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Clinical characteristics of sporadic acute Q fever diagnosed by metagenomic next-generation sequencing: a retrospective analysis and literature review in China

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Abstract

Background Acute Q fever manifests sporadically in mainland China, where its clinical spectrum and optimal diagnostic strategies remain under-recognized. This study aimed to delineate the clinical phenotype and antimicrobial prescribing patterns of sporadic acute Q fever diagnosed via metagenomic next-generation sequencing (mNGS).

Methods We conducted a retrospective, single-center cohort study of adult patients with sporadic acute Q fever. A comprehensive literature review of all published sporadic cases across China was subsequently performed to delineate the national clinical spectrum of sporadic Q fever.

Results The cohort comprised 22 male patients (mean age 36.7±13.5 years). All patients presented with high-grade pyrexia (>39°C) accompanied by a characteristic symptom constellation of headache, fatigue, myalgia, and hepatic involvement (100%, mean ALT 122.2±56.9 U/L). Pneumonia was observed in 2 patients (2/22, 9.1%). A distinct dissociation was observed between markedly elevated C-reactive protein (mean 67.4 ± 33.6 mg/L) and normal leukocyte counts. A pooled analysis of 94 published cases and 22 consecutive patients from our center yielded 116 confirmed Q fever cases (male-to-female ratio 11.9:1, the proportion of hepatitis and pneumonia:87.9% and 24.1%) The median interval from symptom onset to pathogen confirmation was 7.8 ± 2.8 days. mNGS yielded a diagnosis in 77.5 % of 116 patients, the remaining 22.5 % were identified by PCR and antibody testing.

Conclusion Acute Q fever in China predominantly affects young males, presenting as a systemic febrile illness with a distinctive hepatic phenotype (elevated liver enzymes) rather than prominent pneumonia. The clinical triad of high fever, influenza-like symptoms (headache/myalgia), and "WBC-CRP dissociation" (normal white cell count with elevated CRP) serves as a potential clinical indicator. Empiric doxycycline should be initiated promptly in suspected cases. mNGS is a valuable tool for definitive diagnosis, particularly when empiric therapy fails or in severe/complicated cases.

Keywords *Coxiella burnetii*, Acute Q fever, mNGS, Hepatitis

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Q fever, a zoonosis caused by the resilient intracellular bacterium *Coxiella burnetii*, represents a formidable diagnostic challenge globally, particularly in non-endemic regions like mainland China. While the disease is well-characterized in Europe and Australia, where outbreaks often link to livestock reservoirs, sporadic cases in China frequently lack clear epidemiological clues [1–5]. Domestic research on Q fever has primarily concentrated on the livestock sector or isolated case reports [6]. Due to the absence of commercial diagnostic kits, Q fever used to be rarely confirmed by clinicians, when a diagnosis was made, it depended on the Centers for Disease Control or research laboratories. Consequently, nationwide data remained scarce. The disease remains significantly under-recognized, with a substantial proportion of cases misdiagnosed as viral hepatitis or fever of unknown origin (FUO). The clinical presentation of acute Q fever is notoriously pleomorphic, ranging from a self-limiting flu-like illness to severe hepatitis or atypical pneumonia [1–5]. This heterogeneity, compounded by the limited availability of specific serological assay in routine clinical practice, creates a profound "diagnostic gap." [7–8] Patients often endure a prolonged "diagnostic odyssey," subjected to multiple courses of empirical antibiotics—typically β-lactams or fluoroquinolones—that lack efficacy against *Coxiella burnetii*. Although international guidelines recommend doxycycline as first-line therapy, the delay in diagnosis frequently postpones the initiation of effective treatment, increasing the risk of progression to chronic Q fever [7–8]. The advent of metagenomic next-generation sequencing (mNGS) has transformed this landscape, circumventing both the constraints of culture and the seroconversion window to enable earlier detection of a growing number of cases and afford us an unobstructed view of the disease. We combined our own cases with a systematic synthesis of domestic reports to characterize sporadic Q fever across mainland China. Our goal is to raise clinicians' awareness and to promote targeted empirical therapy for febrile patients—doxycycline rather than β-lactams or fluoroquinolones. The findings provide critical real-world evidence to facilitate early recognition and evidence-based, precision therapy of acute Q fever.

Materials and methods

Study design

1. We conducted a retrospective, single-center cohort study at Peking University Third Hospital, a tertiary academic medical center in Beijing, China. We received approval from the Ethics Committee of Peking University Third Hospital [Ethical Approval Number: 2021(214-01)], and given the retrospective nature of the study and the use of de-identified data, the requirement for written informed consent was waived by the ethics.
2. We conducted a systematic literature review of sporadic acute Q fever cases in China to delineate their clinical characteristics to enlarge the sample size and incorporate case analyses from multiple regions.

Study subjects

1. Medical records of all adult patients (≥ 18 years) admitted to the Department of Infectious Diseases between January 2022 and December 2025 were retrospectively reviewed for eligibility. Patients were eligible for inclusion if they met the following criteria: (1) a clinical diagnosis of acute febrile illness, and (2) laboratory confirmation of *Coxiella burnetii* infection via peripheral blood or bronchoalveolar lavage fluid (BALF) mNGS. mNGS testing was conducted in the Molecular Biology Laboratory of Department of Clinical Laboratory following standard operating procedures, and the report reviewed and approved by a professional molecular biologist to confirm *Coxiella burnetii* infection. (3) Comprehensive clinical, laboratory, and radiological data were available for all cases, patients underwent thoracic Computed Tomography (CT), abdominal ultrasound or CT imaging. (4) The diagnosis of acute Q fever attributable to *Coxiella burnetii* infection, hepatitis and pneumonia was adjudicated independently by two infectious-disease specialists.

