



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



Luyan Zhang^a, Zhongtang Zhao^{a,*}, Zhenwang Bi^b, Zengqiang Kou^b, Meng Zhang^a, Li Yang^a, Li Zheng^a

^a Department of Epidemiology and Health Statistics, School of Public Health, Shandong University, 44 Wenhuxi Road, Jinan, Shandong 250012, China

^b Institute for Bacterial Infectious Disease Control and Prevention, Shandong Center for Disease Control and Prevention, Jinan, 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.

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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 infested 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.

* Corresponding author. Fax: +86 0531 88382128.
E-mail address: ztzhao@sdu.edu.cn (Z. Zhao).

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'-TCAAGCTTATTGCTAGTGCAATGCTGCG-3') and 55 (5'-AGGGATCCTGCTGCTGTGCTTGCTGCG-3'), and inner primers, 10 (5'-GATCAAGCTTCTCAGCC-TACTATAATGCC-3') and 11 (5'-CTAGGGATCCGACAGATGCATATTAGGC-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 ± 17.69 years, and that of the control group was 53.35 ± 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

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