Original Article

Severe *Chlamydia psittaci* pneumonia: clinical characteristics and risk factors

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Background: Psittacosis ranges from a mild illness to fulminant severe pneumonia with multi-organ failure. It's crucial to understand the clinical characteristics and identify risk factors for a better outcome.

Methods: We conducted a retrospective analysis designed to identify risk factors for severe *Chlamydia psittaci* pneumonia (C. *psittaci* pneumonia) by comparing the clinical characteristics of patients with severe and less severe forms of the disease. Epidemiological, clinical, laboratory, computed tomography (CT) imaging, and outcome data were collected.

Results: We enrolled 27 patients with C. *psittaci* pneumonia, with a median age of 63 (range, 47–82) years, and 23 of whom (85.2%) had a history of avian exposure. Dyspnea was seen in 15 patients with severe C. *psittaci* pneumonia (100%), and four in 12 non-severe patients (33.3%) (P<0.01). Compared to non-severe patients, those with severe C. *psittaci* pneumonia had significantly higher levels of procalcitonin, urea nitrogen, lactate dehydrogenase, creatine kinase (CK), B natriuretic peptide (BNP), myoglobin, IL-6, and IL-10, as well as lower lymphocyte and CD8+ T cell counts, and P_aO_2/F_iO_2 ratio. Among patients with severe infection, CT showed that 46.7% had multi-lobar (more than two lobes) pneumonia, whereas its incidence was 0% in non-severe patients (P=0.01). Multivariate analysis revealed that the independent risk factors associated with severe C. *psittaci* pneumonia were abnormal CK (OR 15.2, 95% CI: 1.1–204.8, P=0.04) and BNP (OR 22.3, 95% CI: 1.8–281.9, P=0.02).

Conclusions: A history of prior avian exposure in middle-aged patients should serve as a clue in the diagnosis of C. *psittaci* pneumonia, and patients with its severe form are more likely to develop dyspnea and progress into respiratory failure, with involvement of multiple lung lobes. Abnormal CK and BNP levels are risk factors associated with severe C. *psittaci* pneumonia.

Keywords: Pneumonia; psittacosis; *Chlamydia psittaci*; avian exposure

Submitted May 21, 2021. Accepted for publication Jul 13, 2021.
doi: 10.21037/apm-21-1502
View this article at: https://dx.doi.org/10.21037/apm-21-1502

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Introduction

Chlamydia psittaci is an obligate intracellular gram-negative bacterium that primarily infects birds but can also cause zoonotic infection in humans, when it is known as psittacosis (1). Transmission to humans often occurs via the inhalation of contaminated aerosols from the excretions of infected birds. The clinical presentation of psittacosis can range from subclinical or an influenza-like illness to fulminant severe pneumonia with multi-organ failure (2-7). It has been estimated that *C. psittaci* is the causative organism of approximately 1% of cases of community-acquired pneumonia (CAP), when it is known as *C. psittaci* pneumonia (8). With early identification and appropriate antibiotic therapy, the infection is rarely fatal (9). However, in recent years, fulminant severe *C. psittaci* pneumonia has been described more frequently using metagenomic next-generation sequencing (mNGS) in clinical practice (2,3,10), and it is crucial to understand its clinical characteristics and identify its risk factors. There have some case reports or case series reported about clinical manifestations of *C. psittaci* pneumonia, but the sample sizes are limited (11,12). Meanwhile, to the best of our knowledge, there has been little research focusing on the risk factors of severe *C. psittaci* pneumonia.

We conducted a retrospective study comprising 27 patients with *C. psittaci* pneumonia who were diagnosed using mNGS and compared patients with severe pneumonia to those with the non-severe condition, with the aim of investigating the clinical characteristics of severe *C. psittaci* pneumonia and identify its risk factors.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1502).

Methods

Study design

We conducted a retrospective case review of 27 patients with *C. psittaci* pneumonia admitted to the First Affiliated Hospital of Wenzhou Medical University, a 3,380-bed tertiary teaching hospital located in south of Zhejiang province, China, between July 1, 2018 and November 30, 2020. The demographic data, comorbidities, clinical manifestations, laboratory findings, radiological information, treatment modalities, and outcomes were extracted from the electronic medical records of patients.

