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Psittacosis Pneumonia Features, Distinguishing Characteristics, and Outcomes: A Retrospective Study

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Purpose: Psittacosis is an often-neglected cause of community acquired pneumonia (CAP). The limited diagnostic methods for psittacosis pneumonia invariably result in an unfavourable prognosis. Consequently, the early detection of psittacosis pneumonia is crucial. This study aimed to analyse the characteristics, clinical features and treatments of the patients to improve early diagnosis and outcomes.

Patients and Methods: We retrospectively analyzed the clinical features and outcomes of 52 cases of psittacosis pneumonia diagnosed with next-generation sequencing (NGS) from January 2022 to August 2024 in a local tertiary hospital in China.

Results: Of the 52 patients, 18 had a clear exposure to poultry or birds. The main clinical manifestations included fever (100%, 52/52), cough (75.0%, 39/52), fatigue (57.7%, 30/352), and dyspnea (36.5%, 19/52). Significant elevations in neutrophil counts (NEUT), C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer, lactate dehydrogenase (LDH), creatine kinase (CK), interleukin-6 (IL-6) and interferon-γ (IFN-γ), as well as reductions in lymphocyte (LY) and albumin (ALB) were observed. The main chest computed tomography (CT) features were consolidated. Eight patients diagnosed with severe CAP (SCAP) exhibited higher NEUT, CRP, procalcitonin (PCT), blood urea nitrogen (BUN), creatinine, D-Dimer and IL-6 levels, as well as lower oxygen index. The interval between the onset of symptoms and diagnosis was 6–34 days. *C. psittaci* infection was identified by metagenomic NGS (mNGS) or targeted NGS (tNGS) in all cases, and the average length of hospital stay for these patients was 9.4 days. Following the identification of the aetiology, all patients were promptly initiated on tetracycline- or fluoroquinolone-based therapy, with complete recovery observed in all cases.

Conclusion: Patients exposed to poultry should be alert to *Chlamydia psittaci* pneumonia. The application of NGS has improved the diagnostic accuracy of *C. psittaci* pneumonia, reduced unnecessary use of antibiotics, and shortened the course of disease. Patients who received tetracycline-based therapy showed a good prognosis.

Keywords: *Chlamydia psittaci*, next-generation sequencing, community acquired pneumonia, tetracyclines

Introduction

Psittacosis pneumonia is a zoonotic disease caused by the bacterium *Chlamydia psittaci* (*C. psittaci*). Cases of psittacosis pneumonia primarily occur in patients who had contacted with respiratory secretions and aerosols of infected birds.[1] The clinical presentation of psittacosis pneumonia varies from asymptomatic to severe pneumonia to systemic illnesses.[2,3] The routine culture of *C. psittaci* is challenging in a clinical setting due to its time-consuming and the bacterium's requirement for cultivation within either tissue or a chick embryo.[4,5] Notably, the sensitivities of serological assays and real-time polymerase chain reaction tests for detecting *C. psittaci* are low.[5] The lack of highly sensitive and specific methods of detecting the disease may account for the low detection rate of community-acquired pneumonia (CAP) cases attributed to *C. psittaci* previously, which only account for 1%.[6,7]

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Many cases of psittacosis have been reported in recent years. Nearly all of them were confirmed based on the application of metagenomic next-generation sequencing (mNGS) or targeted next-generation sequencing (tNGS).[8,9] As routine diagnostic methods for psittacosis pneumonia are lacking, it is important to identify the clinical characteristics for early detection of patients with psittacosis pneumonia and risk factors for developing severe pneumonia. Currently, clinical studies comparing the patients with non-SCAP and SCAP caused by psittacosis are limited. In this study, the clinical data of 52 patients diagnosed with psittacosis pneumonia were retrospectively analyzed, and the differences between non-severe and severe patients were compared to identify indexes for the early diagnosis of psittacosis pneumonia.

Materials and Methods

Study Population

In this study, clinical data of 52 patients diagnosed with psittacosis pneumonia by mNGS or tNGS of bronchoalveolar lavage fluid (BALF) at Shaoxing People's Hospital between January 2022 and August 2024 were retrospectively analyzed. Symptoms of influenza-like atypical pneumonia and a history of poultry exposure are the main basis for the clinical diagnosis of Psittacosis pneumonia. Suspected patients with associated epidemiological history, clinical and imaging manifestations who meet at least one of the following items can be diagnosed with psittacosis:[10–12] (1) *C. psittaci* is isolated from respiratory or blood samples; (2) The antibody level of serum samples collected 2 weeks apart increases by 4 times or more by complement fixation (CF) or microimmunofluorescence (MIF) test; (3) The single IgM antibody titer detected by MIF is 1:16 or higher; (4) *C. psittaci* nucleic acid is detected in respiratory or blood samples by PCR or mNGS or tNGS. In this study, all patients *with C. psittaci* were identified by BALF mNGS or tNGS. Severe pneumonia was diagnosed according to guidelines of the American Thoracic Society/Infectious Disease Society of America.[13]

Data Collection

The characteristics of the patients, including age, sex, and birds contact history were collected. Clinical manifestations of the disease, including patient vital signs, and laboratory and imaging data were recorded. The antimicrobial treatment and the clinical outcomes were also summarized, including the duration of fever, vital signs, and the time of hospital stay.

