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Original Article

Characteristics of scrub typhus, murine typhus, and Q fever among elderly patients: Prolonged prothrombin time as a predictor for severity

Ko Chang [a,d,g,i], Nan-Yao Lee [b,c], Wen-Chien Ko [b,c], Wei-Ru Lin [g,i], Yen-Hsu Chen [d,e,f,g,**], Jih-Jin Tsai [d,g,i], Tun-Chieh Chen [d,g], Chun-Yu Lin [d,g], Ya-Ting Chang [a,g], Po-Liang Lu [d,g,h,*]

[a] *Department of Internal Medicine, Kaohsiung Municipal Siao-Kang Hospital, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan*
[b] *National Cheng Kung University Medical College and Hospital, Tainan, Taiwan*
[c] *Department of Internal Medicine and Center of Infection Control, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan*
[d] *School of Medicine, Kaohsiung Medical University, Taiwan*
[e] *Graduate Institute of Medicine and Sepsis Research Center, College of Medicine, Kaohsiung Medical University, Taiwan*
[f] *Department of Biological Science and Technology, College of Biological Science and Technology, National Chiao Tung University, HsinChu, Taiwan*
[g] *Division of Infectious Disease, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[h] *Department of Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[i] *Tropical Medicine Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*

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KEYWORDS
Elderly;
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Abstract *Background/purpose:* The clinical manifestations of scrub typhus, murine typhus and acute Q fever in the elderly are not clear.
Methods: We conducted a retrospective study to identify the characteristics of the elderly aged ≥65 years with a comparison group aged 18–64 years among patients with scrub typhus,

* Corresponding author. Department of Internal Medicine, Kaohsiung Medical University Hospital, #100 Tzyou 1st Road, Kaohsiung, Taiwan.
** Corresponding author. Department of Internal Medicine, Kaohsiung Medical University Hospital, #100 Tzyou 1st Road, Kaohsiung, Taiwan.
E-mail addresses: infchen@gmail.com (Y.-H. Chen), d830166@gmail.com (P.-L. Lu).

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Murine typhus;
Complications

murine typhus, or acute Q fever who were serologically confirmed at three hospitals in Taiwan during 2002—2011.
Results: Among 441 cases, including 187 cases of scrub typhus, 166 acute Q fever, and 88 murine typhus, 68 (15.4%) cases were elderly patients. The elderly had a higher severe complication rate (10.3% *vs.* 3.5%, $p = 0.022$), but did not have a significantly higher mortality rate (1.47% *vs.* 0.54%, $p = 0.396$). Compared with those without severe complications, we found the elderly ($p = 0.022$), dyspnea ($p = 0.006$), less relative bradycardia ($p = 0.004$), less febrile illness ($p = 0.004$), prolonged prothrombin time (PT) ($p = 0.002$), higher levels of initial C-reactive protein ($p = 0.039$), blood leukocyte counts ($p = 0.01$), and lower platelet counts ($p = 0.012$) are significantly associated with severe complications. Only prolonged prothrombin time was associated with severe complications in multivariate analysis ($p = 0.018$, CI 95% 0.01—0.66). Among clinical symptoms and laboratory data, multivariate analysis revealed chills was less frequently occurred in the elderly ($p = 0.012$, 95% confidence interval [CI]: 1.33—9.99).
Conclusion: The elderly cases with scrub typhus, murine typhus, or acute Q fever would be more likely to have severe complications, for which prothrombin time prolongation is an important predictor for severe complications.

