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Risk factors associated with severe scrub typhus in Shandong, northern China

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SUMMARY

Objectives: The aim of this study was to identify risk factors associated with severe scrub typhus, in order to provide a reference for clinical decision-making.
Methods: A case–control study was conducted of scrub typhus patients who presented at local hospitals between 2010 and 2013. In total, 46 patients with severe scrub typhus complications (cases) and 194 without severe complications (controls) were included.
Results: There were significant differences in the duration of illness before effective antibiotic therapy, lymphadenopathy, rash, blood platelet count, white blood cell (WBC) count, percentage neutrophils, and percentage lymphocytes between the case and control groups. Multivariate analysis demonstrated that the following four factors were significantly associated with the severe complications of scrub typhus: (1) duration of illness before effective antibiotic therapy (odds ratio (OR) 2.287, 95% confidence interval (CI) 1.096–4.770); (2) the presence of a rash (OR 3.694, 95% CI 1.300–10.495); (3) lymphadenopathy (OR 2.438, 95% CI 1.090–5.458); (4) blood platelet count $<100 \times 10^9$/l (OR 2.226, 95% CI 1.002–4.946).
Conclusions: This study indicates that improved diagnosis and timely treatment are important factors for the prevention of severe scrub typhus. When scrub typhus patients present with a rash, lymphadenopathy, or blood platelet count $<100 \times 10^9$/l, clinicians should be alert to the appearance of severe complications.

1. Introduction

Scrub typhus, an acute febrile infectious disease caused by *Orientia tsutsugamushi*, is widely endemic in the Asia Pacific regions, with an estimated one million cases annually.[1] It is transmitted to humans by the bite of an infected larval mite. Scrub typhus is an infection that may lead to generalized vasculitis, which may cause multiorgan dysfunction syndrome.[2] In China, scrub typhus was first reported in Guangzhou in 1948, while the first outbreak occurred in Shandong in 1986.[3,4] Previous studies have revealed that the incidence of scrub typhus has increased year on year in a nationwide region of China in recent years.[4,5] According to the China information system for disease control and prevention, there were 246, 452, 616, and 628 scrub typhus cases in Shandong Province in the years 2010 to 2013, with one death reported in 2010. Antibiotics of the tetracycline class are effective in preventing fatal complications resulting from scrub typhus if the disease is diagnosed in a timely manner. However, owing to the fact that scrub typhus is a new emerging infectious disease in northern China, the neglect of scrub typhus was unavoidable in most epidemic regions. Cases of misdiagnosis were reported quite frequently.[6,7]

Severe complications such as encephalitis, pneumonia, myocarditis, pericarditis, acute renal failure, acute hepatic failure, acute hearing loss, and acute respiratory distress syndrome (ARDS) have been reported in many cases.[8–10] Some of these complications may lead to death.[11,12] As cases of death have been reported in recent years, it would be of great value to clarify the factors related to severe scrub typhus.[13] However, few studies have been done in China.[5] Thus, we conducted this study to identify the predictors of severe scrub typhus.

2. Materials and methods

2.1. Ethical statement

The study was conducted after obtaining the approval of the Ethics Committee on Preventive Medicine of Shandong University.

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Informed oral consent was obtained from all of the adult participants and from the legal guardians of juveniles.

2.2. Patients and data sources

Considering the incidences and case distribution in different areas of Shandong, stratified cluster sampling was applied to select the areas for investigation. Nine county-level districts were selected randomly for this study (Xintai, Jimo, Jiaonan, Laicheng, Gangcheng, Yiyuan, Yinan, Donggang, and Wendeng). Patients with clinically suspected scrub typhus presenting to hospitals were identified using the diagnostic criteria described below. A structured questionnaire was used to record patient demographic information, hematologic laboratory tests, clinical manifestations and complications, and the outcome of the patients from January 1, 2010 to December 31, 2013. The information listed above was reviewed retrospectively.