   Exclusion criteria included: (1) evidence of co-infection with other pathogens detected by culture, serology, or mNGS, (2) incomplete medical records, or (3) pre-existing decompensated liver cirrhosis or active viral hepatitis, which could confound the assessment of Q fever-associated hepatic injury, (4) immunocompromised hosts (solid-organ or hematopoietic stem-cell transplant recipients, and patients on long-term corticosteroids or other immunosuppressive agents)to avoid confounding factors that could alter the clinical presentation (e.g., atypical manifestations, blunted inflammatory responses, co-infections) and to ensure that the clinical phenotype described reflects immunocompetent hosts.

2. To thoroughly delineate the national clinical spectrum of sporadic Q fever, a systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

A comprehensive search was performed across three major electronic databases: PubMed, the China National Knowledge Infrastructure (CNKI), and Wanfang Data, from database inception up to December 31, 2025. The search strategy was constructed using Boolean operators to combine relevant Medical Subject Headings (MeSH) and free-text terms. For PubMed, the specific search string was: ("Q fever"[Title/Abstract] OR "Coxiella burnetii"[Title/Abstract]) AND ("acute"[Title/Abstract]) AND ("China"[Title/Abstract] OR "Chinese"[Title/Abstract]). Equivalent Chinese search terms and Boolean logic, specifically ("Q 热" OR "贝纳柯克斯体") AND ("急性"), were applied for the CNKI and Wanfang databases. Two independent reviewers screened the titles and abstracts, followed by full-text evaluations to identify eligible studies [10–49].Studies were included if they (1) described sporadic acute Q-fever cases acquired in mainland China, (2) provided information on age, sex, and organ involvement—primarily hepatitis and pneumonia and (3) contained sufficiently complete clinical data. Exclusion criteria were (1) immunocompromised hosts (solid-organ or hematopoietic stem-cell transplant recipients, and patients on long-term corticosteroids or other immunosuppressive agents), (2) outbreak-related cases, and (3) cases reported outside China. patients included in the study. Hepatitis and pneumonia were independently adjudicated by two infectious-disease specialists for the literature. Specifically, during the literature review, we excluded one liver transplant recipient and one kidney transplant recipient to avoid potential confounding effects of underlying conditions and immunosuppressive therapy on the analysis of clinical characteristics and disease severity.

Data collection and definitions

Demographic, clinical, and laboratory data were extracted from electronic medical records. "Hepatitis" was defined as an elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than the 1.5-fold upper limit of normal (ULN). All patients underwent chest CT with complete imaging datasets. Renal involvement was defined as any of the following: elevated serum creatinine, microscopic hematuria, or proteinuria.

Statistical analysis

Statistical analyses were performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). Normally distributed data are presented as mean±standard deviation (SD), while non-normally distributed data are expressed as median and interquartile range (IQR). Categorical variables are summarized as frequencies and percentages.

Results

Demographic and epidemiological characteristics

The study cohort included 22 patients, all of whom were male (100%). The mean age was 36.7 ± 13.5 years. Epidemiologically, only 9 patients (40.9%) reported a clear history of animal contact (cats, sheep, or cattle) or occupational exposure or travel history, underscoring the occult nature of transmission in sporadic cases. A distinct seasonal pattern was observed, with 45% of cases (10/22) occurring in the summer months (June–August), peaking in June (23%). A chi-square goodness-of-fit test was performed to determine whether the seasonal distribution of cases differed significantly from a uniform distribution. The analysis revealed a statistically significant variation in case numbers across seasons($P = 0.013$). Observed cases were highest in summer ($n = 10$), followed by spring ($n = 6$) and autumn ($n = 4$), and lowest in winter ($n = 2$). (Table 1; Fig. 1)

Clinical manifestations

All patients (100%) presented with high-grade pyrexia, with a mean peak body temperature of 39.3 ± 0.5 °C. The clinical presentation was dominated by a characteristic symptom constellation: headache (77.3%), fatigue (68.2%), and myalgia (59.1%). In contrast, cough was reported in only 2 patients (9.1%), and gastrointestinal symptoms such as abdominal pain and diarrhea were similarly uncommon (9.1% each). (Table 1)

Laboratory findings

The Inflammatory Dissociation: Hematological analysis revealed a notable dissociation between systemic inflammatory markers and cellular counts. While C-reactive protein (CRP) levels were markedly elevated (mean 67.4 ± 33.6 mg/L) and procalcitonin (PCT) was moderately increased (0.57 ± 0.42 ng/mL), the white blood cell (WBC) count remained within the normal range, median 4.5 ± 1.5 (10^9/L)) for the majority of patients. Thrombocytopenia was noted in 5 cases (22.7%). (Table 1)

The scatter plot illustrates the relationship between WBC counts (x-axis) and CRP levels (y-axis) in the cohort. The data points are predominantly clustered in the upper-left and center-left quadrants. WBC (x-axis): The majority of patients fall within the normal or low-normal range for leukocytes (approximately 2.0–6.0 × 10^9/L). There is a distinct absence of marked leukocytosis (high WBC), which is typically seen in classical bacterial infections. In contrast to the normal WBC counts, the CRP levels are widely scattered and frequently

