Clinical Analysis of Metagenomic Next-generation Sequencing Confirmed *Chlamydia psittaci* Pneumonia: A Case Series and Literature Review

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Short Report

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Abstract

Introduction: *Chlamydia psittaci* infection is a zoonotic infectious disease, which mainly inhaled through the lungs when exposed to the secretions of poultry that carry pathogenic bacteria. The traditional respiratory specimens or serological antibody testing is slow and the false-negative rate is high. Metagenomic next-generation sequencing gives a promising rapid diagnosis tool.

Methods: We retrospectively summarized the clinical characteristics of five *C. psittaci* pneumonia patients diagnosed by mNGS, conducted a literature review summarizing the clinical characteristics of patients with *C. psittaci* pneumonia reported since 2010.

Results: Five *C. psittaci* pneumonia patients confirmed by mNGS aged from 36 to 66 years with three males. 60% of patients had type 2 diabetes mellitus. And 60% of patients had a history of contact with avian or poultry. All patients had a high fever over 38.5 °C, cough, hypodynamia, hypoxemia, and dyspnea on admission. Two patients had invasive ventilator support and Extracorporeal Membrane Oxygenation support. The levels of C-reactive protein, procalcitonin, and erythrocyte sedimentation rate on admission and follow-up were all higher than normal values. Doxycycline or moxifloxacin monotherapy was accounted for 1/5 (20%) and 2/5 (40%) patients, and combination therapy was accounted for 2/5 (40%) patients. Four patients improved and were discharged, and one patient died due to multiple organ failure and disseminated intravascular coagulation.

Conclusions: mNGS can increase the detection rate of *C. psittaci*, shorten the diagnosis time of *C. psittaci* pneumonia and improve the prognosis of patients.

1. Introduction

Chlamydia psittaci pneumonia is caused by *Chlamydia psittaci* (*C. psittaci*), which can lead to severe pneumonia, adult respiratory distress syndrome, and even death [1]. According to the sequence difference of *C. psittaci* outer membrane protein A gene (ompA), it can be divided into 10 genotypes, namely A-G, WC, E/B, and M56, among which genotype A is the main genotype that causes human infection [2]. About 70% of respiratory tract infections caused by *C. psittaci* are asymptomatic or only with mild symptoms, but 30% of them are severe respiratory illnesses such as community-acquired pneumonia with atypical symptoms, bronchitis, and upper respiratory tract infections [3]. Contacting with birds or poultry is regarded as the main risk factor for psittacosis [1]. The clinical symptoms of *C. psittaci* infection are quite different and lack specificity, which ranges in severity from mild to severe. Cause the clinical manifestations of *C. psittaci* are similar to influenza symptoms, and the extrapulmonary manifestations are similar to Legionella, it needs to be differentiated from influenza and Legionella [4]. Recent publications also reported the co-infection of SARS-CoV-2 with *Chlamydia* [5-7], which makes the infectious diseases more complex.

The culture of *C. psittaci* from respiratory secretions in special media is possible but difficult, and it mainly performed in specialized laboratories only because of the high infectivity of this pathogen. Specific diagnostic testing is serological, which is regarded as the gold standard for *C. psittaci* pneumonia. Moreover, micro-immunofluorescence test (MIF) is the most accurate serologic test for *C. psittaci* pneumonia, but is also performed only in specialty laboratories. Polymerase chain reaction assay (PCR) is used to confirm the strong clinical suspicion of a possible diagnosis of psittacosis especially, to distinguish it from other chlamydial species [8]. And complement fixation (CF) is also an acceptable diagnostic method. Because of its non-specific symptoms and the limitations of traditional tests, *C. psittaci* pneumonia is easily underdiagnosed and misdiagnosed [9].

Metagenomic next-generation sequencing (mNGS) can quickly and accurately identify potential pathogens, whether they are bacteria, fungi, viruses, or parasites [10]. It is increasingly used for the diagnosis of infectious diseases, especially when traditional diagnostic methods have limitations [11]. Studies have shown that mNGS is the most promising comprehensive diagnosis method for infection, especially for severe pneumonia [12]. Recently, several studies have reported the application of

mNGS in diagnosing of *C. psittaci* pneumonia, two literature of case reports describing 5[13] and 9[14] cases of *C. psittaci* diagnosed by mNGS.

