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ORIGINAL RESEARCH

Compare Clinical Characteristics of Psittacosis Pneumonia in 35 Patients and of Non Psittacosis Bacterial Pneumonia in 46 Patients

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Background: We aimed to describe the difference between *Chlamydia psittaci* pneumonia group and non *C. psittaci* bacterial pneumonia group in community acquired pneumonia in this single-center clinical study.

Methods: We collected the data of 35 patients with *C. psittaci* pneumonia cases and 46 patients with non *C. psittaci* bacterial pneumonia cases diagnosed with metagenomic next-generation sequencing assays from February 2019 to December 2021 in Huaihua First People's Hospital in China.

Results: In the *C. psittaci* pneumonia group, 35 patients (100%) had a chance of exposure to poultry or birds, and their body temperature was greater than or equal to 39.0°C. The other common symptoms were a slow pulse (68.6%), cough (65.7%), expectoration (54.3%), chills (51.4%) and a shortness of breath (37.1%). Laboratory tests showed that >90% of the cases had markedly elevated infection indicators, and 97.1% of the cases had markedly declined calcium. The most common imaging finding was patchy shadows (94.3%), pleural effusion (68.6%), bilateral in 54.3% (n = 19) and unilateral in 45.7% (n = 16) participants, and 51.4% (n = 18) of cases met the criteria for severe pneumonia. In the non *C. psittaci* bacterial pneumonia group, 18 patients (39.1%) had a chance of exposure to poultry or birds, and 11 patients (23.9%) body temperature was greater than or equal to 39.0°C. Laboratory tests showed that >67% of cases had a mildly elevated infection indicators, and mildly declined serum albumin.

Conclusion: The following characteristics are more likely to help distinguish *C. psittaci* pneumonia from non *C. psittaci* bacterial pneumonia. Including had a chance of exposure to poultry or birds, high fever, exhibit chills, expectoration, relatively slow pulse, and progress into severe pneumonia. Percentage of neutrophils, C-reactive protein, procalcitonin, lactate dehydrogenase, and myoglobin levels are higher. Blood calcium and corrected calcium are lower. Chest CT showed pleural effusion, pericardial effusion, and mediastinal lymphadenopathy.

Keywords: *Chlamydia psittaci* pneumonia, non *Chlamydia psittaci* bacterial pneumonia, clinical features

Background

Chlamydia psittaci pneumonia is a zoonotic infection caused by *Chlamydia psittaci (C. psittaci*) infection and anthropozoonoses.[1,2] The incubation period of psittacosis is usually 5 to 14 days and can also be several weeks or months.[3] Due to similar clinical symptoms to *C. psittaci* pneumonia and non *C. psittaci* bacterial pneumonia, and less proportion in community-acquired pneumonia, physicians have low perceptions and it is often overlooked, difficult to identify, and misdiagnosed.[4]

Metagenomic next-generation sequencing (mNGS) is fast and accurate, it has been widely used.[5] To date, there have been some case reports and studies that have reported the clinical features of *C. psittacosis* pneumonia. However, there are few articles directly comparing *C. psittaci* pneumonia with non *C. psittaci* bacterial pneumonia. Our study elucidated the clinical features, laboratory examinations, and imaging examination of *C. psittaci* pneumonia and non *C. psittaci*

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bacterial pneumonia. These data will be helpful for clinical physicians in the differential diagnosis of *C. psittaci* pneumonia and non *C. psittaci* bacterial pneumonia.

Patients and Methods

Patients

We conducted a retrospective case review of 35 Patients with *C. psittaci* pneumonia cases and 46 patients with non *C. psittaci* bacterial pneumonia cases admitted to Huaihua First People's Hospital in China, between February 2019 and December 2021. All patients met the diagnostic criteria for community-acquired pneumonia (CAP) and were diagnosed with mNGS by collecting alveolar lavage fluid, lung tissue, or sputum.

Study Design

We collected the clinical data of 81 patients. Sex, age, residing in rural areas (with nearby neighbors feeding poultry), basic diseases, clinical examination indexes such as blood routine, liver function, kidney function, myocardial enzyme, electrolyte, PCT, CRP), IL-6, ESR, and CT were extracted from electronic medical records. We conducted a case–control study on these two groups of patients. The Ethics Committee of the Huaihua First People's Hospital in China (KY-2022052606) approved this study.