The oxygen index was defined as the ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2). Computed tomography (CT) scan characteristics were also recorded, including the location of lung consolidation, the presence of air bronchogram signs, and pleural effusion.

NGS Analysis

BALF samples were sent to WillingMed Technology (Beijing) Co., Ltd, Hangzhou Matridx Biotechnology Co., Ltd and Luoxi Medical Technology (Hangzhou) Co., Ltd, etc for mNGS analysis. Nucleic acid extraction and purification, library construction and quantitative analysis, high-throughput sequencing and bioinformatics data analysis were performed and pathogen reports were generated according to standard procedures.[14,15] BALF samples were sent to Hangzhou DIAN Medical Laboratory for tNGS analysis.[16] To identify background microorganisms, negative controls (NTC) were established for each batch of experiments. *Chlamydia psittaci* with species-specific reads ≥1 was a considered positive if it was consistent with clinical diagnosis by reviewing the original detection information.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software [International Business Machines Corporation (IBM), USA]. Measurement data were expressed as the median (range), and the difference between the two groups was compared with Wilcoxon test. Enumeration data were expressed as the number of cases (percentage), and the difference between the two groups was compared using Fisher's exact test. Statistical significance was indicated by $P < 0.05$.

Results

Demographic and Clinical Characteristics

In total, 52 patients with psittacosis pneumonia infection and diagnosed by BALF mNGS or tNGS were enrolled in this study. The demographic, clinical and imaging characteristics of the patients were presented in Table 1. Of the patients, 29 (55.8%) were female and 23 (44.2%) were male. The patients' ages ranged from 33 to 80, with a median age of 65.5 years old. Among the 52 patients, 18 (34.6%) had a definite history of poultry exposure, which included birds, chickens, or ducks. A total of 75.0% (39/52) of patients had underlying diseases, including hypertension (n = 28), diabetes (n = 9), chronic hepatitis B infection (n = 2), and one each for colon cancer, chronic obstructive pulmonary disease, hyperthyroidism, scleroderma, and chronic gastritis. The majority of disease onset occurred during the autumn-winter season (65.4%, 34/52).

Table 1 Clinical, Demographic, and Imaging Characteristics Patients with Psittacosis Pneumonia

Characteristics	Patients, n (%)	Non-SCAP (n=44)	SCAP (n=8)	*P*-value
Demographic information				
Male/female, n/n	23/29	18/26	5/3	0.441
Age (years), median (range)	65.5 (33–80)	65(33–80)	72.5(60–80)	0.011
History of contact with avian/poultry, n (%)	18/52 (34.6%)	15/44 (34.1%)	3/8 (37.5%)	0.852
Underlying Diseases, n (%)	39/52 (75.0%)	32/44 (72.3%)	7/8 (87.5%)	0.375
Clinical manifestations, n (%)				
Fever	52/52 (100%)	44/44 (100%)	8/8 (100%)	/
Cough	39/52 (75.0%)	32/44 (72.7%)	7/8 (87.5%)	0.662
Sputum	17/52 (32.7%)	13/44 (29.6%)	4/8 (50.0%)	0.413
Fatigue, n (%)	30/52 (57.7%)	23/44 (52.3%)	7/8 (87.5%)	0.118
Dyspnea, n (%)	19/52 (36.5%)	14/44 (31.8%)	5/8 (62.5%)	0.124
Headache, n (%)	12/52 (23.1%)	12/44 (27.3%)	0/8 (0%)	0.174
Nausea, n (%)	5/52 (9.6%)	2/44 (4.6%)	3/8 (37.5%)	0.022
Vomitting, n (%)	3/52 (5.8%)	1/44 (2.3%)	2/8(25.0%)	0.058
Abdominal pain, n (%)	2/52 (3.8%)	2/44 (4.5%)	0/8 (0%)	1.000
Myalgia, n (%)	4/52 (7.7%)	3/44 (6.8%)	1/8 (12.5%)	0.499
Invasive ventilator support, n (%)	1/52 (1.9%)	0/44 (0%)	1/8 (12.5%)	0.154
PaO_2/FiO_2				
300-< 400	13	13/44 (29.5%)	0/8 (0%)	0.177
250-< 300	9	9/44 (20.5%)	0/8 (0%)	0.323
150-< 250	21	15/44 (34.1%)	6/8 (75.0%)	0.049
0-< 150	2	0/44 (0%)	2/8 (25.0%)	0.021
Imaging characteristics, n (%)				
Consolidation of a single lobe	23/52 (44.2%)	23/44 (52.3%)	0/8 (0%)	0.006
Consolidation of two or more lobes	29/52 (57.7%)	21/44 (50%)	8/8 (100%)	0.006
Consolidation in both lungs	20/52 (38.5%)	12/44 (27.3%)	8/8 (100%)	0.000
Consolidation in the left lung	18/52 (34.6%)	18/44 (40.9%)	0/8 (0%)	0.039
Consolidation in the right lung	14/52 (26.9%)	14/44 (31.8%)	0/8 (0%)	0.090
Air bronchogram signs	41/52 (78.8%)	34/44 (77.3%)	7/8 (87.5%)	1.000
Nodules	5/52 (9.6%)	5/44 (11.4%)	0/8 (0%)	1.000
Ground glass opacities	6/52 (11.5%)	4/44 (9.1%)	2/8 (25.0%)	0.227
Enlarged mediastinal lymph nodes	20/52 (38.5%)	16/44 (36.4%)	4/8 (50%)	0.695
Enlarged hilar lymph nodes	3/52 (5.8%)	3/44 (6.8%)	0/8 (0%)	1
Pulmonary embolism	1/52 (1.9%)	0/44 (0%)	1/8 (12.5%)	0.154
Pleural effusion	29/52 (55.8%)	22/44 (50%)	7/8 (87.5%)	0.064