Introduction

Scrub typhus, murine typhus and Q fever (QSM) are common infections in tropical areas worldwide and often present as an acute febrile illness of unclear etiology.[1,2] Scrub typhus is a mite-borne bacterial infection of humans caused by *Orientia tsutsugamushi* that results in vasculitis of organ systems.[1] Murine typhus, caused by *Rickettsia typhi*, is a zoonosis and often presents as acute febrile illness with rash and protean manifestations such as acute hepatitis, pneumonia, and meningitis. The rat flea, *Xenopsylla cheopis*, is the main vector, and rodents and arthropods are natural reservoirs.[3] Q fever, caused by *Coxiella burnetii*, is a zoonosis worldwide.[2] Acute Q fever is more common than chronic infection, presenting with acute febrile illness with acute hepatitis or pneumonia.[4] Scrub typhus, murine typhus and Q fever shared similar clinical presentations at the initial stage of diseases. In Taiwan, these three diseases are the top three common rickettsial and rickettiosis-like diseases. Early differential diagnosis of these diseases is difficult. Usually, the definite diagnosis should have at least a fourfold increase in IgG titers between acute and convalescent sera. It means that the definite diagnosis will be available about two weeks later after admission or first visit. For suspected cases of scrub typhus, murine typhus, and Q fever, doxycycline is empirically prescribed to save lives. Therefore, it would be reasonable to put the three disease entities together with further analysis. However, the characteristics of these three diseases among elderly patients, whose immune status is different from young patients, are not very clear. In the study, we aimed to investigate the clinical and laboratory characteristics of QSM in elderly patients. We also analyzed the potential predictors on severe complications of QSM among elder patients.

Materials and methods

We included cases of scrub typhus, murine typhus, and Q fever from three hospitals in southern Taiwan, including two medical centers and one regional hospital, between 2002 and 2011. Any elderly patient whose age was more than 65 years was referred to one of these.[5] Cases aged less than 18 years were excluded. The characteristics of elderly (age ≧65 years) and non-elderly adults (age, 18—64 years) with scrub typhus, murine typhus, and Q fever (QSM) were retrospectively analyzed.

Ethics statement: This study was approved by the Institute Ethics Committee of Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (KMUH-IRB-970216) and all data analyzed was anonymized.

We evaluated the following clinical presentations, and laboratory findings: fever, chills, headache, dizziness, joint pain, diarrhea, cough, sputum, dyspnea, rhinorrhea, nausea, abdominal pain, skin rash, lymphadenopathy, eschar, initial aspartate aminotransferase (AST), initial alanine aminotransferase (ALT), alkaline-phosphatase, γ-glutamyl transpeptidase, lactic acid dehydrogenase, serum creatinine, initial C-reactive protein, initial white blood cells, initial hemoglobin, and platelets in the blood. We also observed severe complications in these patients. Severe complications of scrub typhus, murine typhus, Q fever were defined if the following conditions were shown: (1) meningitis, (2) acute respiratory distress syndrome (ARDS), (3) acute renal failure, (4) disseminated intravascular coagulopathy (DIC), (5) shock, (6) pancreatitis and (7) death.[6]

All the above three diseases were confirmed by the Centers for Disease Control, Taiwan. The diagnosis of Q fever was made based on the presence of fever and a compatible serologic profile, which included at least a fourfold increase in phase II IgG titers comparing the acute and convalescent sera or the presence of a significant titer of phase II IgM (≥1:50) by indirect immunofluorescence assay.[7] Scrub typhus was diagnosed from patients' blood samples based on the evidence by the method of polymerase chain reaction (PCR), or the serology of indirect microimmunofluorescent (IFA) for *O. tsutsugamushi*. Diagnostic IFA must meet the following criteria: the total antibody titer for Karp, Kato, and Gilliam for strains of *O. tsutsugamushi* must have a fourfold or greater rise in paired

positive serum samples or antibody titer for IgM $\geq$1:80.[8,9] The diagnosis of murine typhus was based on the presence of compatible symptoms and signs, usually a febrile illness, and a significant immunofluorescence antibody assay (IFA) profile against *R. typhi*, which showed at least a four-fold increase in IgG titers between acute and convalescent sera, or the presence of IgM titer $\geq$1:80.[9]

