 g/L in mild group and 119.97 g/L in moderate/severe group. Interestingly, the average platelet count of moderate/severe group (255.95×109/L) was more than that of mild group(220.48×109/L, p<0.01) and the serum creatinine level of moderate/severe group (62.44μmol/L) was lower than that of mild group (67.72μmol/L, p<0.01), which seem to differ from other pneumonia and infectious diseases. The serum lactate dehydrogenase (LDH) and high-sensitivity C-reactive protein (hCRP) of moderate/severe group (LDH 456.82 U/L and hCRP 57.40 mg/L) was higher than that of mild group (LDH 328.65 U/L and hCRP 39.29 mg/L, p<0.01). However, two important parameters of HIV infection, CD4 cell counts and plasma HIV loads were not different between two groups in which CD4 cell counts were 53.53×106/L in mild group vs. 34.19×106/L in moderate/severe group and plasma HIV loads were 5.3 log10 copies/mL in mild group vs. 5.25 log10 copies/mL in moderate/severe group(p>0.05). The mortality of moderate/severe PCP (28.29%) was significantly higher than that of mild PCP (13.06%, p<0.01) (**Table2**).

3. **The strategy and outcome of anti-*pneumocystis* pneumonia therapy**

In this study, 21 days of TMP-SMZ (TMP 15-20 mg/kg/d and SMZ 75-100 mg/kg/d) were selected as standard first-line anti-PCP therapy. Some patients could not tolerate the allergies or various side effects of sulfonamide and had to reduce TMP-SMZ dose or shorten therapeutic course. Here, we did not find the difference in the selection of TMP-SMZ dose or therapeutic course between mild PCP and moderate/severe PCP (**Table3**). Caspofungin was selected as a combined treatment for the severe cases, or alternative medicine for the cases those could not tolerate side-effect of TMP-SMZ due to lack of second-line anti-PCP medicines including primaquine, pentamidine, dapsone and atovaquone in China. It was shown that combined caspofungin treatment was more common in moderate/severe group (72.20%) than that in mild group (52.61%, p<0.01) (**Table3**). Glucocorticoid was recommended for the treatment of moderate/severe PCP as the guideline [2]. In this study, glucocorticoid usage rate in moderate/severe group (29.76%) was significantly higher than that in mild group (16.42%, p<0.01) (**Table3**).

4. **Side-effects of trimethoprim/sulfamethozole administration**

Although sulfonamide has a good anti-*pneumocystis* effect, the facts cannot be denied that the high incidence of intolerable negative reaction occurs during standard dose of trimethoprim/sulfamethozole

usage which usually interrupts anti-*pneumocystis* treatment. In this study, the incidence of TMP-SMZ induced epispasis was 6.34% and mild group was higher than moderate/severe group (8.96% vs. 2.93%, $p<0.01$). TMP-SMZ induced fever was 2.99% and liver injury was 3.38%. TMP-SMZ induced renal injury was rare. TMP-SMZ associated leukopenia was 7.82% and thrombocytopenia was 2.33% and anemia was 2.96%. Severe alimentary tract indisposition was 1.90% (**Table4**). Totally, the incidence of TMP-SMZ associated side-effects was low and mainly focused on epispasis, fever, liver injury and myelosuppression. the incidence of TMP-SMZ associated side-effects was low and mainly focused on epispasis, fever, liver injury and myelosuppression.

5. **Multivariate analysis for predictors of favorable and unfavorable outcome among *pneumocystis* pneumonia patients**

Whether death or not of these patients was selected as the dependent variable, multivariate logistic regression analysis was performed with the variables of demographics, clinical features listed in table 1 and 2 as independent variables to explore the predictors of favorable and unfavorable treatment outcome among PCP. In the multivariate analysis, we found CD4 cell counts were favorable predictor of PCP outcome (OR 0.900, 95% CI 0.813-0.996, $P=0.041$), and lactate dehydrogenase (OR 1.020, 95% CI 1.006-1.033, $P=0.005$), alveolar-arterial O2 difference (OR 1.051, 95% CI 1.005-1.099, $P=0.030$) and neutrophils counts (OR 1.436, 95% CI 1.002-2.060, $P=0.049$) were unfavorable predictors of PCP outcome (**Table5**). Further, we constructed a logistic prognostic model [prognostic index=-11.953+0.049×alveolar-arterial O2 difference+0.019×lactate dehydrogenase level+0.362×neutrophils counts-0.106×CD4 cell counts]. A receiver operating characteristic (ROC) curve was employed to identify the prognostic model and area under curve (AUC) was 0.959 (95%CI 0.914-1.000, cut-off value 0.442, P=0.000), with sensitivity and specificity predictive values of 87.5% and 3.6%, respectively (**Figure2**).

