Journal of Microbiology, Immunology and Infection (2017) 50, 104—111

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Identification of factors for physicians to facilitate early differential diagnosis of scrub typhus, murine typhus, and Q fever from dengue fever in Taiwan

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

[a] *Department of Internal Medicine, Kaohsiung Municipal Hsaio-Kang Hospital, Kaohsiung, Taiwan*
[b] *School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[d] *Tropical Medicine Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[e] *Department of Internal Medicine, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan*
[f] *Center of Infection Control, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan*
[g] *Tropical Medicine Research Center, College of Medicine, Kaohsiung Medical University, Taiwan*
[h] *Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[i] *Department of Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[j] *Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Received 5 January 2014; received in revised form 30 September 2014; accepted 9 December 2014
Available online 26 December 2014

KEYWORDS
dengue fever;
murine typhus;
Q fever;
rainfall;
scrub typhus;
temperature

Background: Dengue fever, rickettsial diseases, and Q fever are acute febrile illnesses with similar manifestations in tropical areas. Early differential diagnosis of scrub typhus, murine typhus, and Q fever from dengue fever may be made by understanding the distinguishing clinical characteristics and the significance of demographic and weather factors.
Methods: We conducted a retrospective study to identify clinical, demographic, and meteorological characteristics of 454 dengue fever, 178 scrub typhus, 143 Q fever, and 81 murine typhus cases in three Taiwan hospitals.

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Number 100 Tzyou 1st Road, Kaohsiung, Taiwan.
E-mail address: d830166@gmail.com (P.-L. Lu).
[k] These two authors have contributed equally to this work.

http://dx.doi.org/10.1016/j.jmii.2014.12.001

Results: Case numbers of murine typhus and Q fever correlated significantly with temperature and rainfall; the scrub typhus case number was only significantly related with temperature. Neither temperature nor rainfall correlated with the case number of dengue fever. The rarity of dengue fever cases from January to June in Taiwan may be a helpful clue for diagnosis in the area. A male predominance was observed, as the male-to-female rate was 2.1 for murine typhus and 7.4 for Q fever. Multivariate analysis revealed the following six important factors for differentiating the rickettsial diseases and Q fever group from the dengue fever group: fever ≥8 days, alanine aminotransferase > aspartate aminotransferase, platelets >63,000/mL, C-reactive protein >31.9 mg/L, absence of bone pain, and absence of a bleeding syndrome.
Conclusion: Understanding the rarity of dengue in the first half of a year in Taiwan and the six differentiating factors may help facilitate the early differential diagnosis of rickettsial diseases and Q fever from dengue fever, permitting early antibiotic treatment.

Introduction

Dengue fever, scrub typhus, murine typhus, and Q fever are common infections in tropical Asia and often present initially as acute febrile illnesses of unclear etiology.[1,2] Many clinical manifestations and laboratory results of dengue fever[2–4] resemble those of rickettsial diseases (such as scrub typhus and murine typhus) and Q fever,[5–9] which makes an early diagnosis difficult. The local data revealed the mortality rate of scrub typhus cases to be 1.5–3%[10,11] and that of murine typhus to be 1.2%.[12] The limited data with regard to Q fever in Taiwan revealed no mortality.[13] The mortality rate of dengue fever is 0.4%, but that of dengue hemorrhagic fever is 8.7%.[14] For suspected cases of scrub typhus, murine typhus, and Q fever, empirical doxycycline is indicated to save lives. In cases of dengue fever, careful observation for the occurrence of dengue hemorrhagic fever is warranted. Therefore, establishing an early differential diagnosis of these diseases is important for providing the appropriate antimicrobial therapy and carefully monitoring anticipated complications.

We retrospectively evaluated cases of dengue fever, rickettsial diseases (scrub typhus and murine typhus), and Q fever from three Taiwan hospitals located south of the Tropic of Cancer. This tropical area has the highest case numbers of dengue fever, rickettsial diseases, and Q fever in Taiwan. In Taiwan, there are case series reports of Q fever, scrub typhus, murine typhus, and dengue fever.[15–17] Our aim was to compare the demographics and clinical characteristics of dengue fever with those of rickettsial diseases and Q fever in order to help with the establishment of an early differential diagnosis. The associated incidence of the four diseases each month and weather factors (i.e., temperature and rainfall) were also analyzed.

