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Original Article

Scrub Typhus: Seven-Year Experience and Literature Review

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Background: Scrub typhus, an emerging rickettsial disease caused by *Orientia tsutsugamushi*, is a clinically important endemic disease on Taiwan.
Methods: From January 1, 2007, to December 31, 2013, 156 patients diagnosed with scrub typhus were admitted to Taitung MacKay Memorial Hospital. Demographic data, clinical features, laboratory results, and outcomes of patients were retrospectively analyzed.
Results: Among 156 cases, 150 survived (96%) and six died (4%). There were 111 males (71%) and 45 females (29%) with a mean age of 47.8 years. The most common clinical features were fever (100%), general malaise (77%), chill (74%), headache (59%), and eschar (55%). No seasonal pattern was observed, with peaks in November and January. The average time to defervescence after appropriate antibiotics for the 150 surviving patients was 2.45 days. The significant risk factors were a delay of initial appropriate antibiotics use within 24 hrs, increased C-reactive protein (CRP), and liver cirrhosis.
Conclusion: Scrub typhus, a growing and emerging disease, is considered in the differential diagnosis of fever of unknown origin, and its diagnosis may be missed if it is not considered owing to its nonspecific clinical presentation. It is important to have a high index of suspicion and to increase awareness in endemic areas. Prompt diagnosis and early treatment with appropriate antibiotics are vital.

Key words: *scrub typhus, eschar, antibiotics*

Introduction

"Scrub typhus" is a chigger-borne disease caused by *Orientia tsutsugamushi* (*O. tsutsugamushi*), an obligate intracellular bacterium in the Rickettsiaceae family. It is an acute febrile illness with the characteristic findings of high fever, maculopapular rash, lymphadenopathy, eschar, headache, myalgia, cough, sore throat, and gastrointestinal symptoms.[1,2] It is easy to be misdiagnosed if it is not considered, and is a unique feature of infection in endemic areas. The literature of the data for scrub typhus in Eastern Taiwan is lacking. Thus, we conducted this retrospective study to analyze the clinical data, laboratory data, complications, and outcomes of 156 patients diagnosed with scrub typhus during a consecutive 7-year period, with a review of the relevant literature.

Methods

Institution and Patients

We retrospectively reviewed all scrub typhus cases at Taitung MacKay Memorial Hospital, a 500-bed teaching hospital in Eastern Taiwan, between January 1, 2007 and December 31, 2013, from the records of the hospital infection control department. Dermographic data, clinical features, complications,

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"chest X-ray (CXR)" findings, laboratory findings, and outcomes were analyzed. A detailed clinical examination, including a careful search for eschar, was conducted. A diagnosis of scrub typhus was required with at least one of the following criteria: (1) a four-fold rise in the indirect immunofluorescent antibody (IFA) test for *O. tsutsugamushi* measured in acute and convalescent paired sera, (2) an Immunoglobulin M (IgM) antibody titre against *O. tsutsugamushi* > 1:80, and/or (3) a positive polymerase chain reaction (PCR) at the Center for Disease Control on Taiwan.[3,4] A total of 51 patients were diagnosed by PCR, and the remainings were diagnosed by serology.

Definitions

A systolic blood pressure below 90 mmHg or a reduction of more than 40 mmHg from the baseline in the absence of other causes of hypotension were defined as septic shock.[2] Acute renal failure was defined as a relative increase of 50% of the baseline serum creatinine concentration. For patients with an unknown baseline serum creatinine concentration, acute renal failure was diagnosed if the patient had a urine output of less than 0.5 ml/kg/hr for more than 6 hrs after treatment.[5] When the partial oxygen pressure of arterial blood (PaO_2) was below 60 mmHg, with a normal or low partial carbon dioxide pressure of arterial blood ($PaCO_2$) in room air, this was diagnosed as acute respiratory failure. CXR positive was defined according to the radiographic interpretations of radiologists. The radiographic findings were classified into pulmonary involvement (reticulonodular opacities, air space consolidation, peribronchial infiltration, and pleural effusion) and cardiovascular involvement (cardiomegaly with pulmonary congestion).[5] Aseptic meningitis and meningoencephalitis were diagnosed by a cerebrospinal fluid study.[6] Blood cultures were obtained at the time of hospitalization. Defervescence was defined as a drop in body temperature to less than 38°C that remains below this level for 24 hrs.[2] The time to defervescence was defined as the duration between the start of antibiotics and the resolution of fever. The duration of hospitalization and in-hospital mortality rate were also documented.