Discussion

Although there was a high prevalence of PCP in HIV/AIDS patients with advanced immunosuppression (25.4% in European and 23–31% in USA) [4, 7], most PCP cases were clinically diagnosed without microbiology evidence in the world, even in the developed countries [8, 9], because of the difficulty of pulmonary specimens acquisition and *pneumocystis* culture [10-12]. Subacute onset of fever, dry cough and exertional dyspnea are usually the main symptoms of PCP, accompanied by typical bilateral GGO with or without cystic lesions on chest computed tomography (CT) scans, which is used as a basis for presumptive diagnosis of PCP. Confirmation of HIV infection and low CD4 cell counts are necessary for HIV associated PCP diagnosis, and serum Lactate dehydrogenase level and arterial oxygen partial pressure are usually used to identify the severity of the disease. In this study, the abnormal signs of respiratory rate, heart rate and body temperature could be found in PCP and moderate/severe PCP had a faster respiratory rate and higher body temperature. It seems that white blood cell count, serum LDH and hCRP but not CD4 cell count or plasma HIV load reflect the severity of PCP. CD4 cell counts, lactate dehydrogenase, alveolar-arterial O2 difference and neutrophils counts were predictors of PCP outcome. World widely, empiric anti-*pneumocystis* treatment with 21 days of TMP/SMX should be initiated as soon

as PCP is suspected, according to the above clinical manifestations [13]. In most case, it does not need to be performed immediately that microbiological tests for *pneumocystis* including microscopic detection of cysts and trophic forms of *pneumocystis jirovecii* and polymerase chain reaction (PCR) [14]. A research in Uganda suggested the high concordance between Giemsa stain and PCR [15]. Even with over 90% sensitivity rates, direct examination and immunofluorescence and PCR are not available in all settings because they require trained personnel [3]. A meta-analysis confirmed the negative diagnosis value of a negative serum (1-3)-β-D-Glucan in ruling out PCP in HIV/AIDS patients. The epidemiological characteristics of PCP in China seem not to differ from other developing countries [16]. A resent research reported that PCP accounted for 11.9 percent of all opportunistic infections in HIV/AIDS patients in Sichuan, a province of Southwest China, and CD4 counts less than 100 cells/mm3 and non-cART were risk factors for high mortality of these patients [17]. Parallel to the imbalance in economy in China, there is the imbalance in medical condition, in which it is developed in the eastern and southern coastal areas of China and developing in other regions.

Globally, TMP/SMX has been used as the first-line agent for anti-PCP given its cost and effectiveness in both treatment and prophylaxis [18]. Over half of patients those admitted TMP/SMX anti-PCP treatment experienced adverse drug reactions (ADRs) of sulfamide, which could lead to discontinuous treatment [19-21]. ADRs of sulfamide included gastrointestinal symptoms, fever, rash, thrombocytopenia, neutropenia, and transaminase elevation [19], rarely severe ADRs including Stevens-Johnson syndrome or toxic epidermal necrolysis [2]. ADRs correlate with sulfamide therapeutic dosage and period [21]. Although epispasis, fever, liver injury and myelosuppression can be found in our study, it is fortunate that they are not common. Mutations within dihydropteroate synthase (DHPS) gene of *pneumocystis* jirovecii render potential resistance to sulfamide, which decreases efficacy of TMP/SMX [18]. It is suggested that the prevalence of DHPS mutations correlate with sulfa-drug usage [22, 23]. Inappropriate treatment of PCP in HIV-positive patients can aggravate sulfamide resistance [24]. The PCP patients with poor therapeutic effects can not be completely excluded from sulfamide resistance in our study, although no drug resistance test is performed. For TMP/SMX intolerance or resistance cases, alternative agents were recommended, including pentamidine, primaquine plus clindamycin, dapsone plus TMP, or atovaquone [2, 4, 13]. However, the status of pentamidine and primaquine out of stock restricts implementation of alternative agents for anti-PCP in China. Caspofungin has also been reported to select as a salvage treatment in PCP [25]. Caspofungin and TMP-SMZ co-treatment had been reported to improve PCP patients' outcome and decrease ADRs of sulfamide in China [26]. Caspofungin combined with clindamycin were also reported to successfully replace TMP-SMZ in anti-PCP treatment [27]. In this study, combined caspofungin was commonly used to anti-PCP treat in North China, especially for moderate/severe PCP. Glucocorticoid can also be found to be used in anti-PCP therapy even if in mild PCP.

