Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Severe Rickettsioses in Critically Ill Adults: Clinical Presentations and Diagnostic Pathways in a Hospital-Wide Case Series

Yue Zhu
Zhejiang University School of Medicine
Xuqin Li
Zhejiang University School of Medicine
Yelin Cao
Zhejiang University School of Medicine
Yangyang Jia
Zhejiang University School of Medicine
Wenqiao Yu
Zhejiang University School of Medicine
Guobin Wang
Zhejiang University School of Medicine
Hongliu Cai
Zhejiang University School of Medicine
Hua Zhou
hua__zhou@163.com

The Second Affiliated Hospital of Zhejiang University School of Medicine

Research Article

Keywords: critical illness, intensive care unit, Japanese spotted fever, metagenomic next-generation sequencing, Orientia tsutsugamushi, Rickettsia japonica, rickettsiosis, scrub typhus

Posted Date: November 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11220208/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Introduction

Severe rickettsioses may progress from nonspecific febrile illness to shock, respiratory failure, neurological dysfunction, and multiorgan failure, while classical cutaneous or exposure clues may be absent. We characterized the clinical presentations, diagnostic pathways, organ-support requirements, and short-term outcomes of critically ill adults with severe rickettsioses identified through hospital-wide screening.

Methods

We conducted a retrospective hospital-wide case series at the First Affiliated Hospital, Zhejiang University School of Medicine, from January 1, 2020 to September 24, 2026. Adults were eligible if mNGS detected *Rickettsia* spp. or *Orientia tsutsugamushi* in a clinically relevant specimen, the clinical syndrome was concordant with the organism, and infection-associated critical illness required ICU-level management. Clinical features, microbiological findings, antimicrobial treatment, organ support, and hospital outcomes were reviewed.

Results

Five patients met the eligibility criteria; all were women aged 55–74 years. Three had *Rickettsia japonica*infection and two had *O. tsutsugamushi* infection. Presentations included septic shock, severe acute respiratory distress syndrome, neurological dysfunction, cardiopulmonary dysfunction, and acute kidney injury. Four patients required invasive mechanical ventilation, two received continuous renal replacement therapy, and one patient with Japanese spotted fever required venovenous extracorporeal membrane oxygenation. Blood mNGS identified the clinically relevant organism in four patients; *R. japonica* was additionally detected in bronchoalveolar lavage fluid in one. Cerebrospinal fluid mNGS identified *O. tsutsugamushi* in the patient with neurological involvement. All patients received doxycycline-containing therapy. Four completed hospitalizations survived to discharge; one patient remained hospitalized at the study cutoff.

Conclusion

Severe rickettsioses presented with heterogeneous forms of critical illness rather than a single ICU syndrome. Rickettsiosis should be considered in unexplained febrile multiorgan dysfunction, particularly with thrombocytopenia, hepatic abnormalities, or compatible outdoor exposure. mNGS provided useful etiologic evidence but required clinical and microbiological interpretation.

Key Summary Points

Why carry out this study?

· Severe rickettsioses may resemble sepsis, severe pneumonia, or neurological infection, while classical clues such as eschar or a clear arthropod exposure may be absent or overlooked.

· Severe *R. japonica* infection remains incompletely characterized in critically ill adults in China.

· This hospital-wide study examined the clinical presentations, diagnostic pathways, organ-support requirements, and contribution of mNGS in critically ill adults with *R. japonica* or *O. tsutsugamushi* infection.

What was learned from the study?

· Five patients showed heterogeneous critical-care presentations; four required invasive mechanical ventilation, two required CRRT, and one patient with Japanese spotted fever required VV-ECMO.

· mNGS provided clinically concordant etiologic evidence from blood, CSF, and BALF, but specimen selection and organism-specific read counts required clinical interpretation and were not suitable for comparative diagnostic inference.

Introduction

Rickettsial diseases are vector-borne infections caused by obligate intracellular bacteria and encompass several clinically and epidemiologically distinct entities. Spotted fever group rickettsioses are caused by *Rickettsia* species, whereas scrub typhus is caused by *Orientia tsutsugamushi*. Both may begin as nonspecific febrile illnesses and progress to systemic disease involving the lungs, cardiovascular system, kidneys, liver, central nervous system, and coagulation system [1–3].

Clinical recognition can be difficult. Rash and eschar are useful diagnostic clues when present but may be absent, overlooked, or develop after the initial presentation. Exposure histories may also be incomplete. Consequently, patients with severe rickettsioses may initially be managed for bacterial sepsis, community-acquired pneumonia, viral infection, or central nervous system infection. This diagnostic uncertainty is particularly relevant in the ICU, where organ dysfunction may evolve before the underlying infection is recognized.

Severe scrub typhus has been relatively well characterized in critically ill populations. In an ICU cohort of 116 patients, respiratory, cardiovascular, renal, hepatic, and neurological dysfunction were frequently observed **[3]**. A recent systematic review involving more than 10,000 hospitalized patients with microbiologically confirmed scrub typhus estimated that acute respiratory distress syndrome (ARDS) occurred in approximately 13% of patients **[4]**. By contrast, severe Japanese spotted fever caused by *R. japonica* remains less well characterized in China. Previous reports have described shock, disseminated intravascular coagulation, neurological involvement, pleural effusion, and multiorgan failure **[5–7]**.