We retrospective summarized the clinical characteristics of five *C. psittaci* pneumonia patients diagnosed by mNGS in our hospital. Besides, we conducted a literature review of patients with *C. psittaci* pneumonia reported since 2010, with the attention to summarize the diagnostic methods and anti-infective drugs of them. We also summarized the clinical outcome and history of exposure to avian or poultry of these infection patients to provide a reference for future *C. psittaci* pneumonia infection patients' diagnosis and treatment. We present the following article in accordance with the CARE reporting checklist.

2. Case Presentations

2.1. Patients information

We carried out a retrospective case series analysis of five patients admitted to the Second Xiangya Hospital of Central South University since 2018. We collected the clinical data of all patients confirmed to have *C. psittaci* pneumonia. Sex, age, clinical examination indexes such as procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), comprehensive computed tomography (CT), and arterial blood gas analysis were extracted from electronic medical records. The treatment of antibiotics, outcomes, and any relevant follow-up data were also collected.

The Ethics Committees of the Second Xiangya Hospital of Central South University (LYF-2020021) approved this study. It was carried out by the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All data were anonymized before analysis.

We identified five *C. psittaci* pneumonia patients all confirmed by mNGS. The median of mNGS detection sequence number of *C. psittaci* was 217(range from 175 to 289). There were three male and two female patients with a median age of 51 years (range from 36 to 66). All patients were positive for *C. psittaci* DNA fragments by mNGS, and culture did not reveal any other respiratory pathogens on admission to our hospital. 60% of patients had underlying diseases Type 2 diabetes. Three of five patients had a history of contact with avian or poultry. All patients had a high fever over 38.5 °C, cough, hypodynamia, hypoxemia, and dyspnea. Two of five patients had a headache. In the course of treatment, two patients had invasive ventilator support and Extracorporeal Membrane Oxygenation (ECOM) support. The medium APACHE II was 17.6(range from 8 to 22). Days from illness to respiratory failure were 4.8(2-8) days.

2.2. Laboratory test

mNGS was conducted using the following operational steps according to the company's operating procedures (The Beijing Genomics Institute, Beijing, China). Briefly, clinical samples (blood or alveolar lavage fluid) were collected by following the standards of aseptic processing procedures. Nucleic acid extraction was conducted and the extracted DNA was subjected to processes of interruption, end repair, library construction, and sequencing. The mapped data were processed for advanced data analysis. Lists of suspected pathogenic microorganisms were produced, which included the numbers of strictly mapped reads, coverage rates, and depth. The clinical diagnosis was determined by considering all the clinical manifestations, possible pathogens identified by mNGS, and other laboratory tests together. On admission and during the hospital, the inflammatory markers such as PCT, CRP, ESR, kidney, and liver function index, CT, and X-ray data were detected according to the patients' condition.

Laboratory inspections parameters of the five patients on admission were shown in **Table 2**. Four patients had lower hemoglobin and the levels were 108.6(range 68-148) g/L. The levels of CRP, PCT and ESR on admission were all higher than normal values. Oxygen partial pressure and partial pressure of carbon dioxide of all patients were significantly lower than normal values.

After admission, follow-up laboratory testing results showed that the levels of inflammatory markers including WBC, percentage of neutrophils, CRP, PCT, ESR were all higher than normal values (**Table 1**). Moreover, the values of CK, lactate

dehydrogenase (LDH), ALT, and AST were all higher than normal values in all five patients. Three patients had hypokalemia and the potassium levels were range from 2.7 to 3.3 mmol/L.

Chest CT and X-ray of patients showed that lungs were exuding consolidation foci, bilateral pectoral effusions, consolidation. After treatment, the image of four patients improved compared with those on admission, and the patients' lung exudation, consolidation, and bilateral pleural effusion were less than before (**Figure 1, Figure 2**).