All patients exhibited remitted fever, with 45 patients can reach to ≥39°C. The most common symptoms observed in patients were cough (75.0%, 39/52), fatigue (57.7%, 30/52), and dyspnea (36.5%, 19/52). A total of 23 patients developed severe hypoxia ($PaO_2/FiO_2 \leq 250$). Eight patients were with severe community-acquired pneumonia (SCAP). Patients with SCAP exhibited a higher age (72.5 (60–80) vs 65 (30–80), $P = 0.011$) and a lower oxygen index (8 patients with oxygen index < 250) (Table 1).

Upon admission, 42.3% (22/52) of patients exhibited elevated white blood cell (WBC) counts, and 67.3% (35/52) had increased neutrophil (NEUT). However, lymphocyte (LYM) counts were decreased in 78.8% (41/52) patients. The infection index C-reactive protein (CRP) was elevated in all patients (100%, 52/52), and procalcitonin (PCT) levels were elevated in 54.8% (23/52) patients. All patients exhibited varying degrees of liver function abnormalities, with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels above the normal range, and all had decreased albumin (ALB) levels. Only 5 patients had elevated serum creatinine (Cr). Forty-two (84.0%) patients had elevated D-dimer, with only one has been diagnosed with pulmonary embolism. This result indicated that elevated D-dimer in psittacosis pneumonia were not primarily due to vascular embolism. Thirty-nine (75.0%) patients exhibited elevated lactate dehydrogenase (LDH) levels, and 27 of them also had increased creatine kinase (CK) levels. Of the 25 patients with serum cytokine levels results, 92.0% (23/25) and 88.0% (22/25) exhibited elevated IL-6 and IFN-γ levels, respectively (Table 2). Higher NEUT count, CRP, PCT, BUN, Cr, D-dimer, IL-6 and TNF-α levels (Table 3) and lower oxygen index (Table 1) were observed in SCAP patients.

Chest CT Findings

All patients underwent chest CT scans. The CT results indicated that lesions were limited to unilateral lung in 32 patients, while lesions were distributed in bilateral lungs in 20 patients.

Pulmonary infiltrates were present in all patients. Of these patients, 23 (44.2%) cases had infiltrates in one pulmonary lobe, 10 (19.2%) had bilobar infiltration, and 19 (36.5%) had multilobar infiltration. Pulmonary consolidation (100%) and