Relative bradycardia is defined as an increase in the heart rate by $<$10 beats/min/°C increase in temperature, in the absence of cardiac arrhythmia, pacemaker, or beta-blocker usage.[10,11] Hyperbilirubinemia was defined as serum levels of total bilirubin $\geq$1.4 g/dL. Prothrombin time (PT) $>$ 12 s signifies PT prolongation. Activated partial thromboplastin time (aPTT) $>$ 33 s signifies aPTT prolongation. Defervescence was defined as an axillary body temperature of less than 37.5°C for three consecutive days. The disappearance of constitutional symptoms was regarded as a clinical response to antimicrobial therapy. A patient with a heart rate of less than 110 beats per minute in conjunction with a high fever ($\geq$38.9°C), in the absence of cardiac arrhythmia, pacemaker or beta-blocker agents usage, was considered as having relative bradycardia.[10,11] Acute renal failure was defined by an increase in serum creatinine of at least 0.5 mg/dL if the baseline was less than 2.5 mg/dL, or an increase in serum creatinine by more than 20% if the baseline was more than 2.5 mg/dL, or the need for acute renal replacement therapy.[12] A diagnosis of ARDS was defined by the presence of all of the following criteria: 1) acute onset; 2) chest radiography showing bilateral lung infiltrates; 3) severe hypoxia with a partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) $\leq$200 mmHg, regardless of the level of positive end-expiratory pressure; and 4) no clinical evidence of increased left atrial pressure with a pulmonary arterial wedge pressure $\leq$18 mmHg.[13] Acute aseptic meningitis was diagnosed in cases with headache and lymphocytic pleocytosis or increased protein levels in cerebrospinal fluid (CSF) without bacterial or viral growth. Shock was defined by a systolic blood pressure less than 90 mmHg (or a fall in systolic blood pressure of $>$40 mmHg). Pancreatitis was defined as clinical features (abdominal pain and vomiting) together with elevation of plasma concentrations of pancreatic enzymes.[14] The DIC was defined as 1) thrombocytopenia, 2) prolongation of PT and aPTT, 3) a low fibrinogen concentration, and 4) increased levels of fibrin degradation products.[15]

Statistical analyses were performed using Chi-square test or Fisher's exact test for categorical variables and the *t*-test for continuous variables. Clinical and laboratory findings were compared using the Statistical Package for Social Sciences (SPSS) Version 12.0 for Windows (Chicago, IL). After finding the selected variables by single variate analysis, we used logistic regression model for multivariate analysis.

Results

The clinical and laboratory features of 441 cases were retrospectively analyzed: 166 with Q fever, 187 patients with scrub typhus, and 88 with murine typhus (QSM) in the period 2002—2011 at three hospitals. Sixty-eight were elderly and 373 were non-elderly adults. Compared with the non-elderly adults, elderly individuals had lower rates of prolongation of activated partial thromboplastin time ($p = 0.007$), fever ($p < 0.0001$), chills ($p = 0.004$), headache ($p = 0.003$), joint pain ($p = 0.022$), diarrhea ($p = 0.029$), cough ($p = 0.020$), and lymphadenopathy ($p = 0.04$); higher incidences of dyspnea ($p = 0.004$), and initial abnormal C-reactive protein ($p = 0.034$) (Table 1). Among clinical manifestations and laboratory data, multivariate analysis showed chills were less common in elderly patients ($p = 0.012$, 95% C.I: 1.33—9.99) and were independently associated with the elderly. The elderly had a significantly higher severe complication rate (10.3% *vs.* 3.49%, $p = 0.022$) but without a significantly higher mortality rate (1.47% *vs.* 0.54%, $p = 0.396$). Among 20 cases with severe complications (Table 3), only one Q fever case (0.6%) had ARF. Five cases (5.7%) of murine typhus development of severe illnesses including meningitis (3 patients, 60%), ARDS (2, 40%), ARF (5, 100%) and death (1, 20%). In scrub typhus group, 14 cases (7.5%) developed severe complications that included meningitis (3 patients, 21.4%), ARDS (5, 35.7%), ARF (5, 35.7%), DIC (5, 35.7%), septic shock (3, 21.4%), pancreatitis (3, 21.4%) and death (2, 14.3%).