2.3 Treatment and outcome

After *C. psittaci* pneumonia was confirmed, one of the three male patients received symptomatic anti-infective treatment with moxifloxacin (400mg ivgtt qd) and with adjuvant non-invasive ventilator therapy. The other two male patients received symptomatic anti-infective therapy with doxycycline (100mg po q12h) and were treated with high flow nasal cannula therapy. All three male patients were improved and discharged after more than 10 days of treatment. Two female patients were transferred to our hospital after invasive ventilator adjuvant treatment with tracheal intubation from other hospitals. They were treated with moxifloxacin (400mg ivgtt qd) combined with doxycycline (100mg po q12h) for symptomatic anti-infective therapy. The two female patients were treated with ECOM and ventilator adjuvant therapy due to their critical illness. One patient was removed ECOM after five days of treatment with blood oxygen saturation and oxygen partial pressure was significantly improved. After 3 days of consecutive treatment, the invasive ventilator was removed. The patient continued to receive treatment and was discharged from the hospital. Another female patient was critically ill and the disease progressed rapidly. She was treated with ECOM five days after admission. One day later after ECOM using, she was died due to multiple organ failure, disseminated intravascular coagulation (DIC).

3. Literature Review

We searched from the databases including PubMed, EMBASE, Web of Science, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) from 1st Jan. 2010 to 1st Oct. 2020. The searching strategy was "*Chlamydia psittaci*" or "*Chlamydia psittaci* pneumonia". Dr. Jian Qu and Dr. Wen-Cheng Gong reviewed all relevant articles to identify potentially eligible studies. We conducted this literature review of patients with *C. psittaci* pneumonia to summarize the diagnostic methods and anti-infective drugs of them, and we also summarized the clinical outcome and history of exposure to avian or poultry of these infection patients to provide a reference for future *C. psittaci* pneumonia infection patients' diagnosis and treatment. The data about authors, reported time, number of cases, ethnics, history of exposure to avian or poultry, anti-infective drugs regiment, and clinical outcome were collected. We found 794 publications. After excluded the full text could not be found or provided no information we needed about *C. psittaci* pneumonia or no original data or the Chlamydia was not specified. Finally, 18 articles were enrolled in further review.

The summary of the detailed information was shown in **Table 3**. The articles were published from 2012 to 2020. With the development of detection technology, the number of articles reported tends to increase (**Figure 3**). Since 2019, there were 12 articles reported *C. psittaci* pneumonia and among them, 8 articles using mNGS to detect *C. psittaci*. There were total of 64 *C. psittaci* pneumonia patients reported and most patients had a history of exposure to avian or poultry. Most patients treated with doxycycline, moxifloxacin, meropenem, or their combinations, and three patients used ECOM support. Most of the patients' treatment improved and four patients died.

4. Discussion

We retrospective analyzed five cases of psittacosis pneumonia diagnosed using mNGS and summarized the clinical characteristics including disease progression, treatments, and outcomes, etc. Moreover, we also carried out a literature review summarized the existing research and reports about *C. psittaci* pneumonia. In our study, five *C. psittaci* pneumonia patients confirmed by mNGS aged from 36 to 66 years with three males. 60% of patients had underlying diseases Type 2 diabetes. Three of these five patients had a history of contact with avian or poultry. All patients had a high fever over 38.5 °C, cough, hypodynamia, hypoxemia, and dyspnea on admission. Two patients had invasive ventilator support and ECOM support. The

levels of CRP, PCT, and ESR on admission and follow-up were all higher than normal values. Doxycycline or moxifloxacin monotherapy was accounted for 1/5 (20%) and 2/5 (40%) patients, and combination therapy was accounted for 2/5(40%) patients. Four patients improved and were discharged, and one patient died due to multiple organ failure and disseminated intravascular coagulation.

The lung manifestations are mainly cough, dry cough, shortness of breath, the rapid progress of lung disease, and occasionally acute respiratory distress syndrome (ARDS) [15]. In the five cases reported in this article, 3 patients had ARDS. And there were even case reports showing only abnormal liver function [16]. In the initial auscultation, the lung lesions of *C. psittaci* pneumonia were often underestimated. The chest radiograph showed infiltrating patches with uneven density, which can seriously affect all lung lobes. CT of the lungs showed consolidation or ground glass-like changes, especially the lower lung, with pleural involvement and pleural effusion [17]. After treatment, the patients' cough and fever improved, but the oxygenation index recovered slowly. According to the reporting of literature, the absorption of the lesion was slow, with an average absorption time of 6 weeks, up to 20 weeks [18].