Mortality of PCP ranges from 10–30% if the diagnosis has not been delayed [3]. Besides sulfamide resistance or intolerance, severe immunodeficiency, high virus load, and wasting/cachexia correlate with poor mortality of PCP [15, 28]. Our research showed that the mortality of these patients was from 13.06% to 28.29%.

Conclusion Our results suggest that high levels of serum-LDH, [A-a] DO2 and neutrophils counts and low CD4 cell counts predict poor outcome of the HIV associated PCP in North China. TMP/SMZ can cure most PCPs in these patients with a low side-effect incidence and caspofungin is an effective alternation. A larger prospective study is needed to obtain better estimates of PCP in China.

Abbreviations

ADRs: adverse drug reactions; ART: antiretroviral therapy; [A-a] DO2: alveolar-arterial O2 difference; BAL: bronchoalveolar lavage; GGO: ground glass obstacle; hCRP: high-sensitivity C-reactive protein; LDH: lactate dehydrogenase; PCP: *pneumocystis* pneumonia; PCR: polymerase chain reaction; SMX: sulfamethoxazole; SMZ: sulfamethozole; TMP: trimethoprim.

Declarations

Acknowledgements

Not Applicable

Funding

Y. Zhang receives funding support from the National Natural Science Foundation of China (81571178, 81873761, 81371399) and the 13th Key Science and Technology Five Year Plan of China (2018ZX10302104). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and material

Not Applicable

Authors' contribution

YZ and CG designed the study; WZ, JZ and ZZ collected the clinical data; WH and Y Y analyzed the data; YZ prepared the manuscript. All authors have read and approved the final manuscript.

Ethic approval and consent to participate

This study was approved by the Ethics Committee of Beijing You An Hospital (2019-003-02-KY). Written informed consents were obtained from all participants

Consent for publication

Not Applicable

Competing interests

The authors declare that they have no conflict of interest.

References

1. Thomas CF, Jr., Limper AH: **Pneumocystis pneumonia**. *The New England journal of medicine* 2004, **350**(24):2487-2498.

2. Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE, National Institutes of H, Centers for Disease C, Prevention, America HIVMAotIDSo: **Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014, **58**(9):1308-1311.

3. Bongomin F, Gago S, Oladele RO, Denning DW: **Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision**. *Journal of fungi* 2017, **3**(4).

4. Huang L, Cattamanchi A, Davis JL, den Boon S, Kovacs J, Meshnick S, Miller RF, Walzer PD, Worodria W, Masur H *et al*: **HIV-associated Pneumocystis pneumonia**. *Proceedings of the American Thoracic Society* 2011, **8**(3):294-300.

5. Thomas CF, Jr., Limper AH: **Current insights into the biology and pathogenesis of Pneumocystis pneumonia**. *Nature reviews Microbiology* 2007, **5**(4):298-308.

6. Wang XL, Wang XL, Wei W, An CL: **Retrospective study of Pneumocystis pneumonia over half a century in mainland China**. *Journal of medical microbiology* 2011, **60**(Pt 5):631-638.

7. Buchacz K, Baker RK, Palella FJ, Jr., Chmiel JS, Lichtenstein KA, Novak RM, Wood KC, Brooks JT, Investigators H: **AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study**. *Aids* 2010, **24**(10):1549-1559.

8. Grabar S, Lanoy E, Allavena C, Mary-Krause M, Bentata M, Fischer P, Mahamat A, Rabaud C, Costagliola D, Clinical Epidemiology Group of the French Hospital Database on HIV: **Causes of the first AIDS-defining illness and subsequent survival before and after the advent of combined antiretroviral therapy**. *HIV medicine* 2008, **9**(4):246-256.

9. Podlasin RB, Wiercinska-Drapalo A, Olczak A, Beniowski M, Smiatacz T, Malolepsza E, Juszczyk J, Leszczyszyn-Pynka M, Mach T, Mian M *et al*: **Opportunistic infections and other AIDS-defining illnesses in Poland in 2000-2002**. *Infection* 2006, **34**(4):196-200.