In the Q fever group, the elderly group had a significantly higher level of CRP (128 *vs.* 84, $p = 0.005$) (Table 4). In the murine typhus group (Table 5), the elderly had lower rates of prolongation of activated partial thromboplastin time ($p = 0.012$), fever ($p = 0.009$), chills ($p = 0.018$), headache ($p = 0.012$), and cough ($p = 0.032$), but a higher rate of dyspnea (23.5% *vs.* 3.2%, $p = 0.018$). For scrub typhus cases (Table 6), the elderly had a higher level of CRP (122.8 *vs.* 82.1, $p = 0.041$), were less male (40% *vs.* 62%, $p = 0.04$), and had lower incidence of lymphadenopathy (12% *vs.* 33%, $p = 0.033$). Among the three diseases, a higher rate of severe complications (21% *vs.* 3%, $p = 0.018$) was only observed in the elderly cases with murine typhus (Table 5).

In addition, we divided cases into two groups: cases with severe complications (20 cases) and the group without severe complications (421 cases) to elucidate the characteristics of cases with severe complications (Table 2). In the severe complications group (Table 2), we found they had higher rates of being elderly ($p = 0.022$), lower rates of relative bradycardia ($p = 0.004$) and fever ($p = 0.004$), higher rates of dyspnea ($p = 0.006$), prolonged prothrombin time (PT) ($p = 0.002$), and a higher level of initial CRP ($p = 0.039$), a higher level of initial white blood cell ($p = 0.01$), and a lower level of initial platelets ($p = 0.012$). In multivariate analysis, only prolonged prothrombin time ($p = 0.018$, C.I 95% 0.013—0.662) was significantly associated with severe complications. Cases with severe complications had a longer hospitalization duration ($p = 0.023$) and had a higher mortality ($p < 0.0001$) (Table 2).

Discussion

For the three tropical diseases, the elderly had less fever and constitutional symptoms (such as chills, headache, and joint pain). The elderly had a significantly higher severe complication rate. A higher mortality trend was also

Table 1 Characteristics of 68 elderly and 373 non-elderly adult cases of Q fever, scrub typhus, murine typhus

Characteristics	Case No./Total case No. (%) or Mean ± standard deviation (No. of case with data)		*p* Values
	Elderly (n = 68)	Non-elderly (n = 373)	
Male	44/68 (64.7)	274/373 (73.5)	0.139
Age, year	71.7 ± 7.05 (68)	44.4 ± 12.6 (373)	P < 0.0001
Initial clinical presentations			
Fever	62/68 (91.18)	368/370 (99.5)	P < 0.0001[a]
Fever before admission, days	6 ± 5.21 (58)	6.95 ± 4.97 (346)	0.180
Chills	29/61 (47.5)	225/338 (66.6)	0.004
Headache	23/62 (37.1)	194/339 (57.2)	0.003
Joint pain	2/60 (3.3)	46/333 (13.8)	0.022
Diarrhea	3/60 (7.01)	52/333 (15.6)	0.029
Cough	12/62 (19.4)	116/338 (34.3)	0.020
Dyspnea	8/61 (13.1)	11/332 (3.3)	0.004[a]
Lymphadenopathy	4/55 (7.27)	56/302 (18.5)	0.04
Relative bradycardia	28/59 (48)	141/307 (46)	0.829
Initial laboratory data			
aPTT prolongation	23/38 (61)	139/172 (81)	0.007
PT prolongation	9/37 (24)	24/158 (15)	0.182
AST, U/L	121.85 ± 162.20 (62)	165.9 ± 408.8 (332)	0.404
ALT, U/L	122.95 ± 143.99 (62)	162.2 ± 304.3 (333)	0.318
Alkaline-phosphatase, U/L	237.93 ± 329.60 (43)	215.4 ± 171.9 (215)	0.517
LDH, U/L	701.6 ± 1333.3 (25)	584.6 ± 714.9 (149)	0.515
Serum creatinine, μmol/L	1.63 ± 1.84 (60)	1.38 ± 3.37 (312)	0.578
CRP, mg/L	109.47 ± 79.59 (52)	84.24 ± 78.04 (297)	0.034
Blood WBC, $\times 10^9$/L	7.24 ± 3.12 (67)	7.00 ± 3.20 (367)	0.59
Blood hemoglobin, g/L	13.48 ± 4.13 (67)	13.93 ± 3.77 (366)	0.377
Blood platelets, $\times 10^9$/L	134.09 ± 69.1 (67)	140.6 ± 71.2 (362)	0.489
Outcome			
Mortality[b]	1/68 (1.47)	2/373 (0.54)	0.396[a]
Severe complications	7/68 (10.3)	13/373 (3.49)	0.022[a]
Duration of hospitalization, days	8.45 ± 5.85 (47)	6.90 ± 4.85 (266)	0.051
Defervescence after effective therapy, days	4.6 ± 4.15 (57)	4.02 ± 5.16 (333)	0.421
Total duration of fever, days	10.2 ± 6.5 (59)	10.8 ± 7.5 (341)	0.552