Diagnostic criteria

Owing to the unavailability of commonly used diagnostic tests for psittacosis, such as serological and polymerase chain reaction-based tests, the diagnostic criteria of *C. psittaci* pneumonia was defined as follows: (I) Individuals fulfilling the diagnostic criteria for CAP according to the stated guidelines (13); (II) the presence of specific *C. psittaci* gene fragments in bronchial alveolar lavage fluid (BALF) samples detected using mNGS, fulfilled the criteria for a positive mNGS result, as described by Miao *et al.* (14); routine microbiological tests, including blood, sputum, and BALF culture were all negative. The diagnosis of severe CAP (SCAP) was confirmed based on the stated guidelines (13), and rhabdomyolysis was defined as a serum creatine kinase (CK) level higher than 1,000 U/L (15).

mNGS

Using previously described methods, mNGS analyses were completed by BGI Genomics Institute (Shenzhen, China) (14). Briefly, BALF samples (0.5–3 mL) were collected following standard procedures then agitated at 2,800–3,200 rpm for 30 min. The DNA from 0.3 mL of each sample was extracted using a TIANamp Micro DNA Kit (DP316, Tiangen Biotech, Beijing, China) following the manufacturer's instructions. DNA libraries were constructed using DNA fragmentation, end-repair, adapter ligation, and PCR amplification. Low-quality and short (length <35 bp) reads were removed to generate high-quality sequencing data, and computational subtraction of human host sequences mapped to the human reference genome (hg19) were performed using the Burrows-Wheeler alignment. The remaining data were classified by removing low-complexity reads, and the sequences were aligned to microbial genome databases for bacteria, fungi, viruses, and parasites downloaded from the US National Center for Biotechnology Information (ftp://ftp.ncbi.nlm.nih.gov/genomes).

Statistical analysis

Continuous variables are presented as means ± standard deviation for normal distribution, or as medians (25^{th}, 75^{th} percentiles) for non-normal distribution, and categorical variables are presented as percentages. Continuous variables were compared using the *t*-test or Mann-Whitney *U*-test and categorical variables were analyzed using the

Table 1 General characteristics of patients with community-acquired C. *psittaci* pneumonia

Characteristics	C. *psittaci* pneumonia (n=27)	Severe C. *psittaci* pneumonia (n=15)	Non-severe C. *psittaci* pneumonia (n=12)	P value
Ages, years	62.6±10.1	65.7±8.7	58.8±10.7	0.07
Male, n (%)	17 (63.0)	11 (73.3)	6 (50.0)	0.26
History of contact with avian or poultry, n (%)	23 (85.2)	12 (80.0)	11 (91.7)	0.60
Current smoker, n (%)	6 (22.2)	5 (33.3)	1 (8.3)	0.18
Current drinker, n (%)	10 (37.0)	7 (46.7)	3 (25.0)	0.42
Chronic underlying diseases, n (%)	18 (66.7)	10 (66.7)	8 (66.7)	1.00
Symptom duration before admission, days	5.6±2.6	6.3±3.1	4.7±1.6	0.10
Season of admission, n (%)				0.60
Spring	7 (25.9)	6 (40.0)	1 (8.3)	
Summer	12 (44.4)	4 (26.7)	8 (66.7)	
Autumn	5 (18.5)	2 (13.3)	3 (25.0)	
Winter	3 (11.1)	3 (20.0)	0 (0.0)	

chi-square or Fisher's exact test. Multivariate logistic regression was performed in a stepwise manner to search for independent risk factors associated with severe *C. psittaci* pneumonia. P<0.1 in univariate analysis was considered for the multivariate model, combined with variables that were considered clinically relevant. Variables were carefully chosen to ensure the parsimony of the final model because of the small number of events available. P<0.05 was considered to be statistically significant, and all statistical analyses were performed using SPSS software (version 26.0, SPSS Inc., Chicago).

Ethics approval and consent to participate

This study received approval from the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (No. 2020-111) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). No informed consent was required due to the retrospective nature of the study.

Results

General characteristics

Of the 27 patients, 15 and 12 individuals were diagnosed with severe and non-severe infections, respectively, and *C. psittaci* DNA fragments were detected in BALF samples of all 27 patients using mNGS. Detailed mNGS results are shown in Table S1. Conventional microbiologic examinations, including blood and BALF cultures, did not reveal any other pathogens. Serological tests to detect IgM and IgG antibodies for *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* were conducted in 25 patients, revealing one positive result for IgM each for *C. pneumoniae* and *M. pneumoniae*. Eleven patients in both acute and convalescent phases underwent the tests, of which one patient exhibited more than a four-fold increase in IgG titers for *C. pneumoniae*. However, DNA fragments of *C. pneumoniae* or *M. pneumoniae* were not detected in these patients using mNGS.