Metagenomic next-generation sequencing (mNGS) allows broad detection of microbial nucleic acid without requiring a predefined target and has increasingly been used in patients with severe infection when conventional microbiological investigations are unrevealing [8–12]. Detection alone, however, does not establish causality, and mNGS findings must be interpreted together with the clinical syndrome, epidemiological information, imaging, and other microbiological data.

We therefore conducted a hospital-wide review of critically ill adults with *R. japonica* or *O. tsutsugamushi* infection at a tertiary referral center in eastern China. Rather than directly comparing these biologically distinct infections, we focused on the clinical pathways by which they presented as critical illness, the associated organ-support requirements, and the role of mNGS in etiologic identification.

Methods

Study Design and Setting

We conducted a retrospective, single-center, hospital-wide observational case series at the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, a tertiary academic referral center providing emergency, infectious diseases, and intensive care services across multiple campuses.

The screening period extended from January 1, 2020 to September 24, 2026. During this period, a total of 12,300 ICU admissions were recorded across six intensive care units within the hospital system, including 1,480 admissions to the Qingchun ICU, 960 to the Surgical ICU, 900 to the Chengzhan ICU, 1,320 to the Yuhang Emergency ICU, 5,240 to the Zhijiang ICU, and 2,400 to the Yuhang ICU. **This ICU admission count was used to characterize the critical-care population during the study period and was not treated as a denominator for estimating the incidence of rickettsiosis.**

Case Ascertainment and Eligibility

Potentially eligible patients were identified through systematic searches of the hospital electronic medical record and microbiology information systems. Search terms included *Rickettsia*, *Rickettsia japonica*, *Orientia tsutsugamushi*, Japanese spotted fever, scrub typhus, rickettsiosis, and metagenomic next-generation sequencing.

The search covered patients managed in emergency departments, general wards, infectious diseases units, and intensive care units and was not restricted to patients initially admitted to an ICU. Duplicate records referring to the same hospitalization were consolidated.

Patients were eligible if they were aged ≥18 years, were hospitalized during the study period, had *Rickettsia* spp. or *O. tsutsugamushi* detected by mNGS in a clinically relevant specimen, had an acute clinical syndrome considered concordant with the detected organism, and required ICU-level management for infection-associated critical illness.

For case ascertainment, infection-associated critical illness was operationally defined as ICU admission with major acute organ dysfunction and/or a requirement for advanced organ support, including vasoactive support, invasive mechanical ventilation, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), or ICU-level management of acute neurological dysfunction.

Patients were excluded if the detected organism was considered unrelated to the acute clinical syndrome, if available clinical data were insufficient to support severe rickettsial disease, or if the infection fell outside the predefined rickettsiosis spectrum. *Coxiella burnetii* infection was excluded because Q fever is clinically and taxonomically distinct from the rickettsial diseases included in this study.

All patients meeting the eligibility criteria were included.

Data Collection and Definitions

Clinical data were extracted from the electronic medical record using a standardized case-report form. Variables included age, sex, major comorbidities, epidemiological exposure, symptom onset, presenting features, rash or eschar, initial working diagnosis, serial laboratory findings, radiological findings, antimicrobial therapy, microbiological results, acute organ dysfunction, ICU interventions, and hospital outcome.

Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores recorded at ICU admission were extracted for all included patients. These scores reflected illness severity at ICU entry and were not intended to represent subsequent peak severity during the clinical course.

For variables that changed during hospitalization, clinically relevant extreme values were recorded, including platelet nadir, peak serum creatinine, peak total bilirubin, peak lactate, and lowest PaO_2/FiO_2 ratio.

ARDS was assessed according to the Berlin definition [13] when adequate arterial blood gas, ventilatory, and radiological data were available. Acute kidney injury was assessed according to Kidney Disease: Improving Global Outcomes criteria [14] when baseline and serial serum creatinine measurements or urine-output data permitted classification.

Neurological involvement was defined as acute encephalopathy, altered consciousness, meningitis, meningoencephalitis, focal neurological dysfunction, or another acute neurological syndrome occurring in temporal association with rickettsial infection. Alternative neurological diagnoses were recorded separately when identified.

Thrombocytopenia was defined as a platelet count <150 × 10^9/L. Coagulation abnormalities were characterized using available prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer measurements.

mNGS and Microbiological Assessment

Metagenomic next-generation sequencing was performed as part of routine clinical care using the in-house clinical mNGS platform of the First Affiliated Hospital, Zhejiang University School of Medicine. The laboratory workflow and clinical interpretation framework used at our institution have been described previously [11].

DNA- and/or RNA-based sequencing workflows were performed according to the institutional clinical laboratory protocol. Following nucleic acid extraction, library preparation, and sequencing quality control, human-derived reads were removed by alignment to the human reference genome. Remaining non-human reads were aligned against the institutional microbial reference database for taxonomic identification.

Specimens were selected according to the clinical presentation and included peripheral blood, cerebrospinal fluid (CSF), and bronchoalveolar lavage fluid (BALF).

mNGS results were interpreted in conjunction with the clinical syndrome, epidemiological exposure, imaging findings, inflammatory markers, conventional microbiological results, and the treating physicians' assessment, consistent with the clinical interpretation framework previously used at our institution [11]. Detection of microbial nucleic acid alone was not considered sufficient to establish etiologic attribution. Organisms judged more likely to represent colonization, latent infection, background contamination, or incidental detection were not classified as the primary pathogen.