Statistical Analysis

The age and time to defervescence after antibiotics were presented by the mean and standard deviation (SD). Owing to the small sample sizes of the deceased group (n = 6), continuous data were presented by the median with an interquartile range (IQR) and were tested with the nonparametric Mann-Whitney test to determine the difference between groups. Categorical data were presented by numbers with percentages, and were tested with Fisher's exact test for the difference between groups. Univariable and multivariable logistic regression models were performed to identify the impact factors for the risk of mortality, and were summarized by the odds ratio (OR) with a corresponding 95% confidence interval (CI). The factors that had significant associations with mortality in the univariable logistic regression models were included in the multivariable logistic regression model by the forward conditional selection method. Statistical assessments were evaluated using a two-sided significance level of 0.05 using SAS 9.4 for Windows® (SAS Institute Inc., Cary, NC, USA).

Results

Clinical Findings

A total of 156 patients with scrub typhus were enrolled and analyzed. Of these patients, 150 survived (96.2%) and six died (3.8%), with a mean age of 47.8 years (with SD of 15.6 years), including 111 males (71.2%) and 45 females (28.8%). No seasonal pattern was observed in our study, with peaks in November and January (Fig. 1).

Table 1 summarizes the clinical data at initial presentation. Common symptoms included fever, chills, general malaise, headache, cough, myalgia, arthralgia, eschar, and maculopapular rash. Septic shock was noted in 22 (14.1%) of the patients, acute renal failure in 12 (7.7%), acute respiratory failure in 8 (5.1%), and congestive heart failure (CHF) in 7 (4.4%). Central nervous system manifestations were not uncommon. Headache was the most common for 92 patients (59%), followed by confusion in 14 (9%) and seizure in 7 (4%) patients. Aseptic meningitis or meningoencephalitis was diagnosed in 12 (7.7%) patients. Gastrointestinal and hepatic involvement was common. A total of 18 patients without any recent history of peptic ulcer disease complained of epigastric pain, received a panendoscopy, and were observed to have a peptic ulcer with or without bleeding. Acute cholecystitis was noted in 15 (9.6%) patients. All of the six deceased patients were CXR positive, but only 45.3% of the surviving patients were CXR positive

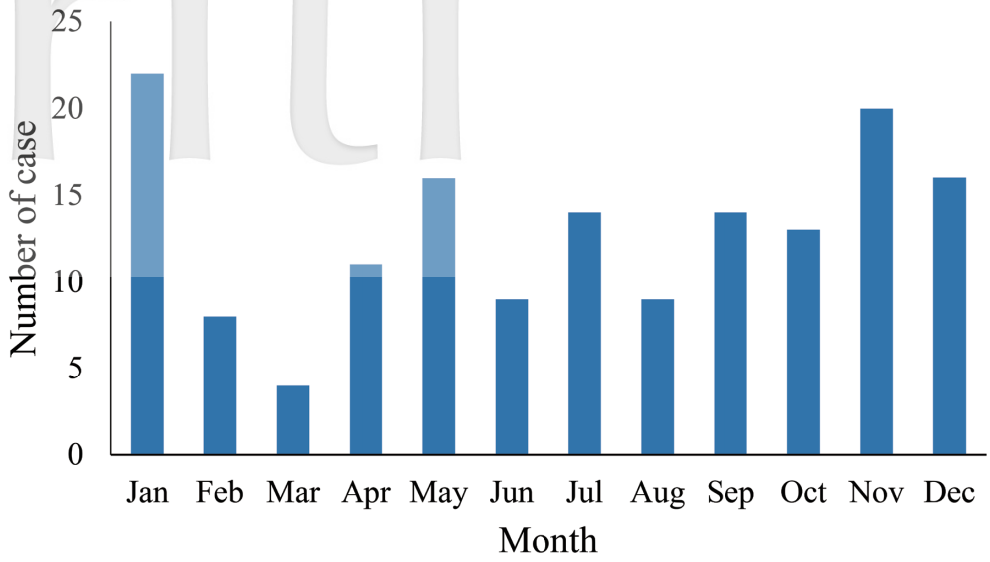

Fig. 1. The distribution of 156 cases of scrub typhus by month of diagnosis.