Table 2 Results of Laboratory Diagnostic Tests

Index	Number of Cases, n (%)	Median (Range)
WBC count (normal range: 3.5–9.5 * 10^9 cells/L)	Elevation, 22 (42.3)	8.9 (3.6–19.3)
NEUT (normal range: 1.8–6.3*10^9/L)	Elevation, 35 (67.3)	7.6 (1.4–18.5)
LYM (normal range: 1.1–3.2*10^9/L)	Lowering, 41 (78.8)	0.8 (0.2–3.4)
CRP (normal range: 0.0–7.0 mg/L)	Elevation, 52 (100),	161.5 (21.3–375.1)
CRP of > 200 mg/L	among which >200, 20 (38.5)	
PCT (normal range: 0–0.5 ng/mL) [a]	Elevation, 23 (54.8)	0.6 (0.1–27.4)
ALT (normal range: 7–40 U/L)	Elevation, 36 (69.2)	58.3 (13.7–299.1)
AST (normal range: 13–35 U/L)	Elevation, 46 (88.5)	75.9 (15.8–539.3)
ALB (normal range: 40–55 g/L)	Lowering, 52 (100)	30.0 (22.9–39.6)
BUN (normal range: 2.86–8.20 μmol/L)	Elevation, 9 (17.3)	5.0 (1.7–15.7)
Cr (normal range: 59.0–104.0 mmol/L)	Elevation, 5 (9.6)	70.9 (37.0–172.6)
D-Dimer (normal range: 0.0–0.70 mg/L) [b]	Elevation, 42 (84.0)	1.7 (0.3–10.2)
CK (normal range: 38.0–174.0 U/L) [c]	Elevation, 27 (61.4)	219.6 (15.4–21,799.0)
CK-MB (normal range: 0.0–25.0 U/L) [c]	Elevation, 10 (23.8)	11.0 (3.9–210.0)
LDH (normal range: 120.0–250.0 U/L)	Elevation, 39 (75.0)	296.2 (148.0–1710.5)
IL-6 (normal range: 0–5.4 pg/mL) [d]	Elevation, 23 (92.0)	51.72 (1.81–729.0)
TNF-α (normal range: 0–16.5 pg/mL) [d]	Elevation, 3 (12.0)	2.0 (0.1–40.3)
IFN-γ (0–23.1 pg/mL) [d]	Elevation, 22 (88.0)	89.4 (5.0–1388.0)

Notes: [a]10 patients had did not undergo PCT analysis. [b]2 patients had did not undergo D-Dimer analysis. [c]8 patients had did not undergo CK, CK-MB analysis. [d] 27 patients had did not undergo IL-6, TNF-α, INF-γ analysis. TNF-α <1.27 were counted as 1.26 in comparison, <2.05 were counted as 2.04 in comparison.

Abbreviations: WBC, white blood cell; NEUT, neutrophil count; LYM, lymphocyte count; CRP, c-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; BUN, blood urea nitrogen; Cr, creatinine; CK, creatinine kinase; CK-MB, creatinine kinase-MB; LDH, lactate dehydrogenase; IL-6, interleukin-6; TNF-α, tumor necrosis-α; IFN-γ, interferon-γ.

Table 3 Comparison of Laboratory Diagnostic Tests Between Patients with Non-Severe Community Acquired Pneumonia and Severe Community Acquired Pneumonia

Index	Non-SCAP (n=44)	SCAP (n=8)	Z	*P* value
WBC (normal 3.5–9.5*10^9/L)	8.4	9.7	−1.915	0.054
NEUT count (normal 1.8–6.3*10^9/L)	7.2	8.7	−2.435	0.013
LYM count (normal 1.1–3.2*10^9/L)	0.9	0.6	−2.029	0.042
CRP (normal 0.0–7.0 mg/L)	148.8	291.8	−2.511	0.010
PCT (0–0.5 ng/mL)	0.5[a]	2.3[b]	−2.692	0.006
ALT (7–40 U/L)	58.5	54.3	−0.330	0.756
AST (13–35 U/L)	67.1	107.1	−1.572	0.120
ALB (40–55 g/L)	31.1	27.3	−2.384	0.016
BUN (2.86–8.20 μmol/L)	4.6	10.0	−4.159	0.000
Cr (59.0–104.0 mmol/L)	67.9	89.3	−2.207	0.026
D-Dimer (0.0–0.70 mg/L)	1.2[b]	2.9	−2.752	0.005
CK (38.0–174.0 U/L)	209.0[c]	630[d]	−0.786	0.432
CK-MB (0.0–25.0 U/L)	9.9[c]	19.0[d]	−2.303	0.020
LDH (120.0–250.0U/L)	289.0	419.0	−1.344	0.187
IL-6 (0–5.4 pg/mL) [e]	42.7[f]	182.9[g]	−2.310	0.019
TNF-α (0–16.5 pg/mL) [h]	2.0	0.9	−2.850	0.002
IFN-γ (0–23.1 pg/mL)	79.9	131.2	−0.204	0.869

Notes: [a]10 patients had not tested PCT. [b]2 patients had not tested D-dimer. [c]7 patients had not tested CK, CK-MB. [d]1 patients had not tested CK, CK-MB. [e]IL-6<1.81 were counted as 1.80 in comparison. [f]24 patients had not tested IL-6, TNF-α, INF-γ. [g]3 patients had not tested IL-6, TNF-α, INF-γ. [h]TNF-α <1.27 were counted as 1.26 in comparison, <2.05 were counted as 2.04 in comparison.