Table 1 Clinical characteristics of the 22 sporadic acute Q fever

Parameter	*N* = 22
Age, years, mean ± SD	36.7 ± 13.5
Sex (Male, n%)	22(100%)
Epidemiological history, n (%)	9(40.5%)
Clinical timeline	
Time from fever onset to hospital admission, days, mean ± SD	6.1 ± 2.3
Time to diagnosis, days, mean ± SD	7.8 ± 2.8
Peak body temperature ℃, mean ± SD	39.3 ± 0.5
Key manifestations (%)	
Fever	22(100%)
Headache	17(72.3%)
Fatigue	15(68.2%)
Myalgia	13(59.1%)
Cough	2(9.1%)
Abdominal pain	2(9.1%)
Diarrhea	2(9.1%)
Organ involvement	
Liver	22(100%)
Kidney	3(13.6%)
Spleen	4(20.3%)
Lung	2(9.1%)
Pancreas	1(4.5%)
Gallbladder	1(4.5%)
Lymph nodes	1(4.5%)
Central nervous system	1(4.5%)
Laboratory results	
WBC count,10^9/L, mean ± SD	4.5 ± 1.5
NE count,10^9/L, mean ± SD	2.8 ± 1.2
LY count,10^9/L, mean ± SD	1.1 ± 0.3
PLT count,10^9/L, mean ± SD	141 ± 69.6
C-reactive protein, mg/L mean ± SD	67.4 ± 33.6
Procalcitonin ng/ml, mean ± SD	0.57 ± 0.42
Ferritin ng/ml, mean ± SD	1479.0 ± 1065.5
ALT, U/L, mean ± SD	122.2 ± 56.9
AST, U/L, mean ± SD	86.0 ± 37.4
GGT, U/L, mean ± SD	120.0 ± 75.2
ALP, U/L, mean ± SD	102.3 ± 31.8
LDH, U/L, mean ± SD	466.7 ± 136.1
TBIL, μmol/L, mean ± SD	16.9 ± 7.5
CK, U/L, mean ± SD	131.5(70.25, 262.8)
Clinical outcomes	
length of hospital days, days, median (IQR)	5.0(3.8–7.3)
clinical cure rate	100%(22/22)

elevated, with many data points exceeding 60 mg/L and some reaching as high as 140 mg/L (Table 1; Fig. 3).

Organ involvement

Hepatic involvement was a ubiquitous feature of the cohort. All 22 patients exhibited mild-to-moderate elevations in liver enzymes, with mean ALT of 122.2 ± 56.9 U/L and AST of 86.0 ± 37.4 U/L. γ-Glutamyl transferase (γ-GT) was also elevated (120.0 ± 75.2 U/L). However, total bilirubin levels remained normal (16.9 ± 7.5 μmol /L), indicating a pattern of anicteric hepatitis. Extra-hepatic involvement included renal abnormalities (microscopic hematuria/proteinuria) in 13.6% (3/22) of patients and splenomegaly in 18.2%. Pneumonia was identified in 2 patients (9.1%) (Table 1). Given that both hepatic injury and myalgia are common clinical manifestations of acute Q fever, and that AST and ALT may be released not only from damaged hepatocytes but also from skeletal muscle, we sought to investigate whether the elevation of aminotransferases in this cohort was confounded by concurrent myalgia or elevated creatine kinase (CK). To address this, we performed two predefined subgroup analyses comparing AST/ALT levels between patients with and without myalgia, and between those with elevated CK and those with normal CK levels.

Myalgia/ without myalgia analysis

The AST/ALT levels were compared between patients with myalgia ($n = 13$) and those without myalgia ($n = 9$) using the Mann–Whitney U test. The median AST/ALT was 0.61 (IQR 0.55–0.83) in the myalgia group vs.0.82 (IQR: 0.60–1.04) in the non-myalgia group. The analysis revealed no statistically significant difference between the two groups ($U = 33.000$, $Z = -1.703$, $P = 0.089$). The exact two-tailed significance was 0.096, consistent with the asymptotic result. This suggests that the presence of myalgia did not significantly influence AST/ALT levels in this cohort.

High CK/normal CK analysis

AST/ALT levels were compared between patients with elevated creatine kinase (CK) ($n = 8$) and those with normal CK ($n = 12$) using the Mann–Whitney U test. The median AST/ALT was 0.84 (IQR:0.64–0.97) in the elevated CK group, compared to 0.66 (IQR: 0.57–0.86) in the normal CK group. The analysis revealed no statistically significant difference between the two groups ($U = 39.000$, $Z = -1.161$, $P = 0.246$). The exact two-tailed significance was 0.267, consistent with the asymptotic result, indicating that CK elevation was not associated with significantly different AST/ALT levels in this cohort.

Therapeutic outcomes

The median time from symptom onset to definitive diagnosis via mNGS was 7.8 ± 2.8 days. Prior to molecular confirmation, 19 patients (86.4%) presented with fever of unknown origin and thus received empirical broad-spectrum antibiotics (β-lactams or fluoroquinolones) without specific indications, exhibiting no special characteristics that distinguished them prior to diagnosis. Upon diagnosis, therapy was switched to oral doxycycline (100 mg twice daily). 90.9% (20/22) of patients defervesced and