Table 1. Clinical manifestations of the 156 scrub typhus patients

Clinical manifestations	Number (%)
Symptoms	
Fever	156 (100)
General malaise	120 (77)
Chills	116 (74)
Headache	92 (59)
Cough	76 (49)
Myalgia/arthralgia	47 (30)
Dyspnea	36 (23)
Abdomen pain	36 (23)
Nausea and vomit	31 (20)
Dizziness	17 (11)
Confusion	14 (9)
Seizure	7 (4)
Signs	
Eschar	86 (55)
Maculopapular rash	45 (29)
Jaundice	22 (14)
Hepatosplenomegaly	22 (14)
Lymphadenopathy	16 (10)
Neck stiffness	5 (3)

(p = 0.010). About half of our patients (49%) had a cough and had evidence of interstitial pneumonitis in their chest roentgenograms. The most frequently CXR abnormalities were diffuse, bilateral, and peribronchial infiltration. Pleural effusion was not uncommon, and 16 patients (21.6%) was presented with pleural effusion (Table 2).

Location of Eschar

An eschar was present in 86 (55.1%) of the patients, with common sites including the groin and perineum (16.2%), lower extrimities (16.2%), axilla (13.9%), upper extremities (11.6%), back (10.4%), and abdomen (9.3%) (Table 3). In male patients, 62/111 (55.9%) of the patients presented with eschar, and for female patients, 24/45 (53.3%) of the patients presented with eschar. The probability of finding eschar during a physical examination seems not significantly different between males and females.

Laboratory Findings

An initial blood count revealed leukocytosis (total white count > 12 × 10^3/μL) in 21 of the 156 patients (13.5%), leucopenia (total white count < 4 × 10^3/μL) in 9 of 156 patients (5.8%), and thrombocytopenia (platelet count < 150 × 10^3/μL) in 76 of 156 patients (48.7%). Hemoglobin of < 10 mg/dL was noted in 5 of 156 patients (3.2%). Prothrombin and activated partial thromboplastin time (> 12 s and > 36 s, respectively) were prolonged in 14 (8.9%) and 16 (10.2%) of the

Table 2. Abnormal chest radiographic findings in 74 scrub typhus patients[a]

Radiographic findings	n (%)	Distribution		Zone	
		bilateral	unilateral	upper	lower
Pulmonary involvement					
Reticulonodular opacities	8/74 (10.8)	8	0	0	8
Air space consolidation	17/74 (22.9)	10	7	3	14
Peribronchial infiltration	35/74 (47.2)	32	3	0	35
Pleural effusion	16/74 (21.6)	11	5		
ARDS	5/74 (6.7)	5	0		
Cardiovascular involvement					
Cardiomegaly with pulmonary edema	7/74 (9.4)	7	0		

ARDS: acute respiratory distress syndrome.
[a]Individual patients may have had more than one features.

Table 3. Eschar distributions of scrub typhus cases

Location of eschar	Total number (%)	Right	Left	Male	Female
Groin and perineum	14 (16.2)	5	9	13	1
Lower extrimities	14 (16.2)	7	7	8	6
Axilla	12 (13.9)	9	3	9	3
Upper extrimities	10 (11.6)	5	5	5	5
Back	9 (10.4)	4	5	6	3
Upper abdomen	8 (9.3)	5	3	7	1
Lower abdomen	8 (9.3)	5	3	7	1
Chest wall	6 (6.9)	2	4	5	1
Head and neck	4 (4.6)	3	1	2	2
Buttock	1 (1.2)	0	1	0	1
Total	86 (100)	45	41	62	24

156 patients, respectively. Acute renal failure was diagnosed in 12 of the 156 patients (7.7%). Although the serum potassium remained normal in most cases, serum sodium was slightly low and was < 130 mg/dL in 26 of 156 patients (16.6%). In 47 cases (30.1%), the serum albumin level was below 3 g/dL, and proteinuria was noted in 95 cases (60.9%). A total bilirubin of > 2 mg/dL was found in 25 of 156 patients (16%).

Microbiological Findings and Treatment

Routine blood cultures of all patients revealed no growth since *O. tsutsugamushi* can only be grown on mouse or chicken embryos or tissue cultures. All patients were treated with minocycline or doxycycline. The average time to defervescence after antibiotics for the 150 survived patients was 2.45 days (with SD of 1.16 days).