Abbreviations: WBC, white blood cell; NEUT, neutrophil count; LYM, lymphocyte count; CRP, c-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; BUN, blood urea nitrogen; Cr, creatinine; CK, creatinine kinase; CK-MB, creatinine kinase-MB; LDH, lactate dehydrogenase; IL-6, interleukin-6; TNF-α, tumor necrosis-α; IFN-γ, interferon-γ.

air bronchogram signs (78.8%, 41/52) were the most common findings, followed by pleural effusion (55.8%, 29/52) and enlarged mediastinal lymph nodes (38.5%, 20/52). Other findings included nodules (9.6%, 5/52), enlarged hilar lymph nodes (5.8%, 3/52), ground glass opacities (11.5%, 6/52), and pulmonary embolism (1.9%, 1/52). Detailed CT scan results can be found in Figure 1. The CT scan demonstrated more lobe consolidations in SCAP patients.

Etiological Results

All patients underwent bronchoscopy, and BALF samples were collected and sent for NGS examination. All patients showed *C. psittaci* positive, and 41 patients had other pathogens detected by BALF NGS or culture (Table 4). Of the pathogens identified by NGS, only *Haemophilus influenzae, Influenza A virus*, and *Mycoplasma pneumoniae* were considered as the co-infective pathogens based on the comprehensive diagnosis criteria, while the others were classified as colonization. Of the culture result, *Penicillium* was identified as contaminated bacterium, while the others were classified as colonization. The detailed results of NGS for all the samples were listed in (Supplementary Table 1).

Treatment and Prognosis

Before the confirmed diagnosis of psittacosis pneumonia, 44 patients were treated with fluoroquinolones or a combination of fluoroquinolones and other antibiotics, 1 patient received piperacillin-tazobactam, and 3 patients were treated with omadacycline due to the suspicion of psittacosis infection, 4 patients transferred from fluoroquinolones to omadacycline due to recurrent symptoms. All patients received tetracycline- or fluoroquinolone-based therapy following a diagnosis of psittacosis. Among the 8 patients diagnosed with SCAP, 6 were adjusted to tetracycline-based therapy, while two continued to receive moxifloxacin-based therapy.

The mean duration from the onset of illness to admission to Shaoxing People's Hospital was 5.6 days. The duration from symptom onset to diagnosis was 6–34 days, with a median duration of 10 days. The average length of hospital stay for the included patients was 9.4 days. One patient was admitted to the intensive care unit and received invasive