According to the control requirements of *C. psittaci* issued by the National Public Health Veterinary Association, the confirmed diagnosis of human *C. psittaci* pneumonia only needs to meet one of the following two standards: 1). Isolate *C. psittaci* from respiratory specimens (sputum, pleural fluid, tissue, etc.) or blood specimens 2). Serological examination: Measure the *C. psittaci* IgG antibody in the acute and convalescent phases during the interval of 2-4 weeks, the convalescent phase is more than four times higher than the acute phase. If the patient meets one of the following two standards, it may be infected: 1). Serum examination, *C. psittaci* IgM ≥ 32 ; 2). *C. psittaci* DNA can be detected through PCR amplification of respiratory specimens (sputum, pleural fluid, tissue, etc.) [19]. Since *C. psittaci* is strictly intracellular parasitic, its direct isolation and cultivation are very difficult and cannot be carried out routinely. At present, MIF [20] and PCR gene expansion detection has become an auxiliary detection of molecular biological diagnosis due to its high sensitivity and specificity [21]. mNGS can be used to detect pathogens that cannot be detected by traditional methods[22]. Patients introduced in this article were all severely infected when they were admitted to our hospital, with respiratory failure, and dry cough without sputum. Due to the high risk of bronchoscopy and difficulty in taking respiratory tract specimens, the blood of patients was sent out for mNGS testing and finally reported *C. psittaci* infection. Early pathogenic diagnosis can greatly benefit patients, and of the 5 patients reported in this article, 4 patients improved and were discharged. Our literature review also found that with the development of technology, the number of *C. psittaci* detected increased year by year, and the articles reported *C. psittaci* pneumonia via mNGS increased year by year (**Figure 3** and **Table 3**).

Tetracyclines, macrolides, and quinolones can interfere with DNA and protein synthesis, therefore, these three kinds of antibiotics can be used to treat *C. psittaci* [23]. At present, tetracyclines are the first choice for the treatment of *C. psittaci* pneumonia including tetracycline, doxycycline, and minocycline [24, 25]. In severe cases, doxycycline can be administered intravenously. The treatment of the patient in case 2 with doxycycline is also effective. Macrolide drugs such as azithromycin and fluoroquinolones have been confirmed to have antibacterial activity against *C. psittaci* in vitro [25, 26], In particular, moxifloxacin has strong antibacterial activity against Chlamydia, and there are case reports at home and abroad that the use of fluoroquinolone drugs is effective [27-30]. Given of the lack of experience in the use of tetracyclines in our hospital, Chlamydia trachomatis, which is the same species as *C. psittaci* in my country, is highly resistant to tetracycline [31], so the treatment for case 1 patient used moxifloxacin and it was effective. After five patients were treated, four patients were improved and discharged. Among them, one patient was treated with moxifloxacin, two patients were treated with doxycycline, and the other two patients were treated with moxifloxacin plus doxycycline. Current *C. psittaci* Pneumonia treatment guidelines recommend addition of macrolide or quinolone to the initial regimen of severe *C. psittaci* in any case. According to current reports, it is unclear whether combination medication is more effective than single medication for patients. Further case-control studies with larger samples are needed to find the optimal treatment.

In this article, we have searched the relevant literature. At present, most cases of human infection with *C. psittaci* are reported in scattered cases and details are listed in **Table 3**. With the development of detection technology, mNGS became a routine examination for etiology. Therefore, more and more *C. psittaci* pneumonia was diagnosed and treated according to guidelines.

Our literature review summarized 18 articles including 64 *C. psittaci* pneumonia patients and found that most patients had a history of exposure to avian or poultry. Therefore, epidemiological data combined with mNGS detection is helpful for the early diagnosis of *C. psittaci* pneumonia. Most patients are treated with doxycycline, moxifloxacin, or their combinations. There were three patients who used ECOM support and they are all improved. Among these 64 patients in our literature review, 60 patients of *C. psittaci* pneumonia improved and four patients died.

5. Conclusions

mNGS can increase the detection rate of *C. psittaci*, shorten the diagnosis time of *C. psittaci* pneumonia and improve the prognosis of patients.