For this study, the organism reported in the finalized clinical mNGS report and the corresponding organism-specific read count, when available, were extracted. Read counts were reported descriptively and were not compared quantitatively across patients or specimen types.

Because specimen selection was clinically directed and paired specimens were not obtained systematically, diagnostic sensitivity or yield was not compared among blood, CSF, and BALF.

Antimicrobial Treatment and Organ Support

Antimicrobial treatment was reviewed from initial presentation through the acute infectious episode. Use and timing of doxycycline were recorded, together with other antimicrobial agents administered during etiologic treatment, including azithromycin, moxifloxacin, and omadacycline.

Use of invasive mechanical ventilation, vasoactive agents, CRRT, and ECMO was recorded. For the patient who received ECMO, the ECMO configuration, indication, concurrent organ support, and outcome after decannulation were documented.

Treatment regimens and organ-support strategies were determined according to individual clinical circumstances; no comparative treatment-effect analysis was performed.

Outcomes and Statistical Analysis

Clinical outcomes of interest included in-hospital survival, ICU and hospital length of stay, requirement for invasive mechanical ventilation, vasoactive support, CRRT, and ECMO, and successful liberation from organ support when applicable.

For patients who remained hospitalized at the prespecified cutoff, hospital status and lengths of stay were reported as of September 24, 2026; these patients were not classified as having survived to discharge.

All analyses were descriptive. Continuous variables were reported as individual values or as median (range), as appropriate, and categorical variables as counts. No hypothesis testing, regression analysis, survival modeling, or imputation of missing data was performed.

Ethics

The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (**[2026B] IIT Ethics Approval No. 0874**).

The requirement for individual informed consent was waived because of the retrospective study design and the use of routinely collected, de-identified clinical data. The study was conducted in accordance with the Declaration of Helsinki.

Results

Patient Identification and Baseline Characteristics

During the study period, 12,300 admissions were recorded across six ICUs within the hospital system. Hospital-wide screening identified five adults who met the prespecified criteria for severe rickettsiosis. One additional patient with *Coxiella burnetii* infection was excluded because Q fever was outside the predefined rickettsiosis spectrum.

All five included patients were women, with a median age of 65 years (range, 55–74 years). Three patients had *Rickettsia japonica* infection and two had *Orientia tsutsugamushi* infection. Although the

screening period extended from January 2020 to September 2026, all eligible cases occurred between April 2024 and September 2026.

Fever was present in all five patients. Epidemiological clues suggesting possible vector exposure were documented in several cases. One patient reported a recent insect bite during a mountain excursion, one developed symptoms after collecting bamboo shoots, and one had been collecting walnuts before symptom onset. Another patient reported a tick bite approximately four months before admission; given the long interval, its relevance to the acute illness was uncertain. No characteristic eschar was documented in the available records.

Initial working diagnoses included sepsis, pulmonary infection, central nervous system infection, and undifferentiated febrile illness. All patients received empirical antibacterial therapy before or during etiologic evaluation.

At ICU admission, SOFA scores ranged from 8 to 11 (median, 10), and APACHE II scores ranged from 8 to 18 (median, 16) (Table 1).

Clinical Presentations and Organ Dysfunction

The pattern and severity of organ dysfunction varied across the cohort (Table 1). The lowest PaO_2/FiO_2 ratio ranged from 45.2 to 216 mmHg (median, 92.1 mmHg), and peak lactate ranged from 2.1 to 9.9 mmol/L (median, 4.1 mmol/L). Thrombocytopenia was present in all patients, with platelet nadirs ranging from 13 to 42 × 10^9/L (median, 33 × 10^9/L). Peak serum creatinine ranged from 61 to 230 μmol/L and peak total bilirubin from 11.1 to 77.1 μmol/L.

Among the three patients with Japanese spotted fever, the 65-year-old patient presented with hypotension, thrombocytopenia, hepatic injury, and acute kidney injury (AKI), and required vasoactive support during the early ICU course. Renal function subsequently recovered without CRRT.

The 55-year-old patient developed septic shock, severe acute respiratory distress syndrome (ARDS), AKI, hepatic dysfunction, thrombocytopenia, and coagulopathy. Her lowest PaO_2/FiO_2 ratio was 45.2 mmHg. She required invasive mechanical ventilation, vasoactive support, venovenous extracorporeal membrane oxygenation (VV-ECMO), and CRRT.

The 74-year-old patient initially presented with fever and transient confusion and subsequently developed septic shock, respiratory failure, metabolic acidosis, cardiac dysfunction, thrombocytopenia, and anuric AKI. Her lowest PaO_2/FiO_2 ratio was 85.7 mmHg and peak lactate was 9.9 mmol/L. She required invasive mechanical ventilation, multiple vasoactive agents, and CRRT.

The two patients with scrub typhus had different dominant manifestations. The 72-year-old patient developed progressive cognitive impairment, disorientation, and respiratory failure after more than 10

days of fever and required invasive mechanical ventilation. Brain magnetic resonance imaging also showed an acute infarction adjacent to the right lateral ventricle.

The 59-year-old patient developed respiratory failure accompanied by pulmonary edema, pleural effusion, and impaired cardiac contractility. Her lowest PaO_2/FiO_2 ratio was 92.1 mmHg. She required invasive mechanical ventilation and pleural drainage. Coronary computed tomographic angiography showed no obstructive coronary artery disease.