Methods

We retrospectively reviewed the charts of all the patients with dengue fever, scrub typhus, murine typhus, or Q fever in three Taiwan hospitals KMUH (Kaohsiung Medical University Hospital), KMHKH (Kaohsiung Municipal Hsaio-Kang Hospital), and NCKUH (National Cheng Kung University Hospital) from 1995 to 2009. The three hospitals that provide about 20% of the hospital beds in the Kaohsiung and Tainan regions are located in a region that is home to about 4,643,000 persons in an area of 5138 km^2. This work was approved by the Institute Ethics Committee of Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (KMUH-IRB-960195 and KMUH-IRB-970216). The Institute Ethics Committee of Kaohsiung Medical University Hospital waived the need for written informed consent from the participants because of the nature of the study and the retrospective collection of routine medical practice data. We collected data including demographic characteristics (including age, gender, and location), clinical manifestations, and laboratory results. All data analyzed were anonymized. The characteristics of murine typhus cases in the study have already been reported.[12] Relative bradycardia was defined as an increase in heart rate by <10 beats/min/°C increase in temperature in the absence of cardiac arrhythmia, a pacemaker, or administration of beta-blockers.[18]

Case definitions

All the laboratory diagnostic methods were performed at the laboratories of the Center for Disease Control and Prevention, Taiwan. The diagnosis of dengue fever was confirmed if one of the following criteria was met: (1) virus isolation; (2) positive result of real-time polymerase chain reaction; (3) positive result of higher-titer dengue-specific immunoglobulin (Ig)M and IgG antibodies in a single serum specimen, in which cross-reaction to Japanese encephalitis had been excluded; or (4) positive seroconversion or ≥4-fold rise in dengue-specific IgM or IgG antibody from the acute phase compared with the convalescent phase.[19] The diagnosis of Q fever was made based on the presence of fever and a compatible serologic profile, which included at least a 4-fold increase in Phase II IgG titers between the acute and convalescent sera or the presence of a significant titer of Phase II IgM (≥1:50) by indirect immunofluorescence assay at the Centers for Disease Control, Taiwan.[6,20] Scrub typhus was diagnosed from patients' blood samples based on a polymerase chain reaction analysis[21] or the serology result of an indirect microimmunofluorescence assay for *Orientia tsutsugamushi*. Diagnostic immunofluorescence assay must have met the following criteria: the total antibody titer for

Karp, Kato, and Gilliam for strains of *O. tsutsugamushi* must have had a $\geq$4-fold rise in paired positive serum samples or antibody titer for IgM $\geq$1:80.[9] The diagnosis of murine typhus was based on the presence of compatible symptoms and signs (usually a febrile illness) and a significant serologic profile, which required at least a 4-fold increase in IgG titers between the acute and convalescent sera or the presence of a significant immunofluorescence assay result against *Rickettsia typhi* of IgM ($\geq$1:80).[22]

Statistical analysis

Statistical analyses were performed using a 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 SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Selected variables in univariate analysis were examined with the receiver-operating characteristic (ROC) curve for choosing the best cut-point value. ROC curves were generated using MedCalc version 9.3.2.0 (MedCalc Software, Mariakerke, Belgium). A logistic regression model for multivariate analysis was generated for the significant variables in the univariate analysis. The monthly average temperatures (°C) and rainfall (mm) in the Tainan and Kaohsiung areas were obtained from the Central Weather Bureau, Taiwan (http://www.cwb.gov.tw/V5e/index.htm), and the average values of the two areas were arbitrarily used to represent the outdoor temperature and rainfall. The degree of linear relationship between case numbers of dengue fever, rickettsial diseases, Q fever, and average temperature (°C) per month was calculated using Spearman's rank correlation, and the correlation was considered significant at the level of 0.01 (2 tailed).

