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CASE SERIES

Fatal Rickettsia Japonica Infection Complicating Disseminated Intravascular Coagulation in Yichang, China

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Background: Severe complications may cause a fatal or disabling outcome in patients with *Rickettsia japonica* infection but are poorly understood.

Methods: We identified 11 patients with only *Rickettsia japonica* infection with metagenomics next generation sequencing (mNGS) during April to November 2021 at Yichang Central People's Hospital, China. Clinical data were obtained through review of medical records.

Results: Most patients realized that they had symptoms about one or two days after being bitten. Fever (91%), pulmonary effusion (91%), rash or erythema (100%), abnormal urine (100%), neutropenia (100%), lymphopenia (100%), and thrombocytopenia (100%) were the most common clinical signs. Six severely ill patients were admitted to the intensive care unit and five had mild symptoms. Systemic manifestations such as vomiting (83%), neurological manifestations (100%), and disseminated intravascular coagulation (100%) were more frequently observed in the severe cases, 33.3% of whom developed purpura fulminans requiring amputation or skin graft, and 16.6% died two days after admission. Some patients experienced sequelae.

Conclusion: Our study found that patients with critical *Rickettsia japonica* infection complicating disseminated intravascular coagulation had high risk of poor outcome.

Keywords: Rickettsia japonica, Japanese spotted fever, infection, tick, disseminated intravascular coagulation, purpura fulminans

Introduction

Rickettsia japonica (*R.japonica*), first reported in Japan in 1984, causes severe tick-borne rickettsiosis named Japanese spotted fever (JSF).[1] JSF usually manifests as high fever, erythema and eschar and leukocytosis; thrombocytopenia, increased levels of C-reactive protein and creatine kinase are observed.[2,3] Clinical cases of *R.japonica* infection are mainly concentrated in Japan, and mostly reported in adjacent countries like South Korea, the Philippines and Thailand.[4–6] However, cases of *R.japonica* infection in humans are scarce in China and its outbreak is sporadic and limited. Furthermore, little is known about its clinical course and data, especially for severe or fatal cases which may require prolonged hospitalization and intensive care support, are scarce. Therefore, in this presented case series, we analyzed 11 Chinese patients with JSF who were healthy before, focusing on the severe/fatal cases and differences between severe and mild patients. Investigating these cases would help us to have a better understanding of the risk factors on admission for JSF which may potentially cause poor outcomes.

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Methods

Study Population

To determine the evolution and clinical characteristics of patients with confirmed infection with *R.japonica*, we conducted a single-center, retrospective observational study between April and November 2021, in a tertiary teaching hospital. The study population of 11 patients, without significant underlying disease, had only *R.japonica* infection.

Study Design

According to Sepsis-3,[7] patients with septic shock were defined as severe cases, others were mild cases. Septic shock was defined as: vasopressors required to maintain MAP ≥ 65 mmHg and serum lactate level >2 mmol/L. Chest computed tomography (CT) scans were performed for each patient on admission. Laboratory findings were included only within 24 hours of admission. The patients' Acute Physiology and Chronic Health Evaluation II (APACHE-2) and disseminated intravascular coagulation / the international society of thrombosis and hemostasis (DIC / ISTH) were calculated.[8,9] Acute kidney injury (AKI) was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) definition.[10] Ethics review committee of our hospital certified that this retrospective observational study was exempt from ethical approval. The identifiable part of patients for figures was hidden and informed consent was obtained.

Metagenomic Next Generation Sequencing

Whole blood samples were collected at admission or during hospitalization with standard procedures and promptly stored in sterile containers and transported on dry ice to the laboratory for metagenomic next generation sequencing (mNGS). Information about all DNA and RNA present in the sample was recorded. All raw reads were quality filtered including removing low-quality reads, adapter contamination, duplicated reads, and reads shorter than 35 bp, and the human DNA was also filtered out. Finally, all reference genomes were from NCBI (ftp://ncbi.nlm.nih.gov/genomes/). The results of only *R.japonica* infection with no other evidence of any other pathogen, were included in the study.

Statistical Analysis

All data analyses were completed using Statistical Package for the Social Sciences (SPSS) for Windows (version 24; SPSS Inc, IBM, Chicago, IL, USA). The categorical demographic features, early clinical symptoms, and categorical variables are reported as frequencies and percentages. Continuous variables are presented as median and interquartile ranges (IQRs).