2.3. Case definition

Patients who had three or more of the following items could be diagnosed as a case of scrub typhus: (1) a history of field exposure 1–3 weeks before symptom onset, (2) symptoms including high fever, lymphadenopathy, skin rash, splenomegaly, hepatomegaly, or multiorgan dysfunction, (3) typical cutaneous lesions, such as eschars or ulcers, (4) rapid defervescence with appropriate antibiotics, and (5) Weil–Felix OX-K agglutination titer $\geq$1:80. Patients were confirmed by nested PCR test targeting the 56-kDa gene of *O. tsutsugamushi* or by rapid immunochromatographic immunoassay with a positive result for IgM or IgG.[14]

Scrub typhus patients with one or more of the following manifestations were defined as severe scrub typhus cases: bronchopneumonia, meningoencephalitis, toxic hepatitis, acute nephritis or renal failure, acute gastritis, gastrointestinal bleeding, myocarditis, shock, and death. Controls in this study were scrub typhus patients without the severe complications listed above.

2.4. Nested PCR

DNA was extracted from the patient blood samples, and coding sequences targeting part of the 56-kDa gene of *O. tsutsugamushi* were amplified using nested PCR. The following two sets of primers were used in this study: outer primers, 34 (5′-TCAAGCTTATTGC-TAGTGCAATGTCTGC-3′) and 55 (5′-AGGGATCCCTGCTGCTGTGC TTGCTGCG-3′), and inner primers, 10 (5′-GATCAAGCTTCCTCAGCC-TACTATAATGCC-3′) and 11 (5′-CTAGGGATCCCGACAGATGCAC-TATTAGGC-3′).[15] The expected length of the product was 481–507 bp.

The initial round of PCR was started with a 5 min denaturation at 94 °C, followed by 30 cycles of 95 °C for 30 s, 57 °C for 2 min, and 70 °C for 2 min, and then a final extension at 72 °C for 10 min. Three microliters of the product was used as the template for the second round of PCR, which used the same reaction conditions as the initial one. The nested PCR products were visualized with an ultraviolet transilluminator after agarose gel electrophoresis and staining with ethidium bromide.

2.5. Statistical analysis

Epidata 3.1 was used to set up a database (Jens M. Lauritsen, Odense, Syddanmark, Denmark), and the accuracy was ensured with double data entry and logistic consistency checking. SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous data were expressed as the mean $\pm$ standard deviation (SD), and the unpaired Student *t*-test was used to compare the means between the two study groups. Categorical data were expressed as the frequency or proportion, and the statistical significance of the difference in proportions between the two groups was determined by Chi-square test or Fisher's exact test. Two-sided *p*-values of <0.05 were considered statistically significant. The associations between markers and severe scrub typhus were determined by Chi-square test and univariate logistic regression analysis. Input variables for the multivariate analysis were selected from significant variables derived from the univariate analysis. Multivariate analysis was then performed with the independent variables that were significantly associated with severe scrub typhus in the univariate analysis. The linearity of continuous variables, such as age and days of duration of illness before effective antibiotic therapy, were dichotomized with the mean as the cut-off point. Other continuous laboratory variables, such as the platelet count, white blood cell (WBC) count, percentage of neutrophils, percentage of lymphocytes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and direct bilirubin, were dichotomized with the point at the normal range for the laboratory index. The odds ratio (OR) with 95% confidence intervals (95% CI) was presented to examine statistical significance.

3. Results

A total of 317 patients were recruited into this study, among whom 240 met the criteria for scrub typhus infection and had complete questionnaires. Severe scrub typhus such as bronchopneumonia, toxic hepatitis, acute gastritis, myocarditis, pleurisy, meningoencephalitis, heart failure, and emphysema was observed in 46 of the 240 patients (19.2%); these patients formed the case group in this study. The remaining 194 patients without severe scrub typhus formed the control group. Bronchopneumonia and toxic hepatitis were the predominant complications, with percentages of 41.3% and 21.7%, respectively.