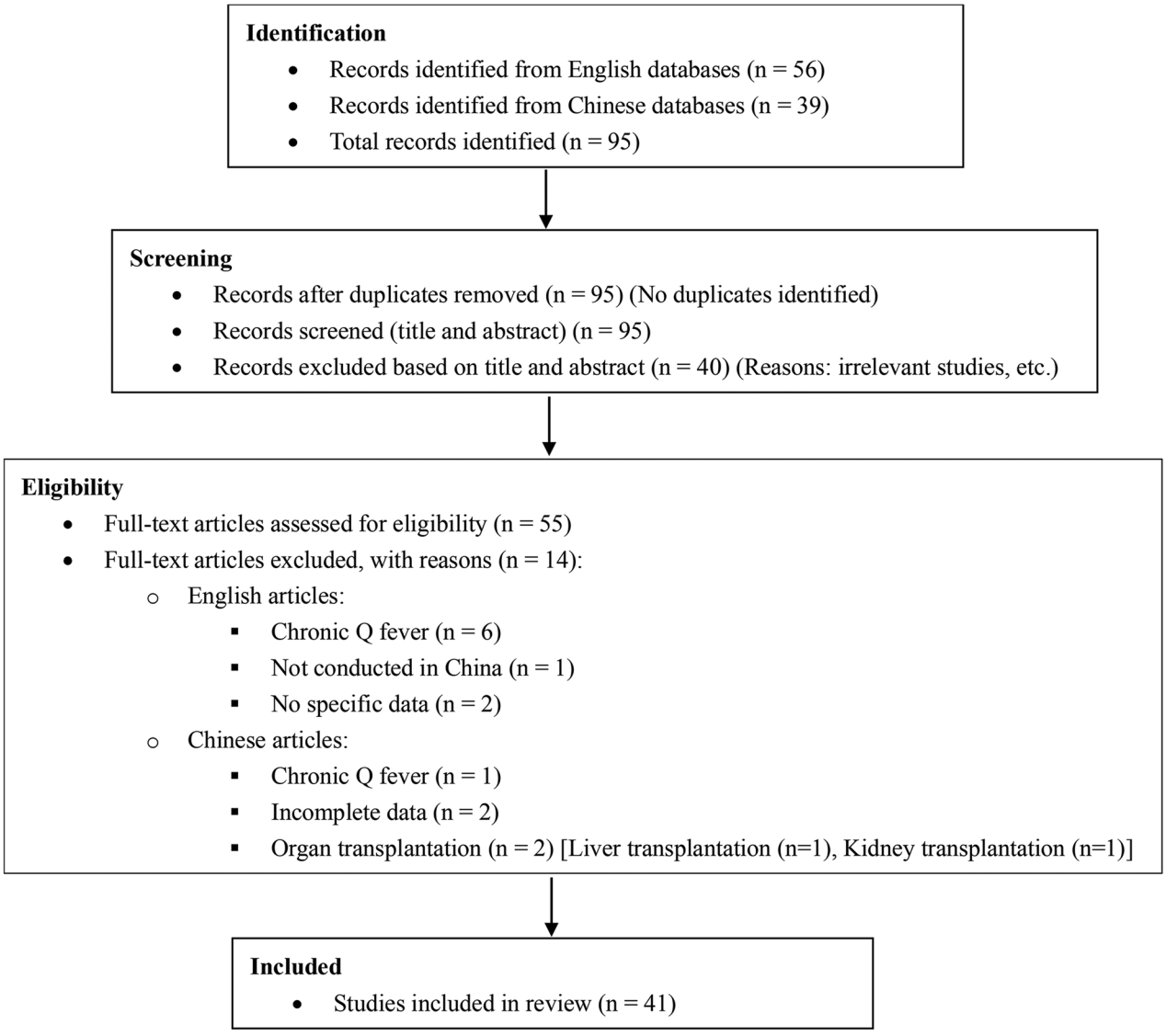

Fig. 1 PRISMA 2020 Flow Diagram for Study Selection

showed clinical improvement within 48 h of doxycycline initiation. The median length of hospital stay was 5.0 days (IQR 3.8–7.3). All patients received a 2-week course of doxycycline and achieved complete recovery. (Table 1; Fig. 4)

Radiological findings

Chest CT findings in our center revealed pneumonia in two patients. One patient exhibited subpleural consolidation in the right upper lobe, while the other showed patchy consolidation in the right lower lobe (Fig. 5).

Literature review: demographic and clinical characteristics

Ultimately, 41 publications comprising [9–49] 94 sporadic acute Q-fever patients met all eligibility criteria (Fig. 1). A total of 116 patients were included in the comparative analysis, comprising an institutional cohort of 22 patients from our study and a literature review cohort of 94 patients. Both cohorts demonstrated a strong male predominance, with males accounting for 100% (22/22) of our study group and 90.4% (85/94) of the literature cohort, revealing no statistically significant difference in sex distribution between the two groups ($P = 0.204$). However, a highly significant discrepancy was observed in the geographic origin of the cases ($P < 0.001$). All 22 patients in our study were located in Northern regions, whereas the vast majority of cases identified in the literature review (76/94) originated from Southern regions.

Regarding clinical manifestations, hepatic involvement was the most prominent feature, affecting 100%