Results

Patient Characteristics

We identified 11 cases with *R.japonica* infection: six severe cases (Patient No.1–6) and five mild cases (Patient No.7–11). The six severe cases were all admitted to the intensive care unit (ICU) due to shock. All cases were from Yichang, Hubei province, China, which covers 21,227 square kilometers and occurred in April to November, 2021 which just coincides with active period of ticks. Most of the cases occurred after tick bite or mountain tourism and eschar was a specific sign. Ages ranged from 48 to 74 years with a median age of 58 years. Duration of symptoms before admission varied but mild patients had a significantly shorter median duration (5 days, 4–7) than severe patients (7 days, 6.25–7.75). Characteristics of these patients on admission are shown in Table 1.

Most patients realized that they had symptoms about one or two days after being bitten. Regarding the initial symptoms and signs, fever (10/11, 91%) and rash or erythema (11/11,100%) were the most frequent complaints. Almost every case had pulmonary effusion (10/11, 91%) and abnormal urine (11/11, 100%). Meanwhile, systemic manifestations were observed in severe cases, namely vomiting (5/6, 83%), anuria or oliguria (3/6, 50%) and neurological manifestations (6/6100%). That was rarely observed as first symptom in other reports. Moreover, at the first contact, dark erythema could be observed in some critical patients and timely and effective treatment was started. However, these symptoms infrequently occurred in mild patients.

Table 1 Characteristics of the 11 Patients with R.japonica Infection on Admission, April 20, to November 20, 2021, Yichang, China

	Patient No.										
	1	2	3	4	5	6	7	8	9	10	11
Age/Gender	68 F	48 M	54 M	58 M	69 F	55 F	70 F	56 F	58 M	74 M	71 F
Evidence of insect bites (site)	Eschar (Right waist)	History of mountain tourism	Eschar (Right inguinal region)	Eschar (Back)	Not found	Redness and swelling (Right hand)	Eschar (Right shoulder)	Eschar (Left lower abdomen)	Eschar (Left knee)	Eschar (Right thigh)	Eschar (Right lower abdomen)
Duration of symptoms before admission	10 days	6 days	7 days	8 days	7 days	6 days	7 days	7 days	2 days	4 days	5 days
Constitutional symptom	Fatigue	Fever	Fever, myalgia	Fever	Fever,	Fever, myalgia	Fever	Fever	Fever	Fever	Fever
Dermatological manifestations (site)	Erythema (all-over body)	Rash (all-over body)	Erythema (all-over body)	Erythema (all-over body)	Rash (abdomen)	Rash (abdomen and limbs)	Rash (all-over body)	Rash (all-over body)	Rash (all-over body)	Rash (all-over body)	Rash (all-over body)
Circulatory condition (within 24 hours)	Shock	Shock	Shock	Shock	Shock	Shock	Stable	Stable	Stable	Stable	Stable
Respiratory manifestations	Shortness of breath, extensive pulmonary effusion	Shortness of breath, extensive pulmonary effusion	Shortness of breath, partial consolidation in lungs	Dyspnea, pulmonary effusion and consolidation	Shortness of breath, local pulmonary effusion	Shortness of breath, local pulmonary effusion	None	Little pulmonary effusion	Little pulmonary effusion	Little pulmonary effusion	Little pulmonary effusion
Neurological manifestations (within 24 hours)	Confusion	Coma, limb twitching	Deep coma	Limb twitching, deep coma	Incidental delirium	Delirium	None	Headache	None	Acute cerebral infarction	Headache
Gastrointestinal symptoms	Nausea, vomiting	Nausea, vomiting	None	Nausea, vomiting	Abdominal pain, vomiting	Anorexia, diarrhea	Anorexia, vomiting	None	None	None	Nausea
Renal manifestations (within 48 hours)	Anuria	Oliguria	Urine protein	Oliguria	Urine protein	Low urine output	Urine protein	Urine protein	Urine protein	Urine protein	Urine protein
Lymphadenopathy[a]	NA	None	NA	NA	Yes	Yes	NA	Yes	Yes	Yes	Yes
Underlying conditions	Hypertension	None	None	Coronary heart disease	Chronic bronchitis	None	Old pulmonary tuberculosis	None	None	Hypertension	None

Note: Lymphadenopathy[a] included enlarged cervical, axillary and inguinal lymph nodes.
Abbreviation: NA, not available.