Table 1 presents the main characteristics and laboratory findings of the study patients. The mean age of the case group was 57.33 $\pm$ 17.69 years, and that of the control group was 53.35 $\pm$ 19.13 years. No significant difference was found in age, gender, AST, ALT, total bilirubin, direct bilirubin, the presence of an eschar, or fever between the two groups. However, there were significant differences in the duration from disease onset to effective antibiotic therapy, the presence of a rash, lymphadenopathy, platelet count, WBC count, percentage of neutrophils, and percentage of lymphocytes between the two groups.

A univariate logistic regression model was fitted to test for significant correlations between the above factors and severe scrub typhus. Table 2 shows the significant factors for severe scrub typhus, which were as follows: (1) duration of illness before effective antibiotic therapy, (2) lymphadenopathy, (3) the presence of a rash, (4) platelet count $<100 \times 10^9$/l, (5) percentage of neutrophils $<$50%, (6) percentage of lymphocytes $>$40%, (7) total bilirubin $>$0.024 mmol/l, and (8) direct bilirubin $>$0.009 mmol/l.

Multivariate unconditional logistic regression was applied to estimate the association between the risk of severe scrub typhus and the eight factors above. The results demonstrated that the following four factors were significantly associated with severe scrub typhus: (1) duration of illness before effective antibiotic therapy (OR 2.287, 95% CI 1.096–4.770, $p = 0.027$), (2) lymphadenopathy (OR 2.438, 95% CI 1.090–5.458, $p = 0.030$), (3) the presence of a rash (OR 3.694, 95% CI 1.300–10.495, $p = 0.014$), and (4) platelet count $<100 \times 10^9$/l (OR 2.226, 95% CI 1.002–4.946, $p = 0.050$). The results are detailed in Table 3.

4. Discussion

Scrub typhus was once considered a traditional tropical disease. However, it has emerged in the temperate zone in northern China

Table 1
Demographic and clinical characteristics of the study subjects

Subject characteristics	Cases ($n=46$)				Controls ($n=194$)			
	Mean	SD	n	%	Mean	SD	n	%
Age, years	57.33	17.69			53.35	19.13		
Gender								
Female			25				90	46.39
Male			21				104	53.61
Time taken to diagnosis, days	1.33	1.86			2.43	3.43		
Duration of illness before effective antibiotic therapy, days[a]	6.17	4.74			4.15	3.67		
Fever			46	100.00			194	100.00
Lymphadenopathy[a]			16	34.78			39	20.10
Rash[a]			40	86.78			127	65.46
Eschar			37	80.43			157	80.93
Platelet count, cells $\times 10^9$/l[a]	130.45	62.49			159.26	67.72		
WBC count, cells $\times 10^9$/l[a]	6.36	2.39			7.07	2.98		
Neutrophil count, %[a]	54.18	19.04			48.95	18.81		
Lymphocyte count, %[a]	32.38	15.30			39.88	17.96		
AST, IU/l	74.19	49.81			83.58	95.72		
ALT, IU/l	93.50	80.72			93.72	96.53		
Total bilirubin, mmol/l	0.012	0.008			0.011	0.005		
Direct bilirubin, mmol/l	0.005	0.006			0.004	0.002		

SD, standard deviation; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a] There was a significant difference between the two groups ($p<0.05$).