Diagnostic Criteria

1. CAP: (1). Community onset. (2). Clinical manifestations related to pneumonia: newly developed cough, expectoration, or worsening symptoms of existing respiratory diseases with purulent sputum, with or without chest pain, difficulty breathing, or hemoptysis; Fever; Signs of lung consolidation and/or moist rales; WBC > 10 $*10^9$/L or <4 * 10^9/L. (3). A pulmonary imaging examination shows patchy, patchy infiltrating shadows or interstitial changes, with or without pleural effusion. Conforming a, c, and any one of, excluding tuberculosis, lung tumors, non infectious pulmonary interstitial diseases, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophil infiltration, pulmonary vasculitis, etc.

2. *C. psittaci* pneumonia: Individuals fulfilling the diagnostic criteria for CAP, the *C. psittaci* was found in alveolar lavage fluid, lung tissue, or sputum through mNGS.

3. Non *C. psittaci* bacterial pneumonia: Individuals fulfilling the diagnostic criteria for CAP, the non *C. psittaci* bacteria were found in alveolar lavage fluid, lung tissue, or blood through mNGS, >30% relative abundance at the genus level in bacteria,[6] and other pathogen infections were excluded.

Definition of Relative Slow Pulse

The acceleration of a pulse is not proportional to the degree of temperature increase. For every 1°C increase in the patient's body temperature, the corresponding pulse does not increase by more than 15 beats per minute.[5]

Treatment and Outcomes of Patients with C. psittaci Pneumonia

Record the types and efficacy of medication used before and after diagnosis, divided into groups using tetracyclines (Doxycycline), quinolones (Levofloxacin or Moxifloxacin), and others, the time from onset to diagnosis, the antipyretic time, whether to receive oxygen therapy, and the method of oxygen therapy in patients with *C. psittaci* pneumonia. Record the patients outcome (improvement or unprepared) and hospitalization time.

Statistical Analysis

All data were statistically analyzed using SPSS version 26.0 software (IBM, Armonk, New York). The independent sample *t* test was used for continuous variables with normal distributions and homogeneity of variance, the results were expressed as mean ± standard deviation. Nonnormal distributions expressed as median (interquartile range [IQR]), uses the Mann–Whitney *U*-test. The $\chi 2$ test and Fisher exact test were used for inter-group comparison of categorical variables; the results were expressed as ratios or composition ratios. $P < 0.05$ was considered statistically significant.

Results

Demographic Data, Clinical Symptoms and Signs

A total of 35 patients with *C. psittaci* pneumonia cases and 46 patients with non *C. psittaci* bacterial pneumonia were enrolled.

In the *C. psittaci* pneumonia group, most patients had underlying diseases (hypertension, diabetes, autoimmune disease, chronic hepatitis, coronary heart disease, or atrial fibrilation) before admission. Two patients had a clear history of contact with birds more than 10 days before the onset of the disease, All patients neighbors feeding poultry. The most common symptom was fever (35/35 [100.0%]). In the non *C. psittaci* bacterial pneumonia group, the most common symptom was cough, 23/46 [50.0%] patients have fever. The demographic features, clinical symptoms and signs are shown in Table 1.

Laboratory Examination Results

On admission, in the *C. psittaci* pneumonia group, 12 of 35 (34.3%) had an elevated WBC count, 94.3% (33/35) had elevated N%, and >90% of the cases had markedly elevated CRP, PCT, ESR, and IL-6. More than 60% of the cases had elevated ALT, AST, LDH and MYO. About 97.1% (34/35) had markedly declined ALB, serum calcium, and corrective calcium. The laboratory results are shown in Table 2.

In the non *C. psittaci* bacterial pneumonia group, 22 of 46 (47.8%) had elevated WBC, and >60% of the cases had elevated N%, CRP, PCT, ESR, IL-6, and IL-6. About 80.4% (37/46) had declined ALB.