Abbreviations

<i>C. psittaci</i>	<i>Chlamydia psittaci</i>
PCR	Polymerase chain reaction assay
CF	complement fixation
mNGS	Metagenomic next-generation sequencing
PCT	procalcitonin
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
CT	computed tomography
ECOM	Extracorporeal Membrane Oxygenation
LDH	lactate dehydrogenase
DIC	disseminated intravascular coagulation
ARDS	acute respiratory distress syndrome

Declarations

Ethics approval and consent to participate

The Ethics Committees of the Second Xiangya Hospital of Central South University (LYF-2020021) approved this study. Informed consent was obtained by the treating physicians from each patient for being included in the publication.

Consent for publication

All authors have read and approved the manuscript.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JQ designed the study, assisted in data collection and approved the manuscript. XQT and WCG assisted in data collection and drafted, revised and approved the manuscript. QQ, GHL, and QL revised and approved the manuscript.

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Tables

Table 1.

Clinical characteristics of the five *C. psittaci* pneumonia cases

Characteristics	Abnormal patients/Total patients, <i>n</i> (%)	Median value (range)
Demographics		
Age, median (range, years)		51(36-66)
History of exposure to avian or poultry	3/5(60)	
Underlying disease	3/5(60)	
Clinical manifestations		
Fever > 38.5 °C	5/5(100)	39.1 (38.7–40.5)
Cough, hypodynamia, dyspnea	5/5(100)	
Headache	2/5(40)	
Hypoxemia	5/5(100)	
Invasive ventilator support	2/5(40)	
ECOM support	2/5(40)	
APACHE II		17.6(8-22)
Days from illness to respiratory failure		4.8(2-8)
NGS detection sequence number		217(175-289)
Laboratory testing		
WBC (normal 4–10, × 10 ⁹ /L)	4/5(80)	14.35(10.4-20.08)
Neutrophil ratio (normal 45–75%)	5/5(100)	93.03(80.5-97.7)
CRP (normal 0–8 mg/L)	5/5(100)	129.83(16.8-423)
PCT (normal 0–0.05 ng/mL)	5/5(100)	10.12(0.058-100)
ESR (normal 0–15mm/h)	5/5(100)	65.64(25-100)
CK (normal 30–135 U/L)	5/5(100)	2261.18(14-8842.2)
LDH (normal 109–245 U/L)	5/5(100)	737.96(252.9-1433.1)
ALT (normal 9–50 U/L)	5/5(100)	310.17(65.7-2889.7)
AST (normal 15–40 U/L)	5/5(100)	1554.11(40.4-23553.3)
Hypokalemia (normal 3.5–5.3 mmol/L)	3/5(80)	3.1(2.7-3.3)*
Hemoglobin		
Treatment		
Doxycycline	2/5(40)	
Moxifloxacin	1/5(20)	
Moxifloxacin+Doxycycline	2/5(40)	
Treatment result		
Survive	4/5(80)	

ECOM, Extracorporeal Membrane Oxygenation; APACHE, The Acute Physiology and Chronic Health Evaluation; CK, creatine kinase; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; PCT, procalcitonin; ALT, alanine transaminase; AST, Aspartate aminotransferase; WBC, white blood cell; ESR, erythrocyte sedimentation rate. *The potassium levels just analyzed the values of hypokalemia patients.

Table 2.

Laboratory inspections parameters of the five patients on admission

Inspection items	Case 1	Case 2	Case 3	Case 4	Case5	Reference value
PH	7.504	7.47	7.52	7.4	7.53	7.35-7.45
Oxygen partial pressure (mmHg)	64.6	42	53.1	59	58	80-100
Partial pressure of carbon dioxide (mmHg)	28.8	29	26.7	27	29	35-45
White blood cell count ($\times 10^9/L$)	16.88	8.43	13.56	5.66	2.1	3.5-9.5
Hemoglobin (g/L)	128	127	68	148	72	130-175
Platelets ($\times 10^9/L$)	183	129	325	83	100	125-350
C reactive protein (mg/L)	423	109.12	434	179.5	191.59	0-8
Procalcitonin (ng/mL)	18.17	8.1	13.89	58.5	2.75	0-0.05
Erythrocyte sedimentation rate (mm/h)	68	100	none	82	32	0-15
Alanine aminotransferase (IU/L)	146.7	91.7	237	33.4	79.2	9-50
Aspartate aminotransferase (IU/L)	139	115.8	587.6	60	246	15-40
Total bilirubin ($\mu\text{mol/L}$)	20.4	8.9	16.3	12.6	5.8	3.4-17.1
Serum creatinine ($\mu\text{mol/L}$)	71.4	79.7	48.6	338	53.5	44-133
Outcome	survival	survival	survival	survival	death	

Table 3.

