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Original Article

Clinicoepidemiologic characteristics of scrub typhus and murine typhus: A multi-center study in southern Taiwan

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KEYWORDS
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Abstract *Background:* This study aimed to offer key features to differentiate scrub typhus (ST) and murine typhus (MT) at the early stage of the diseases and provide clinicoepidemiologic characteristics of ST and MT in southern Taiwan, a region where both diseases are endemic. Comparison of doxycycline treatment efficacy between the two diseases by matching disease severity and delayed treatment had never been investigated.
Methods: We reviewed the medical records of cases of ST and MT in four hospitals in southern Taiwan. Propensity-score matching was used to analyze the defervescence curves between patients with doxycycline-treated ST and MT by log-rank test.
Results: Between 2004 and 2016, 265 ST and 63 MT cases were diagnosed. The number of cases of ST was significantly related to temperature (Rs = 0.77) and rainfall (Rs = 0.63). Island area exposure, arthropod bite, eschar, and lymphadenopathy were only recorded in ST patients. Multivariate analysis revealed that mountainous area exposure (odds ratio [OR], 11.0; 95% confidence interval [CI], 4.4—27.2) was an independent predictor for ST, while contact with rats (OR, 8.4; 95% CI, 3.3—21.3) was that for MT. After propensity-score matching, there was no

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difference in defervescence curves between these two rickettsioses treated with doxycycline ($p = 0.24$).
Conclusion: In the present study, island area exposure, arthropod bite, eschar, and lymphadenopathy were unique manifestations of ST. Mountainous area exposure is a predictive factor for ST, while contact with rats predicted MT. There was no difference in defervescence time between these two rickettsioses after doxycycline treatment.

Introduction

Rickettsioses are a group of zoonotic febrile diseases caused by obligate intracellular bacteria, Rickettsiae.[1] Although rickettsiae have their own epidemic areas, they do not only affect local people, but are also important pathogens of imported fever among international travelers.[1] In the Asia–Pacific region, including Taiwan, both murine typhus (MT) and scrub typhus (ST) are common rickettsioses.[2] MT is a flea-borne disease caused by *Rickettsia typhi*. Both rodents and arthropods are natural reservoirs. It is an acute febrile illness that may be complicated with pneumonia, respiratory failure, central nervous system (CNS) involvement, and even death.[3] ST is a mite-borne infection of humans caused by *Orientia tsutsugamushi*. The disease could involve multiple organs including the lung, CNS, and heart, and also cause mortality.[4] Early differential diagnosis of these two diseases is difficult because ST and MT share similar clinical characteristics at the initial stage of the diseases.[2] Serological diagnosis is usually used in the clinical setting and includes the determination of seroconversion or a four-fold increase in specific IgG or IgM titers between acute and convalescent sera. This means that the definite diagnosis might be available about two weeks after the initial visit. However, pneumonia is a common manifestation of these two rickettsioses,[3,4] which may lead clinicians to prescribe fluoroquinolones as empirical treatment.[5] For *R. typhi, in vitro* susceptibility to ciprofloxacin and levofloxacin[6] is documented and fluoroquinolone treatment might reduce the duration of fever in MT.[3] On the other hand, fluoroquinolones are not recommended in the treatment of ST[7] and intrinsic fluoroquinolone resistance in *O. tsutsugamushi* has been reported.[8] As a result, higher mortality has been reported in patients with levofloxacin treatment in severe ST, when compared to patients with tetracycline treatment.[9] There are concerns of inappropriate empirical antibiotic therapy with fluoroquinolones for ST patients with pneumonia as initial presentation. Therefore, it would be reasonable to put the two disease entities together for further analysis to differentiate ST from MT. For suspected cases of ST and MT, doxycycline is empirically prescribed to save lives,[3,7] but a comparison of the doxycycline treatment efficacy between the two diseases by matching of disease severity and delayed treatment had never been investigated.

This study aimed to offer key features to differentiate ST from MT at the initial stage of the diseases in a region where both diseases are endemic and provide clinicoepidemiologic characteristics of ST and MT in southern Taiwan. In the second part of the present study, we conducted a propensity score matching study for defervescence comparison between the two diseases after doxycycline treatment.

Methods

Patient identification and enrollment

We included cases of ST and MT from four hospitals in southern Taiwan: Kaohsiung Chang Gung Memorial Hospital, E-Da Hospital, Pingtung Christian Hospital, and Paochien Hospital, between 2004 and 2016. For cases in which the patient experienced more than one episode, only the first episode was included. The Institutional Review Board of the Chang Gung Memorial Hospital approved the study protocol (no. 201800591B0) and waived the need for patient consent due to the retrospective nature of the study. Patient data were anonymized to maintain confidentiality.