Chest Computed Tomographic

Computed tomography (CT) imaging Performed in all patients. In the *C. psittaci* pneumonia group, 19 of 35 (54.3%) patients had bilateral lesions. The most common patterns of lesions were patchy or patchy shadows (94.3%), followed by pleural effusion (68.6%), pleural thickening (51.4%), pericardial effusion (31.4%), mediastinal lymph node enlargement (40.0%), nodular changes in the lungs (17.1%), and bronchial inflation sign (14.3%). Pleural effusion was evident in 9 patients (Figure 1). In the non *C. psittaci* bacterial pneumonia group, 40 of 46 (87.0%) patients had bilateral lesions. The most common patterns of lesion were patchy or patchy shadows (71.7%). Followed by mediastinal lymph node enlargement (67.4%), pleural thickening (47.8%), pleural effusion (32.6%), nodular changes in the lungs (15.2%), pericardial effusion (17.1%), and all of the patients had bronchial inflation sign.

Table 1 Demographic Data, Clinical Symptoms and Signs of Patients with *Chlamydia psittaci* Pneumonia or Bacterial Pneumonia

Characteristic	Chlamydia psittaci pneumonia (n = 35)	Bacterial pneumonia (n = 46)	P value
Age, y, median (IQR)	62.31±10.96	58.5 (45.0–71.0)	0.248
Sex (males /female)	22/13	26/20	0.565
Reside in rural areas	35 (100%)	18 (39.1%)	0.000
Underlying disease	19 (54.3%)	28 (60.9%)	0.335
Fever (°C)	39.60 (39.2–40.0)	37.1 (36.5–39.0)	0.000
Cough	23 (65.7%)	39 (84.8%)	0.140
Expectoration	19 (54.3%)	35 (76.1%)	0.070
Chills	18 (51.4%)	5 (10.9%)	0.000
Shortness of breath	13 (37.1%)	21 (45.7%)	0.804
Coarse breathing sound	22 (62.9%)	26 (56.5%)	0.442
Low breath sound	9 (25.7%)	12 (26.1%)	0.803
Moist rale	23 (65.7%)	25 (54.3%)	0.442
Slow pulse	24 (68.6%)	4 (8.7%)	0.000

Table 2 Laboratory Tests of Patients with Chlamydia Psittaci Pneumonia and Bacterial Pneumonia

Laboratory Test (Unit)	Chlamydia psittaci pneumonia (n = 35)	Bacterial pneumonia (n = 46)	P value
WBC (*10^9/L)	8.45±2.91	10.0 (8.2–13.5)	0.014
PLT (*109/L)	165.23±76.70	219.07±115.77	0.020
N(%)	88.30±8.38	79.66±9.78	0.000
CRP (mg/L)	162.15±76.78	82.80 (16.01–122.00)	0.000
PCT (ug/L)	2.46 (0.57–6.51)	0.18 (0.08–0.97)	0.000
ESR (mm/h)	58.63±30.75	45.0 (19.0–98.0)	0.685
IL-6 (pg/mL)	106.55 (63.94–362.35)	52.19 (13.83–1665.75)	0.092
ALT (IU/L)	54.0 (32.5–89.5)	18.0 (11.0–30.0)	0.000
AST (IU/L)	82.0 (41.0–122.5)	23.0 (16.0–36.0)	0.000
ALB (g/L)	29.24±7.24	34.12±6.17	0.002
TBIL (umol/L)	13.90 (8.05–26.50)	7.70 (5.68–13.60)	0.002
DBIL (umol/L)	7.30 (4.05–16.55)	3.45 (2.30–5.80)	0.000
CREA-S (umol/L)	96.0 (77.5–128.0)	70.0 (56.0–97.0)	0.002
UA (umol/L)	213.0 (167.0–304.0)	315.42±127.89	0.007
LDH (U/L)	363.0 (282.5–528.5)	195.5 (166.0–284.0)	0.000
CK (U/L)	216.5 (97.0–498.0)	58.5 (35.5–105.0)	0.000
CK-MB (IU/L)	15.0 (10.0–22.0)	9.5 (8.0–13.0)	0.001
MYO (ug/L)	207.0 (94.5–630.0)	57.5 (41.5–120.0)	0.000
Na (mmol/L)	134.4 (131.7–140.0)	139.79±6.97	0.007
Ca (mmol/L)	1.99±0.16	2.28 (2.14–2.36)	0.000
Corrective Ca (mmol/L)	2.04±0.14	2.28 (2.16–2.36)	0.000