Table 2
Unadjusted relative risks of each factor for severe scrub typhus

Factors	Severe scrub typhus ($n=46$)	Non-severe scrub typhus ($n=194$)	p-Value	OR	95% CI
Age, >54 years	27 (58.7%)	109 (56.5%)	0.785	1.095	0.570–2.102
Gender					
Female	25 (54.3%)	90 (46.4%)	0.333	1.376	0.722–2.622
Male	21 (45.7%)	104 (53.6%)	-	1.000	-
Time taken to diagnosis, days	12 (26.1%)	69 (35.6%)	0.671	1.275	0.415–3.991
Duration of illness before effective antibiotic therapy, >4.5 days	30 (65.2%)	85 (43.8%)	0.010	2.404	1.231–4.698
Lymphadenopathy	16 (34.78%)	39 (20.10%)	0.036	2.120	1.052–4.273
Rash	40 (87.0%)	127 (65.5%)	0.007	3.517	1.419–8.717
Eschar	37 (80.4%)	157 (80.9%)	0.939	0.969	0.430–2.182
Platelet count, $<100 \times 10^9$/l	16 (34.8%)	34 (17.9%)	0.014	2.447	1.202–4.983
WBC count, $>10 \times 10^9$/l	5 (10.9%)	33 (17.4%)	0.287	0.580	0.213–1.579
Percentage of neutrophils					
50–70[a]	22 (47.8%)	67 (35.4%)	-	1.000	-
≤49.99	15 (32.6%)	97 (51.3%)	0.042	0.471	0.228–0.974
≥70.01	9 (19.6%)	25 (13.2%)	0.841	1.047	0.667–1.643
Percentage of lymphocytes					
20–40[a]	26 (56.5%)	78 (41.3%)	-	1.000	-
<20	9 (19.60%)	25 (13.2%)	0.864	1.080	0.447–2.608
>40	11 (23.9%)	86 (45.5%)	0.015	0.619	0.422–0.910
AST, >37 IU/l	38 (82.6%)	132 (75.9%)	0.334	1.511	0.654–3.493
ALT, >40 IU/l	35 (76.1%)	130 (74.7%)	0.848	1.077	0.504–2.300
Total bilirubin, >0.024 mmol/l	4 (8.7%)	4 (2.1%)	0.043	4.357	1.047–18.133
Direct bilirubin, >0.009 mmol/l	6 (13.0%)	7 (3.7%)	0.021	3.857	1.230–12.096

OR, odds ratio; CI, confidence interval; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Normal range for neutrophils 50–70%; normal range for lymphocytes 20–40%.

and there has been a rapid increase in cases in Shandong Province over the past two decades. Since scrub typhus is not one of the notifiable infectious diseases in mainland China, it is widely neglected by both physicians and residents in epidemic foci.

Scrub typhus is usually contracted in rural areas, where most of the residents are farmers. Poor sanitary conditions and long-time exposure in the field increase the chances of a farmer being bitten by chigger mites harboring *O. tsutsugamushi*. The first place a farmer will seek medical help is usually the village clinic or a township hospital. According to our investigation, the average number of days before the patients received effective antibiotic therapy was 4.5 days. There are at least two reasons for this delay: first, the patients themselves may not have been aware that the disease may lead to severe complications without prompt treatment, and second, the neglect of scrub typhus and delayed diagnosis may have contributed to the misdiagnosis of scrub typhus.[6] The mean value for the duration of illness before effective antibiotic therapy was 6.17 days in the case group and 4.15 days in control group, and the difference was significant. This result indicates that, on average, patients in the case group received effective treatment after the onset of scrub typhus 2 days later than patients in the control group. Jang et al. also found that delays in diagnosis and treatment were associated with complications and mortality in scrub typhus patients.[16]

In recent years, a few studies on severe complications and the mortality rate of scrub typhus have been published in some countries.[17,18] Kim et al. reported that age ≥60 years was an independent predictive variable for the occurrence of severe scrub typhus.[17] In our study, the mean age of the patients was 54 years, and multivariate logistic analysis indicated that age was not an

Table 3
Multivariate logistic regression analysis of risk factors for severe scrub typhus[a]

Factors	*p*-Value	OR	95% CI
Duration of illness before effective antibiotic therapy, >4.5 days	0.027	2.287	1.096–4.770
Rash	0.014	3.694	1.300–10.495
Lymphadenopathy	0.030	2.438	1.090–5.458
Platelet count, $<100 \times 10^9$/l	0.050	2.226	1.002–4.946
Total bilirubin, >24 mmol/l	0.382	2.733	0.286–26.096
Direct bilirubin, >8.6 mmol/l	0.514	1.768	0.319–9.818
Percentage of neutrophils			
≤49.99	0.766	0.854	0.301–2.422
≥70.01	0.632	1.344	0.402–4.492
Percentage of lymphocytes			
<20	0.791	1.176	0.355–3.891
>40	0.164	0.456	0.151–1.379

OR, odds ratio; CI, confidence interval.
[a] Only the significant risk factors in Table 2 were selected for this analysis.

independent predictive variable for the occurrence of severe scrub typhus; this is in contrast to the result of Kim et al. Further studies are needed to confirm the relationship between age and the occurrence rate of severe scrub typhus.