10. Prebil SE, Andrews J, Cribbs SK, Martin GS, Esper A: **Safety of research bronchoscopy in critically ill patients**. *Journal of critical care* 2014, **29**(6):961-964.

11. Damiani C, Le Gal S, Da Costa C, Virmaux M, Nevez G, Totet A: **Combined quantification of pulmonary Pneumocystis jirovecii DNA and serum (1->3)-beta-D-glucan for differential diagnosis of pneumocystis pneumonia and Pneumocystis colonization**. *Journal of clinical microbiology* 2013, **51**(10):3380-3388.

12. Esteves F, Cale SS, Badura R, de Boer MG, Maltez F, Calderon EJ, van der Reijden TJ, Marquez-Martin E, Antunes F, Matos O: **Diagnosis of Pneumocystis pneumonia: evaluation of four serologic biomarkers**. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2015, **21**(4):379 e371-310.

13. Salzer HJF, Schafer G, Hoenigl M, Gunther G, Hoffmann C, Kalsdorf B, Alanio A, Lange C: **Clinical, Diagnostic, and Treatment Disparities between HIV-Infected and Non-HIV-Infected Immunocompromised Patients with Pneumocystis jirovecii Pneumonia**. *Respiration; international review of thoracic diseases* 2018.

14. Song Y, Ren Y, Wang X, Li R: **Recent Advances in the Diagnosis of Pneumocystis Pneumonia**. *Medical mycology journal* 2016, **57**(4):E111-E116.

15. Taylor SM, Meshnick SR, Worodria W, Andama A, Cattamanchi A, Davis JL, Yoo SD, Byanyima P, Kaswabuli S, Goodman CD *et al*: **Low prevalence of Pneumocystis pneumonia (PCP) but high prevalence of pneumocystis dihydropteroate synthase (dhps) gene mutations in HIV-infected persons in Uganda**. *PLoS One* 2012, **7**(11):e49991.

16. Chen M, Xu Y, Hong N, Yang Y, Lei W, Du L, Zhao J, Lei X, Xiong L, Cai L *et al*: **Epidemiology of fungal infections in China**. *Frontiers of medicine* 2018, **12**(1):58-75.

17. Pang W, Shang P, Li Q, Xu J, Bi L, Zhong J, Pei X: **Prevalence of Opportunistic Infections and Causes of Death among Hospitalized HIV-Infected Patients in Sichuan, China**. *The Tohoku journal of experimental medicine* 2018, **244**(3):231-242.

18. Huang YS, Yang JJ, Lee NY, Chen GJ, Ko WC, Sun HY, Hung CC: **Treatment of Pneumocystis jirovecii pneumonia in HIV-infected patients: a review**. *Expert review of anti-infective therapy* 2017, **15**(9):873-892.

19. Gordin FM, Simon GL, Wofsy CB, Mills J: **Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome**. *Annals of internal medicine* 1984, **100**(4):495-499.

20. Goldman JL, Jackson MA, Herigon JC, Hersh AL, Shapiro DJ, Leeder JS: **Trends in adverse reactions to trimethoprim-sulfamethoxazole**. *Pediatrics* 2013, **131**(1):e103-108.

21. Yang JJ, Huang CH, Liu CE, Tang HJ, Yang CJ, Lee YC, Lee KY, Tsai MS, Lin SW, Chen YH *et al*: **Multicenter study of trimethoprim/sulfamethoxazole-related hepatotoxicity: incidence and associated factors among HIV-infected patients treated for Pneumocystis jirovecii pneumonia**. *PLoS One* 2014, **9**(9):e106141.

22. Ponce CA, Chabe M, George C, Cardenas A, Duran L, Guerrero J, Bustamante R, Matos O, Huang L, Miller RF *et al*: **High Prevalence of Pneumocystis jirovecii Dihydropteroate Synthase Gene Mutations in Patients with a First Episode of Pneumocystis Pneumonia in Santiago, Chile, and Clinical Response to Trimethoprim-Sulfamethoxazole Therapy**. *Antimicrobial agents and chemotherapy* 2017, **61**(2).

23. Kazanjian PH, Fisk D, Armstrong W, Shulin Q, Liwei H, Ke Z, Meshnick S: **Increase in prevalence of Pneumocystis carinii mutations in patients with AIDS and P. carinii pneumonia, in the United States and China**. *The Journal of infectious diseases* 2004, **189**(9):1684-1687.