Summary of case series and case report of *C. psittaci* pneumonia

Author	Reported time	Number of reported cases	Reported area	Methods	Anti-infective drugs	Clinical outcome	History of exposure to avian or poultry
Gacouin A[4]	2012	13	France	mNGS	Tetracycline ± Erythromycin/(Left) Ofloxacin	11 patients improved, 2 patients died	Yes
Laroucau K[32]	2013	8	France	PCR	Macrolides + Cephalosporins	Improved	Yes
Chau S[33]	2015	3	Hong Kong	PCR	Doxycycline	Improved	Yes
Mair-Jenkins J [34]	2015	4	United Kingdom	serology and PCR	Not stated	Improved	No history of direct contact, but someone raises pigeons near the office building
Spoorenberg SM[35]	2016	7	Netherlands	PCR, MIF	2 patients used tetracycline, macrolide or quinolone; 1 patients used β -lactam	Improved	6 patients had an exposure history
Cipriano A[36]	2016	1	Portugal	IIF	Amoxicillin/Clenauic Acid, Azithromycin	Improved	Yes
Qiu C[28]	2019	1	China	mNGS	Doxycycline + Moxifloxacin	Improved	No
Zhu RS[37]	2019	1	China	mNGS	Moxifloxacin	Improved	Yes
Shi LP[38]	2019	1	China	PM-seq	Piperacillin Tazobactam + Minocycline	Improved	Yes
Liu L[27]	2019	1	China	antibody test	Moxifloxacin	Improved	Yes
Gu L[13]	2019	5	China	mNGS, IIF	1 patient used Minocycline + Erythromycin	Improved	4 patients had an exposure history
					2 patients used Doxycycline+ moxifloxacin		
					2 patients used Moxifloxacin		
Chen X[14]	2020	9	China	mNGS	Minocycline	8 patients improved, 1 patient died	7 patients had an exposure history

He XY[39]	2020	1	China	mNGS	Doxycycline	Improved	Yes
Chen, Q[29]	2020	1	China	mNGS	Moxifloxacin +Cefoperazone Sodium Sulbactam/ Meropenem	Improved	Not stated
Katsura D[40]	2020	1	Japan	PCR	Meropenem+Gamma globulin	Died	Yes
Zhang G[41]	2020	1	China	mNGS	Doxycycline +Moxifloxacin	Improved	Yes
Zhang H[42]	2020	1	China	mNGS	doxycycline + ceftazidime/meropenem	Improved	No
Fernández P[43]	2020	5	Murcia	mNGS	3 patients used Levofloxacin	Improved	Yes
					+ doxycycline		
					2 patients used cephalosporin		
					+ doxycycline		

mNGS, metagenomics next-generation sequencing; PCR, polymerase chain reaction; MIF, micro-Immunofluorescence; IIF, indirect immunofluorescence; PM-seq, pathogenic microorganisms sequencing.

Figures

Figure 1

Chest computed tomography (CT) scans of a 66-year-old man with *C. psittaci* pneumonia. Lungs were exuding consolidation foci, bilateral pectoral effusions, consolidation on the 8th day of hospitalization (a). After treatment, on the 18th day of

hospitalization (b), the image of four patients improved, and the patients' lung exudation, consolidation, and bilateral pleural effusion were less than before.

Figure 2

Chest X-ray of A 36-year-old pregnant female patient with *C. psittaci* pneumonia and died of septic shock, DIC, and multiple organ failure. (a) on the first day of hospitalization, (b) on the third day of hospitalization, (c) on the sixth day of hospitalization, (d) on the seventh day of hospitalization.

Figure 3

The summary of *C. psittaci* pneumonia literature review from 2010 to 2020 year.

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