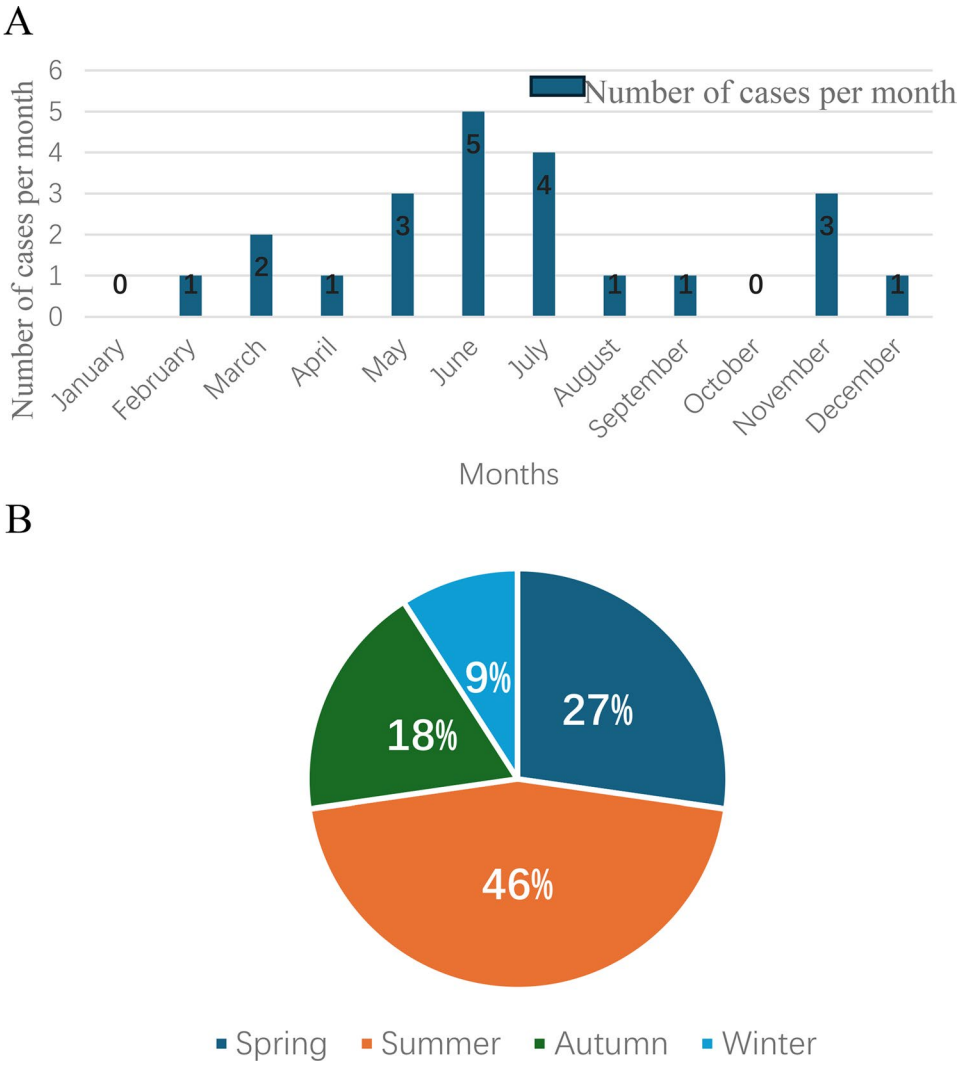

Fig. 2 Monthly and seasonal distributions of Acute Q fever cases. **A.** Monthly Distribution of Acute Q Fever Cases. **B.** a seasonal distribution of acute Q fever cases

(22/22) of our study group compared to 85.1% (80/94) of the literature cohort (95% CI for the difference: 7.7% to 22.1%; $P = 0.07$). Conversely, pulmonary involvement was observed less frequently in our study (9.1%, 2/22) than in the literature review (27.7%, 26/94) (95% CI for the difference: -33.6% to -3.5%; $P = 0.096$) (Table 2).

Finally, the diagnostic modalities utilized for pathogen detection differed significantly between the two groups ($P = 0.020$). Our study relied exclusively on mNGS for all 22 cases. In contrast, the literature cohort utilized a more diverse range of detection methods, including mNGS ($n = 68$), polymerase chain reaction (PCR, $n = 25$), and serology ($n = 1$) (Table 2).

Discussion

This retrospective study provides a detailed characterization of sporadic acute Q fever in China, diagnosed definitively through the application of next-generation sequencing. The clinical phenotype observed—a constellation of high-grade fever, severe headache, myalgia, and universal anicteric hepatitis—stands in contrast to the pneumonia-predominant presentations frequently reported in North America and parts of Europe (60–75%) [50–52]. Further analysis in the 116 acute Q fever cases, hepatic involvement was documented in 102 patients (87.9%), and pneumonia in 28 (24.1%). In Europe, pneumonia is the predominant clinical phenotype of acute Q fever. Pneumonia was the most common clinical presentation. Pneumonia rate was 62% in 2007 and 2008 Q fever epidemic. This hepatic phenotype aligns more closely with cohorts reported in southern Europe and Taiwan, China [51–53] suggesting potential geographic variations in *C. burnetii* strain virulence or host genetic susceptibility factors that favor hepatic over pulmonary tropism.

These findings underscore that Q fever should be routinely considered in the differential diagnosis of male