The demographic data and general characteristics of patients are shown in *Table 1*. The median age was 63 (range, 47–82) years and 23 of the 27 patients with psittacosis (85.2%) had a history of avian exposure. Sixteen patients (59.3%) raised poultry, such as chickens and ducks, at home, while five patients raised pigeons and one raised a parrot. One of the patients admitted to visiting live poultry markets. There were no significant differences in general characteristics and underlying diseases between the groups.

Clinical characteristics

Clinical manifestations of the enrolled patients are shown in *Table 2*. Patients were febrile with a mean temperature

Table 2 Clinical manifestations of patients with community-acquired C. *psittaci* pneumonia

Characteristics	C. *psittaci* pneumonia (n=27)	Severe C. *psittaci* pneumonia (n=15)	Non-severe C. *psittaci* pneumonia (n=12)	P value
Fever, n (%)	27 (100)	15 (100)	12 (100)	–
Temperature, ℃	39.9±0.5	39.9±0.5	39.8±0.5	0.50
Rigors, n (%)	18 (66.7)	11 (73.3)	7 (58.3)	0.45
Myalgia, n (%)	4 (14.8)	2 (13.3)	2 (16.7)	1.00
Fatigue, n (%)	13 (48.1)	8 (53.3)	5 (41.7)	0.70
Cough, n (%)	22 (81.5)	14 (93.3)	8 (66.7)	0.14
Sputum, n (%)	17 (63.0)	12 (80.0)	5 (41.7)	0.06
Dyspnea, n (%)	19 (70.4)	15 (100)	4 (33.3)	<0.01
Extrapulmonary findings, n (%)				
Relative bradycardia	16 (59.3)	8 (53.3)	8 (66.7)	0.70
Neurological symptoms (headache, dizziness)	12 (44.4)	7 (46.7)	5 (41.7)	1.00
Gastrointestinal symptoms (vomiting and diarrhea)	5 (18.5)	5 (33.3)	0 (0.0)	0.05
Rhabdomyolysis	4 (14.8)	3 (20.0)	1 (8.3)	0.60

of 39.9 ℃. Fifteen patients (100%) with severe *C. psittaci* pneumonia had dyspnea whereas it was present in only four (33.3%) patients with the non-severe condition (P<0.01). Except for dyspnea, patients in both groups had similar symptoms which were not significantly different.

Laboratory results conducted upon admission are shown in *Table 3*. Compared to patients with the non-severe infection, those with severe *C. psittaci* pneumonia exhibited significantly lower lymphocyte and CD8+ T cell counts, and P_aO_2/F_iO_2 ratio. Procalcitonin (PCT), urea nitrogen, lactate dehydrogenase (LDH), CK, B natriuretic peptide (BNP), and myoglobin levels were significantly higher in patients with the severe condition than in those with the non-severe variant. While serum IL-6 and IL-10 levels were significantly higher in patients with severe infection than in those with non-severe infections, white blood cell (WBC) count and C-reactive protein (CRP) levels were not significantly different between the groups.

The radiological manifestations observed during admission are shown in *Table 4*. Using CT, we found that 46.7% of patients with the severe condition had multi-lobar pneumonia (more than two lobes) whereas this condition was not observed in patients with non-severe infections. Consolidation was detected in all patients, and inflammatory exudates, ground-glass opacities, bronchiectasis, and lymphadenopathy were common in patients in both groups without any significant differences (*Figures 1*,*2*). It is noteworthy that pleural effusion was found in 20 of 27 patients (74.1%) with *C. psittaci* pneumonia and presented mostly with unilateral small pleural effusions.

Treatment and outcomes

The antimicrobial treatments used are listed in *Table 5*. Antibiotics that were not active against *C. psittaci* were administered empirically on admission to 11.5% of patients with psittacosis. While one patient with severe disease received carbapenem as the initial empirical antibiotic and developed acute kidney failure, he refused hemodialysis owing to financial constraints and succumbed within 24 hours before receiving the mNGS result. Quinolone (moxifloxacin, 0.4 g intravenously q.d.) was administered to 65.4% of patients, and the median fever-clearance time in the severe group (3.5 days) did not significantly differ from that in the non-severe group (2.5 days). Eight patients with the severe form of the infection (53.3%) underwent invasive ventilation. And patients in severe group had a higher pneumonia severity index (PSI) than the non-severe patients. About 86.7% of patients with severe infection developed sepsis whereas there were no instances of sepsis in the non-severe group. The median length of hospital stay was longer in the severe group (12 days) than in the non-severe group (7.5 days).