Some studies have not analyzed lymphadenopathy. However, in our study, scrub typhus patients with lymphadenopathy (55 patients in total) appeared to have a 2.438 times higher risk of severe scrub typhus than patients without lymphadenopathy (85 patients in total). Scrub typhus has no specific clinical presentations, which makes it hard to identify. In epidemic regions, most of which are rural areas in Shandong Province, lymphadenopathy together with fever, eschar (or skin ulcer), and a skin rash are the indications of scrub typhus for the experienced clinician. According to our multivariate logistic analysis, it is also an independent risk factor for severe scrub typhus. Scrub typhus patients with lymphadenopathy should be taken good care of, in case severe complications occur.

As well as the duration of illness before effective antibiotic therapy and lymphadenopathy, two other factors were found to be independently predictive of the occurrence of severe scrub typhus by multivariate analysis in our study. These were the presence of a rash and a platelet count $<100 \times 10^9$/l. According to various reports, the occurrence of skin rash as well as eschar has been shown to differ among epidemic regions.[2,18,19] The occurrence rate of skin rash has been reported to be as high as 93% in the study by Ogawa et al. in Japan,[2] and also as low as 22% in the study by Mathai et al. in South India.[19] However, in our study we found that 87.0%, 65.5%, and 69.6% of severe scrub typhus patients, non-severe scrub typhus patients, and all 240 patients, respectively, had a rash. In contrast to our study, Kim et al. reported that skin rash was not a relative risk for severe scrub typhus, while the absence of an eschar was a relative risk.[17] These differences could be attributed to the local prevalent genotypes of *O.tsutsugamushi*.[20] Similar to lymphadenopathy, if a scrub typhus patient develops a rash, the clinician should be aware of the possible complications and intensive care should be given to the patient.

Univariate analysis showed that the platelet count in the severe scrub typhus group was significantly lower than in the non-severe scrub typhus group (platelet count $<100 \times 10^9$/l: 34.8% in the case group and 17.9% in the control group, $p < 0.05$), with a similar WBC count. Tsay and Chang[21] and Mathai et al.[19] reported thrombocytopenia in severe scrub typhus patients. However, Mathai et al. found that when the combination of elevated transaminases, thrombocytopenia, and leukocytosis was used, their specificity and positive predictive value were around 80%, but thrombocytopenia itself was not sensitive enough to predict scrub typhus.[19] The present study and that by Su et al., identified thrombocytopenia as being associated with severe complications.[22] Thrombocytopenia leads to problems with coagulation, and has been identified as a risk factor for the development of ARDS, which is a rarely reported but serious complication that may lead to death.[23] Therefore, thrombocytopenia is a plausible risk factor for severe scrub typhus.[9]

There are several limitations to this study. First, the patient clinical information was retrieved retrospectively. Thus, clinical information is not integrated to some degree. A few values such as the amount of albumin and creatinine were not assessed.[17,18] Second, we performed this study in Shandong Province, where the main genotype of *O. tsutsugamushi* is Kawasaki-related; the application of our results to other epidemic areas with different genotypes could therefore be limited. Third, selection bias is unavoidable with a hospital-based design. Nevertheless, our results could be representative of Shandong and some other epidemic regions that share the same genotype, and they provide reference information for other epidemic areas. As well as the duration of illness before effective antibiotic therapy, the other three parameters reported in this study could be checked in most medical institutions, even in township hospitals.

In summary, health education should be carried out in epidemic zones to raise the residents' awareness of this disease, so that they attend hospital as soon as they feel sick. Further, better physician awareness and improved diagnosis could effectively speed diagnosis. Once a scrub typhus patient presents a skin rash, lymphadenopathy, platelet count $<100 \times 10^9$/l, or thrombocytopenia, the clinician should be aware of the possibility of severe complications. Close observation should be applied to these patients to prevent severe complications and mortality.

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