Results

A total of 178 scrub typhus, 143 Q fever, 81 murine typhus, and 454 dengue fever cases were included in the study. The majority of dengue fever cases (309 cases, 68.06%) appeared between August and October (Fig. 1). The case numbers of murine typhus and Q fever peaked in July, but for scrub typhus it occurred in September. The overall case numbers of Q fever, murine typhus, and scrub typhus per month ranged from 11 cases in February to 57 cases in September. The majority of rickettsial disease and Q fever cases (251 cases, 62.43%) appeared between June and October (Fig. 1). The distribution of temperature, rainfall, and case numbers of the four diseases is presented in Fig. 1. A significant correlation was noted between monthly average temperatures (°C) and overall case numbers of the rickettsial diseases and Q fever group [correlation coefficient (Rs) $= 0.851$, $p < 0.001$]. The associations of temperature to the four diseases were as follows: Rs $= 0.823$, $p = 0.001$ for murine typhus; Rs $= 0.643$, $p = 0.024$ for scrub typhus; Rs $= 0.721$, $p = 0.008$ for Q fever; and Rs $= 0.336$, $p = 0.285$ for dengue fever. The association with rainfall was as follows: Rs $= 0.697$, $p = 0.012$ for the rickettsial diseases and Q fever group. The associations of rainfall with the four individual diseases were as follows: Rs $= 0.622$, $p = 0.031$ for murine typhus; Rs $= 0.427$, $p = 0.167$ for scrub typhus; Rs $= 0.717$, $p = 0.009$ for Q fever, and Rs $= 0.126$, $p = 0.696$ for dengue fever. Among demographic factors, the majority of cases of rickettsial diseases and Q fever were 40–59 years old (Fig. 2A). However, the majority of dengue fever cases were 30–69 years of age (Fig. 2B). Male predominant is obvious in rickettsial diseases and Q fever (Fig. 2C), and the male-to-

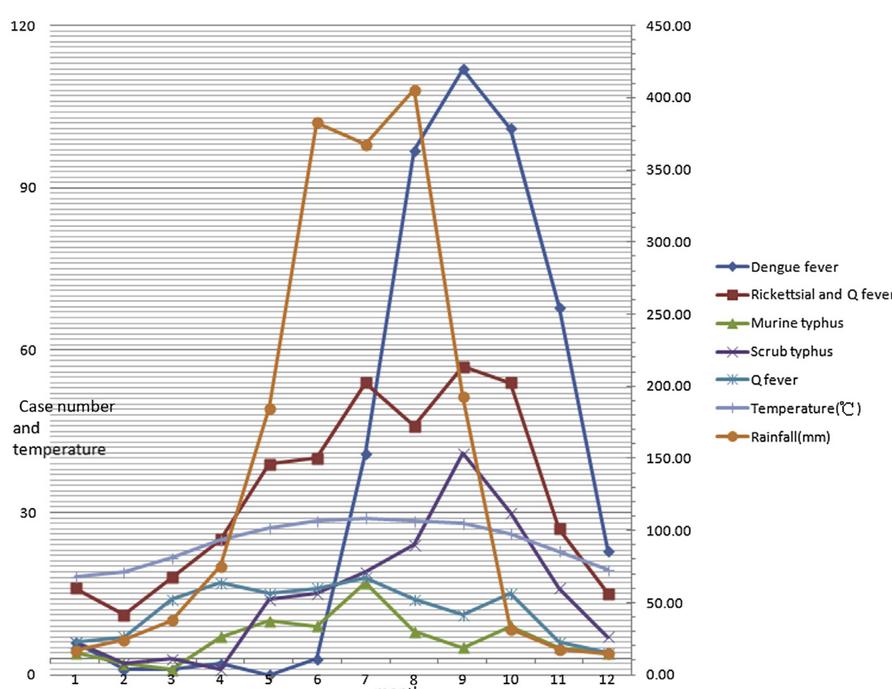

Figure 1. Monthly distribution of the 402 cases of rickettsial infection and Q fever, and the 454 cases of dengue fever (1992–2009), and their correlation with average temperature (°C) and rainfall (mm) in the Tainan and Kaohsiung areas.