24. Denning DW, Perlin DS, Muldoon EG, Colombo AL, Chakrabarti A, Richardson MD, Sorrell TC: **Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities**. *Emerging infectious diseases* 2017, **23**(2):177-183.

25. Armstrong-James D, Stebbing J, John L, Murungi A, Bower M, Gazzard B, Nelson M: **A trial of caspofungin salvage treatment in PCP pneumonia**. *Thorax* 2011, **66**(6):537-538.

26. Maximova N, Schillani G, Simeone R, Maestro A, Zanon D: **Comparison of Efficacy and Safety of Caspofungin Versus Micafungin in Pediatric Allogeneic Stem Cell Transplant Recipients: A Retrospective Analysis**. *Advances in therapy* 2017, **34**(5):1184-1199.

27. Li H, Huang H, He H: **Successful treatment of severe Pneumocystis pneumonia in an immunosuppressed patient using caspofungin combined with clindamycin: a case report and literature review**. *BMC pulmonary medicine* 2016, **16**(1):144.

28. Guo F, Chen Y, Yang SL, Xia H, Li XW, Tong ZH: **Pneumocystis pneumonia in HIV-infected and immunocompromised non-HIV infected patients: a retrospective study of two centers in China**. *PLoS One* 2014, **9**(7):e101943.

Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section

Figures

Figure 1

Distribution of pneumocystis pneumonia cases in mainland China. Pneumocystis pneumonia cases were mainly reported from North China, although they came from 23 provinces, 3 municipalities and 4 autonomous regions in mainland China. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

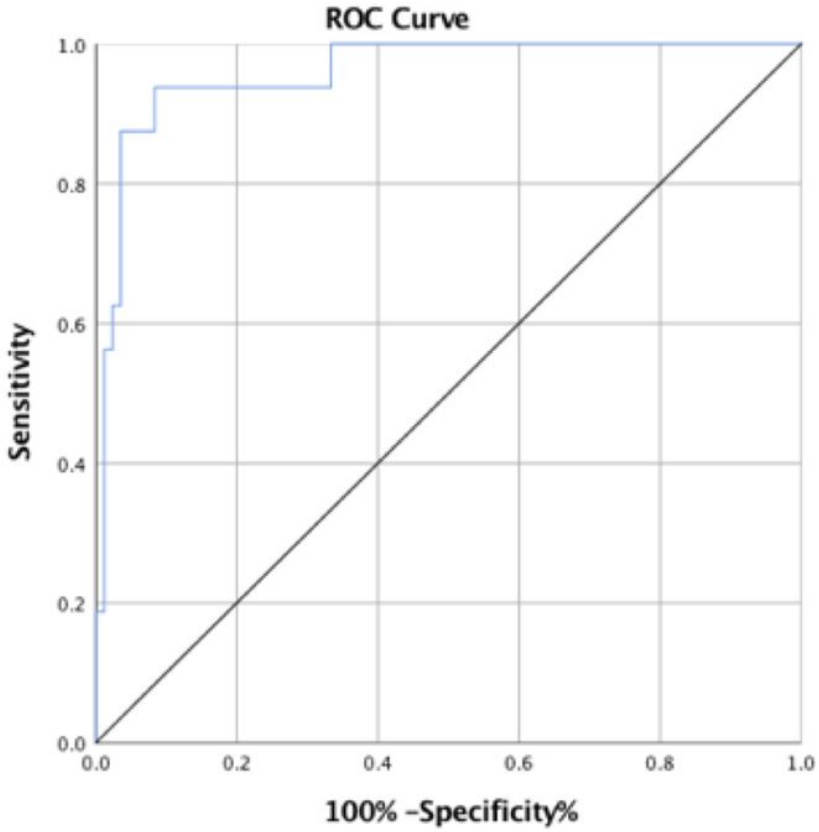

Figure 2

Identification of the logistic prognostic model to predict Pneumocystis pneumonia outcome. A receiver operating characteristic (ROC) curve showed that area under curve (AUC) was 0.959 (95%CI 0.914-1.000, cut-off value 0.442, P=0.000), with sensitivity and specificity predictive values of 87.5% and 3.6%.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.docx
- supplement2.docx
- supplement3.docx
- supplement4.docx
- supplement4.docx