Diagnostic Pathways and Antimicrobial Treatment

mNGS provided etiologic evidence in all five patients. Blood was tested in four patients, including one who also underwent bronchoalveolar lavage fluid (BALF) sequencing, and cerebrospinal fluid (CSF) was tested in one patient (Table 2).

Among the three patients with Japanese spotted fever, mNGS performed on April 20, 2024 identified *R. japonica* in both blood and BALF in the 55-year-old patient, with 11 and 5 organism-specific reads, respectively. Epstein–Barr virus (EBV; human herpesvirus 4 [HHV-4]) was also detected at 25 reads. In the 65-year-old patient, blood mNGS performed on May 8, 2024 detected *R. japonica* with 3 reads. In the 74-year-old patient, blood mNGS performed on September 23, 2026 detected *R. japonica* with 35 reads; EBV (HHV-4) was also detected at 3 reads.

Among the two patients with scrub typhus, CSF mNGS performed on August 7, 2025 detected *O. tsutsugamushi* with 23 organism-specific reads in the patient with neurological involvement. In the 59-year-old patient, blood mNGS performed on September 5, 2025 detected *O. tsutsugamushi* with 191 reads after persistent fever and clinical deterioration despite conventional antibacterial therapy.

Organism-specific read counts were reported descriptively. Because specimen type was selected according to clinical indication, read counts were not compared quantitatively across patients and were not interpreted as direct measures of pathogen burden. EBV detected concurrently in two patients was not classified as active coinfection on the basis of sequencing findings alone.

All five patients received doxycycline-containing therapy. Both patients with scrub typhus received doxycycline plus azithromycin. The 55-year-old patient with Japanese spotted fever received doxycycline with moxifloxacin during the severe ICU phase. The 65-year-old patient received doxycycline in the ICU followed by omadacycline after transfer to the infectious diseases ward. The 74-year-old patient received doxycycline plus azithromycin after identification of *R. japonica* by blood mNGS.

Organ Support and Outcomes

All five patients received vasoactive support during their ICU course. Four required invasive mechanical ventilation, two received CRRT, and one received VV-ECMO (Table 2).

The 55-year-old patient with Japanese spotted fever required concurrent invasive mechanical ventilation, vasoactive support, VV-ECMO, and CRRT. VV-ECMO was discontinued on April 24, 2024, CRRT was subsequently stopped after recovery of urine output and renal function, and the patient was extubated on April 30. She was transferred from the ICU to the infectious diseases ward on May 2. ICU and total hospital lengths of stay were 15 and 23 days, respectively.

The 65-year-old patient with Japanese spotted fever did not require invasive mechanical ventilation or renal replacement therapy. She was discharged after improvement in fever, thrombocytopenia, hepatic dysfunction, and renal function. ICU and total hospital lengths of stay were 5 and 9 days, respectively.

The 72-year-old patient with neurological scrub typhus was extubated on August 14, 2025 and discharged from hospital on August 20. ICU and total hospital lengths of stay were 6 and 10 days, respectively. Residual focal neurological deficits were present at discharge in the setting of the concomitant cerebral infarction.

The 59-year-old patient with cardiopulmonary scrub typhus was extubated on September 8, transferred from the ICU on September 9, and discharged on September 15, 2025. ICU and total hospital lengths of stay were 6 and 13 days, respectively.

At the prespecified study cutoff, the 74-year-old patient with Japanese spotted fever remained hospitalized in the ICU with septic shock, respiratory failure, and AKI requiring invasive mechanical ventilation, vasoactive support, and CRRT. Her ICU and hospital lengths of stay were therefore not final, and her ultimate hospital outcome was unavailable.

Among the four patients with completed hospitalizations, ICU length of stay ranged from 5 to 15 days and total hospital length of stay ranged from 9 to 23 days. All four survived to hospital discharge. The fifth patient remained hospitalized at the study cutoff.

Discussion

This hospital-wide series describes the different routes by which severe rickettsial infections presented as critical illness. Although all five patients had an acute febrile illness, the dominant clinical problem at ICU presentation varied considerably, including septic shock, severe hypoxemic respiratory failure, neurological dysfunction, cardiac dysfunction, and kidney injury. In several patients, the initial diagnostic focus was directed toward the affected organ system rather than an underlying vector-borne infection. This is an important feature of severe rickettsioses in critical care, where organ failure may obscure the infectious syndrome that preceded it.

The heterogeneity of organ involvement has a plausible biological basis. Pathogenic *Rickettsia* species primarily involve the microvascular endothelium, and endothelial injury is central to the vascular pathology of rickettsial disease [1]. *O. tsutsugamushi* can involve both endothelial cells and mononuclear phagocytes, with vascular dysfunction and dysregulated inflammatory responses implicated in

pulmonary and systemic organ injury [2]. Disruption of vascular integrity may contribute to pulmonary edema, circulatory failure, coagulation abnormalities, and multiorgan dysfunction. These mechanisms may help explain why clinically similar febrile illnesses subsequently evolved into different predominant organ syndromes.

The two patients with scrub typhus showed markedly different patterns of severe disease. One developed progressive neurological dysfunction and respiratory failure, whereas the other presented with respiratory failure, pulmonary edema, pleural effusion, and impaired cardiac contractility. Neurological involvement is well recognized in scrub typhus; a prospective cohort of 198 patients reported neurological manifestations in approximately one-third of patients, most commonly meningitis or meningoencephalitis [13]. In our patient with neurological disease, the concomitant cerebral infarction complicated attribution of persistent focal deficits, which could not be ascribed solely to the infection.