Diagnoses of ST and MT

ST and MT are notifiable diseases in Taiwan, and clinicians are required to report patients who are clinically suspected of these diseases to the Taiwan Centers for Disease Control (CDC-TW). Paired blood specimens (acute and convalescent phases) are collected and sent to the contracted laboratories of the CDC-TW for laboratory confirmation or exclusive diagnosis. In brief, acute ST and MT were confirmed either by serological assessment using an indirect immunofluorescence antibody assay (IFA) or by molecular methods. Diagnostic IFA was considered positive for ST and MT if a 4-fold or greater increase or seroconversion in specific antibodies against the Karp, Kato, and Gilliam strains of *O. tsutsugamushi* and *R. typhi*, respectively. The diagnosis could also be established by IFA for *O. tsutsugamushi* or *R. typhi* if the IgG and IgM titers were more than 320 and 80, simultaneously. Polymerase chain reaction could be employed to detect the DNA of the causative pathogen in the blood, with a positive result confirming the diagnosis.[10–12]

Data collection and definitions

We collected the patients' demographic data, including age, gender, residence, environmental exposure history, occupation, arthropod bite history, animal contact history, underlying disease, days from disease onset to hospital visit, hospitalization or not, initial sequential organ failure assessment (SOFA) score if available, and days from doxycycline treatment to defervescence. The patients' initial symptoms, signs, initial image studies, hemogram, blood chemistry and serological markers of hepatitis B and C viruses were recorded if available.

The first day of the highest body temperature lower than 37.5 °C for more than 3 consecutive days was defined as the date of defervescence.[12] SOFA score parameters were retrieved and calculated according to the definition of the European Society of Intensive Care Medicine.[13] Relative bradycardia was defined as a body temperature higher than 38.9 °C and a heart rate less than 110 beats per minute occurred simultaneously, in the absence of beta-blockers, calcium blockers or other antiarrhythmic medications.[14] Pulmonary findings on chest radiographs were assessed for the presence and location, and categorized into unilateral or bilateral reticulonodular infiltration and unilateral or bilateral consolidation.[15] A gallbladder wall thickness more than 5 mm was considered gallbladder wall thickening.[16]

To analyze the relationship between case numbers and climate, we obtained the monthly average temperature and rainfall data in twenty years (1981—2010) from the website of Central Weather Bureau of Taiwan (http://www.cwb.gov.tw/V7/climate/monthlyMean/Taiwan_tx.htm). The exact temperature and rainfall data used in this study were the regional averages of Kaohsiung, Pingtung, and Penghu in Taiwan.

Geographic distribution of ST and MT cases

The residential addresses of the confirmed cases were recorded according to districts, and maps of the geographic distributions of cases were created using SuperGIS Desktop software (Supergeo Technologies Inc., Taipei, Taiwan). The locations of Kaohsiung City, Pingtung County and Penghu County were marked on the map. It's worth mentioning that Penghu County is a group of offshore islands, and lies in the Taiwan Strait, west of the Taiwan main island.

Statistical analysis

Spearman's rank correlation coefficient analysis was used to evaluate the association between case numbers and climate parameters. Chi-square test or Fisher's exact test were used for categorical variables, and the Student's *t*-