Clinical Outcomes and Factors Predictive of Death

Of the 156 patients, 6 (3.8%) died, and 150 (96.2%) survived. There were 106 males (70.7%) and 44 females (29.3%) with a median age of 46.5 years (IQR of 37–58 years) in the surviving group, and five males (83.3%) and one female (16.7%) with a median age of 54 years (IQR of 48–76 years) in the deceased group, respectively. Comparisons between the surviving and deceased scrub typhus patients are summarized in Table 4. The deceased group had a significantly longer duration of illness before admission (11.0 vs. 4.0 days, $p < 0.001$) and a prolonged hospitalization time (10.0 vs. 6.0 days, $p < 0.001$). Anemia, leukocytosis, thrombocytopenia, prolonged prothrombin time and activated partial thromboplastin time, jaundice,

Table 4. Differences between the survival and died patients of scrub typhus

	Scrub typhus		*p*
	Survival (n = 150)	Death (n = 6)	
Age (year)	46.5 (37.0, 58.0)	54.0 (48.0, 76.0)	0.067
Gender[a]			
Male	106 (70.7)	5 (83.3)	0.674
Female	44 (29.3)	1 (16.7)	
Hematuria[a]	51 (34.0)	3 (50.0)	0.418
Proteinuria[a]	91 (60.7)	4 (66.7)	1.000
CXR positive[a]	68 (45.3)	6 (100.0)	0.010*
Eschar[a]	85 (56.7)	1 (16.7)	0.090
Skin rash[a]	44 (29.3)	1 (16.7)	0.674
Duration of illness before admission (day)	4.0 (3.0, 7.0)	11.0 (9.0, 14.0)	< 0.001*,**
Initiating of appropriate antibiotic within 24 hrs	130 (86.7)	3 (50.0)	0.042*
Comorbidity			
DM	13 (8.7)	0	1.000
HTN	26 (17.3)	3 (50.0)	0.078
LC	24 (16.0)	5 (83.3)	< 0.001*,**
CVD	19 (12.7)	4 (66.7)	0.005*
CRD	7 (4.7)	2 (33.3)	0.039*
HB < 10 g/dL	3 (2.0)	2 (33.3)	0.012*
WBC > 10,000/μL	32 (21.3)	5 (83.3)	0.003*
PLT < 150,000/μL	70 (46.7)	6 (100.0)	0.012*
PT > 12 s	8 (5.3)	6 (100.0)	< 0.001*,**
APTT > 36 s	10 (6.7)	6 (100.0)	< 0.001*,**
AST > twice of normal U/L	59 (39.3)	4 (66.7)	0.222
ALT > twice of normal U/L	46 (30.7)	3 (50.0)	0.379
TB > 2 mg/dL	19 (12.7)	6 (100.0)	< 0.001*,**
ALB < 3 g/dL	41 (27.3)	6 (100.0)	< 0.001*,**
BUN > 20 mg/dL	19 (12.7)	6 (100.0)	< 0.001*,**
Cr > 2.0 mg/dL	7 (4.7)	5 (83.3)	< 0.001*,**
Na^+ < 130 mEq/L	26 (17.3)	0	0.590
K^+ > 5 mEq/L	3 (2.0)	3 (50.0)	< 0.001*,**
CRP > 10 mg/dL	5 (3.3)	4 (66.7)	< 0.001*,**
Hospitalization (day)	6.0 (4.0, 8.0)	10.0 (8.0, 13.0)	0.014*

ALB: albumin; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; CRD: chronic renal disease; CRP: C-reactive protein; CVD: cardiovascular disease; CXR: chest X-ray interpretation; DM: diabetes mellitus; HB: hemoglobin; HTN: hypertension; K: potassium; LC: liver cirrhosis; Na: sodium; PLT: platelet; PT: prothrombin time; TB: total bilirubin; WBC: white blood cell.

[a]Data are presented by median with inter-quartile range except for categorical data are presented by number with percentage.

*$p < 0.05$ indicates a statistically significant difference between the two groups.