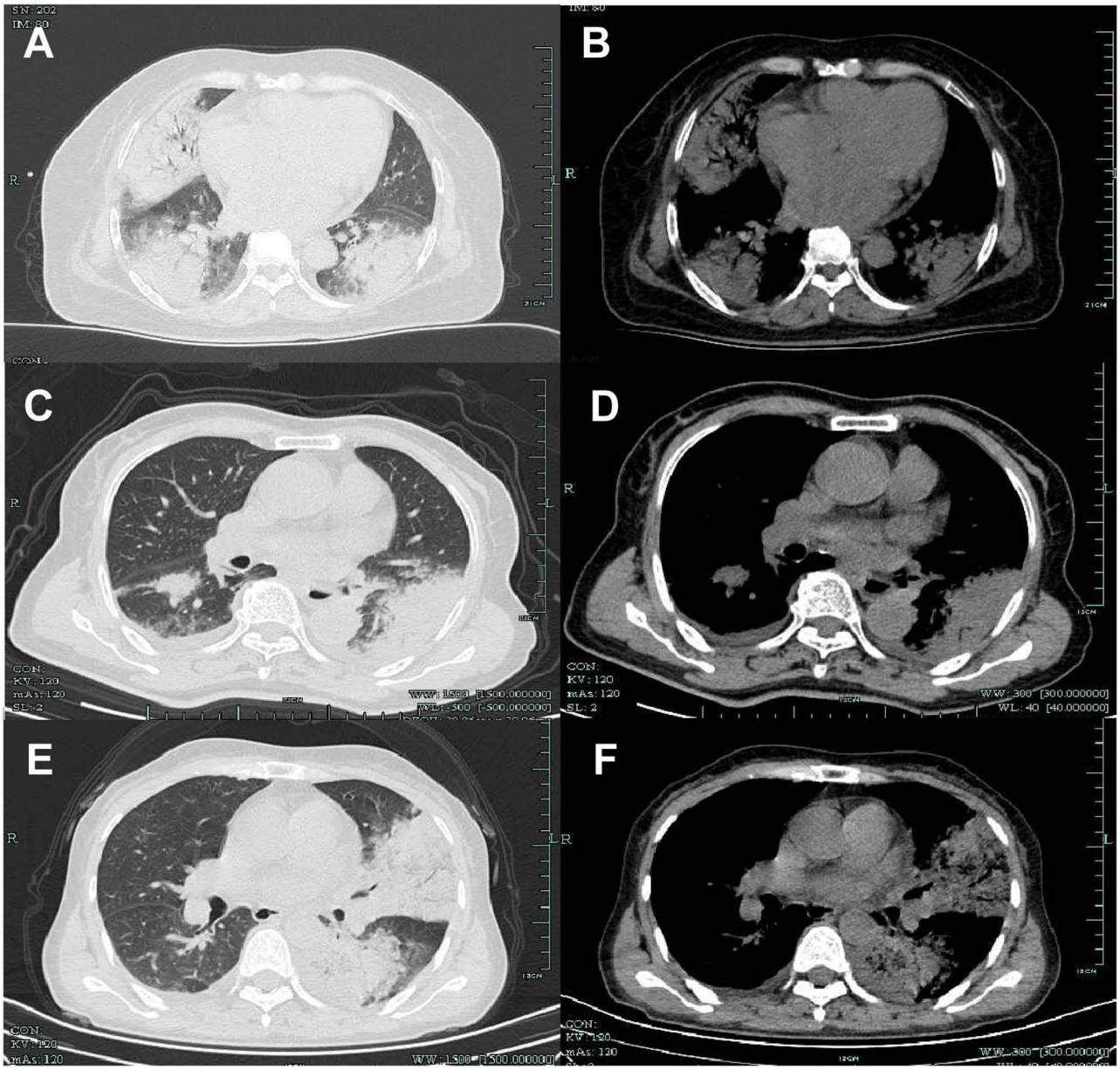

Figure 1 Chest computed tomography (CT) images of representative cases with psittacosis infection. Chest CT findings of a patient with multiple lobar consolidation are shown in (**A**) and (**B**). Chest CT findings of a patient with lobar consolidation, pleural effusion and nodule-like patchy consolidation are shown in (**C**) and (**D**). Chest CT findings of a patient with unilateral lobar consolidation are shown in (**E**) and (**F**).

mechanical ventilatory support, 13 patients received high-flow oxygen therapy in the general ward. One patient experienced sudden drop of oxygen saturation to 60% and turned unconscious, yet he had not transferred to intensive care unit due to his family members' decision. The patient continued to receive therapy in the general ward and received noninvasive mechanical ventilation, but recovered and was discharged after 20-day admission.

At discharge, all patients are stabilized and have normal vital signs (temperature ≤ 37.8°C, heart rate ≤ 100 times/min, breath rate ≤ 24 times/min, diastolic blood pressure ≥ 90 mmHg, oxygen saturation ≥ 90%).

Discussion

Psittacosis is a zoonotic disease that is caused by *C. psittaci*.[17] Infection can result from contact with common domestic poultry such as chickens and ducks, and mammals such as pigeons, cats, cattle, sheep, pigs, or horses.[18] This study

Table 4 Microorganisms Identified by BALF NGS and Culture

Class	Species	NGS	Culture
Bacteria	*Chlamydia psittaci*	52	
	Staphylococcus aureus	5	
	Stenotrophomonas maltophilia	5	
	Haemophilus influenzae	4	
	Klebsiella pneumoniae	4	
	Mycoplasma pneumoniae	5	
	Enterococcus faecalis	3	
	Moraxella catarrhalis	2	
	Pseudomonas aeruginosa	2	
	Acinetobacter baumannii	1	
	Corynebacterium accolens	1	
	Staphylococcus hominis	1	
	Streptococcus pneumoniae	1	
Fungi	*Candida albicans*	8	4
	Aspergillus flavus	3	1
	Aspergillus fumigatus	1	3
	Candida lusitaniae	1	1
	Penicillium	0	2
	Candida parapsilosis	1	
Virus	Human betaherpesvirus 5	1	
	Human gammaherpesvirus 4	5	
	Human rhinovirus	1	
	Influenza A virus	1	

summarized the clinical features and laboratory results of 52 cases of *C. psittaci* pneumonia treated in our hospital and analyzed the imaging features of the disease. Psittacosis infection has been reported in European countries, China, the United States, Japan, and other developing or developed countries.[19,20] It is likely that there are regional differences in the awareness of psittacosis. The epidemiology of psittacosis pneumonia in Zhejiang province remains uncertain.