Table 3 Laboratory findings on admission of patients with community-acquired C. *psittaci* pneumonia

Characteristics	C. *psittaci* pneumonia (n=27)	Severe C. *psittaci* pneumonia (n=15)	Non severe C. *psittaci* pneumonia (n=12)	P value
WBC (normal 4×10^9–10×10^9/L)	6.9 (5.3, 10.8)	10.3 (5.3, 15.7)	6.6 (5.3, 7.8)	0.22
Neutrophils (normal 1.8–6.3×10^9/L)	5.5 (4.5, 10.2)	9.3 (4.5, 15.2)	5.3 (4.4, 6.1)	0.21
Lymphocyte (normal 1.1–3.2×10^9/L)	0.7±0.2	0.6±0.2	0.8±0.3	0.02
CRP (normal 0–8 mg/L)	188.7±85.4	214.9±94.6	156.0±61.3	0.07
PCT (normal 0–0.5 ng/mL)	0.4 (0.2, 6.3)	2.3 (0.4, 7.8)	0.2 (0.1, 0.4)	<0.01
ALT (normal 7–50 U/L)	46.0 (33.0, 116.0)	58.0 (30.0, 118.0)	46.0 (34.3, 75.5)	0.70
AST (normal 13–40 U/L)	79.0 (45.0, 213.0)	140.0 (58.0, 220.0)	63.0 (32.0, 136.8)	0.12
Urea nitrogen (normal 2.8–7.2 mmol/L)	5.1 (3.7, 9.0)	7.0 (4.8, 20.0)	3.9 (3.5, 5.4)	0.02
Creatinine (normal 35–97 μmol/L)	71.0 (60.0, 118.0)	74.0 (62.0, 215.0)	64.0 (53.0, 79.5)	0.12
LDH (normal 0–247 U/L)	392.0 (316.3, 563.3)	494.0 (390.0, 661.0)	302.0 (288.0, 393.0)	<0.01
CK (normal 26–174 U/L)	232.0 (96.0, 708.0)	456.0 (232.0, 715.0)	97.0 (57.5, 186.5)	<0.01
BNP (normal 0–100 pg/mL)	139.0 (45.0, 204.0)	182.0 (135.0, 256.0)	44.0 (34.5, 120.3)	<0.01
Elevated troponin	5 (20.0)	5 (33.3)	0 (0.0)	0.06
Myoglobin (normal 0–154.9 ng/mL)	99.1 (48.5, 780.4)	322.8 (99.1, 1,110.8)	42.3 (24.3, 53.6)	<0.01
Decreased LVEF (50–70%)	1 (3.7)	1 (6.7)	0 (0)	1.00
CD4+ T cell (normal 432–1,341/μL)	278.2±168.0	236.1±149.6	337.1±182.3	0.15
CD8+ T cell (normal 238–1,075/μL)	116.9±69.4	79.2±33.7	169.7±73.1	<0.01
IL-6 (normal 0–3 pg/mL)	130.6 (58.4, 491.4)	345.9 (63.1, 948.0)	72.8 (25.4, 117.1)	0.01
IL-10 (normal 0–4.1 pg/mL)	5.6 (3.3, 11.0)	7.6 (5.4, 18.7)	3.5 (2.4, 4.8)	<0.01
IFN-γ (normal 0–2.2 pg/mL)	31.5 (8.3, 136.3)	41.5 (4.9, 188.3)	13.5 (8.6, 49.2)	0.33
P_aO_2/F_iO_2 ratio, mmHg	219.7±111.6	152.3±36.7	350.0±92.3	<0.01

WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BNP, B natriuretic peptide; LVEF, left ventricular ejection fraction.

Risk factors associated with severe C. psittaci pneumonia

Results from the multivariate analysis indicated that elevated CK and BNP significantly increased the risk of severe *C. psittaci* pneumonia (OR 15.2, 95% CI: 1.1–204.8, P=0.04; and OR 22.3, 95% CI: 1.8–281.9, P=0.02, respectively) (*Table 6*).