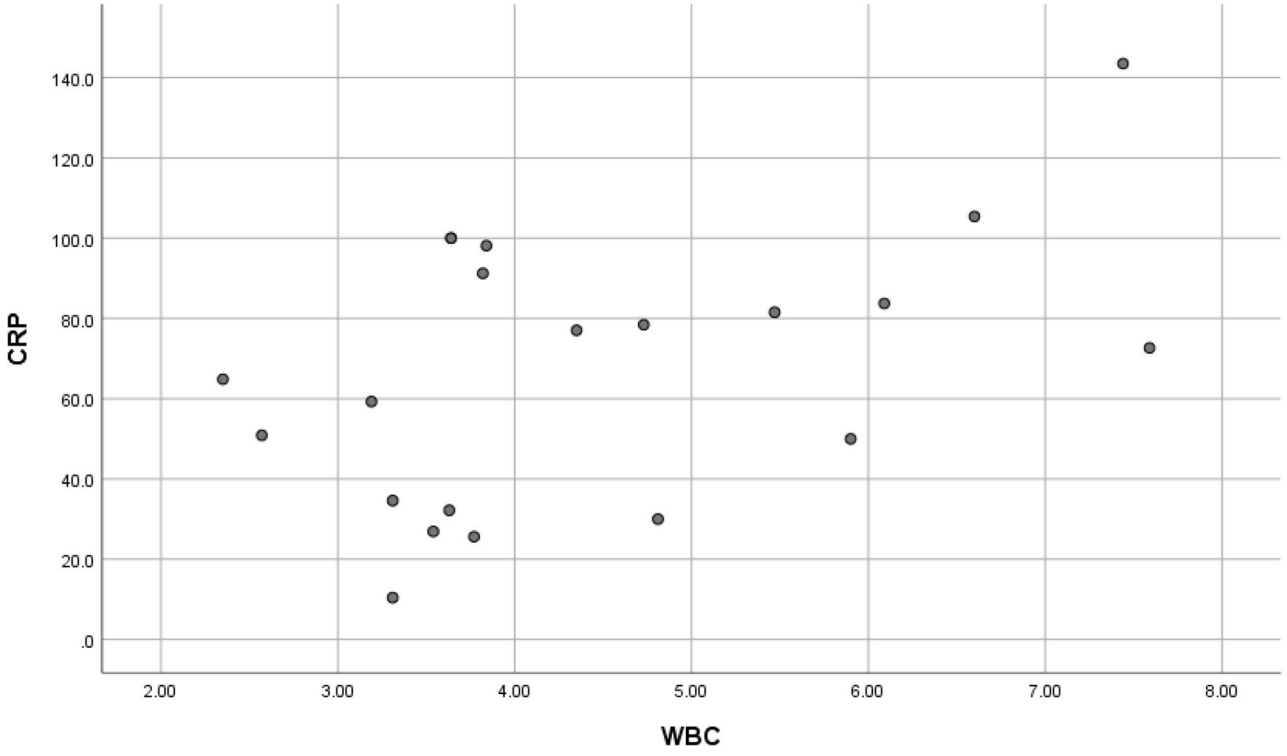

Fig. 3 Scatter-plot analysis of WBC-CPR

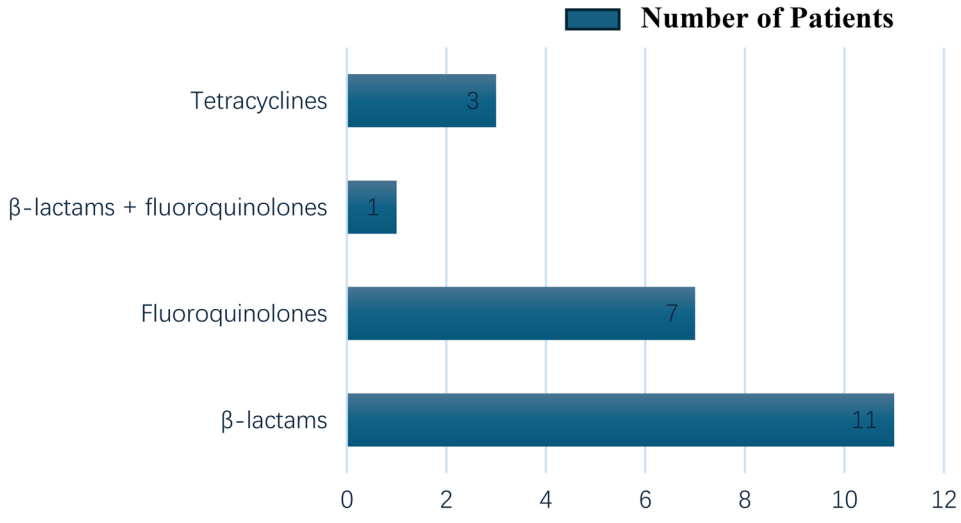

Fig. 4 Initial antimicrobial therapy analysis

patients presenting with fever of unknown origin accompanied by elevated liver enzymes or pneumonia, so that prompt serologic testing, early treatment, and prevention of potential outbreaks can be achieved.

An interesting observation in this study is the potential diagnostic utility of the "WBC-CRP dissociation." The observation of marked systemic inflammation (CRP > 60 mg/L) in the presence of a normal leukocyte count may serve as a "red flag" for intracellular pathogens. The Scatter-plot analysis of WBC-CRP visually confirms the "Inflammatory Dissociation" phenomenon. It demonstrates that despite causing a robust systemic inflammatory response (high CRP), *Coxiella burnetii* infection does not trigger the massive mobilization of neutrophils (leukocytosis) typically seen with extracellular bacteria. This specific pattern (Normal WBC + High CRP) serves as a valuable visual heuristic for clinicians to suspect intracellular pathogens like *Coxiella burnetii*.