PT = prothrombin time; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = Lactic acid dehydrogenase; CRP = C-reactive protein; WBC = white blood cells.

[a] Fisher's exact test.

[b] Murine typhus 1 case (70 years old), scrub typhus 2 cases (60 years old and 37 years old).

observed but without statistical significance in the study of 441 cases. In general, the aging-adherent co-morbidities and waning immunity posed a substantial risk for fatality in elderly patients with active infection.[16] The cause of high mortality of the elderly infected was possibly because of more comorbidities in this population.[17,18] Besides, older age could be a factor leading to delayed diagnosis of scrub typhus.[18] Our findings on the three tropical diseases cases revealed a similar poor prognosis when the elderly became infected.

Taking the age distribution of cases of scrub typhus as an example, 62% cases were 51—75 years old, and 14% cases were ≧ 76 years old and the oldest case was 91 years old in a Japan study [1]. In this study, conducted in southern Taiwan, 52.4% (98/187) cases were 51—75 years of age, and 4.3% (8/187) cases were ≧76 years old and the oldest cases was 81 years old. In an eastern Taiwan study,[19] 50- to 69-year-olds reached 47.4%, and 60- to 69-year-olds reached 23.9%. All the above revealed a significant proportion of scrub typhus cases were elderly. It may be due to the fact that most young people move to urban areas for work and the elderly are left to work as farmers on their own land. It is therefore necessary to understand the clinical manifestations of the elderly.

Regarding the severe complications, we found the elderly had lower rates of relative bradycardia and fever, higher rates of dyspnea with worse laboratory value (prolonged prothrombin time, a higher level of initial CRP, a higher level of initial white blood cell, and a lower level of initial platelets). As a result, cases with severe complications had a longer hospitalization duration and a higher mortality. Only one 70-year-old with murine typhus and two cases of scrub typhus (60 y/o, 37 y/o) developed ARDS and died. The overall mortality rate of scrub typhus, murine typhus and Q fever was 0.68% in this study. A higher mortality trend of the elderly was found, but without statistical

Table 2 Comparison of the characteristics of cases with and without severe complications