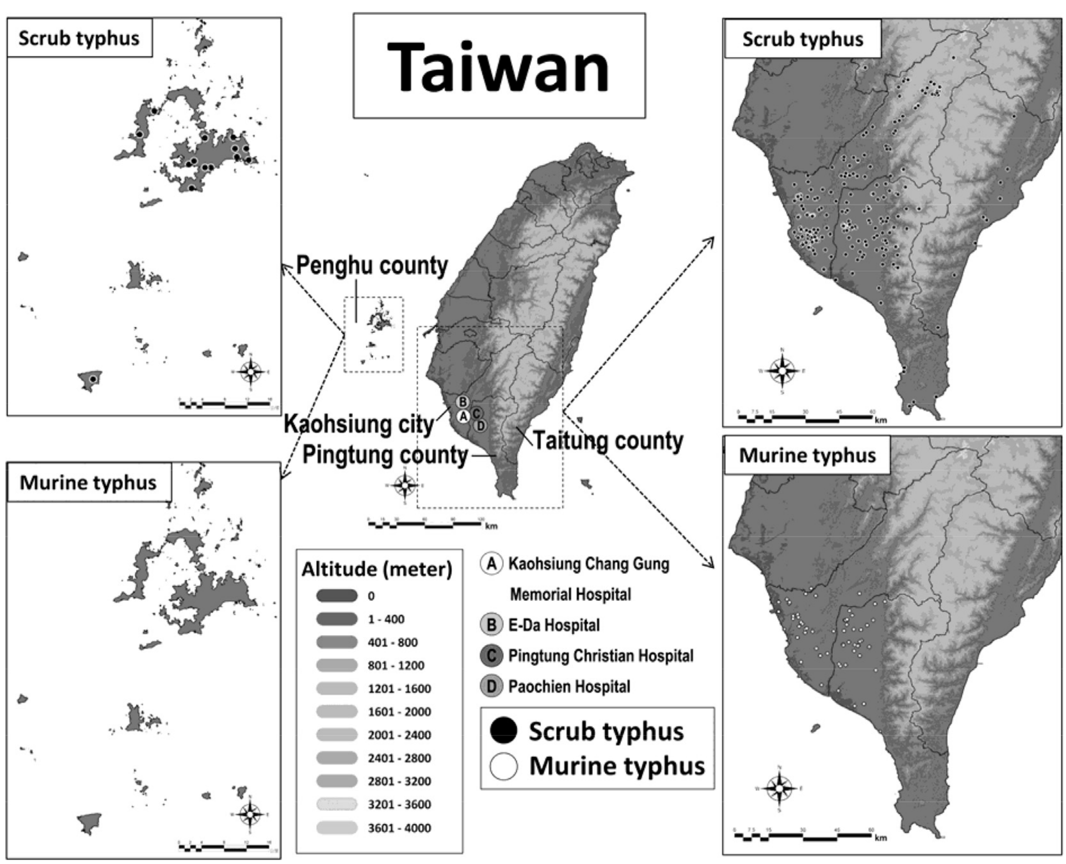

Figure 1. Geographical distributions of residence of two rickettsioses patients in an altitude map of Kaohsiung-Pingtung-Penghu region (where 94.5% of our patients originated) in Taiwan, with marking of locations. The white dots represent the residences of patients with murine typhus (MT), who lived mainly in flatland areas of Kaohsiung-Pingtung region. The distribution of patients with scrub typhus (ST), represented as black dots, extended into the mountainous areas of Kaohsiung-Pingtung region and appeared in the island-composed Penghu County.

test was used for continuous variables. To survey the independent predictive factors between ST patients and MT patients, multivariate logistic regression was conducted for all variables with $p < 0.1$ noted in the univariate analysis. However, due to the limitation of the test, those items with zero cases were excluded in the multivariate analysis.

We managed to analyze the fever defervescence pattern after doxycycline treatment between ST and MT. To minimize the potential confounding effects of delay extents, disease severity and non-random assignment of patients, the NCSS software version 10 (NCSS, LLC., Kaysville, UT, USA) was used to calculate the propensity score based on the duration from symptom onset to the first hospital visit and SOFA score. We excluded the cases without defervescence date, doxycycline treatment, or SOFA score. A 1:2 matched study population (doxycycline-treated MT patients versus doxycycline-treated ST patients) was created by the optimal method. Afterward, the study population was evaluated via Kaplan—Meier survival curve analysis and the log-rank test. Statistical analyses other than the generation of propensity score-matched groups were conducted using SPSS version 22 (IBM Corp., Armonk, NY, USA). All statistical analyses were two-sided, and values of p less than 0.05 were considered significant.

Results

The clinical and laboratory features of 328 cases including 265 with ST and another 63 with MT were retrospectively analyzed. No patient had concomitant ST and MT in this study population. A total of 310 patients (94.5%) lived in Kaohsiung City, Pingtung County and Penghu Country of Taiwan. The patients' residence distribution was presented in an altitude map (Fig. 1). More patients with ST lived in the mountainous area of Kaohsiung-Pingtung Region and Penghu County, while patients with MT were scattered in the flat land areas of Kaohsiung-Pingtung Region. The monthly distribution of cases, together with 20-year average temperature and rainfall data, are shown in Fig. 2. The temperature and rainfall data reached higher points in the summer months (June, July, and August). The number of cases of ST was correlated with temperature (correlation coefficient: Rs = 0.77, $p < 0.01$) and rainfall (Rs = 0.63, $p = 0.03$). However, no significant correlation was found between the number of cases of MT and temperature (Rs = 0.30, $p = 0.34$) or rainfall (Rs = 0.32, $p = 0.32$).