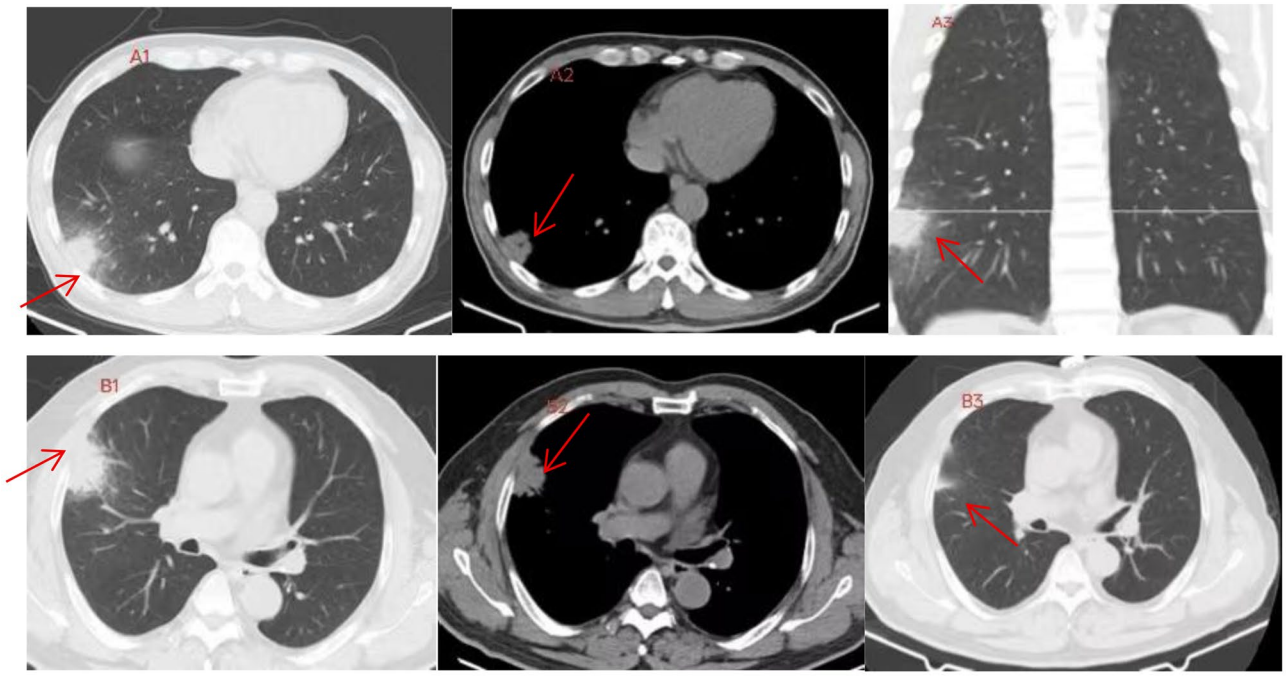

Fig. 5 Chest CT findings in two patients with acute Q fever pneumonia. Figure **A**. A 62-year-old male patient with right upper lobe consolidation. (A1) Axial lung window image shows subpleural consolidation in the right upper lobe (arrow). (A2) Axial mediastinal window image reveals no mediastinal lymphadenopathy or pleural effusion, with the subpleural consolidation also visible (arrow). (A3) Coronal reformatted image (lung window) demonstrates the craniocaudal extent of the consolidation (arrow). Figure **B** A 53-year-old male patient with right lower lobe consolidation. (B1) Axial lung window image shows patchy consolidation in the right lower lobe (arrowhead). (B2) Axial mediastinal window image shows no associated mediastinal abnormality, with the subpleural consolidation also visible (arrowhead). (B3) Follow-up axial lung window CT obtained 2 weeks after treatment (doxycycline) demonstrates partial resolution of the consolidation (arrowhead)

Table 2 Analysis of cases identified through literature review and pooled results of all cases

Characteristic	Literature Review (*N* = 94)	Our Study (*N* = 22)	Total (*N* = 116)	*p*-value*
Sex (male/female)	85/9	22/0	107/9	0.20
Geographic distribution (Northern/Southern)	18/76	22/0	40/76	< 0.05
Hepatic involvement, n (%)	80 (85.1%)	22 (100%)	102 (87.9%)	0.07
Pulmonary involvement, n (%)	26 (27.7%)	2 (9.1%)	28 (24.1%)	0.10
Detection methods (Serology/PCR/mNGS)	1/25/68	0/0/22	1/25/90	< 0.05

Note: P-values for Sex, Geographic distribution, Hepatic involvement, and Pulmonary involvement were calculated using Fisher's exact test due to small expected frequencies. The P-value for Detection methods was calculated using the Pearson Chi-square test. The 95% confidence intervals (CIs) for the difference in proportions between our study and the literature cohort (calculated using the standard Wald method) are [7.7%, 22.1%] for hepatic involvement and [-33.6%, -3.5%] for pulmonary involvement

Mechanistically, *C. burnetii* resides within macrophages and may not trigger the massive neutrophilic leukocytosis typical of extracellular bacterial sepsis [54–55]. Clinicians encountering this dissociation in the context of FUO should maintain a high index of suspicion for Q fever, even in the absence of overt epidemiological links.

The clinical characteristics of the patients in our study are summarized as follows: ① the triad of high-grade fever (> 39 °C), headache and myalgia without focal signs reinforcing that acute Q fever often masquerades as a non-specific febrile illness. ② normal leukocyte counts coupled with marked C-reactive protein elevation (mean 67 mg/L) created a "dissociation" pattern that has been repeatedly described in rickettsial and viral infections. This discrepancy should prompt clinicians in non-endemic areas to add Q fever to the differential of fever of unknown origin even when routine blood cultures are negative. Five of 22 patients (22.7%) developed thrombocytopenia ($< 100 \times 10^9$/L, nadir 62×10^9/L). ③moderate elevations of ALT, AST and γ-GT with preserved total bilirubin are consistent with a sub-clinical hepatitis phenotype previously labelled "Q fever hepatitis". ④Renal involvement—microscopic haematuria and/or proteinuria.

In the present study, the diagnosis of acute Q fever relied on laboratory tests performed at the time of hospital admission. Given the retrospective design, we defined the onset of illness based on patients' self-reported fever

onset, with a median interval of approximately 6 days from fever onset to admission and initial blood sampling. It is important to acknowledge that CRP and WBC counts exhibit different kinetics following an inflammatory stimulus. CRP typically rises within 24–48 hours and peaks rapidly, whereas leukocytosis may follow a slightly different trajectory [55–56]. Consequently, the normal WBC count observed around day 6 of illness may not reflect the WBC count at the very onset of fever, representing a limitation of our cross-sectional sampling. Nevertheless, we believe this observation retains substantial clinical relevance. The time of presentation—approximately day 6 of illness—is precisely the moment when clinicians must make initial diagnostic and therapeutic decisions. At this typical stage, the finding of high fever accompanied by a markedly elevated CRP (~60 mg/L) yet a normal WBC count serves as a practical "red flag." This pattern is characteristic of intracellular pathogens such as *Coxiella burnetii* and contrasts with the leukocytosis expected in common extracellular bacterial infections at a similar symptomatic phase. Thus, even with the kinetic caveat, the "WBC–CRP dissociation" may represent a useful clinical clue for considering doxycycline empiric therapy in suspected acute Q fever. However, because this observation is based on a small cohort without a comparator group of other febrile infections, its specificity and diagnostic validity require further validation in larger, controlled studies.