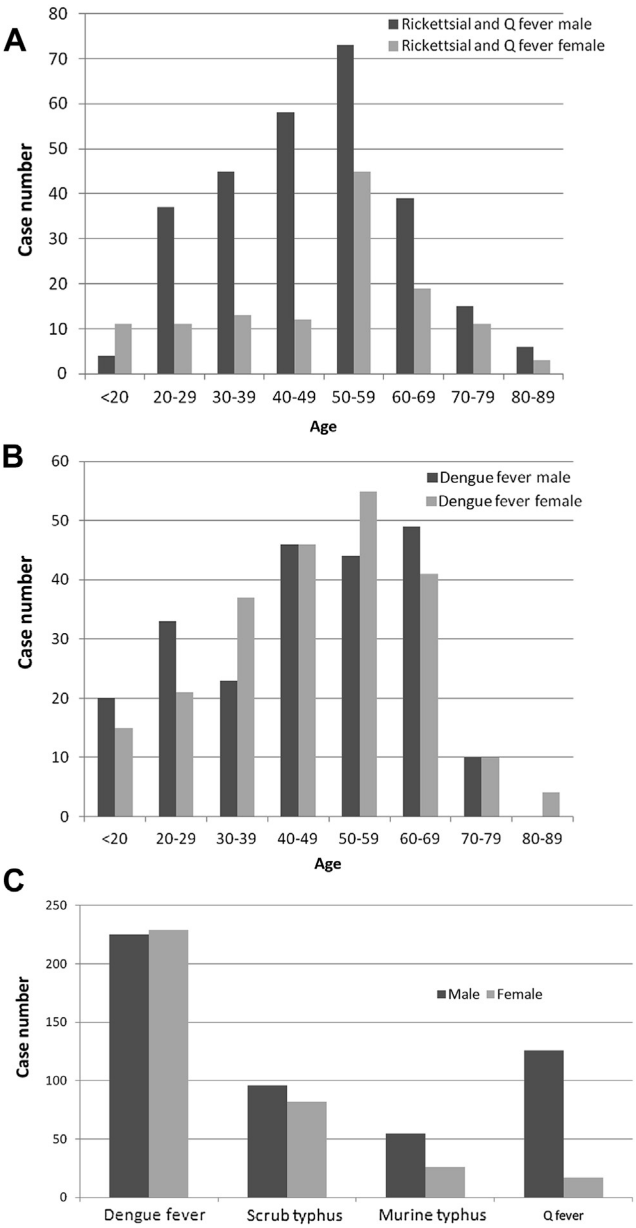

Figure 2. (A) Annual case numbers of rickettsial infection and Q fever in the study sites (1992–2009). (B) Annual case numbers of dengue fever in the study sites (1992–2009). (C) Male-to-female ratios of the four diseases.

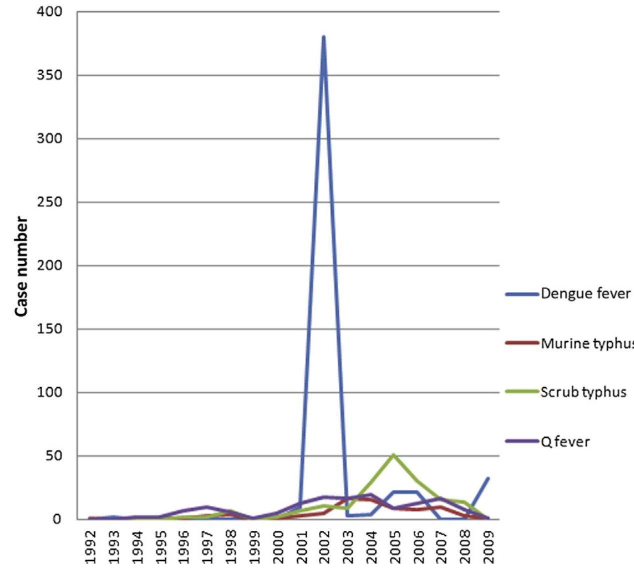

Figure 3. Age and gender distribution of the 402 cases of rickettsial infection and Q fever, and the 454 cases of dengue fever in southern Taiwan (1992–2009).

female ratio was 1.2 for scrub typhus, 2.1 for murine typhus, and 7.4 for Q fever cases.