Pulmonary involvement was prominent across both infections. A recent systematic review of 68 studies involving 10,330 hospitalized patients with microbiologically confirmed scrub typhus estimated that ARDS occurred in 13% overall and 15% of adults [4]. In our series, severe hypoxemia occurred in patients with both scrub typhus and Japanese spotted fever. One patient with *R. japonica* infection required VV-ECMO in addition to invasive mechanical ventilation and CRRT. ECMO experience in Japanese spotted fever remains limited; Yamamoto et al. reported VA-ECMO in a patient with refractory septic shock and impending cardiac arrest [14]. In contrast, VV-ECMO was used in our patient because refractory respiratory failure was the predominant indication. This case does not establish a disease-specific role for ECMO, but it shows that pulmonary involvement in severe *R. japonica* infection can progress to a level requiring extracorporeal respiratory support.

Japanese spotted fever remains less well characterized in critically ill patients in China than scrub typhus. Previous reports from Yichang and Zhejiang Province have described disseminated intravascular coagulation, shock, neurological involvement, pleural effusion, and multiorgan failure [5–7]. The three patients in our series ranged from hypotension with AKI and thrombocytopenia to severe ARDS and septic shock requiring VV-ECMO and CRRT. In clinical practice, severe *R. japonica* infection may therefore be encountered in the context of septic shock, severe pneumonia, or otherwise unexplained multiorgan dysfunction rather than as a readily recognizable spotted fever syndrome.

Recognition was further complicated by the absence of consistent bedside clues. No characteristic eschar was documented in the five included patients, and a clearly relevant recent arthropod exposure was not elicited in every case. Fever, thrombocytopenia, hepatic dysfunction, AKI, coagulation abnormalities, and pulmonary infiltrates are individually nonspecific. Their coexistence, however, may provide a useful diagnostic pattern when the clinical course is not adequately explained by more common infections, particularly in patients with compatible outdoor exposure. The absence of an eschar therefore does not reliably exclude rickettsiosis. Similar diagnostic difficulties have been reported in Japanese spotted fever, where prompt recognition of compatible clinical and epidemiological features is important for timely treatment [15].

mNGS was clinically useful because it narrowed the etiologic differential when the presenting syndrome was nonspecific. Its findings, however, should not be interpreted in isolation. Blood yielded the clinically relevant organism in four patients, while CSF identified *O. tsutsugamushi* in the patient with neurological involvement and BALF additionally identified *R. japonica* in the patient with severe pulmonary disease. These findings are descriptive rather than comparative. Specimen selection was clinically driven, paired specimens were not obtained systematically, and the study was not designed to determine the relative diagnostic yield of blood, CSF, or BALF.

The organism-specific read counts also require cautious interpretation. Read abundance in clinical mNGS is influenced by specimen type, host nucleic-acid background, timing of sampling, prior antimicrobial exposure, sequencing workflow, and bioinformatic processing [8–10]. The differences in read counts observed in this series therefore should not be interpreted as quantitative measures of pathogen burden or disease severity. EBV was detected concurrently in two patients, but viral nucleic-acid detection alone did not establish active coinfection. Etiologic attribution depended on concordance between the detected organism, the acute clinical syndrome, and the overall microbiological and clinical context rather than on read count alone.

All patients received doxycycline-containing therapy, but the heterogeneity of treatment precludes comparison of antimicrobial regimens. Additional therapy reflected individual clinical circumstances rather than a predefined protocol. Available evidence has not established a clear outcome benefit from routinely adding fluoroquinolones to tetracycline therapy for Japanese spotted fever [16,17]. Improvement in individual patients in this series therefore cannot be attributed to a specific antimicrobial combination, particularly because antimicrobial treatment was delivered alongside mechanical ventilation, vasoactive support, CRRT, ECMO, and other supportive interventions.

A strength of this study is its ascertainment strategy. Cases were identified through a prespecified hospital-wide search rather than selected because of an unusual clinical presentation. During the study period, the six ICUs collectively recorded 12,300 admissions, providing a broad critical-care population within which eligible cases were ascertained. This approach may reduce selective case reporting within the mNGS-defined population, although it does not eliminate ascertainment bias. The use of the same institutional mNGS framework also allowed a consistent approach to interpretation of sequencing findings across patients.

Several limitations are important. First, this was a retrospective, single-center series of only five patients and cannot estimate incidence, prognostic factors, treatment effects, or mortality. Second, microbiological eligibility required mNGS detection; patients diagnosed exclusively by targeted PCR, serology, or clinical criteria may therefore have been missed. The concentration of eligible cases after 2024 may also reflect temporal changes in mNGS use or other diagnostic practices rather than a true increase in severe rickettsial disease. Third, Japanese spotted fever and scrub typhus are biologically distinct infections and were considered together because the clinical question concerned their recognition and presentation in critical illness, not because they were assumed to represent a

homogeneous disease entity. Fourth, pathogen identification was not uniformly confirmed by targeted PCR or paired serology, and specimen type and timing were determined by clinical judgment rather than a standardized protocol. Exposure history and examination for eschar were not uniformly documented. Finally, all five patients were women, but this small sample provides no basis for inference regarding sex-specific susceptibility, and one patient remained hospitalized at the study cutoff.