Characteristics	Case No./Total case No. (%) or Mean ± standard deviation (No. of case with data)		*p* Values
	With severe complications n = 20 (%)	Without severe complications n = 421 (%)	
Male	12/20 (60)	306/421 (72.7)	0.217
Age, year	56.2 ± 19.2 (20)	48.3 ± 15.2 (421)	0.027
Elderly patients	7/20 (35)	61/421 (14.5)	0.022*
Initial clinical presentation			
Fever	17/20 (85)	413/418 (98.8)	0.004*
Fever before admission, days	7.35 ± 3.94 (17)	6.80 ± 5.05 (387)	0.653
Cough	10/19 (52)	118/381 (30.9)	0.074
Dyspnea	4/17 (23.5)	15/376 (3.9)	0.006
Relative bradycardia	2/17 (11.8)	167/349 (47.9)	0.004
Initial laboratory data			
PT prolongation	6/10 (60)	27/185 (14.6)	0.002
aPTT prolongation	10/10 (100)	152/200 (76)	0.070
Maximal AST, U/L	672.2 ± 1663.5 (20)	155.6 ± 188.6 (400)	0.18
Maximal ALT, U/L	476.3 ± 1157.9 (20)	159.0 ± 157.2 (401)	0.236
Serum creatinine, μmol/L	2.39 ± 2.50 (18)	1.37 ± 3.20 (354)	0.181
CRP, mg/L	129.1 ± 88.9 (15)	86.3 ± 77.8 (334)	0.039
Blood white blood cell, $\times 10^9$/L	10.1 ± 5.00 (20)	6.90 ± 3.00 (414)	0.01
Blood hemoglobin, g/L	12.7 ± 2.82 (20)	13.9 ± 3.86 (413)	0.151
Blood platelets, $\times 10^9$/L	100.6 ± 79.1 (20)	141.5 ± 69.9 (409)	0.012
Outcome			
Duration of hospitalization, days	13.6 ± 9.90 (14)	6.82 ± 4.49 (299)	0.023
Defervescence after effective therapy, days	4.60 ± 4.69 (15)	4.08 ± 5.05 (375)	0.695
Total duration of fever, days	11.65 ± 6.33 (16)	10.7 ± 7.39 (384)	0.606
Mortality	3/20 (15)	0 (0)	P < 0.0001*

* Fisher's exact test.

significance, which might be due to the small case number. In previous studies, the mortality rates of scrub typhus cases were 1.5—3%, but the mortality rate for the scrub typhus patients with ARDS was 25% in Taiwan.[20—22] Watt G et al. reported the case fatality rate of 15%—30% in scrub typhus patients from Thailand.[21] The mortality of murine typhus was 1.2% in Taiwan.[23] Though a recent study of murine typhus in returned travelers and child murine typhus showed no deaths,[24,25] the mortality rate was 0.86% in a large study of murine typhus.[26] With regard to the mortality rate of Q fever, the limited data of Q fever in Taiwan has revealed no mortality,[27] but the largest Q fever study showed a mortality rate of 2.42% in the world.[4] In short, the overall mortality of these three tropical diseases in our study was lower than most previous studies. It could be attributed to the physicians' alertness to these diseases and the easy access of medical help in Taiwan.

Delayed discharge was mainly associated with cognitive impairment, and functional dependence in elderly hospitalized medical patients[28] and high C-reactive protein level independently predicted prolonged hospital length of stay in hospitalized elderly patients found in previous studies.[29] In our study, we found the elderly individuals had higher level of initial CRP, but the hospitalization period was not significantly prolonged. A careful observation of the elderly cases with these tropical diseases is required for the higher

Table 3 Severe complications among the 441 cases of Scrub typhus, murine typhus and Q fever

Severe complications	Cases/Total No. (%)	Q fever	Murine typhus	Scrub typhus
	20/441	N = 1	N = 5	N = 14
Meningitis	6 (1.36%)	0	3 (60%)	3 (21.4%)
ARDS	7 (1.598%)	0	2 (40%)	5 (35.7%)
Acute renal failure	11 (2.51%)	1	5 (100%)	5 (35.7%)
DIC	5 (1.13%)	0	0	5 (35.7%)
Septic shock	3 (0.68%)	0	0	3 (21.4%)
Pancreatitis	3 (0.68%)	0	0	3 (21.4%)
Death	3 (0.68%)	0	1 (20%)	2 (14.3%)

Table 4 Comparison of the characteristics of 24 elderly and 142 non-elderly Q fever cases