To provide a more comprehensive framework for clinical treatment, we also summarized and analyzed the characteristics of psittacosis pneumonia cases in Zhejiang province. We summarised 178 cases from 28 articles published after 2018 in Zhejiang Province (Supplementary Table 2). Of these cases, the most common clinical symptoms observed were fever, cough, myalgia, nausea, headache, and vomiting. The most common imaging results were consolidation. Cases of meningitis and myocarditis caused by *C. psittaci* were also reported.[21,22] In our study, high-grade fever, cough, fatigue, and dyspnea were common symptoms (Table 1), segmental consolidation with air bronchogram sign was the major feature of psittacosis pneumonia, and SCAP patients had higher age and lower oxygen saturation. Pulmonary consolidation was also a feature of CAP caused by bacterial, viral or fungal pathogens, including COVID-19, which made it difficult to distinguish the type of infection.[23,24] Furthermore, the proportion of pleural effusion in patients with psittacosis pneumonia was higher than that in patients with COVID-19.[25] Pleural effusion is associated with higher mortality in pneumonia patients.[26] Therefore, when a patient presents with pleural effusion and symptoms similar to psittacosis infection, it is necessary to prevent the development of severe disease.

Of the 178 cases, all patients received fluoroquinolone or doxycycline-based therapy, with only four patients having a poor prognosis, resulting in a mortality rate of 2.25%.[27–29] In our study, patients received tetracyclines or fluoroquinolone-based therapy, and all patients improved and discharged in a good condition. Tetracyclines, especially doxycycline and minocycline, are considered the first choices for treating psittacosis.[9,30] Omadacycline and tigecycline have been employed in cases of severe psittacosis pneumonia.[31,32] Large-sample clinical research comparing antibiotic effectiveness is lacking. However, numerous studies have indicated that tetracycline-based therapy is associated with a good prognosis.[32,33] Notably, a retrospective cohort study of patients with SCAP caused by psittacosis revealed no

difference in outcomes when patients were treated with fluoroquinolone initially and after diagnosis, fluoroquinolone initially and tetracycline thereafter, or fluoroquinolone combined with tetracycline.[34] Further cohort studies are required to evaluate the effectiveness of tetracyclines and fluoroquinolones in the treatment of psittacosis pneumonia.

In order to more comprehensively analyze the differences in clinical characteristics between patients with severe and non-severe psittacosis pneumonia and the risk factors for severe disease, we conducted a meta-analysis of previous studies. We searched electronic databases including PubMed, Embase, and Google Scholar for the published research articles with keywords "Psittacosis" OR "C. psittaci" OR "Chlamydia psittaci" OR "Chlamydophila psittaci" OR "risk factors" or "risk assessment", limited to the English language from January 2014 to October 2024, and 10 articles were extracted. Characteristics of the 10 included studies and our study were showed in Supplementary Table 3. All the studies belong to China, all the patients in the studies were adults. The main methods for identifying *C. psittaci* infection was mNGS, tNGS and PCR. Among the 11 studies, the levels of NEUT, NEUT%, neutrophil-to-lymphocyte ratio (NLR), CRP, C-reactive protein to albumin ratio (CAR), PCT, ALT, AST, LDH, Hydroxybutyrate Dehydrogenase (HBDH), BUN, Cr, CK, CK-MB, D-dimer, BNP, myoglobin (MB), cardiac troponin I (cTnI), IL-2, IL-6, and IL-10 were significantly increased in severe cases compared to the non-severe cases, while the level of LYM, LYM%, PLT, ALB, TNF-α, CD3+T cell, CD4+T cell, CD8+T cell and CD4+/CD8+T cell ratio were significantly decreased (Table 5). Risk factors for severe psittacosis pneumonia predicting including age, male, LYM, NEUT%, NLR, CRP, CAR, PCT, CK, BNP, LDH, AST, CR, ALB and globulin (Glo) were identified through logistic regression analysis (Table 6).

Besides PCT, D-dimer and LDH were the most commonly identified elevated indicators in severe psittacosis pneumonia patients (Table 5). Clinical disorders associated with elevated D-dimer include thrombosis, inflammation, DIC (disseminated intravascular coagulation), age, infection, and others.[35] In our study, higher D-dimer levels was observed in SCAP group compared to non-SCAP group, which confirmed that D-dimer to be a potential predictor of pneumonia severity. High LDH levels are features of psittacosis infection, while previous studies have demonstrated that

Table 5 Proportion of Significant Different Clinical Test Results Between Severe and Non-Severe Cases in the Meta-Analysis Studies

Significant Increased Clinical Indicators in Severe Cases	Number of Studies (n=11)	Percentage (%)	Significant Decreased Clinical Indicators in Severe Cases	Number of Studies (n=11)	Percentage (%)
NEUT	4	36.36%	LYM	8	72.73%
NEUT%	2	18.18%	LYM%	2	18.18%
NLR	4	36.36%	PLT	2	18.18%
CRP	6	54.55%	ALB	6	54.55%
CAR	1	9.09%	TNF-α	1	9.09%
PCT	10	90.91%	CD3 + T cell	1	9.09%
ALT	2	18.18%	CD4 + T cell	1	9.09%
AST	2	18.18%	CD8+ T cell	1	9.09%
LDH	7	63.64%	CD4+/CD8 + T cell ratio	1	9.09%
HBDH	1	9.09%			
BUN	3	27.27%			
Cr	3	27.27%			
CK	4	36.36%			
CK-MB	2	18.18%			
D-dimer	7	63.64%			
BNP	2	18.18%			
MB	2	18.18%			
cTnI	1	9.09%			
IL-2	1	9.09%			
IL-6	3	27.27%			
IL-10	2	18.18%			