**p was presented as < 0.001 when its value was 0.000 (given to three decimal places).

hypoalbuminemia, lower renal function, hyperkalemia, and higher C-reactive protein (CRP) were significantly more common in the deceased group. Liver cirrhosis patients had a significantly higher mortality compared to non-cirrhosis patients ($p < 0.001$). There were no malignant patients in our study. All six deceased patients were CXR positive, but only 45.3% of the surviving patients were CXR positive ($p = 0.010$). The deceased group had a significantly lower early initiation of appropriate antibiotics within 24 hrs compared to the surviving group (50 vs. 86.7, $p = 0.042$).

In our study, the overall case fatality was 3.8%. According to the univariable logistic regression models, the risk of mortality increased with a longer duration before admission by an OR of 2.13 per day ($p < 0.001$). The risk of mortality increased with an increasing white cell count, creatinine, potassium, CRP, and comorbidities such as liver cirrhosis, cardiovascular disease, and chronic renal disease (with OR and 95% CI > 1), and decreased with the early initiation of appropriate antibiotics (minocycline or doxycycline) within 24 hrs (with OR and 95% CI < 1). In addition, given the associations of the three factors of early initiation of appropriate antibiotics within 24 hrs, liver cirrhosis and increased CRP remained statistically significant in the multivariable logistic regression model. After adjusting for each other, the risk of mortality decreased with the early initiation of appropriate antibiotics within 24 hrs (OR = 0.03 with 95% CI of 0–0.63, $p = 0.023$) and increased with increasing CRP (OR = 122.69 with 95% CI of 6.13–2,454.12, $p = 0.002$) and in liver cirrhotic patients (OR = 62.7 with 95% CI of 2.58–1,523.94, $p = 0.011$) (Table 5). A limitation of our study is the small sample size of the deceased group.

Discussion

Scrub typhus is a zoonotic disease that is endemic to a part of the world known as the Tsutsugamushi Triangle. This extends from Japan to Taiwan, China, South Korea, Nepal, Northern Pakistan, Papua New Guinea, and the Australian states of Queensland and Northern New South Wales.[1,2,7] *O. tsutsugamushi* is a gram-negative, obligate intracellular bacterium that infects various cells, including endothelial cells and phagocytes, and causes acute vasculitis.[1] It is transmitted to humans by the bite of the larval thrombiculid mite, commonly known as a chigger, especially Leptotrombidium deliense on Taiwan. It is common in some parts of Taiwan, especially in Kinmen, Nantou, Penghu, Hualian, and Taitung counties, where our hospital is located. When humans are bitten by the infectious mites, rickettsia begins to grow at the location of the bite. Initially it forms a papule, which becomes a vesicle and then an ulcer, and which is finally covered by black eschar surrounded by red erythema. This forms after 9–12 days, and patients show clinical symptoms such as fever, maculopapular rash, headache, gastrointestinal symptoms, and lymphadenopathy. A total of 72% of patients with eschar were male, which may be a result of occupational exposure or outdoor activities in rural areas. Although the presence of an eschar is highly suggestive of scrub typhus, it was reported in variable proportions in various studies. Therefore, its presence confirms the disease, but its absence does not exclude the possibility. In a study in India, the absence of eschar was revealed as a poor prognostic factor because it was more difficult to make a diagnosis.[3,8,9] Five of six deceased patients had no eschar in our series, but no significant *p* value was noted. In a previous report, researchers used an eschar PCR for useful diagnostic tests on patients with scrub typhus. The nested PCR method for eschar might be both a rapid diagnostic test for tsutsugamushi disease in the early acute stage and a differential test for a crust is a scrub typhus eschar.[10] Scrub typhus is a notifiable disease in Taiwan, and the Center for Disease Control does not perform eschar PCR for the diagnosis of scrub typhus.

Fever is frequent in scrub typhus cases, with fever noted in 100% of the patients in our study. The systemic involvement of various organs results in complications such as meningoencephalitis, acute renal failure, myocariditis, interstitial pneumonia, adult respiratory distress syndrome (ARDS), and even multiple organ failure. Elevated aspartate aminotransferase, alanine aminotransferase, and bilirubin are common. Scrub typhus may be frequently overlooked as liver and biliary tract infections. Clinicians should be alert to the possibility that scrub typhus is intrinsically resistant to common antibiotics. Only effective appropriate antibiotic treatment can reduce the morbidity and mortality rates. Aseptic meningitis and meningoencephalitis are serious complications of scrub typhus. We found 12 cases (7.7%) of central nervous system involvement in our series. The findings of slight pleocytosis with mild protein elevation and normal sugar values in the cerebrospinal fluid in our cases are similar to those found in other studies.[6,11]