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Laboratory Data

The most common laboratory abnormalities are detailed in Table 2. The data of laboratory tests were collected only within 24 hours of admission. Therefore, partial data were not available because some laboratory tests were not performed on admission.

For all patients, neutrophil percentage (NEUT %) was increased. Red blood cell (RBC) count, platelet (PLT) count, and lymphocytes percentage (LY %) were decreased. White blood cell (WBC) count was increased in all severe patients but normal in most mild patients (4/5 80%). Among them, PLT count, NEUT% and WBC count seemingly correlated with severity of disease and the median value of platelet count (26.5, 24.5–31.5) in severe patients was significantly lower than in mild patients (76, 68–87). In contrast, IL-6, CRP, PCT, SAA and FER, as indicators of inflammatory severity, suggested weak correlations with clinical severity. D-Dimer and fibrin degradation products (FDP) increased simultaneously with available data. In addition, fecal occult blood tested positive in three severe patients (3/6, 50%).

Therapies During Hospitalization

The main treatment regimen was Doxycycline (DO). Considering that we were in a highly endemic area of tick-borne disease, DO was empirically almost given every 12 hours from admission. In severe cases, five patients (5/6, 83%) were treated with DO and steroid hormones. Two severe patients (2/6, 33%) received extra quinolones. Five severe patients (5/6, 83%) were intubated and presented with concurrent hypotension requiring vasopressors. Continuous renal replacement therapy (CRRT), plasma exchange (PE) and transfusion were also employed. Regarding mild patients, they all recovered with oral DO alone. Additional adjunctive therapies are presented in Table 3.

Clinical Outcome

The incidence of poor outcome was remarkably high for our severe JSF cases, reaching 50%. Besides, what was really troublesome was follow-up complications and organ failure. That significantly increased the length of hospital stay and treatment cost.

Patient No.1 and 3 were admitted directly to the ICU through the emergency department and later presented with purpura fulminans. Patient No.1 developed gangrene and underwent amputation. Patient No.3 avoided amputation, but got extensive cutaneous necrosis of extremities and required skin grafting. Patient No.4 died after four days. Other remaining patients were all cured and discharged. Schematic description of disease course and outcomes is shown in Figure 1.

Disseminated intravascular coagulation (DIC) was a common complication for our severe cases, two of whom suffered from purpura fulminans. Deep venous thrombosis was demonstrated in Patients No.1–3 and 6. Intracranial hemorrhage was diagnosed in two severe cases and one mild case. And this mild patient was diagnosed with acute cerebral infarction the day before admission. In addition, we also detected arrhythmias in three severe patients (3/6, 50%) who never had it before (Table 4). Comparing with mild cases, multiple organ dysfunction was merely noted in severe patients. Without exception, they showed higher APACHE-2 score and longer hospital stay and length of ICU stay.

Discussion

We described homochronous combined mild and severe cases of JSF in China that reflect the largest number of serious *R. japonica* infections described by far. JSF is generally considered to cause mild symptoms. However, we found it continues to have potential for developing poor outcomes when neglected. Therefore, we summarized the clinical characteristics, laboratory findings, therapies and outcomes of 11 patients. Our study demonstrated that DIC carrying a risk of death and disability should cause concern in JSF patients.

In fact, it is first comprehensive case study in China region. Specifically, the first Chinese clinical case of *R.japonica* was discovered in Anhui Province, in 2013.[11] Since then, 14 and 16 Japanese spotted fever cases occurred in Xinyang city and Zhejiang Province respectively during 2014–2017.[12,13] Reportedly, *R.japonica* was broadly identified from *H. longicornis*, a tick from China, in Shandong Province, in 2015.[12] Although, the presence and distribution of *R.japonica* are not very clear, previous studies suggested that *R.japonica* might be more frequent in China than is believed.[13]

Table 2 Laboratory Tests of the 11 Patients with R.japonica Infection on Admission, April 20, to November 20, 2021, Yichang, China