Characteristics	Case No./Total case No. (%) or Mean ± standard deviation (No. of case with data)		*p* Values
	Elderly (n = 24)	Non-elderly (n = 142)	
Male	21/24 (87.5)	126/142 (88.7)	0.741
Fever	22/24 (91.7)	139/141 (98.6)	0.101
Fever before admission, days	6.33 ± 5.18 (18)	7.24 ± 5.46 (125)	0.508
Chills	10/19 (52.6)	82/110 (74.6)	0.051
Headache	7/19 (36.8)	64/110 (58.2)	0.084
Initial laboratory data			
PT prolongation	8/13 (61.5)	52/65 (80)	0.164
aPTT prolongation	2/13 (15.4)	7/51 (13.7)	1.0
AST, U/L	150.8 ± 265.6 (20)	126.0 ± 104.1 (116)	0.463
ALT, U/L	148.5 ± 200.6 (20)	147.0 ± 122.3 (116)	0.963
Alkaline-phosphatase, U/L	273.2 ± 504.4 (17)	228.3 ± 176.2 (88)	0.722
LDH, U/L	375.3 ± 237.1 (19)	401.9 ± 230.3 (45)	0.755
Serum creatinine, μmol/L	1.45 ± 1.65 (23)	1.1 ± 0.77 (118)	0.12
CRP, mg/L	128.2 ± 76.4 (16)	84.0 ± 53.9 (107)	0.005
Blood white blood cell, $\times 10^9$/L	5.97 ± 2.73 (23)	6.85 ± 2.75 (139)	0.158
Blood hemoglobin, g/L	13.65 ± 1.49 (23)	14.3 ± 4.99 (138)	0.511
Blood platelets, $\times 10^9$/L	146.6 ± 74.1 (23)	160.3 ± 69.7 (136)	0.389
Outcome			
Duration of hospitalization, days	8.54 ± 4.96 (13)	7.78 ± 5.50 (73)	0.644
Defervescence after effective therapy, days	5.85 ± 4.33 (20)	5.69 ± 6.70 (124)	0.916
Total duration of fever, days	11.5 ± 6.93 (21)	12.8 ± 9.84 (26)	0.887

Table 5 Comparison of the characteristics of 9 elderly and 69 non-elderly murine typhus cases

Characteristics	Case No./Total case No. (%) or Mean ± standard deviation (No. of case with data)		*p* Values
	Elderly (n = 19)	Non-elderly (n = 69)	
Male	13/19 (68)	48/69 (70)	0.924
Initial clinical presentations			
Fever	16/19 (84.2)	67/67 (100)	0.009
Fever before admission, days	5.35 ± 7.2 (17)	6.60 ± 4.86 (62)	0.405
Chills	6/17 (35.2)	44/66 (66.6)	0.018
Headache	5/18 (27.7)	41/67 (61.1)	0.012
Cough	1/18 (5.5)	21/66 (31.8)	0.032
Dyspnea	4/17 (23.5)	2/61 (3.2)	0.018
Initial laboratory data			
PT prolongation	5/13 (38)	35/44 (80)	0.012
aPTT prolongation	5/13 (38)	11/42 (26)	0.489
AST, U/L	79.8 ± 50.9 (17)	125.3 ± 96.0 (63)	0.064
ALT, U/L	119.6 ± 145.6 (17)	119.6 ± 86.3 (63)	0.999
Alkaline-phosphatase, U/L	222.6 ± 135.5 (15)	231.9 ± 167.1 (40)	0.847
LDH, U/L	1137.4 ± 2207.3 (9)	733.5 ± 835.6 (33)	0.604
Serum creatinine, μmol/L	2.24 ± 2.57 (19)	1.06 ± 0.34 (58)	0.06
CRP, mg/L	74.04 ± 72.5 (16)	90.0 ± 101.8 (63)	0.558
Blood WBC, $\times 10^9$/L	8.29 ± 3.17 (19)	7.51 ± 4.10 (68)	0.447
Blood hemoglobin, g/L	13.09 ± 2.24 (19)	13.6 ± 1.40 (68)	0.340
Blood platelets, $\times 10^9$/L	131.2 ± 71.2 (19)	135.1 ± 67.9 (68)	0.827
Outcome			
Duration of hospitalization, days	10.8 ± 8.34 (14)	7.49 ± 3.81 (56)	0.162
Defervescence after effective therapy, days	5.44 ± 4.49 (16)	3.89 ± 3.50 (62)	0.141
Total duration of fever, days	10.5 ± 8.5 (17)	9.9 ± 5.11 (67)	0.722