The demographic data and the difference between ST and MT are shown in Table 1. By univariate analysis, the mountainous area exposure history (55.8% vs. 9.5%, $p < 0.01$) and island area exposure history (12.5% vs. 0%, $p < 0.01$), rural area travel history (39.2% vs. 9.5%, $p < 0.01$), and arthropod bite history (12.5% vs. 0%, $p < 0.01$) were more common in ST. Contrastively, animal husbandry (11.1% vs. 3.0%, $p = 0.01$), animal contact history (49.2% vs. 23.4%, $p < 0.01$), contact with cats (7.9% vs. 1.9%, $p = 0.03$), and contact with rats (30.2% vs. 3.8%, $p < 0.01$) were more dominant among patients with MT. For the underlying diseases, only chronic renal disease

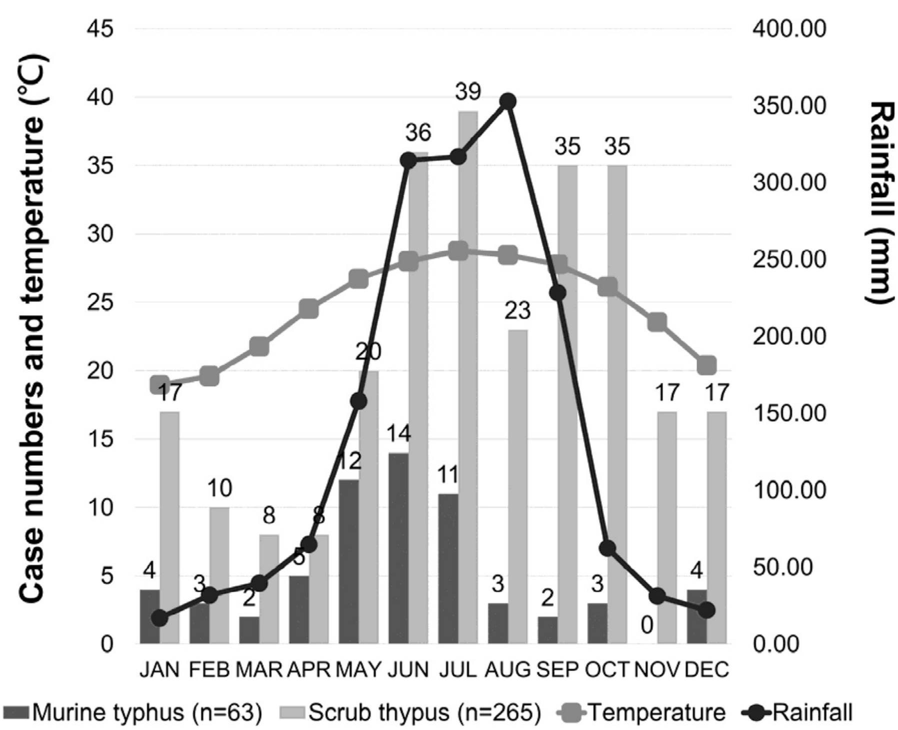

Figure 2. Monthly distribution of the 63 cases with murine typhus (MT) and 265 cases with scrub typhus (ST) together with average temperature (in degrees Celsius) and average rainfall level (in millimeters) in Kaohsiung-Pingtung-Penghu region of Taiwan. The analysis of Spearman's rank correlation coefficients showed that the monthly distribution of patients with ST was associated with both temperature (Rs = 0.77, $p < 0.01$) and rainfall (Rs = 0.63, $p = 0.03$). These relationships were not significant in patients with MT. Abbreviation: mm, millimeter.

Table 1 Comparison of demographic variables between patients with murine typhus (MT) and scrub typhus (ST).