	Reference Ranges[a]	Patient No.										
		1	2	3	4	5	6	7	8	9	10	11
WBC(10^9/L)	3.5–9.5	16.22	11.07	12.07	15.18	11.86	10.81	6.15	15.05	3.64	6.64	5.44
RBC(10^{12}/L)	3.8–5.1	3.62	3.55	4.91	4.20	3.66	2.14	3.33	2.75	3.95	4.24	3.40
PLT (10^9/L)	125–350	26	23	27	33	34	24	48	68	76	102	87
NEUT%	40.0–75.0	95.4	96.7	95.5	91.3	88.8	91.3	80.6	90.7	90.4	90.7	85.1
LY%	20.0–50.0	3.6	2.2	3.5	5.7	7.4	5.7	13.8	7.4	6.9	5.9	7.9
IL-6(pg/mL)	0–7	1965	>5000	198.8	203.6	208.6	571.9	NA	35.32	30.54	204.9	501.6
CRP (mg/L)	0–10	172.8	292.9	160.67	248.7	155.2	121.1	115.7	97.7	154.6	142.7	234.4
PCT (ng/mL)	0–0.05	NA	22.79	154.66	5.24	2.12	3.98	2.32	2.94	1.82	2.01	0.76
SAA (mg/L)	0–10	NA	NA	NA	625.0	588.2	NA	NA	501.1	884.0	837.2	670.7
FER (ng/mL)	25–350	1277.9	>3000	NA	>3000	>3000	2596	NA	>3000	2296	NA	>3000
D-Dimer(ug/mL)	0–0.5	NA	>20	NA	>20	12.37	13.62	>10	NA	NA	5.07	NA
FDP (mg/L)	0–5	81.26	53.78	NA	NA	11.98	59.23	NA	NA	NA	NA	NA
LDH (IU/L)	120–250	894	793	522	907	680	501	681	815	898	562	468
α-HBDH(IU/L)	95–250	561	543	266	571	468	377	479	565	455	400	321
CK (IU/L)	40–200	724	NA	1121	397	76	NA	39	160	844	315	243
NT-proBNP (pg/mL)	0–300	NA	9419	NA	11517	915	8041	1249	NA	NA	NA	NA
AST (U/L)	13–35	134	193	166	495	126	90	681	105	399	54	45
ALT (U/L)	7–40	36	117	93	220	60	42	106	49	189	37	13
TBIL (umol/L)	5.1–28.0	29.1	133	41.0	28.5	15.5	12.8	11.4	8.64	14.8	22.1	6.57
DBIL (umol/L)	0–10.0	22.9	85.79	29.1	22.2	9.1	7.2	4.18	3.85	7.6	7.8	3.71
SCr(umol/L)		237	739	111	239	93	85	60.6	65	104	121	86
CHOL(mmol/L)	2.8–6.0	NA	1.94	NA	2.71	2.07	2.63	3.31	NA	NA	NA	NA

(*Continued*)

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Table 2 (Continued).

	Reference Ranges[a]	Patient No.										
		1	2	3	4	5	6	7	8	9	10	11
TG (mmol/L)	0.3–2.1	NA	3.46	NA	1.38	3.94	1.89	2.54	NA	NA	2.38	NA
TP(g/L)	65–85	29.26	50.58	44.83	50.57	43.70	46.6	52.02	44.42	60.0	61.62	53.44
ALB(g/L)	40–55	10.55	27.23	21.76	24.51	22.44	20.14	27.02	22.42	33.49	33.35	27.56
PT(s)	11.0–15.0	21.5	16.5	16.2	16.3	14.9	13.1	10.8	12.9	14.3	13.6	12.5
PTA(%)	70–150	42	64	66	66	78	102	120	103	83.0	94	111
INR	0.80–1.20	1.86	1.33	1.3	1.3	1.17	0.99	0.84	0.98	1.12	1.04	0.94
Fib (g/L)	2.00–4.00	1.07	3.76	3.77	5.22	1.91	2.30	3.08	2.46	4.56	5.18	3.95
APTT(s)	32.0–45.0	81.6	90	58.9	66.1	63.3	56.8	35.6	47.1	36.0	43.4	48.1
TT(s)	14.0–20.0	22.2	23.6	18.3	81.3	15.2	17.2	13.8	21.6	16.5	16.7	20.1
FOB[b]		+	-	+	+	-	-	-	-	-	-	-
3P (+)		+	-	NA	-	-	+	NA	NA	NA	NA	NA

Notes: [a]Reference ranges refer to those of Yichang Central People's Hospital. [b]FOB measured by fecal occult blood cards. - showed negative result; + showed positive result.