Discussion

In this study, we found that *C. psittaci* pneumonia presented with clinical characteristics, such as non-specific hyperpyrexia, fatigue, and cough, which are similar to pneumonia caused by other pathogens. However, in cases of *C. psittaci* pneumonia, the majority (85%) of patients admitted to instances of exposure to birds, which is a crucial diagnostic clue for the development of psittacosis. This condition presents in middle-aged adults (average 63 years), and the results in our study were similar to previously reported findings on the disease (2,16,17). However, some characteristics and clinical findings in our study differed from those reported in others. Dyspnea was seen in 70% of patients in our study, including 100% of patients with severe disease, which was significantly more frequent than the incidence in the non-severe group, and 53% of patients with severe infection required invasive medical ventilation. In a study comprising 135 patients with psittacosis, dyspnea was a reported symptom in 24% of patients, and none developed fulminant multiorgan failure and no fatalities were reported (17). In another endemic study conducted in Australia

Table 4 Radiological findings on admission of patients with community-acquired C. *psittaci* pneumonia

Characteristics	C. *psittaci* pneumonia (n=27)	Severe C. *psittaci* pneumonia (n=15)	Non severe C. *psittaci* pneumonia (n=12)	P value
Lobes involvement >2, n (%)	7 (25.9)	7 (46.7)	0 (0)	0.01
Consolidation, n (%)	27 (100)	15 (100)	12 (100)	–
Inflammatory exudation, n (%)	25 (92.6)	13 (86.7)	12 (100)	0.49
Ground-glass opacities, n (%)	19 (70.4)	9 (60.0)	10 (83.3)	0.24
Bronchiectasis, n (%)	6 (22.2)	3 (20.0)	3 (25.0)	1.00
Lymphadenopathy, n (%)	10 (37.0)	7 (46.7)	3 (25.0)	0.42
Pleural effusions, n (%)				0.46
No pleural effusions	7 (25.9)	3 (20.0)	4 (33.3)	
Unilateral	12 (44.4)	7 (46.7)	5 (41.7)	
Bilateral	8 (29.6)	5 (33.3)	3 (25.0)	

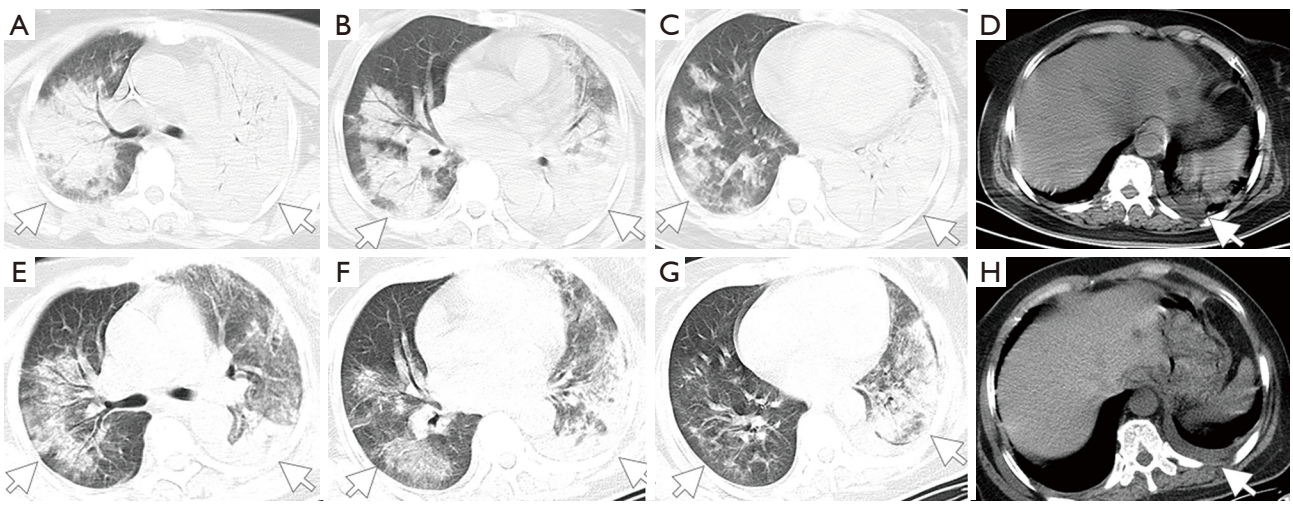

Figure 1 Serial chest computed tomography (CT) scans of a 58-year-old woman with severe C. *psittaci* pneumonia. The initial CT scan shows air-space consolidation with inflammatory exudates in five lobes of the lung with left small pleural effusion (white arrows) on 2020-4-15, eight days after onset (A,B,C,D). On 2020-4-26, after 11 days of moxifloxacin therapy, a repeat CT scan shows resolution of the consolidation leaving behind ground-glass opacities and inflammatory exudates along with left small pleural effusion (white arrows) (E,F,G,H).

and comprising 44 patients with community-acquired psittacosis, only one patient (2%) was reported as receiving invasive ventilatory support, and eventually succumbed to respiratory failure (16). However, a recent study focusing on severe pneumonia caused by *Chlamydia psittaci* reported that 100% of patients had dyspnea and 66.7% needed invasive ventilator support, which is consistent with our results (2). Researchers in the Netherlands reviewed the case reports of patients with severe psittacosis requiring respiratory support and found that eight of 12 patients with severe respiratory failure perished (7). Collectively, these findings indicate that respiratory failure requiring ventilatory support is not a rare occurrence and can lead to fatalities.