Abbreviations: NEUT, neutrophil count; NEUT%, neutrophil ratio; LYM, lymphocyte count; LYM%, lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CRP, c-reactive protein; CAR, C-reactive protein to albumin ratio; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; HBDH, Hydroxybutyrate Dehydrogenase; BUN, blood urea nitrogen; Cr, creatinine; CK, creatinine kinase; CK-MB, creatinine kinase-MB; BNP, B natriuretic peptide; MB, myoglobin; cTnI, cardiac troponin I; IL, interleukin; PLT, platelet; ALB, albumin; TNF-α, tumor necrosis-α.

Table 6 Risk Factors for Severe Psittacosis Pneumonia in the Meta-Analysis Studies

Risk Factors	Number of Studies (n=6)	Percentage (%)
Age	2	33.33%
Male	1	16.67%
LYM	1	16.67%
NEUT%	1	16.67%
NLR	1	16.67%
CRP	2	33.33%
CAR	1	16.67%
PCT	1	16.67%
CK	2	33.33%
BNP	1	16.67%
LDH	1	16.67%
AST	1	16.67%
Cr	1	16.67%
ALB	1	16.67%
Glo	1	16.67%

Abbreviation: Glo, globulin.

elevated LDH levels usually indicate viral infections or *Pneumocystis jirovecii* pneumonia rather than bacterial pneumonia.[36,37] In our study, increased LDH levels were observed in 75% of patients (Table 2), but no significant difference was found between SCAP and non-SCAP patients (Table 3). One of the possible reasons may be the disparity in sample size between the groups.

Elevated ALT and AST levels were also observed in severe psittacosis cases than non-severe cases (Table 5), and AST also may be a risk factor for severe psittacosis (Table 6). Other studies have also demonstrated that most patients exhibited on-severe impairment of liver function.[9,38,39] Our study indicated mild elevated ALT and AST levels in patients with psittacosis pneumonia compared to the reference range in healthy people. The above results demonstrated that in psittacosis infection patients, it is necessary to pay attention to the prevention and treatment of liver damage.

High CK levels may be also a features of severe psittacosis infection.[40] And CK was a most sensitive indicator of muscle injury.[41] In our study, increased CK levels were observed in more than 60% of patients (Table 2), but no significant difference was found between SCAP and non-SCAP patients (Table 3). These results indicated that muscle injury may be present in psittacosis patients, while the possible mechanism is still unclear. The importance of CK levels in psittacosis patients needs to be further studied.

Elevated levels of cytokine, particularly increased levels of IL-6 and INF-γ, warrant consideration. This result is in accordance with a prior study that indicated a remarkable rise in pro-inflammatory cytokines in the serum of patients with psittacosis pneumonia.[42] Another study observed increased IL-6 levels severe cases compared to non-severe cases of psittacosis infection.[8]

Our research has a limited number of cases, which may introduce a degree of bias into the statistical comparison. Besides, a retrospective study is inherently limited in its ability to evaluate the effectiveness of therapy. We found that clinical test results may have the potential for distinguishing psittacosis pneumonia from other types of CAP. Further studies should be multi-centre, prospective and focus on assessing the utility of clinical laboratory results in disease differentiation.

Conclusion

This retrospective study identified several clinical features of psittacosis pneumonia infection, such as pre-exposure to birds, high fever, respiratory failure, pulmonary consolidation, and elevated serum CK, D-dimer and LDH levels. Patients exhibited positive responses to therapy with omadacycline and doxycycline. The timely utilization of NGS significantly aids in the clinical diagnosis and prompt treatment of patients.

Statement Covering Patient Data Confidentiality

To protect patients' personal information and maintain the security of Shaoxing People's Hospital's patient information, we are committed to fulfilling our obligation to keep patients' personal information confidential.

Data Sharing Statement

The datasets utilized and/or analyzed during the present study can be obtained from the corresponding author.

Ethics Approval

The research followed the principles of the Declaration of Helsinki. The Ethics Committee of Shaoxing People's Hospital approved this study (2023-Scientific research project 080-01) and waived the requirement for informed written consent, given its nature of retrospective study. All data were processed anonymously.

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Disclosure

The authors declare no competing interests in this work.

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