Because clinical and routine laboratory features are non-specific, physicians frequently default to fluoroquinolone or β-lactam agents. The present data argue for an earlier transition to doxycycline once Q fever is suspected—particularly in young males with fever–headache–myalgia, normal white count and disproportionately high CRP. Only 3 patients received doxycycline as first-line therapy, the remaining were exposed to β-lactams and/or fluoroquinolones for a median of 4–5 days while inflammatory markers continued to rise. The guideline recommendation that a tetracycline should be introduced within the first week of symptom onset to shorten duration of fever and prevent complications such as hepatitis or pneumonia [8].

Q-fever diagnosis traditionally relies on serology. Culture is hazardous and insensitive, PCR is largely confined to research laboratory and may be negative if effective treatment with antibiotics like doxycycline have been started or if the bacterial load is low. Antibodies, moreover, are usually undetectable until 2–3 weeks after symptom onset, so paired acute- and convalescent-phase sera are required for reliable confirmation. For decades the complement-fixation (CF) test was the mainstay. CF is specific but laborious and relatively insensitive. Seroconversion generally occurs 7–15 days after symptoms appear, and 90% of patients have converted by the third week. Heat-inactivated serum was reacted with phase I or phase II *Coxiella burnetii* antigens, an anti-phase II titre ≥ 1:40 indicated acute infection, whereas an anti-phase I titre ≥ 1:200 suggested chronic disease. During this window a negative serological result does not exclude Q fever [57–60]. Because diagnosis was delayed, doxycycline initiation was also markedly postponed, in a 2007 study, the first 200 mg dose was given a median of 111 days (IQR 96.5–209.0) after symptom onset [61].

mNGS enables definitive diagnosis within 48 hours, offering a culture-independent method for early pathogen detection, particularly in non-endemic regions where Q fever is rarely suspected. As acute Q fever often presents as fever of unknown origin, mNGS broadens pathogen spectrum, increases microbial confirmation, and provides high negative predictive value, shortening time-to-diagnosis, reducing hospital stay, and curbing unnecessary antibiotics [62–63]. Crucially, mNGS results facilitate immediate precision de-escalation—e.g., switching from ineffective β-lactams or fluoroquinolones to doxycycline—leading to prompt clinical improvement. In severe/complicated cases, mNGS should be considered. mNGS is most valuable in: (1) patients with FUO failing empirical antibiotics; (2) severe or atypical presentations; (3) immunocompetent patients with diagnostic uncertainty. This approach balances cost, availability, and clinical utility.

Epidemiological Insights: Gender and Seasonality. The exclusive male composition of our cohort (100%) is a striking finding that warrants discussion. Recognizing the limited size of our local cohort, we expanded the literature search to capture the broadest possible case series, thereby minimizing selection bias that could arise from small-sample estimates. Our pooled analysis of sporadic acute Q-fever cases in mainland China—derived from a systematic literature review plus our own cohort—revealed an overwhelming male predominance, with a male-to-female ratio of 11.9:1. This marked skew differs substantially from the gender distribution reported in outbreaks outside China, where Q fever globally exhibits a milder male predilection (typically 2.5-3:1) [64]. Earlier studies indicate that men and women are equally susceptible to *C. burnetii*, yet infection manifests more severely in males, driving a higher proportion to present for care and thus be diagnosed [65–66]. Compelling animal work further shows that oestrogen exerts a protective, immunomodulatory effect against *C. burnetii*, supplying a credible biological underpinning for the striking male predominance observed in reported Q-fever cases [65–66].Furthermore, the summer peak (June/July) observed here similar with European studies. In European Centre for Disease Prevention and Control. reports: Cases are reported all year round, numbers show an increase between April and October and a peak in June/July

[67–68]. The seasonal increase corresponds to the lambing which shows a peak during the summer months. In addition, climatic factors such as heat and drought during the summer may facilitate the spread of the bacteria and increase the risk of transmission[67.68].

Our study is limited by its retrospective design and the small sample size from a single center. As a tertiary referral center, our cohort is inherently subject to selection bias, potentially skewing towards more severe or complex presentations. Furthermore, the reliance on mNGS for diagnosis introduces diagnostic bias, as this testing modality may not be uniformly available or applied in all settings. The study is also subject to sampling bias given the localized geographical catchment.These constraints are partially offset by our pooled analysis of sporadic acute Q-fever cases identified through the Chinese literature, yet large-scale, multicenter investigations are still required to fully elucidate the epidemiological characteristics of acute Q fever in China.

Conclusions

In summary, sporadic acute Q fever in China presents as a systemic febrile illness with a distinct hepatic phenotype and. more common in males than in female. The integration of mNGS into the diagnostic algorithm is critical for early pathogen identification and the initiation of targeted doxycycline therapy. Recognizing the potential "WBC-CRP dissociation" and the characteristic symptom tetrad may help shorten the diagnostic odyssey and improve patient outcomes.

Abbreviations

ALT	Alanine aminotransferase
BALF	Bronchoalveolar lavage fluid
CRP	C-reactive protein
CT	Computed Tomography
FUO	Fever of unknown origin
γ-GT	γ-Glutamyl transferase
IQR	Interquartile range
LY	Lymphocyte
mNGS	Metagenomic Next-Generation Sequencing
NE	Neutrophil
PCT	Procalcitonin
PLT	Platelet
SD	Standard deviation
AST	Aspartate aminotransferase
ULN	Upper limit of normal

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and data analysis were carried out by Jing Chen, Xiaoguang Li, Zhonghua Deng, Yingqiu Ying, and Ming Lu. The first draft of the manuscript was written by Jing Chen. Study design, conduct, and oversight were the responsibility of Yingqiu Ying and Ming Lu.

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Data availability

The datasets generated and analyzed during the current study are available from Dr. Lu.

Declarations

Ethics approval and consent to participate

We received approval from the Ethics Committee of the Peking University Third Hospital [Ethical Approval Number: 2021(214-01)]. We confirm that their study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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