For critical care clinicians, the principal implication is diagnostic rather than prognostic. Severe rickettsioses may initially present as sepsis-like illness, severe respiratory failure, neurological disease, cardiopulmonary dysfunction, or multiorgan failure. An acute febrile illness accompanied by thrombocytopenia, hepatic abnormalities, otherwise unexplained organ dysfunction, and compatible epidemiological exposure should prompt consideration of rickettsial infection even when classical cutaneous findings are not documented. In this setting, targeted testing or mNGS may provide etiologic evidence, but sequencing findings should be interpreted together with the clinical syndrome and other microbiological data.

Conclusion

Severe *R. japonica* and *O. tsutsugamushi* infections presented with distinct forms of critical illness, including shock, severe respiratory failure, neurological involvement, cardiac dysfunction, and AKI. Rickettsiosis should remain in the differential diagnosis of unexplained febrile multiorgan dysfunction, particularly when thrombocytopenia, hepatic abnormalities, or compatible outdoor exposure are present. mNGS provided useful etiologic evidence in this series but required interpretation together with the clinical syndrome and other microbiological findings.

Declarations

Ethical Approval

This retrospective observational study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (**[2026B] IIT Ethics Approval No. 0874**). The requirement for individual informed consent was waived because of the retrospective study design and the use of routinely collected, de-identified clinical data. The study was conducted in accordance with the Declaration of Helsinki.

Funding

This work was supported by the National Science and Technology Major Project Young Scientists Program (**grant number 2025ZD0549000**). The funding source had no role in study design; data

collection, analysis, or interpretation; preparation of the manuscript; or the decision to submit the manuscript for publication.

Data Availability

Patient-level data underlying this study are not publicly available because they contain potentially identifiable clinical information. De-identified data may be made available from the corresponding author upon reasonable request and subject to institutional and ethical approval.

Author Contributions

Yue Zhu: Conceptualization, methodology, investigation, data curation, formal analysis, writing—original draft.
Yelin Cao: Investigation, validation, data curation, formal analysis.
Xuqin Li: Investigation, data curation, writing—original draft.
Yangyang Jia: Validation, microbiological data interpretation.
Wenqiao Yu: Clinical data interpretation, imaging review.
Guobin Wang: Clinical data interpretation, writing—review and editing.
Hongliu Cai: Clinical data interpretation, writing—review and editing.
Hua Zhou: Supervision, methodology, writing—review and editing.

All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Acknowledgements
None.

References

1. Sahni A, Fang R, Sahni SK, Walker DH. Pathogenesis of rickettsial diseases: pathogenic and immune mechanisms of an endotheliotropic infection. Annu Rev Pathol. 2019;14:127–152. doi:10.1146/annurev-pathmechdis-012418-012800.
2. Trent B, Fisher J, Soong L. Scrub typhus pathogenesis: innate immune response and lung injury during Orientia tsutsugamushi infection. Front Microbiol. 2019;10:2065. doi:10.3389/fmicb.2019.02065.
3. Griffith M, Peter JV, Karthik G, Ramakrishna K, Prakash JAJ, Kalki RC, et al. Profile of organ dysfunction and predictors of mortality in severe scrub typhus infection requiring intensive care

admission. Indian J Crit Care Med. 2014;18(8):497–502. doi:10.4103/0972-5229.138145.

4. Chaudhuri S, Das Adhikari S, Boodman C, Schmiedel Y, Grobusch MP, Gupta N. Acute respiratory distress syndrome in scrub typhus: a systematic review and meta-analysis. Infection. 2026. doi:10.1007/s15010-026-02907-7.
5. Gao S, Li L, Zhou X, Dai X, Lu L, Chen Y, et al. Fatal Rickettsia japonica infection complicating disseminated intravascular coagulation in Yichang, China. Infect Drug Resist. 2022;15:6613–6623. doi:10.2147/IDR.S383917.
6. Ren Y, Jiang Y, Xiang Z, Cheng Q, Chen K, Ma J, et al. Sporadic human infections with Rickettsia japonica in Yichang, China, 2021–2023. Transbound Emerg Dis. 2025;2025:4832524. doi:10.1155/tbed/4832524.
7. He K, Chen S, Yu L, Wei D, Xu X. Japanese spotted fever complicated with pleural effusion in Zhejiang province, China: a case report and literature review. J Infect Dev Ctries. 2024;18(7):1135–1140. doi:10.3855/jidc.18354.
8. Gu W, Miller S, Chiu CY. Clinical metagenomic next-generation sequencing for pathogen detection. Annu Rev Pathol. 2019;14:319–338. doi:10.1146/annurev-pathmechdis-012418-012751.
9. Simner PJ, Miller S, Carroll KC. Understanding the promises and hurdles of metagenomic next-generation sequencing as a diagnostic tool for infectious diseases. Clin Infect Dis. 2018;66(5):778–788. doi:10.1093/cid/cix881.
10. Miao Q, Ma Y, Wang Q, Pan J, Zhang Y, Jin W, et al. Microbiological diagnostic performance of metagenomic next-generation sequencing when applied to clinical practice. Clin Infect Dis. 2018;67(Suppl 2):S231–S240. doi:10.1093/cid/ciy693.
11. Zhu Y, Jia Y, Zhang C, Li H, Ding P, Huang L, et al. Clinical characteristics and prognosis of patients with severe pneumonia with neurological dysfunction: a regional multicenter retrospective study in mainland China. Infect Drug Resist. 2025;18:4215–4226. doi:10.2147/IDR.S537406.
12. Teng Z, Shi Y, Peng Y, Zhang H, Luo X, Lun X, et al. Severe case of rickettsiosis identified by metagenomic sequencing, China. Emerg Infect Dis. 2021;27(5):1530–1532. doi:10.3201/eid2705.203265.
13. Majumdar S, Benjamin RN, Ralph R, Mahasampath G, Abhilash KPP, Samson N, et al. Neurological manifestations of scrub typhus: the clinical spectrum, determinants, and outcome. Neurol India. 2025;73(1):88–94. doi:10.4103/ni.ni_139_22.
14. Yamamoto N, Narita M, Hiwatari C, Yano K. Septic shock due to severe Japanese spotted fever that could be saved by using VA-ECMO: a case report. J Jpn Assoc Acute Med. 2022;33(3):116–120. doi:10.1002/jja2.12688.
15. Sato R, Yamada N, Kodani N, Makiishi T, Iwashita Y. Prompt diagnosis and appropriate treatment of Japanese spotted fever: a report of three cases. Heliyon. 2024;10(1):e23462. doi:10.1016/j.heliyon.2023.e23462.
16. Itoh K, Kabata D, Shigemi H, Hirota T, Sakamaki I, Tsutani H, et al. Evaluation of tetracycline and fluoroquinolone therapy against Japanese spotted fever: analysis based on individual data from