Demographics	MT N = 63 n (%)	ST N = 265 n (%)	*p* values
Age[a]	47.2 ± 13.0	46.4 ± 16.9	0.67
Male	49 (77.8)	182 (68.7)	0.16
Environmental exposure			
Mountainous area	6 (9.5)	148 (55.8)	<0.01
Island area	0	33 (12.5)	<0.01
Flood	2 (3.2)	2 (0.8)	0.17
Rural area travel history	6 (9.5)	104 (39.2)	<0.01
Occupation			
Farmer	11 (17.5)	58 (21.9)	0.44
Animal husbandry	7 (11.1)	8 (3.0)	0.01
Slaughter	2 (3.2)	3 (1.1)	0.25
Arthropod bite history	0	33 (12.5)	<0.01
Animal contact history	31 (49.2)	62 (23.4)	<0.01
Dogs	9 (14.3)	31 (11.7)	0.57
Cats	5 (7.9)	5 (1.9)	0.03
Rats	19 (30.2)	10 (3.8)	<0.01
Underlying diseases			
Hypertension	8 (12.7)	41 (15.5)	0.58
Diabetes mellitus	8 (12.7)	25 (9.4)	0.44
Congestive heart failure	0	3 (1.1)	>0.99
COPD	0	3 (1.1)	>0.99
Liver cirrhosis	1 (1.6)	14 (5.3)	0.32
Chronic renal disease	0	19 (7.2)	0.03
Hemodialysis	1 (1.6)	1 (0.4)	0.35
Malignancy	1 (1.6)	8 (3.0)	>0.99
Collagen disease	0	2 (0.8)	>0.99
Days from disease onset to hospital visit[a]	6.3 ± 2.9	6.1 ± 3.5	0.67
Hospitalization	60 (95.2)	244 (92.1)	0.59
Initial SOFA score[a]	2.1 ± 2.0[b]	2.5 ± 2.1[c]	0.25
Days from doxycycline treatment to defervescence[a]	2.8 ± 1.9[d]	2.3 ± 2.4[e]	0.14

[a] Presented as mean value ± standard deviation (case numbers).
[b] n = 43.
[c] n = 161.
[d] n = 50.
[e] n = 215.
Abbreviations: COPD, chronic obstructive pulmonary disease; MT, murine typhus; SOFA, sequential organ failure assessment; ST, scrub typhus.

predominated in patients with ST than those with MT was found (7.2% vs. 0%, $p = 0.03$). There was no difference between days from disease onset to hospital visit, hospitalized patient proportions, initial SOFA score and days from doxycycline treatment to defervescence.

Table 2 displays the symptoms and signs and the difference between ST and MT. By univariate analysis, eschar (26.8% vs. 0%, $p < 0.01$) and lymphadenopathy (9.1% vs. 0%, $p < 0.01$) were significantly more common in ST patients. Patients with MT had a higher proportion with headache (69.8% vs. 53.2%, $p = 0.02$) and relative bradycardia (55.6% vs. 41.5%, $p = 0.04$). The results of laboratory data and image studies are shown in Table 3. There were no differences between patients with ST or MT in the hemogram parameters, blood chemistry results, and positive serology for hepatitis B or hepatitis C. There was more pulmonary involvement on plain chest radiographs in patients with ST (48.1% vs. 24.2%, $p < 0.01$). Bilateral reticulonodular infiltration was the most common abnormal pulmonary findings on chest radiograph in ST.

To obtain the independent predictive factors between MT and ST, we conducted a multivariate logistic regression analysis. To reduce error, the following items with zero cases were excluded from the analysis: island area exposure history, arthropod bite history, chronic renal disease, presence of eschar, and lymphadenopathy. History of mountainous area exposure was a significant predictive factor for ST (odds ratio [OR] = 11.0; 95% confidence interval [CI], 4.4–27.2, $p < 0.001$). History of contact with rats (OR, 8.4; 95% CI, 3.3–21.3, $p < 0.001$) was a predictive factor for MT.

Propensity score matched patients were selected to reduce the effect of differences in delay extent and disease severity. The flow chart of the propensity score matching process is shown in Fig. 3. Of a total of 63 patients with MT, 6 were excluded due to the absence of the date of

Table 2 Comparison of symptoms and signs between patients with murine typhus (MT) and scrub typhus (ST).

Symptoms/signs	MT N = 63 n (%)	ST N = 265 n (%)	*p* values
Symptoms			
Fever	61 (96.8)	255 (96.2)	>0.99
Chills	35 (55.6)	167 (63.0)	0.27
Headache	44 (69.8)	141 (53.2)	0.02
Cough	24 (38.1)	82 (30.9)	0.28
Sore throat	4 (6.3)	24 (9.1)	0.49
Jaundice	6 (9.5)	20 (7.5)	0.61
Nausea	9 (14.3)	51 (19.2)	0.36
Abdominal pain	11 (17.5)	61 (23.0)	0.34
Diarrhea	5 (7.9)	32 (12.1)	0.35
Arthralgia	3 (4.8)	20 (7.5)	0.59
Myalgia	19 (30.2)	91 (34.3)	0.53
Bone pain	2 (3.2)	8 (3.0)	>0.99
Signs			
Icteric sclera	5 (7.9)	27 (10.2)	0.59
Conjunctival suffusion	0	2 (0.8)	>0.99
Skin rash	13 (20.6)	67 (25.3)	0.44
Eschar	0	71 (26.8)	<0.01
Lymphadenopathy	0	24 (9.1)	<0.01
Hepatomegaly	2 (3.2)	9 (3.4)	>0.99
Splenomegaly	4 (6.3)	21 (7.9)	0.79
Relative bradycardia	35 (55.6)	110 (41.5)	0.04