Laboratory findings in our study showed that PCT, urea nitrogen, LDH, CK, BNP, myoglobin, IL-6, and IL-10 levels were significantly higher, and the lymphocyte and CD8+ T cell counts, and P_aO_2/F_iO_2 ratio were lower in patients with the severe form of the infection than in those with the

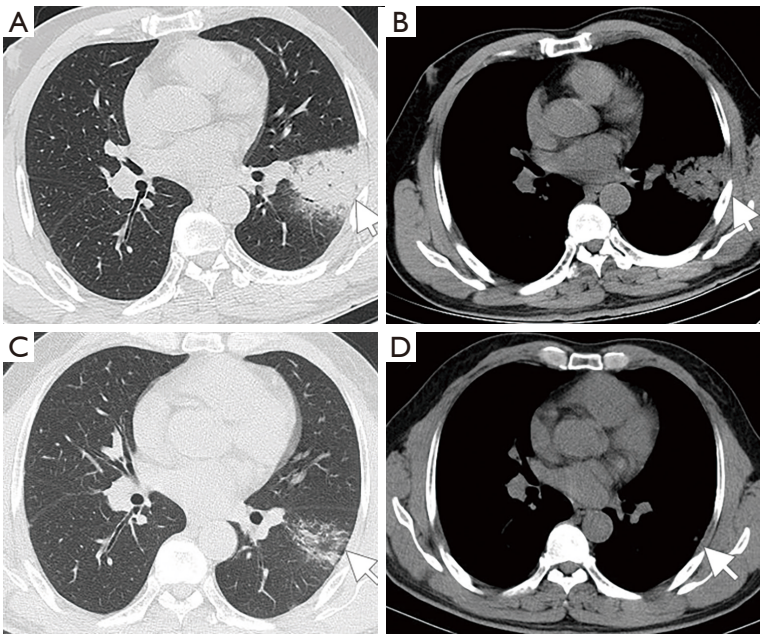

Figure 2 Serial chest CT scans of a 56-year-old man with non-severe C. *psittaci* pneumonia. The initial CT scan shows consolidation in the lower lobe of the left lung (white arrows) on 2020-7-20, four days after onset (A,B). On 2020-8-3, 18 days after the onset, a repeat CT scan shows almost complete resolution of the consolidation 2 weeks after azithromycin therapy (white arrows) (C,D).

Table 5 Treatment and outcomes of patients with community-acquired C. *psittaci* pneumonia

Variable	C. *psittaci* pneumonia (n=27)	Severe C. *psittaci* pneumonia (n=15)	Non severe C. *psittaci* pneumonia (n=12)	P value
Empirical antibiotics not covered	3 (11.5)	2 (13.3)	1 (8.3)	1.00
Antimicrobial therapy				0.27
Tetracycline	1 (3.8)[a]	1 (7.1)[b]	0 (0)	
Macrolides	7 (26.9)[a]	3 (21.4)[b]	4 (33.3)	
Quinolones	17 (65.4)[a]	9 (64.3)[b]	8 (66.7)	
Combination of above antibiotics	1 (3.8)[a]	1 (7.1)[b]	0 (0)	
Fever clearance time, days	3.0 (1.8, 5.0)	3.5 (2.8, 6.8)	2.5 (1.0, 4.0)	0.05
Respiratory support, n (%)				0.75
Invasive ventilation	8 (29.6)	8 (53.3)	0 (0)	
Non-invasive ventilation	1 (3.7)	1 (6.7)	0 (0)	
Oxygen therapy	14 (51.9)	6 (40.0)	8 (66.7)	
No respiratory support	4 (14.8)	0 (0)	4 (33.3)	
Sepsis, n (%)	13 (48.1)	13 (86.7)	0 (0)	<0.01
Pneumonia severity index	110.4±45.4	144.6±28.0	67.6±16.4	<0.01
Hemodialysis, n (%)	3 (11.1)	3 (20.0)	0 (0)	0.23
Median length of hospital stay, days	10.0 (7.0,13.0)	12.0 (10.0, 17.0)	7.5 (6.3, 9.8)	0.01
Death, n (%)	2 (7.4)	2 (13.3)	0 (0)	0.49

a=26; b=14.