Abbreviations: WBC, White blood cells; RBC, Red blood cell; PLT, Platelet; NEUT, Neutrophils; LY, Lymphocytes; IL-6, Interleukin-6; CRP, C-reactive protein; PCT, Procalcitonin; SAA, Serum amyloid a; FER, Serum ferritin; FDP, Fibrinogen and fibrin degradation products; LDH, Lactate dehydrogenase; α-HBDH, α-hydroxybutyrate dehydrogenase; CK, Creatine kinase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; AST, Aspartic transaminase; ALT, Alanine transaminase; TBIL, Total bilirubin; DBLL, Direct bilirubin; SCr, Serum creatinine; CHOL, Cholesterol; TG, Triglyceride; TP, Total protein; ALB, Albumin; FOB, Fecal occult blood; 3P, Plasma protamine paracoagulation test.

Table 3 Therapies of the 11 Patients with R.japonica Infection During Hospitalization, April 20, to November 20, 2021, Yichang, China

	Patient No.										
	1	2	3	4	5	6	7	8	9	10	11
Main medication*	DO 100mg po q12h	DO 100mg po q12h	DO 100mg IV q12h + LVX 0.5g IV qd	DO 100mg IV q12h + MXF 0.4g IV q12h	DO 100mg IV q12h	DO 100mg IV q12h	DO 100mg po q12h	DO 100mg po q12h	DO 100mg po q12h	DO 100mg po q12h	DO 100mg po q12h
Steroid hormones	MP 0.7mg/kg/d IV×11d	HC 2mg/kg/d IV×20 d	MP 0.7mg/kg/d IV×9d	MP 0.7mg/kg/d IV×4d	None	DEX 0.2mg/kg/d IV ×14d	None	None	None	None	None
Vasopressors	Yes	Yes	Yes	Yes	Yes	None	None	None	None	None	None
Respiratory support	MV	MV	ECMO	MV	NC	HFNC	NC	NC	None	None	NC
CRRT	Yes	Yes	Yes	Yes	None	Yes	None	None	None	None	None
PE	Yes	Yes	Yes	None	None	None	None	None	None	None	None
Transfusion*	Yes	Yes	Yes	None	None	Yes	None	None	None	None	None

Note: *Transfusion referred to the transfusion of blood components.

Abbreviations: DO, Doxycycline; po, per os; IV, Intravenous drip; q12h, every 12 hours; qd, every day; LVX, Levofloxacin; MXF, Moxifloxacin; ECMO, Extracorporeal membrane oxygenation; MP, Methylprednisolone; HC, Hydrocortisone; DEX, Dexamethasone; MV, Mechanical ventilation; HFNC, High-flow nasal cannula oxygen therapy; NC, Nasal catheter oxygen inhalation; CRRT, Continuous renal replacement therapy; PE, Plasma exchange.

Only individual cases with DIC and multiple organ dysfunction had been reported in JSF.[14,15] In our case series, six severe cases rapidly developed DIC and multiple organ failure, including one fatal case and two cases which suffered from purpura fulminans.

Purpura fulminans is a disabling and even life-threatening disorder with cardinal manifestations presenting skin discoloration, DIC, fever, and septic shock.[16] Several studies have documented that its mortality is extremely high and most survivors have poor outcomes and require amputation.[17] Acute infectious purpura fulminans is the most common form of purpura fulminans. Rickettsia infection associated with purpura fulminans is recorded rarely, and seen only in *R. rickettsii, R.australis, R.conorii, israelensis* and probably *indica*.[18–20] We described two cases of acute infectious purpura fulminans which, to the best of our knowledge, were the first discovered cases in *R.japonica*.