Table 6 Comparison of the characteristics of 25 elderly and 162 non-elderly scrub typhus cases

Characteristics	Case No./Total case No. (%) or Mean ± standard deviation (No. of case with data)		*p* Values
	Elderly (n = 25)	Non-elderly (n = 162)	
Male	10/25 (40)	100/162 (62.0)	0.04
Initial clinical presentations			
Fever	24/25 (96)	162/162 (100)	0.133*
Fever before admission, days	6.22 ± 3.41 (23)	6.87 ± 4.6 (159)	0.516
Chills	13/25 (52)	990/162 (61)	0.387
Headache	11/25 (44)	89/162 (55)	0.307
Lymphadenopathy	3/25 (12)	53/160 (33)	0.033
Initial laboratory data			
PT prolongation	10/12 (83.3)	53/63 (84)	1.0*
aPTT prolongation	2/11 (18.1)	6/65 (9.2)	0.32
AST, U/L	127.3 ± 85.5 (25)	212.8 ± 587.8 (153)	0.471
ALT, U/L	104.7 ± 76.2 (25)	191.6 ± 430.0 (154)	0.316
Alkaline-phosphatase, U/L	204.4 ± 140.9 (11)	195.0 ± 169.4 (87)	0.863
LDH, U/L	560.7 ± 267.5 (7)	631.1 ± 833.0 (71)	0.825
Serum creatinine, μmol/L	1.22 ± 0.805 (18)	1.76 ± 5.04 (136)	0.651
CRP, mg/L	122.8 ± 81.9 (20)	82.1 ± 82.1 (127)	0.041
Blood WBC, $\times 10^9$/L	7.6 ± 3.1 (25)	6.9 ± 3.1 (160)	0.323
Blood hemoglobin, g/L	13.6 ± 6.4 (25)	13.7 ± 3.2 (160)	0.914
Blood platelets, $\times 10^9$/L	124.8 ± 63.7 (25)	126.1 ± 70.4 (158)	0.931
Outcome			
Duration of hospitalization, days	6.75 ± 3.57 (20)	6.20 ± 4.79 (137)	0.625
Defervescence after effective therapy, days	2.76 ± 3.10 (21)	2.66 ± 3.67 (147)	0.904
Total duration of fever, days	8.57 ± 3.25 (21)	9.21 ± 5.16 (149)	0.579

* Fisher's exact test.

chances of severe complications. A significantly higher rate of severe complications was only observed in the elderly cases with murine typhus among these three diseases. However, the exact mechanism for this cannot be elucidated in the study.

Concerning complications of these diseases, the complications in Q fever were mainly jaundice and pneumonia,[27] and the largest Q fever cohort study showed case fatality was due to ARDS and heart failure.[4] Murine typhus could develop into severe illness, such as ARDS, aseptic meningitis, and ARF.[23] Scrub typhus might be complicated with pneumonia, hyperbilirubinemia, ARDS, DIC and ARF.[20,22] For scrub typhus, severe complications have been found in cases of age ≥60 years, the absence of eschar, WBC counts >10,000/mm^3 and albumin ≤3.0 g/dL[22] and risk factors leading to fatal outcome including absence of eschar, event of intensive care unit admission and higher APACHE II score.[30] In our analysis, PT prolongation was the only independent factor significantly associated with the severe complications of QSM. The prolonged PT could be a warning sign for severe complications among these elder patients.

The limitations of this study are as follows. First, this is a retrospective study, so some data about underlying diseases were missing. Second, the case number for analysis of the cause of death is small.

In summary, we found that the elderly had a significantly higher rate of severe complications. Prolonged prothrombin time is an independent prediction factor for severe complications for these diseases among elderly patients.

Conflicts of interest

The authors declare that they have no conflict of interest.

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