Table 6 Multivariate logistic regression analysis of factors associated with severe community-acquired C. *psittaci* pneumonia

Variables	Odds ratio	95% confidence interval	P value
CK (>174 U/L)	15.2	1.1–204.8	0.04
BNP (>100 pg/mL)	22.3	1.8–281.9	0.02

The area under the curve was 0.88. CK, creatine kinase; BNP, B natriuretic peptide.

non-severe infection. The independent risk factors associated with severe *C. psittaci* pneumonia were CK and BNP.

CK is distributed in many tissues, including cardiac and skeletal muscle. Its lack of specificity has resulted in it not being used in the diagnosis of myocardial damage for several years, despite it being the most sensitive indicator of muscle injury (18). Previously published case reports suggest the occurrence of rhabdomyolysis in psittacosis presented with a high level of CK (19,20), although the mechanism by which this occurs is unknown. Our study shows that psittacosis-associated rhabdomyolysis is not rare both in severe and non-severe groups, and abnormal CK levels (higher than 174 U/L) is a predictive factor of severe *C. psittaci* pneumonia, which indicated the presence of muscle injury in psittacosis patients.

While BNP is a marker for heart failure, it is also thought to be a biomarker to determine the severity and outcome of CAP (21-24), and our results suggest abnormal BNP is also an independent risk factor associated with severe *C. psittaci* pneumonia. BNP secretion is triggered by hypoxia, and its levels are increased in patients with severe sepsis and septic shock (25). Moreover, the activation of proinflammatory cytokines has also been identified as a factor inducing BNP secretion (24). In our study, patients with severe infection were found to have a significantly lower P_aO_2/F_iO_2 ratio and higher levels of PCT, IL-6, and IL-10 compared to those with non-severe infection. Additionally, 86.7% of patients with severe infection developed sepsis, whereas none developed septic complications in the non-severe group. Collectively, these data may help interpret the BNP levels.

Involvement of the heart in psittacosis is uncommon, and conditions such as endocarditis, myocarditis, and pericarditis have rarely been reported. Case studies suggest that myocarditis may lead to elevated troponin levels, left ventricular dilatation, and severely decreased left ventricular ejection fraction (LVEF) (26,27). However, in our study, only one patient with severe infection had a decreased LVEF of 45%. Although 33.3% of patients with severe infection exhibited elevated troponin levels, this increase was not statistically significant compared to those with non-severe infections. We have no direct evidence to prove the occurrence of myocardial injury in our study, and cardiac involvement cannot adequately explain the independent results of CK and BNP levels. Moreover, the serological results indicating the presence of IgM and IgG antibodies for *C. pneumoniae* and *M. pneumoniae* suggest the possibility of cross-reactivity of these diagnostic tests, which is consistent with other findings (1,28).

Based on CT results in our study, 46.7% of patients with severe infection exhibited involvement of more than two lung lobes. Air-space consolidation, inflammatory exudates, ground-glass opacities, and bronchiectasis were common. Pleural effusions were present in 74% of patients. This was much higher than the figure reported in an Australian study (13%) (16), and the 44.4% seen in a study on severe *C. psittaci* pneumonia in China (2), and, indicates pleural effusions may be more common than generally reported.

Tetracyclines are first-line antibiotics for the treatment of psittacosis (9,13), and severely ill patients may require intravenous doxycycline, which is unavailable in our hospital. In the present study, 17 patients with psittacosis received quinolones, one of whom succumbed. Another patient with severe psittacosis who died 24 hours after admission, received carbapenem as the initial empirical antibiotic. These findings suggest it may be better to follow the prescribed guidelines and administer a β-lactam plus a macrolide, or a β-lactam plus a respiratory fluoroquinolone, before identifying the causative pathogen in patients with severe CAP (29). Owing to the unavailability of doxycycline in the majority of hospitals in China, quinolones are frequently administered as the first choice, and while some experimental models report the efficacy of quinolones in *C. psittaci* infections, further prospective clinical studies are needed to confirm their efficacy (30).

Our retrospective study has several limitations. Firstly, this was a single-center study in a tertiary teaching hospital, and bias may exist as patients with a mild illness would not have been admitted. Secondly, the sample size was small, and thirdly, the diagnosis of *C. psitt*aci pneumonia was made solely using mNGS without confirmation using other

diagnostic methods. Future studies with a larger population in multiple centers are needed.