Abbreviations: MT, murine typhus; ST, scrub typhus.

defervescence, 7 were excluded because they did not receive doxycycline treatment, and 16 were excluded due to lack of SOFA score data. Among 265 patients with ST, 32 were excluded due to the absence of the date of defervescence, 18 were excluded because they did not receive doxycycline treatment, and 74 were excluded due to lack of SOFA score data. Propensity scores for individual patients were created according to the duration from symptom onset to hospital visit and SOFA score. Finally, 34 doxycycline-treated MT patients were matched with 68 doxycycline-treated ST patients. In the propensity score-matched population, the median and mean times to defervescence for ST patients were 2 days and 2.4 days, respectively. For MT patients, the median and mean times to defervescence were 2 days and 2.9 days, respectively. The proportion of patients defervesced after receiving doxycycline is shown in Fig. 4. The defervescence curves showed no significant difference between these two groups ($p = 0.24$ by log-rank test).

Discussion

In this study, the prevalence of ST was related to higher temperature and increased rainfall levels. This result was consistent with previous literature.[17,18] It might relate to the seasonal existence of vector mites in the warmer temperatures[19] and wetter months,[20] as did human activity in the field. The environment exposure history may conceal important clues to distinguish these two rickettsioses in the early stage. Since ST is transmitted by chigger bites, human activity involving its habitat increase the risk for *O. tsutsugamushi* inoculation.[21] Chiggers are widely distributed in Taiwan, including fields, mountainous areas and offshore islands, including the island-composed Penghu County.[22] In our study, mountainous area exposure history was an independent predictive factor for ST. It was worth noting that all our patients with offshore island exposure history were diagnosed with ST. However, island exposure history was not included in the multivariate analysis due to the lack of cases with island exposure history in the MT patient group. Also, history of contact with rats was a predictive factor for MT rather than ST. From an ectoparasite and seroepidemiological survey of MT prevalence among mouse-like animals in Taiwan, *Rattus norvegicus* was the most commonly-captured animal and the most common ectoparasite was *Xenopsylla cheopis* (the main vector for *R. typhi*).[23] Kaohsiung Harbor with MT seropositive rates of 32.08% was found.[23] In contrast, the prevalence of *O. tsutsugamushi* infection in small mammals active around Kaohsiung Harbor was only 6.67%.[24] This might explain why the proportion of history of contact with rats was significantly higher among MT patients than among ST patients.

The common manifestations of ST and MT found in our study included fever, chills, headache, cough, myalgia, and relative bradycardia, which were similar findings as previous studies.[15,17,25] Among these manifestations, eschar and lymphadenopathy were exclusively noted in patients with ST. In agreement with previous studies,[15,26,27] abnormal chest radiograph findings were present in about 59.4–72.0% of patients with ST. The most frequent finding was bilateral reticulonodular infiltration. Although abnormal chest radiograph findings were also present in patients with MT in this study, the percentage (17.0–30.6%) was not as high as

Table 3 Comparison of laboratory data and imaging findings between patients with murine typhus (MT) and scrub typhus (ST).

	MT A/B[a] (%)	ST A/B[a] (%)	*p* values
Hemogram			
Leukocytosis[b]	12/63 (19.0)	67/262 (25.6)	0.28
Leukopenia[c]	7/63 (11.1)	33/262 (12.6)	0.75
Anemia[d]	1/63 (1.6)	15/261 (5.7)	0.33
Thrombocytopenia[e]	38/63 (60.3)	180/260 (69.2)	0.18
Blood chemistry			
BUN (mg/dL)[f]	17.2 ± 17.2[g]	19.4 ± 22.0[h]	0.54
Creatinine (mg/dL)[f]	1.2 ± 0.7[i]	1.4 ± 1.1[j]	0.15
ALT (U/L)[f]	182 ± 258[k]	127 ± 130[l]	0.10
AST (U/L)[f]	154 ± 121[m]	137 ± 178[n]	0.50
Total bilirubin (mg/dL)[f]	1.8 ± 3.2[o]	1.9 ± 3.5[p]	0.90
CRP level (mg/L)[f]	86.8 ± 66.8[q]	100.7 ± 86.1[r]	0.31
Serology			
Seropositive for HBsAg	6/45 (13.3)	21/143 (14.7)	0.82
Seropositive for anti-HCV Ab	2/45 (4.4)	8/143 (5.6)	>0.99
Image finding			
Plain chest radiograph			
Pulmonary involvement	15/62 (24.2)	115/239 (48.1)	<0.01
Unilateral reticulonodular infiltration	3/62 (4.7)	34/239 (14.2)	0.05
Bilateral reticulonodular infiltration	9/62 (14.5)	73/239 (30.5)	0.01
Unilateral consolidation	2/62 (3.2)	2/239 (0.8)	0.19
Bilateral consolidation	1/62 (1.6)	15/239 (6.3)	0.21
Abdominal sonography or computed tomography			
Gallbladder wall thickening	5/59 (8.5)	27/207 (13.0)	0.34
Hepatomegaly	6/59 (10.2)	23/207 (11.1)	0.84
Splenomegaly	13/59 (22.0)	64/207 (30.9)	0.18