Treatment and Outcomes of Patients with C. psittaci Pneumonia

All patients with *C. psittaci* pneumonia detected psittaci sequences in Bronchoalveolar Lavage Fluid (BALF), lung tissue, or sputum. There were 18 patients diagnosed with severe pneumonia. 5 of 35(14.3%) patients unrecovered and this patients with severe pneumonia. All patients have been treated with antibiotics before specimen extraction. Chest CT was re-examined in 18 patients at some time after treatment, of which 2 patients had significant changes in chest CT (Figure 2).

Patients were started on empirical antibiotic therapy with penicillins, fluoroquinolones, or semisynthetic supplementary carbapenems. The average time from onset to diagnosis is 12 days. When *C. psittaci* infection was confirmed, the antibiotic was changed to tetracyclines for about 2 weeks. The average time from onset to use of sensitive antibiotics in all patients was 9.8 days. Thirty-three (94.3%) patients' fevers generally subsided about 5.7 days. Thirty (85.7%) patients' other clinical symptoms generally subsided. The average hospitalization time for patients is 14.7 days. Thirty-one (88.6%) patients were treated with oxygen therapy, of which 13 were only treated with central tube oxygen inhalation, and 18 were treated with ventilator-assisted breathing.

In 35 patients, 100% (35/35) of the patients with *C. psittacosis* pneumonia developed their illness in winter, 30 (85.7%) patients showed improvement in symptoms and eventually recovered, and 5(14.3%) patients were unrecovered. Among these 5 patients, 3 had already used doxycycline before diagnosis, and 1 had used levofloxacin. Patients in the unrecovered *C. psittacosis* pneumonia were older than those in the recovered *C. psittacosis* pneumonia. The number of patients with underlying diseases in the unrecovered *C. psittacosis* pneumonia was higher than that in the recovered *C. psittacosis* pneumonia. The median time from onset to use of sensitive antibiotics was shorter than in the recovered *C. psittacosis* pneumonia 7.0 days vs 10.2. Patients in the unrecovered *C. psittacosis* pneumonia had a percentage of neutrophils, c-reactive protein, procalcitonin, erythrocyte sedimentation rate, and interleukin 6 markedly than those in the recovered *C. psittacosis* pneumonia. Moreover, there is more severe organ damage.The laboratory results are shown in Table 3.