The annual case numbers of the four diseases are presented in Fig. 3. Among Q fever and rickettsial diseases, Q fever is the most common disease in NCKUH, but scrub typhus is the predominant disease in KMUH. All three diseases are almost equivalent in KMHKH. The clinical and laboratory parameters in the dengue group and the rickettsial diseases and Q fever group are presented in Table 1. For the dengue fever group, the mean age was 46.26 years and 225 participants (49.6%) were male. For the rickettsial diseases and Q fever group, the mean age was 47.93 years and 277 individuals (68.9%) were male. Laboratory parameters of the dengue and the rickettsial diseases groups are presented in Table 2. Patients in the rickettsial diseases and Q fever groups had significantly higher mean values than dengue patients for initial alanine aminotransferase (ALT), maximum ALT, initial aspartate aminotransferase (AST), maximum AST, γ-glutamyl transpeptidase, initial C-reactive protein (CRP), initial white blood cells, initial platelet, initial blood urea nitrogen, fever prior to admission, duration of hospitalization, defervescence after effective therapy (days), and total duration of fever. Patients with dengue fever had significantly lower mean values of leukocyte and platelet counts.

The clinical characteristics of the patients with rickettsial diseases and Q fever are presented in Table S1. Patients with Q fever had a significantly longer fever duration after effective treatment ($p < 0.001$) and total duration of fever ($p < 0.001$). The difference in laboratory parameters between the Q fever and rickettsial diseases groups are presented in Table S2. Patients in both groups had abnormal liver function, but patients with Q fever had significantly higher mean values of platelet counts. Patients in the rickettsial diseases group had higher lactic acid dehydrogenase (LDH) levels than patients with Q fever ($p = 0.003$). The patients with Q fever usually had LDH levels two times higher than the upper normal limit (mean, 211 IU/L). The patients with scrub typhus or murine typhus tended to have LDH levels 3.5 times that of the upper normal limit. Based on ROC curve analysis, the sensitivity was 77.2% and specificity was 74.2% when an LDH level of 651 IU/L was used as a criterion to differentiate between Q fever and rickettsial diseases (area under curve: 0.772, 95% confidence interval: 0.706–0.829, $p = 0.0001$).

After identifying the significant variables using univariate analysis (Tables 1 and 2), multivariate analysis was performed with logistic regression. The variables selected in the univariate analysis were further examined with the ROC curve to choose the most suitable cut-point value (Table 3). The cut-point value was 63,000/mL for platelet

Table 1 Comparison of the clinical characteristics between the rickettsial diseases and Q fever group, and the dengue fever group in southern Taiwan during 1995–2009

Characteristics	QSM group[a]	Dengue fever	p[b]
Fever	394/400 (98.5)	414/421 (98.3)	0.852
Chills	232/361 (64.3)	180/223 (80.7)	<0.001
Headache	200/363 (55.1)	221/290 (76.2)	<0.001
Bone pain	45/355 (12.7)	209/272 (76.8)	<0.001
Retrobulbar pain	12/354 (3.4)	77/218 (35.3)	<0.001
Diarrhea	53/355 (14.9)	98/243 (40.3)	<0.001
Cough	115/362 (31.8)	113/282 (40.1)	0.03
Nausea	73/325 (23.4)	141/259 (54.4)	<0.001
Abdominal pain	70/330 (21.2)	101/226 (44.7)	<0.001
Skin rash	86/355 (24.2)	185/339 (54.6)	<0.001
Petechia	3/402 (0.75)	130/223 (58.3)	<0.001[c]
Gum bleeding	0/302 (0)	56/215 (26)	<0.001[c]
Eschar	74/320 (23.1)	0/454 (0)	<0.001[c]
Age (y)	47.93 ± 16.51	46.26 ± 16.93	0.146
Male	277/402 (68.9)	225/454 (49.6)	<0.001
Relative bradycardia	151/330 (45.8)	90/218 (41.3)	0.302
Bleeding syndrome[d]	5/340 (1.5)	188/309 (60.8)	<0.001[c]
Pain syndrome[e]	224/345 (64.9)	319/359 (89.1)	<0.001
No upper respiratory infection syndrome	103/334 (30.8)	308/424 (72.6)	0.002
Fever prior to admission (d)	7.0 ± 4.9	3.4 ± 1.7	<0.001
Duration of hospitalization (d)	7.3 ± 5.2	6.0 ± 2.5	<0.001
Defervescence after effective therapy (d)	4.2 ± 5.2	2.9 ± 2.4	0.003
Duration of fever (d)	10.8 ± 7.4	6.2 ± 2.5	<0.001
Fever ≥8 d	240/375 (64)	70/337 (20.8)	<0.001