[a] A/B: "A" represents the number of cases with positive results, while "B" represents the number of cases with available data.
[b] Leukocytosis: white blood cell count >10,000/μL.
[c] Leukopenia: white blood cell count <4000/μL.
[d] Anemia: hemoglobin level <10 g/dL.
[e] Thrombocytopenia: platelet count <150,000/μL.
[f] Presented as mean value ± standard deviation.
[g] n = 44.
[h] n = 177.
[i] n = 63.
[j] n = 245.
[k] n = 63.
[l] n = 251.
[m] n = 62.
[n] n = 250.
[o] n = 43.
[p] n = 173.
[q] n = 46.
[r] n = 182.
Abbreviations: ALT, alanine aminotransferase; anti-HCV Ab, anti-hepatitis C antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; HBsAg, hepatitis B surface antigen; MT, murine typhus; ST, scrub typhus.

that of ST.[25,28,29] However, these findings did not showed significance after multivariate analysis.

Doxycycline was suggested and widely used for the treatment of MT and ST.[3,7,30] MT often presents as a mild febrile disease, but patients with untreated MT still require 12–21 days to defervesce.[3] The duration of fever was significantly shorter post doxycycline treatment, with a median of 3 days[28] and a mean of 2.89 days.[31] For ST without treatment, the median duration of fever was 14.4 days.[4] The median time to defervescence after starting doxycycline treatment was 29–48 h.[32–34] Within 48 h after the initiation of antimicrobial therapy, 59.3–71.7% of patients with ST became afebrile.[32,33] This wide range reflected the diversity of disease severity and the duration from disease onset to hospital visit. To compare the efficacy of doxycycline treatment between the two diseases, matching of disease severity and extent of delay treatment was needed. To our knowledge, this current report might be the first study comparing defervescence patterns post doxycycline treatment in patients with ST or MT after propensity-score matching. In our study, the duration of febrile post-doxycycline treatment revealed no difference