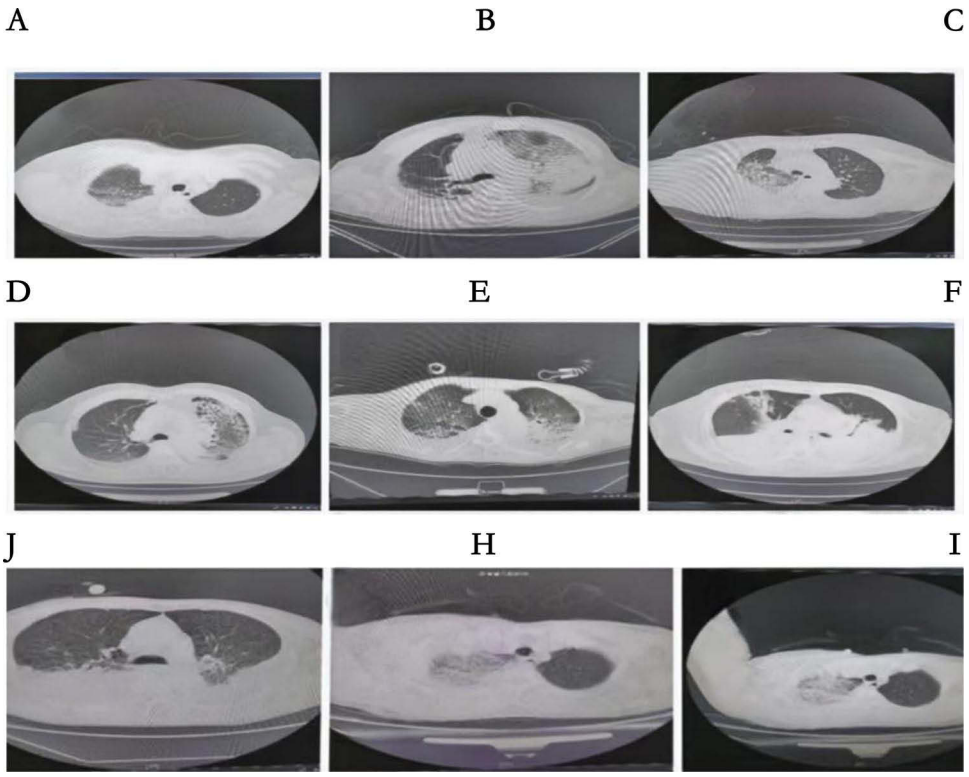

Figure 1 Computed tomographic scan showing markedly pleural effusion in 9 patients with C. psittaci pneumonia (**A**) a 70-year-old man, hospitalized due to fever and cough for 4 days. (**B**) a 69-year-old man, hospitalized due to fever for 4 days. (**C**) a 70-year-old woman, hospitalized due to fever for 3 days. (**D**) a 73-year-old man, hospitalized due to fever, cough, and Expectoration for 7 days. (**E**) a 67-year-old woman, hospitalized due to fever and Chills for 8 days. (**F**) a 79-year-old woman, hospitalized due to fever and cough for 13 days. (**G**) a 72-year-old man, hospitalized due to fever and Chills for 10 days. (**H**) a 49-year-old woman, hospitalized due to fever for 20 days. (**I**) a 48-year-old woman, hospitalized due to fever for 5 days.

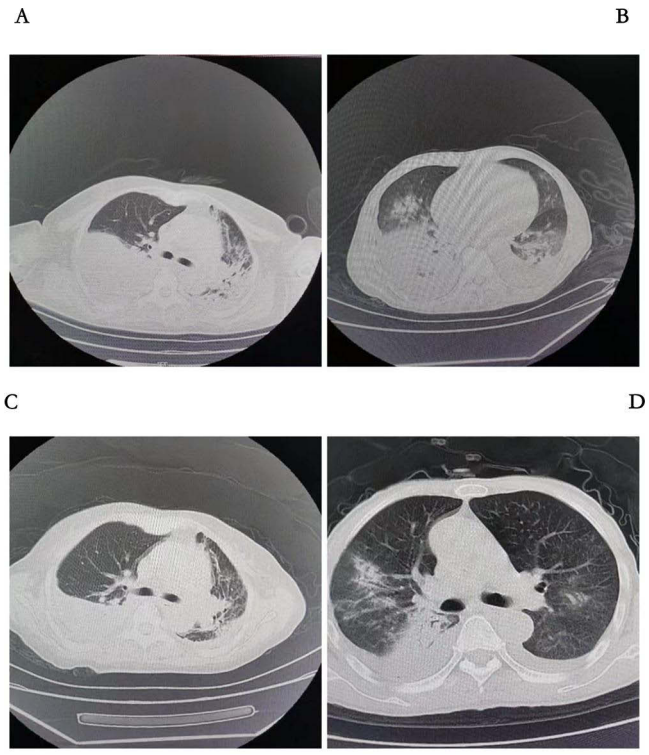

Figure 2 Computed tomographic images from a 54-year-old woman (**A and B**) and a 78-year-old man (**C and D**) A, Image obtained on day 1 hospital. B, Image obtained on day 13 hospital. C, Image obtained on day 1 hospital. B, Image obtained on day 7 hospital.

Table 3 Demographic Data and Laboratory Tests with Recovered Psittacosis Pneumonia and Unrecovered Psittacosis Pneumonia