[a] QSM group includes 132 patients with scrub typhus, 119 with Q fever, and 64 with murine typhus in three Taiwan hospitals during the period of 1995–2009.
[b] Determined using χ^2 test.
[c] Determined using Fisher's exact test.
[d] Bleeding syndrome definition: positive tourniquet test, petechiae, gum bleeding, epistaxis, menorrhalgia, or gastrointestinal bleeding.
[e] Pain syndrome definition: headache, retro-orbital pain, bone pain, muscle pain, and arthralgia; upper respiratory infection syndrome definition: cough, sputum, rhinorrhea, or sore throat.
Data are presented as *n*/*N* (%).
QSM group = rickettsial diseases and Q fever group.

counts (sensitivity: 89.6, specificity: 34.2), 31.9 mg/L for CRP (sensitivity: 79.7%, specificity: 82.2%), 12.4 g/dL for Hb (sensitivity: 27.7%, specificity: 79.4%), and 4670/mm^3 for white blood cell counts (sensitivity: 80%, specificity: 64.9%). Multivariate analysis revealed six factors useful for differentiating the rickettsial diseases and Q fever group from the dengue fever group, which include fever ≥8 days, ALT > AST, platelet counts, CRP levels, absence of bone pain, and absence of a bleeding syndrome (Table 3).

Discussion

For the differential diagnosis of dengue fever versus rickettsial diseases and Q fever, clinicians may first consider the difference in local disease incidence each month. Rickettsial diseases and Q fever were constantly seen in southern Taiwan in every month of the year. By contrast, the occurrence of dengue fever was primarily observed in the latter half of the year. The rarity of dengue fever cases from January to June in Taiwan would be helpful in making a tentative diagnosis. However, the occurrences of rickettsial diseases and Q fever in these months were less too. Therefore, the six clinical characteristics identified in the study for an early differential diagnosis will be more important.

Our results revealed that the occurrences of murine typhus and Q fever correlated significantly with temperature and rainfall; scrub typhus was only significantly related with temperature. Neither temperature nor rainfall correlated with the case numbers of dengue fever. The fact that temperature had a strong impact on the occurrence of murine typhus and scrub typhus is consistent with a finding in southern France that warmer weather is associated with tick attacks and occurrences of rickettsioses.[23] It has also been demonstrated that rainfall, minimum temperature, and relative humidity were with 3-month lag and 1-month lag of high mosquito larval density and were significant predictors of dengue fever incidence in Kaohsiung, a major city in southern Taiwan.[24,25] It is likely that suitable weather conditions for a period of time are essential for the mosquito vectors to adequately proliferate for an endemic dengue fever outbreak to occur. However, we did not assess a time-lag effect with regard to weather factors on the case

Table 2 Comparison of clinical laboratory data between the rickettsial diseases and Q fever group, and the dengue fever group in southern Taiwan during 1995–2009

Characteristics	QSM group[a]	Dengue fever	*p*
Initial AST (IU/L)	144.68 ± 164.5	112.39 ± 1684.4	0.009
Maximum AST (IU/L)	170.28 ± 258.93	114.27 ± 168.18	<0.001
Initial ALT (IU/L)	148.4 ± 145.46	78.01 ± 111.7	<0.001
Maximum ALT (IU/L)	165.2 ± 182.3	79.6 ± 112.13	<0.001
AST/ALT >1 (%)	141/278 (50.7)	305/350 (87.1)	<0.001
Alkaline-phosphatase (IU/L)	226.52 ± 212.36	205.75 ± 193.46	0.517
γ-Glutamyl transpeptidase (mg/dL)	167.83 ± 145.66	79.01 ± 85.23	<0.001
LDH (IU/L)	597.84 ± 699.64	852.71 ± 422.45	0.052
Serum creatinine (g/L)	1.46 ± 3.35	1.27 ± 1.53	0.339
Initial CRP (mg/L)	86.29 ± 79.24	20.50 ± 21.88	<0.001
Initial WBC (/mm^3)	7.08 ± 3.19	4.38 ± 2.29	<0.001
Initial hemoglobin (g/L)	13.81 ± 3.97	13.7 ± 1.7	0.658
Initial platelets (/mm^3)	137.63 ± 71.4	101.79 ± 65.53	<0.001
Prolongation of aPTT (%)	140/188 (74.5)	225/255 (88.2)	<0.001
Initial blood urea nitrogen	15.47 ± 17.99	13.0 ± 7.92	0.024