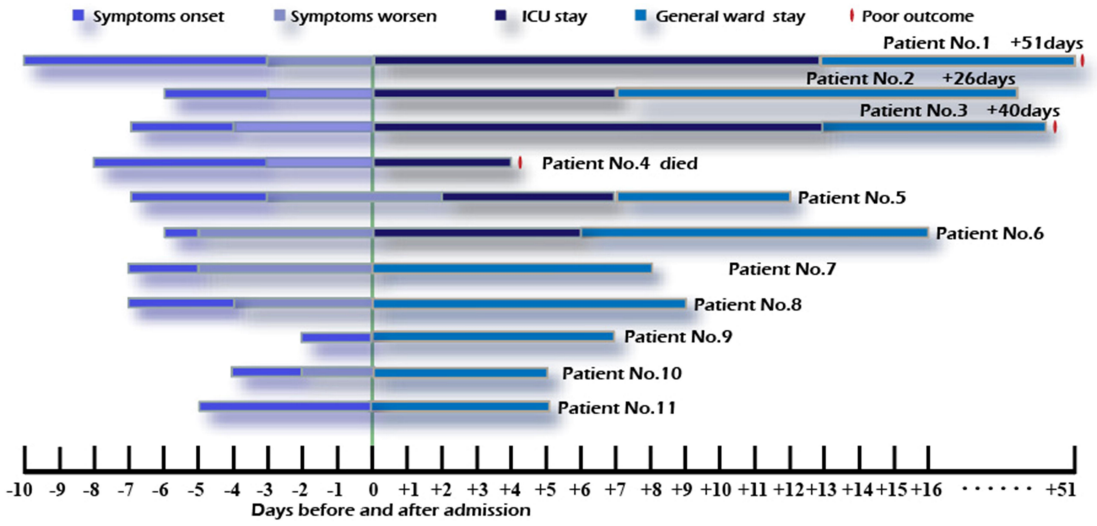

Figure 1 Schematic description for individual patients.

Table 4 Clinical Outcome of the 11 Patients with R.japonica Infection, April 20, to November 20, 2021, Yichang, China*

	Patient No.										
	1	2	3	4	5	6	7	8	9	10	11
Duration from symptoms' onset to medication	10 days	6 days	7 days	8 days	7 days	6 days	7 days	7 days	2 days	4 days	5 days
Duration from admission to ICU	0 hours	5 hours	0 hours	10 hours	2 days	4 hours	None	None	None	None	None
Length of stay ICU	16 days	12 days	13 days	4 days	5 days	6 days	None	None	None	None	None
Hospital stay	51 days	26 days	40 days	4 days	12 days	16 days	8 days	9 days	7 days	5 days	5 days
APACHE-2 score	36	36	39	36	26	18	NA	NA	NA	NA	NA
DIC/ISTH score	7	6	NA	6	5	5	6	NA	NA	3	NA
Organ failure	HF, RF, AKI	HF, RF, AKI	HF, RF, AKI	HF, RF, AKI	None	RF	None	None	None	None	None
Cerebral involvement	Intracranial hemorrhage	Arachnoid hemorrhage	None	None	None	None	None	NA	NA	Acute cerebral infarction	NA
Arrhythmia	Yes	None	None	Yes	Yes	None	None	None	None	None	None
Deep venous thrombosis	Yes	Yes	Yes	None	None	Yes	None	NA	None	None	NA
Other involvement	Limb gangrene	Hyperlipemia	Skin Infection	None	Hyperlipemia	None	Hyperlipemia	None	None	Hyperlipemia	None
Outcome	Amputation	Cured	Cutaneous necrosis	Died	Cured	Cured	Cured	Cured	Cured	Cured	Cured

Abbreviations: HF, Heart failure; RF, Respiratory failure.

They initially manifested as cutaneous circumscribed ecchymosis and formation of bullae (Figure 2A), which was linked to the obstruction of small blood vessels in the superficial skin leading to telangiectasia and congestion.[21] Later enhanced vascular permeability and extravasation of blood in the center of petechial lesions enlarged ecchymosis and extremities blackened (Figure 2B and C),[22] which marked disease progression. In comparison with Patient No.1 who underwent amputation, blackened extremities gradually recovered owing to aggressive management in our Patient No.3. Consequently, full knowledge of the disease initiation and progression, prompt identification remain essential to prognosis.