Table 5. Logistic regression models for the risk of mortality

	Univariable		Multivariable	
	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age (year)	1.05 (1.00–1.11)	0.068		
Gender (female to male)	0.48 (0.05–4.24)	0.511		
Hematuria	1.94 (0.38–9.96)	0.427		
Proteinuria	1.30 (0.23–7.30)	0.768		
CXR positive	—			
Eschar	0.15 (0.02–1.34)	0.090		
Skin rash	0.48 (0.05–4.24)	0.511		
Hospitalization (day)	1.33 (1.06–1.67)	0.015*		
Duration before admission (day)	2.13 (1.36–3.32)	< 0.001*,**		
Initiating of appropriate antibiotic within 24 hrs	0.15 (0.03–0.82)	0.028*	0.03 (0.00–0.63)	0.023*
Comorbidity				
HTN	4.77 (0.91–24.96)	0.064		
LC	26.25 (2.93–234.77)	0.003*	62.70 (2.58–1,523.94)	0.011*
CVD	13.79 (2.36–80.48)	0.004*		
CRD	10.21 (1.59–65.56)	0.014*		
HB < 10 g/dL	24.50 (3.17–189.63)	0.002*		
WBC > 10,000/μL	18.44 (2.08–163.48)	0.009*		
PLT < 150,000/μL	—			
AST > twice of normal U/L	3.08 (0.55–17.38)	0.202		
ALT > twice of normal U/L	2.26 (0.44–11.63)	0.329		
Cr > 2.0 mg/dL	102.11 (10.48–995.09)	< 0.001*,**		
K^+ > 5 mEq/L	49.00 (6.86–350.16)	< 0.001*,**		
CRP > 10 mg/dL	58.00 (8.53–394.53)	< 0.001*,**	122.69 (6.13–2,454.12)	0.002**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval;Cr: creatinine; CRD: chronic renal disease; CRP: C-reactive protein; CVD: cardiovascular disease; CXR: chest X-ray interpretation; HB: hemoglobin; HTN: hypertension; K: potassium; LC: liver cirrhosis; OR: odds ratio; PLT: platelet; WBC: white blood cell.

*$p < 0.05$ indicates a statistically significant association with mortality.

**p was presented as < 0.001 when its value was 0.000 (given to three decimal places).

Radiological abnormalities in scrub typhus are not rare (74/156, 47.4%), and the findings vary. Reticulonodular opacities were found in eight patients (10.8%), airspace consolidation in 17 patients (22.9%), and peribronchial infiltrates in 35 patients (47.2%). In previous studies, pleural effusion was a common radiographic feature in 12–43% of patients.[12,13] Pleural effusion was found in 16 patients (21.6%) in our study, mostly combined with other parenchymal lesions. It is important to note that ARDS may develop in scrub typhus, and to be aware of the possible risk factors, because it is treatable if considered and diagnosed early. A total of 5 of 156 patients were found to have ARDS in our study. Park et al.[14] reported on pathological findings of open lung biopsies that showed interstitial edema with mononuclear cell infiltration, mainly lymphocytes without any evidence of vasculitis or perivasculitis. Thus, not only vasculitis owing to direct invasion of the rickettsial organism but also an immunological mechanism may participate in the pathogenesis of the pulmonary involvement of scrub typhus.[5,14-16] No autopsy or open-lung biopsy was done in our series.

Cardiovascular complication has rarely been described in the past. Symptoms of myocardial involvement are usually subclinical. However, acute fulminant myocarditis leading to severe cardiogenic shock and fatalities was found in other studies. Cardiomegaly could be secondary to myocardial and pericardial involvement owing to the infection, and scrub typhus

myocarditis may contribute to CHF. Acute onset of CHF was found in seven patients (9.4%) in our study, although no myocarditis was evaluated.[17,18]

In our study, scrub typhus had a predilection for males (male 111/156, 71.1%, female 45/156, 28.8%). This is similar to what has been reported in other series, and is assumed to result from the fact that men are the major workers and participants in field activities in Taiwan, as in many other countries. Thus, an increase in the risk of acquiring scrub typhus was noted in males. The high risk groups were the elderly, farmers, and males.