[a] QSM group includes 178 patients with scrub typhus, 143 with Q fever, and 81 with murine typhus in three Taiwan hospitals from 1995 to 2009.
Data are presented as *n*/*N* (%) or mean ± SD.
ALT = serum alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = serum aspartate aminotransferase; CRP = C-reactive protein; LDH = lactic acid dehydrogenase; QSM group = rickettsial diseases and Q fever group; WBC = white blood cells.

numbers of the four tropical diseases owing to the small case numbers of dengue fever in this study.

Among the demographic factors, male predominance was apparent among the rickettsial diseases in our study cohort. The male-to-female ratio for scrub typhus in our study was 1.2. This ratio was 2.1 for murine typhus and 7.4 for Q fever cases. In the related literature, the ratio for scrub typhus is in the range of 0.518–1.1,[26–28] for murine typhus cases 0.67–1.50,[29,30] and for Q fever 1.6–2.5.[31–33] The male-to-female ratio for Q fever was higher than murine typhus and scrub typhus in our study and in other reports. A possible explanation for this observation is presented in a study on mice with Q fever, which revealed a protective role for 17 beta-estradiol,[34] and the predisposition of scrub typhus, murine typhus, and Q fever in men may be related to more chances of staying outdoors. By contrast, dengue fever did not have this feature of male predominance.

Based on the analysis of the clinical and laboratory characteristics of the patients in this study, 27.2% of patients with scrub typhus had eschar, which was very helpful for the early diagnosis of this disease. Skin rash was more common for patients with dengue fever (54.6%) as compared to those with rickettsial diseases and Q fever (24.2%). Only a minority (2.8%) of patients with Q fever had a skin rash, indicating that the absence of a rash may be a marker for Q fever. With multivariate analysis, six factors were significantly different between the dengue group and the rickettsial diseases and Q fever groups. CRP levels of >31.9 mg/L had the highest odds ratio (OR), and this may have been due to an elevated CRP response to bacterial infection (rickettsial diseases and Q fever group) relative to virus infection (dengue fever group). The cut-point of the platelet counts for not suspecting dengue fever was found to be 63,000/mL, with an OR of 24.69. Although ALT > AST was significantly associated with dengue fever, this factor may not be clinically practical because both percentages were >50%. The absence of bone pain and bleeding syndromes were useful for predicting a lower likelihood of dengue infection (OR: 87.56 and 89.34, respectively). If a patient had a fever for >7 days, dengue fever was less likely than rickettsial infections or Q fever (OR: 14.67).

Table 3 Multivariate logistic regression analysis for differentiation of rickettsiosis/Q fever and dengue fever

Variables	Odds ratio	95% CI	*p*
Total fever ≥8 d	14.68	2.81–76.63	0.001
ALT/AST >1	13.18	2.15–80.86	0.005
Platelets >63,000/mL	24.69	3.66–166.40	0.001
C-reactive protein >31.9 mg/L	44.93	7.401–272.73	<0.001
No bone pain	87.56	14.25–538.06	<0.001
No bleeding syndrome	89.34	7.18–1111.55	<0.001

CI = confidence interval.

Despite some of the above differences, these four diseases may appear frequently from late summer to autumn, and some febrile cases can be extremely difficult to differentially diagnose clinically. At this time, clinicians may consider treating febrile cases with tetracycline/doxycycline first, under the suspicion of dengue fever, Q fever, or rickettsial diseases, as rickettsial disease and Q fever cases can benefit from this early empirical therapy.

There is an increasing trend of case numbers of dengue, Q fever, and rickettsial diseases from 1992 to 2009. This phenomenon can partly be attributed to the fact that clinicians are gaining experience and have a heightened alertness level in terms of the diagnosis of tropical diseases. In addition, the average temperature in Taiwan increased by 0.8°C in the past 100 years, according to the data of Central Weather Bureau of Taiwan [The Central Weather Bureau, Taiwan. Available at: http://www.cwb.gov.tw/V7/climate/climate_info/statistics/pdf/other.pdf (date accessed: May 28, 2014)].