Name	Recovered (n = 30)	Unrecovered (n = 5)
Age, y, median	62.5	69
Underlying disease	16 (53.3%)	3 (60%)
Fever (°C)	39.6 (39.0–42.0°C)	39.6 (39.0–42.0°C)
WBC (*109/L)	7.75	12.2
PLT (*109/L)	145	117
N (%)	88.2	96.4
CRP (mg/L)	159.7	320.6
PCT (ug/L)	1.43	18.03
ESR (mm/h)	55.5	62
IL-6 (pg/mL)	75.78	1032.6
ALT (IU/L)	46.5	66
AST (IU/L)	81.5	221
ALB (g/L)	30.05	26.6
TBIL (umol/L)	12.9	29.4
DBIL (umol/L)	6.4	19.6
UREA (mmol/L)	6.16	13.96
CREA-S (umol/L)	95	150
UA (umol/L)	207	266
LDH (U/L)	341	564
CK (U/L)	171	700
CK-MB (IU/L)	15	25
MYO (ug/L)	151.5	839
Na (mmol/L)	135.3	132.9
Cl (mmol/L)	103.1	96.8
Ca (mmol/L)	1.98	1.86
Corrective Ca (mmol/L)	2.03	1.95

Discussion

Previous studies have shown that *C. psittaci* pneumonia's primary infected host was parrot-like bird, poultry, and pigeon.[7,8] *C. psittaci* can be prevalent in poultry markets, with prevalence rates of 13%, 39%, and 31% for chickens, ducks, and pigeons, respectively. Contact methods include inhaling aerosols formed by dried secretions or excretions in the respiratory tract of infected birds, bird bites, mouth-to-mouth contact, and handling of infected bird feathers and tissues.[7,9] The main methods for diagnosing *C. psittaci* pneumonia include respiratory secretion culture, serology, and polymerase chain reaction (PCR).[10] The result of a positive culture is relatively reliable, but it takes a long time and is mainly performed on specialized equipment. Serological testing is regarded as the gold standard for chlamydia psittaci pneumonia. The micro immunofluorescence test (MIF) is the most accurate serologic method for Chlamydia psittaci pneumonia,[11] but almost all serologic tests require acute and recovery serum and are also performed only in specialized laboratories. PCR is fast, sensitive, and specific, but its high sensitivity only occurs in the acute phase, experimental reagents are not easily obtainable and most hospitals in China lack PCR testing programs for *C. psittaci* pneumonia.[6] According to statistics, the proportion of *C. psittaci* pneumonia in CAP ranges from 0.5% to 15%, with an average of 1%.[11] Among severe pneumonia patients in the intensive care unit, *C. psittaci* pneumonia accounts for 8%.[12] With the development and promotion of mNGS, reports on *C. psittaci* pneumonia and non *C. psittaci* bacterial pneumonia are gradually increasing. Our study elucidated the clinical features, laboratory examinations, and imaging examination of *C. psittaci* pneumonia and non *C. psittaci* bacterial pneumonia. These data will be helpful for clinical physicians in the differential diagnosis of *C. psittaci* pneumonia and non *C. psittaci* bacterial pneumonia.

C. psittaci pneumonia occurs throughout the year but is more common in winter. It mostly occurs between the ages of 35 to 55[13] and more male patients than female patients.[14] non *C. psittaci* bacterial pneumonia often occurs when the

body's immune system decreases. The main risk factor for human infection is contact with birds or poultry.[15] In this study, all patients with *C. psittacosis* pneumonia occurred in winter and are over 40 years old (average 62 years old). *C. psittacosis* pneumonia patients are more common in males. All *C. psittacosis* pneumonia patients reside in rural areas and neighborhoods feeding poultry. Because chickens and ducks are common poultry in rural areas, the prevalence of *C. psittacosis* pneumonia in this study is considered to be more common in chickens and ducks.

C. psittacosis pneumonia not only manifested as respiratory symptoms but also other systemic symptoms such as myalgia, headache, and CNS symptoms. The symptoms of *C. psittaci* pneumonia range from mild to severe, which can lead to asymptomatic pneumonia, mild pneumonia, and severe pneumonia. Its typical clinical manifestations include mild cough, fever, headache, and myalgia.[7] The most common symptoms are fever, difficulty breathing, dry cough, and headache.[15] Common signs include lung dryness, moist rales, and a relatively slow pulse.[16,17] In this study, compared to non *C. psittaci* bacterial pneumonia, the clinical characteristics of *C. psittaci* pneumonia mainly include (1) The most common symptoms of patients with *C. psittaci* pneumonia are high fever, cough, expectoration, and chills; (2) More than half of the patients accompanied by relatively slow pulse. (3) The disease progresses rapidly, with a high proportion of severe cases, and half of the patients develop severe pneumonia.