case reports and case series. Int J Antimicrob Agents. 2023;62(2):106895. doi:10.1016/j.ijantimicag.2023.106895.

17. Sando E. Japanese spotted fever and adjunctive fluoroquinolones: a critical appraisal of hard outcome evidence. Fukushima J Med Sci. 2026. Advance online publication. doi:10.5387/fms.26-00024.

Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

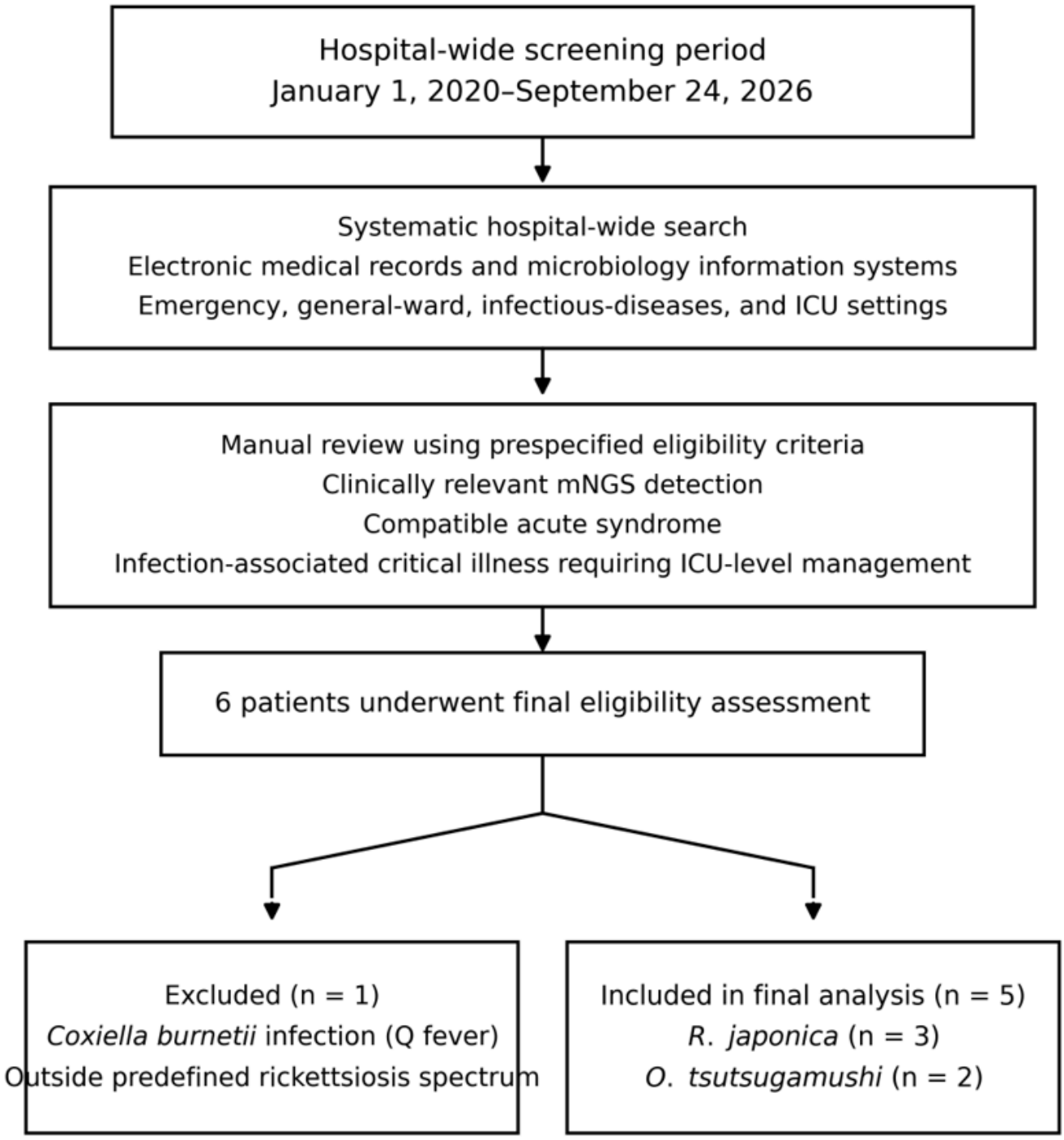


Figure 1

Hospital-wide case ascertainment of severe rickettsioses.
Flow diagram showing the prespecified screening period, systematic hospital-wide search of electronic medical records and microbiology information systems, manual review using prespecified eligibility criteria, exclusion of one patient with *Coxiella burnetii* infection (Q fever), and final inclusion of five critically ill adults with *Rickettsia japonica* or *Orientia tsutsugamushi* infection. During the study period,