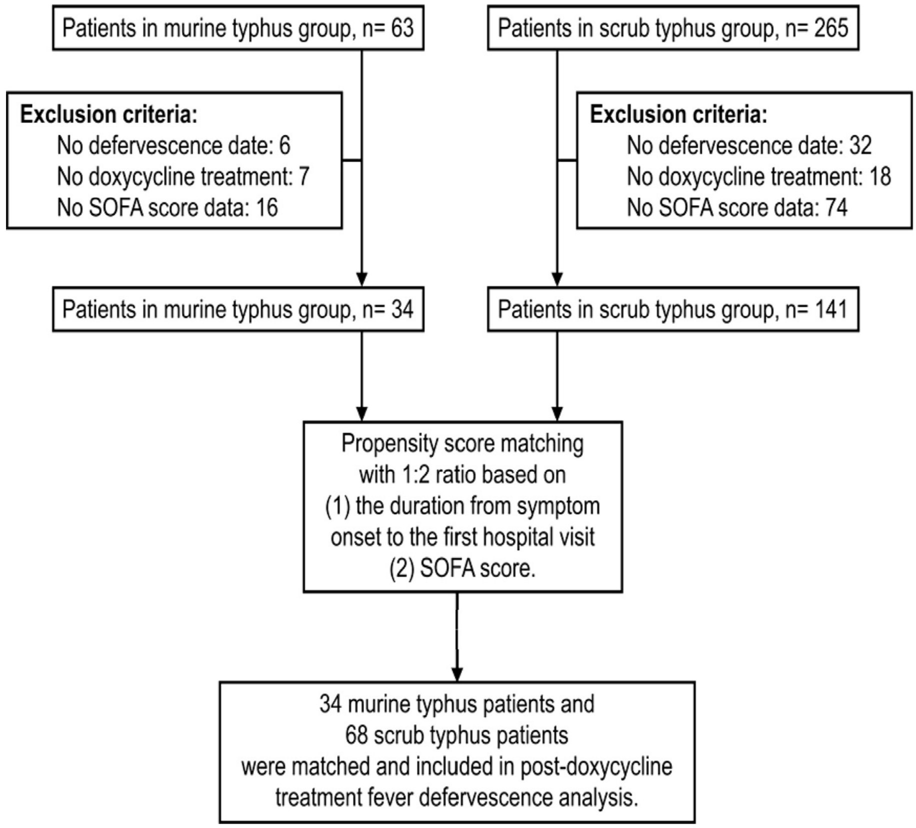

Figure 3. The flow chart of the propensity score matching study to determine the difference in defervescence between patients with scrub typhus (ST) and those with murine typhus (MT) after receiving doxycycline treatment.

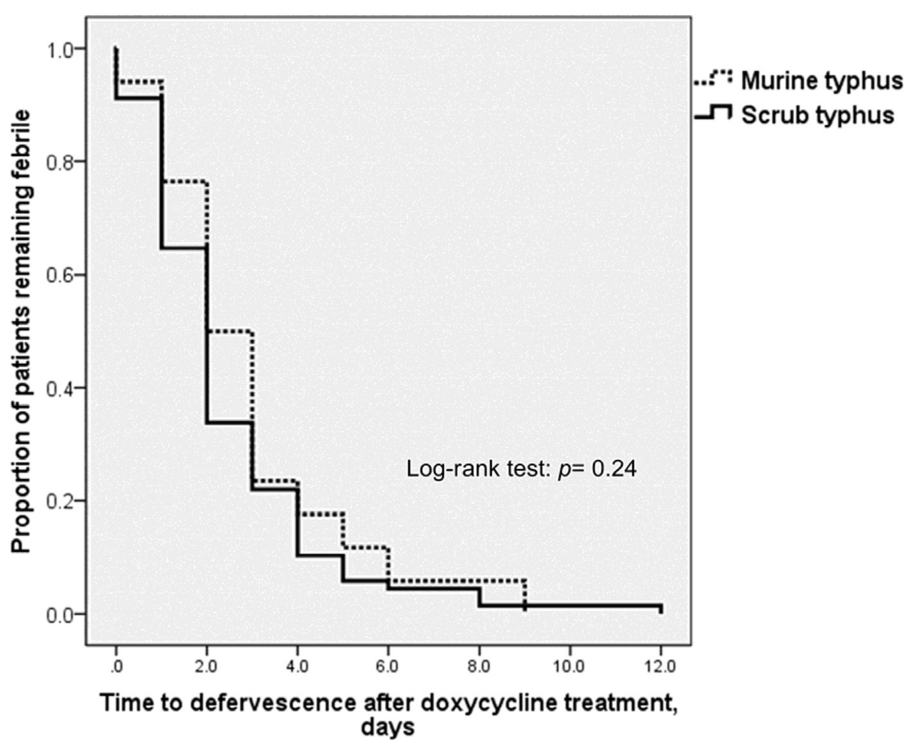

Figure 4. The proportion of defervesced patients presented in a Kaplan—Meier plot. There was no statistical significance between these two rickettsioses after receiving doxycycline treatment in the propensity score-matched population.

between these two rickettsioses before or after propensity-score matching.

Our study still had several limitations. First, not all the included patients underwent serological tests for both ST and MT; thus co-infection may be under-estimated. Second, due to the retrospective nature of the study, the bias of clinical information including exposure history, symptoms and signs may exist. Third, several factors showed significance in univariate analysis but some cases with one of these two diseases could not be investigated in the multivariate analysis. Those factors would potentially become independent predictive factors between these two diseases, such as island area exposure history, arthropod bite history, eschar and lymphadenopathy for ST.

In summary, our findings suggested that mountainous area exposure history was an independent predictive factor for ST and history of contact with rats was an independent predictive factor for MT. Of note, island area exposure history, arthropod bite history, eschar and lymphadenopathy were only reported from ST patients. In the post-doxycycline treatment analysis of propensity score-matched patients, the treatment responses were good and the median time to defervescence was 2 days for both diseases. There was no difference in post-doxycycline defervescence curves between the two rickettsioses.

Ethical approval

The Institutional Review Board of the Chang Gung Memorial Hospital approved the study protocol (no. 201800591B0).

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2019.04.004.