Systemic symptoms were found more frequently in severe than mild cases. These implied critical patients showed a propensity for multiple organ involvement. Even though pulmonary effusion secondary to microvascular leakage is always seen, the more extensive effusion may indicate more severe disease. Similarly, not only urine protein but also anuria and oliguria were present in severe cases. Consistent with a published study,[23] we also found SCr had a strong correlation with serious infection.

The clinical manifestations seem to be consistent with the pathophysiology described in a murine model of rickettsiosis. Mice with *R.australis* infection acquired progressively severe vasculitis, multifocal hepatic necrosis, renal and pulmonary involvement.[24] In another study, hematogenous dissemination, multifocal inflammatory lesions, interstitial pneumonitis and cerebral hemorrhages were exhibited in *R.heilongjiangensis* infected mice model.[25] For severe patients, this endothelial inflammation leads to microvascular dysfunction increasing the likelihood of DIC and invasion of multiple organs including heart, brain, lungs and kidney, which suggests *R.japonica* may cause more severe rickettsiosis.

Noticeably, our observations were comparable to previous studies with some differences. Patient No.1 complained firstly of vomiting and did not have fever until the sixth day of admission. Therefore, we deem that lack of fever should not preclude the possibility of JSF. Nonspecific gastrointestinal symptoms may also be first and prominent in afebrile patients.

Comparing mild and severe cases, we found duration from symptoms' onset to medication, PLT count, NEUT%, WBC count, D-Dimer, FDP, APACHE-2 score and multiple organ dysfunction might reveal severity of disease, which might be tested in future prospective studies. Unlike the most common sequelae of neurological involvement caused by Rocky Mountain spotted fever,[26] JSF caused arrhythmias in three severe patients, which has not been previously reported. The combination therapy of DO and steroid hormones is workable and quinolones can be added if necessary.

Although our study has limitations, ie, the results were based on a small quantity of cases and the only methods depended on mNGS, a sample with relatively balanced population in mild and severe groups and a population with almost the same underlying condition enabled us to illustrate the different courses, and provide some relevant factors regarding the severity of disease.

We believe that these results will contribute to better understanding of severe *R.japonica* infection. Definitive treatment should be instituted on the basis of clinical and epidemiological clues as early as possible to avoid severe disease and poor outcome.

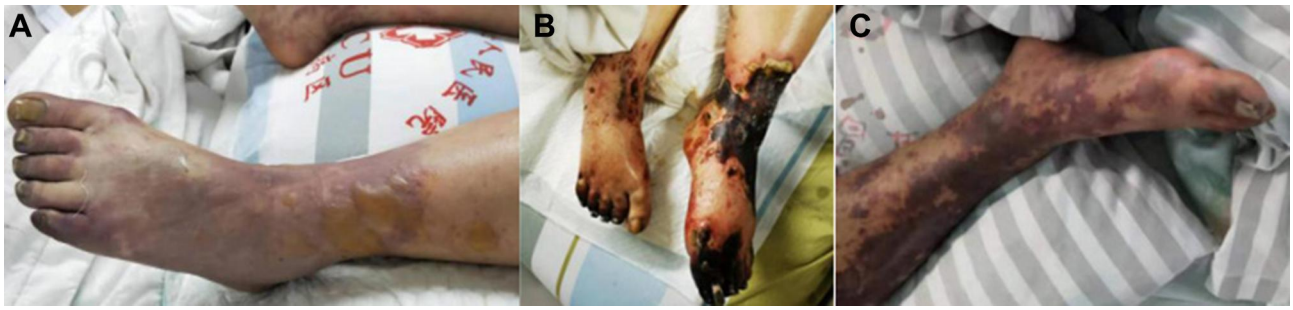

Figure 2 Cutaneous circumscribed ecchymosis and formation of bullae in Patient No.1 (**A**); gangrene in both lower extremities in Patient No.1 (**B**); extravasation of blood in the center of petechial lesions and enlargement of ecchymosis in Patient No.3 (**C**).

Consent Statement

Written informed consent was provided by all patients to allow the case details and any accompanying images to be published.

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Disclosure

Siyu Gao and Lingfeng Li are co-first authors for this study. The authors report no conflicts of interest in this work.

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