In general, hypoalbuminemia, thrombocytopenia, hepatic impairment, and acute renal insufficiency are associated with complications and mortality in patients with acute infectious diseases. In previous studies, a decreased albumin level, prolonged prothrombin time, and elevated creatinine levels were found to be predictors of mortality.[19,20] Although the mechanism of hypoalbuminemia in patients with scrub typhus is still not well known, it is considered to be associated with plasma protein leakage from the blood vessels owing to increased vascular permeability.[4,21-23] A delay of initial appropriate antibiotics use within 24 hrs, increased CRP, and liver cirrhosis were found to be our independent predictors of mortality.

In vitro, *O. tsutsugamushi* is susceptible to doxycycline and minocycline. In previous studies, a higher Acute Physiology and Chronic Health Evaluation (APACHE) II score was linked to high mortality for scrub typhus, and nearly all patients (93.6%) became afebrile within 72 hrs after the use of tetracycline antibiotics.[24,25] In our study, the average time to defervescence after antibiotics for the 150 surviving patients was 2.45 days (with SD of 1.16 days). The time to start tetracycline antibiotics after admission was the most important factor for scrub typhus patients.

Although scrub typhus is rare in pregnant females, when present, it can lead to serious repercussions for both the mother and fetus. The clinical features of pregnant females were the same as for non-pregnant females. The pregnancy outcome was closely related to the therapeutic outcome of each patient. Stillbirths and abortions were mainly observed in females whose scrub typhus was poorly controlled. Therefore, effective and safe therapeutic regimens are critical for avoiding adverse pregnancy outcomes. Kim et al. reported on eight pregnant women with scrub typhus who were treated successfully with a single 500-mg dose of azithromycin. All of the women delivered healthy babies at term without congenital or neonatal complications.[26] Since this is uncommon, no pregnant women were noted in our study.

In a study by Tsai and Yeh,[27] no significant correlation between scrub typhus incidence and surface temperature was observed in the endemic southeastern regions of Taiwan, including Taitung, whereas a similar significant correlation was found in low-incidence areas of the central-western and southwestern regions of Taiwan.[27,28] Our findings show that cases were found year-round and exhibited no climatic effects. However, the number of incidences during the cold season was higher than during the warm season. Peaks occurred in November and January in our study. This weather is suitable for outdoor activities, thus increasing the contact between infected mites and human hosts.

To improve self-recognition and encourage early visits to the hospital, it is important to provide intensive health education to local residents in endemic areas in order to increase awareness of clinical symptoms such as fever, eschar, headache, and skin rash. To reduce the risk of infection during epidemic periods, people should also be alerted to apply repellents to skin and clothes, to avoid contact with overgrown grasses and bushes, and to wear long pants, long sleeves, and long socks. Taiwan has a well-established public health system, so door-to-door health education by local public health nurses will be effective for prevention. We suggest that better vector control can also reduce the incidence of the disease.[29]

Although the rates of fatality have shown a considerable variation of about 14–17% between studies, the mortality rate was only 3.8% in our series. This might result from the high awareness of clinical physicians and thorough physical examinations of febrile patients in endemic areas. A limitation of our study was the small sample size of the deceased group. Further and larger studies will help to clarify more information regarding scrub typhus fever.

Scrub typhus, a growing and emerging disease, is considered a differential diagnosis of fever of unknown origin, and diagnosis may be missed if it is not considered owing to its nonspecific clinical presentations. Laboratory findings and clinical courses may also vary significantly, making diagnosis and appropriate treatment difficult. The possibility of scrub typhus, which is intrinsically resistant to common empirical antibiotics, should be kept in mind with regard to fever patients with abnormal liver function and

jaundice. It may be frequently overlooked as a biliary tract infection. Travel history to endemic areas of Taiwan is also important in these patients. Our retrospective study highlights that a delayed diagnosis and treatment may be fatal. Therefore, it is important to have a high index of suspicion and to increase awareness in endemic areas at initial presentation. Prompt diagnosis and early treatment with appropriate antibiotics are crucial for patient survival.

Conflicts of Interest Statement

None to declare.

Declaration of Interest

There are no commercial relationship or potential conflict of interest, no sources of funding and the study was not supported by any institutions.

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