Previous studies have shown that *C. psittaci* pneumonia can cause normal or mild elevation of white blood cells in patients,[18] as well as an increase in CRP and ESR.[19] In this study, compared to non *C. psittaci* bacterial pneumonia, the laboratory examination results of *C. psittaci* pneumonia mainly include (1) Most patients have normal white blood cells; (2) The percentage of neutrophils, CRP, PCT, ESR, IL-6, myocardial enzymes, and liver enzymes in most patients with *C. psittaci* pneumonia are significantly elevated. (3) patients showed a marked decrease in albumin, blood calcium, and corrected calcium. This may be due to insufficient dietary intake, fever consumption, and decreased albumin production due to abnormal liver function.

In this study, compared to non *C. psittaci* bacterial pneumonia, the CT imaging results of *C. psittaci* pneumonia mainly have little difference on one or both sides, with 68.6% of patients having pleural effusion, which may be due to increased vascular permeability and decreased plasma colloid osmotic pressure caused by decreased albumin.

Previous studies have shown that most cases of *C. psittacosis* pneumonia recover well, and with timely and correct treatment, the mortality rate can be reduced to 1%. Conversely, it can reach 10% to 20%.[20] *C. psittacosis* pneumonia is treated with tetracycline or quinolone antibiotics. In this study, most patients who use penicillin or semi-synthetic carbapenem antibiotics have less significant symptom relief. After switching to sensitive antibiotics, most patients improved, 5 (14.3%) patients did not anticipate. Considering that most of the patients were diagnosed through mNGS only after a period of experience with ineffective anti-infection treatment.

In summary, this study compared the clinical characteristics of two groups and summarized some characteristics of *C. psittacosis* pneumonia patients, which is convenient for distinguishing from non *C. psittaci* bacterial pneumonia. These features include there are opportunities for contact with birds or poultry, body temperature greater than or equal to 39.0°C, cough, chills, relatively slow pulse, mostly normal white blood cells, significantly elevated inflammatory indicators, and abnormalities in liver and kidney function, myocardial enzymes, and electrolytes. The imaging manifestations of the lungs are patchy and patchy shadows. The use of penicillin or semi-synthetic carbapenem antibiotics has poor efficacy. *C. psittacosis* pneumonia has a high rate of severe disease. Metagenomic next-generation sequencing differential diagnosis is rapid and accurate. Tetracycline therapy had a high cure rate.

The main limitation of this study is that it included only 30 cases of recovered *C. psittacosis* pneumonia and 5 cases of unrecovered *C. psittacosis* pneumonia. This relatively small sample size is not enough to prove all the relevant features of recovered *C. psittacosis* pneumonia and cases of unrecovered psittacosis pneumonia. The study was a retrospective and single-center study. We did not use PCR or MIF to confirm the diagnosis.

Conclusions

All patients with *C. psittaci* pneumonia had a chance of exposure to poultry or birds, their body temperature was greater than or equal to 39.0°C and high incidence of severe illness. *C. psittaci* pneumonia cases are more likely to exhibit chills, expectoration, relatively slow pulse, and progress into severe pneumonia compared to patients with non *C. psittaci* bacterial pneumonia. Percentage of neutrophils, C-reactive protein, procalcitonin, lactate dehydrogenase, and

myoglobin levels are higher. Blood calcium and corrected calcium are lower. Chest CT showed pleural effusion, pericardial effusion, and mediastinal lymphadenopathy.

Abbreviations

mNGS, metagenomic next-generation sequencing; PCR, polymerase chain reaction; MIF, micro immunofluorescence test; CAP, community-acquired pneumonia; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6; ESR, erythrocyte sedimentation rate; CT, computed tomography; WBC, white blood cell; N%, percentage of neutrophils; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; MYO, myoglobin; ALB, albumin; BALF, Bronchoalveolar Lavage Fluid.

Ethics Approval and Informed Consent

The Ethics Committees of Hunan Medical College General Hospital (Original name: Huaihua First People's Hospital. LYF-2022052606) approved this study. Informed consents were obtained from patients and guardians. The study complies with the Declaration of Helsinki.

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Authors'contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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