Conclusions

A history of avian exposure in middle-aged patients could be suggestive of *C. psittaci* pneumonia. Respiratory failure is not a rare occurrence and can prove to be fatal. Abnormal CK and BNP are independent risk factors for severe *C. psittaci* pneumonia.

Acknowledgments

The authors would like to thank MJEditor (www.mjeditor.com) for its linguistic assistance during the preparation of this manuscript.
Funding: This work was supported by the Project of National Natural Science Foundation of China (Grant number 81970066).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1502

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-1502

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1502). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study received approval from the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (NO. 2020-111) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). No informed consent was required due to the retrospective nature of the study.

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(English Language Editor: B. Draper)

Cite this article as: Su S, Su X, Zhou L, Lin P, Chen J, Chen C, Zhou Y, Li Y. Severe *Chlamydia psittaci* pneumonia: clinical characteristics and risk factors. Ann Palliat Med 2021;10(7):8051-8060. doi: 10.21037/apm-21-1502

Supplementary

Table S1 Detail mNGS results of 27 cases

Patient ID	Sex	Age	Group	mNGS results and reads from BALF
01	Male	67	Severe	Chlamydia psittaci (92)
02	Male	52	Severe	Chlamydia psittaci (168)
03	Male	68	Non-severe	Chlamydia psittaci (20)
04	Male	56	Non-severe	Chlamydia psittaci (2)
05	Female	55	Non-severe	Chlamydia psittaci (18)
06	Female	52	Non-severe	Chlamydia psittaci (53)
07	Female	47	Non-severe	Chlamydia psittaci (15)
08	Female	63	Non-severe	Chlamydia psittaci (900)
09	Female	47	Non-severe	Chlamydia psittaci (180)
10	Female	61	Severe	Chlamydia psittaci (271), Chlamydia abortus (20)
11	Male	51	Severe	Chlamydia psittaci (3686), Chlamydia abortus (194)
12	Male	71	Severe	Chlamydia psittaci (4458), Chlamydia abortus (369)
13	Male	79	Severe	Chlamydia psittaci (182), Chlamydia abortus (18)
14	Male	68	Non-severe	Chlamydia psittaci (254), Chlamydia abortus (5)
15	Male	78	Severe	Chlamydia psittaci (1219), Candida tropicalis (9)
16	Male	68	Severe	Chlamydia psittaci (75), Chlamydia abortus (5), Actinomyces (3)
17	Male	74	Severe	Chlamydia psittaci (728), Chlamydia abortus (40), Staphylococcus hominis (25)
18	Male	57	Severe	Chlamydia psittaci (3521), Chlamydia abortus (13), Tropheryma whipplei (450)
19	Male	64	Severe	Chlamydia psittaci (45), Chlamydia abortus (3), streptococcus mitis (6), Veillonella parvula (3)
20	Female	72	Severe	Chlamydia psittaci (71), Acinetobacter baumannii (23), Acinetobacter johnsonii (3)
21	Female	71	Severe	Chlamydia psittaci(138), Pseudomonas aeruginosa (4), Candida albicans (77):
22	Female	58	Severe	Chlamydia psittaci (105), Achromobacter xylosoxidans (4), Pseudomonas monteilii (3), Stenotrophomonas maltophilia (3)
23	Male	63	Severe	Chlamydia psittaci (586), Chlamydia abortus (28), Enterococcus faecium (261), Enterococcus durans (4), Corynebacterium accolens (53), Campylobacter rectus(4), Lautropia mirabilis (4), Tannerella forsythia (3)
24	Male	50	Non-severe	Chlamydia psittaci (106), Prevotella melaninogenica (9), Human alphaherpesvrus 1 (11)
25	Male	66	Non-severe	Chlamydia psittaci (403), Chlamydia abortus (15), Klebsiella pneumoniae (2099), Klebsiella variicola (69), Olsenella uli(28)
26	Male	51	Non-severe	Chlamydia psittaci (6), Aggregatibacter segnis (60), Aggregatibacter Aphrophilus(3), Gemella morbillorum (14), Dolosigranulum pigrum (8), Mycobacteroides abscessus (3)
27	Female	82	Non-severe	Chlamydia psittaci (232), Chlamydia abortus (16), Ureaplasma parvum (4), Moraxella Catarrhalis (29), Haemophilus influenzae (8), Human gamma herpesvirus 4 (6)

https://dx.doi.org/10.21037/apm-21-1502