12,300 admissions were recorded across six ICUs; this number is provided only to characterize the background critical-care population and was not used as a denominator for incidence estimation.

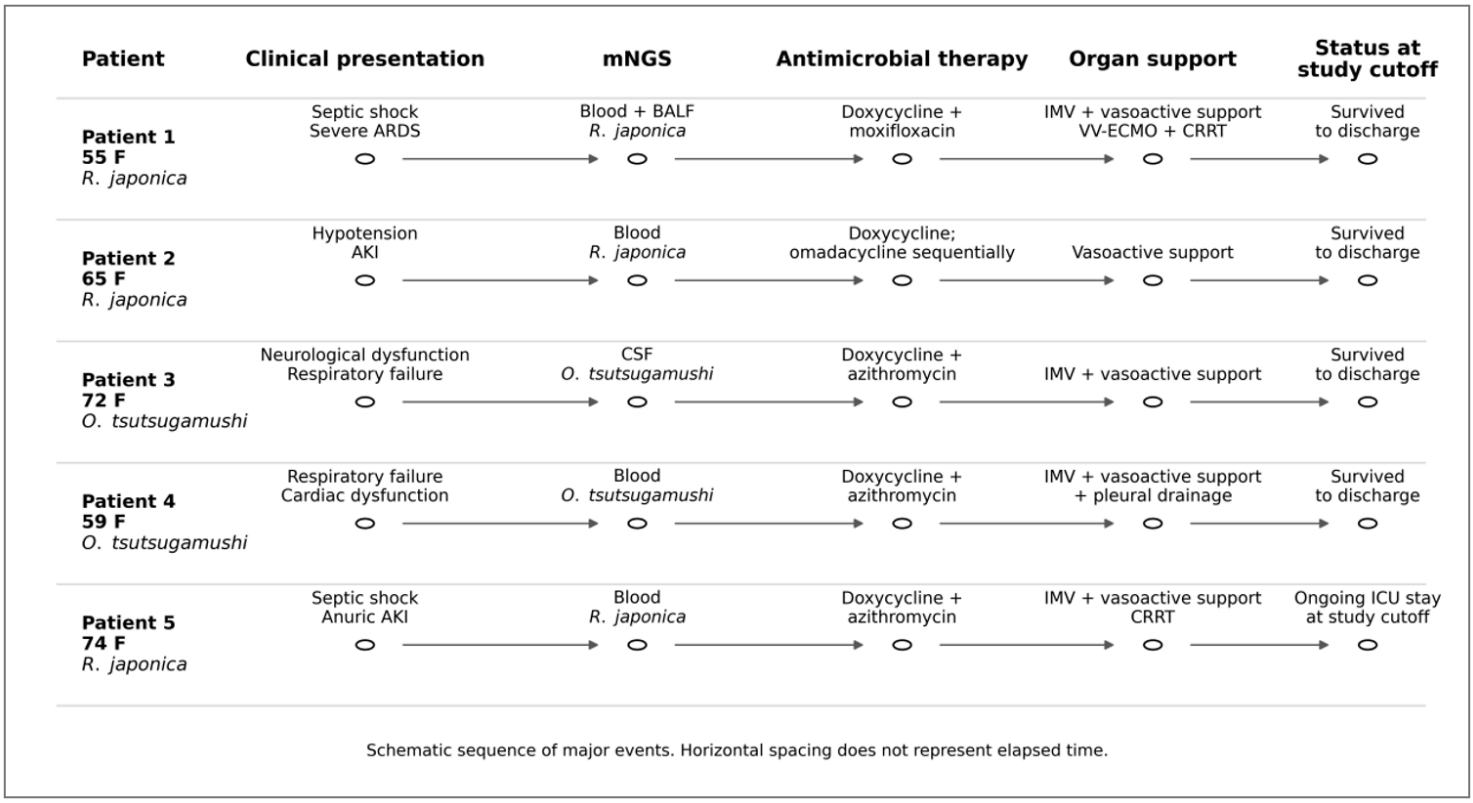


Figure 2

Clinical and diagnostic pathways of patients with severe rickettsioses.
Schematic patient-level summary of the major clinical presentations, mNGS findings, antimicrobial therapy, organ-support requirements, and status at the study cutoff for the five included patients. Horizontal spacing is schematic and does not represent elapsed time. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; CRRT, continuous renal replacement therapy; CSF, cerebrospinal fluid; ICU, intensive care unit; IMV, invasive mechanical ventilation; mNGS, metagenomic next-generation sequencing; VV-ECMO, venovenous extracorporeal membrane oxygenation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table2.docx