According to the related literature a number of factors influence the transmission of Q fever, including vegetation, soil humidity, low groundwater level, and wind direction.[35] Rainfall and vegetation will influence soil humidity, which will reduce the amount of dust available for dispersion of bacteria. In addition, the effect of temperature and moisture on the *Rickettsia felis* infection in *Ctenocephalides* fleas had been reported.[36] It could be possible that the increase in temperature is also a cause of the increased case numbers of these four tropical diseases. However, the exact impact of weather change on these tropical diseases in Taiwan clearly requires further investigation.

Scrub typhus is transmitted to humans by the larval mite, and murine typhus is transmitted by the fleas of rodents.[12] There is an extensive wildlife and arthropod (mainly ticks) reservoir of *Coxiella burnetii*, and cattle, sheep, and goats are common sources of transmitting this microorganism to humans.[37] Therefore, occupational groups including abattoir workers and veterinarians are at risk of *C. burnetii* infection, while rural activity is regarded as a risk factor for rickettsiosis.[38,39] Furthermore, suspected patients who have been active in outdoor leisure activities with increased exposure to and contact with vectors should also be considered for early differential diagnosis.[12,13,40]

Our study had the following limitations. The male predominance in the rickettsial diseases group could be affected by the difference in travel and occupational exposure between genders, but this could not be elucidated because detailed travel, occupation, and rural life histories of most of the patients were lacking. In this study, imported dengue cases were excluded from analysis; it was appropriate to exclude imported cases to correlate the dengue case numbers with weather factors. The relationship between the occurrence of diseases and the meteorological data by season category was not analyzed due to the vague differences in weather factors over the typical four seasons in such tropical areas.

In summary, our findings suggested methods for clinicians to distinguish between these two types of infections. Based on the six factors that help differentiate between the rickettsial diseases and dengue fever groups (fever $\geq$ 8 days, ALT/AST $>$ 1, platelet count $>$ 63,000/mL, CRP $>$ 31.9 mg/L, absence of bone pain, and absence of a bleeding syndrome), an early suspicion of rickettsial diseases would allow for the early administration of antibiotic treatment in an effort to help save lives.

Ethical approval

This work was approved by the Institute Ethics Committee of the Kaohsiung Medical University Hospital (KMUH-IRB-960195 and KMUH-IRB-970216).

Conflicts of interest

None declared.

Acknowledgments

This work was supported by grants from the foundation of the Kaohsiung Municipal Hsaio-Kang Hospital, Kaohsiung Medical University (KMHK-96-013), and the National Science Council (NSC 97-2321-B-037-004). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2014.12.001.

References

1. Silpapojakul K. Scrub typhus in the Western Pacific region. *Ann Acad Med Singapore* 1997;**26**:794—800.
2. Watt G, Jongsakul K, Chouriyagune C, Paris R. Differentiating dengue virus infection from scrub typhus in Thai adults with fever. *Am J Trop Med Hyg* 2003;**68**:536—8.
3. Jensenius M, Fournier PE, Raoult D. Rickettsioses and the international traveler. *Clin Infect Dis* 2004;**39**:1493—9.
4. Daumas RP, Passos SR, Oliveira RV, Nogueira RM, Georg I, Marzochi KB, et al. Clinical and laboratory features that discriminate dengue from other febrile illnesses: a diagnostic accuracy study in Rio de Janeiro, Brazil. *BMC Infect Dis* 2013; **13**:77. http://dx.doi.org/10.1186/1471-2334-13-77.
5. Chadwick D, Arch B, Wilder-Smith A, Paton N. Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: application of logistic regression analysis. *J Clin Virol* 2006;**35**:147—53.
6. Ko WC, Liu JW, Chuang YC. Acute Q fever as a cause of acute febrile illness of unknown origin in Taiwan: report of seven cases. *J Formos Med Assoc* 1997;**96**:295—7.
7. Lai PC, Lee SS, Kao CH, Chen YS, Huang CK, Lin WR, et al. Characteristics of a dengue hemorrhagic fever outbreak in 2001 in Kaohsiung. *J Microbiol Immunol Infect* 2004;**37**: 266—70.
8. PicKard AL, McDaniel P, Miller RS, Uthaimongkol N, Buathong N, Murray CK, et al. A study of febrile illnesses on the Thai—Myanmar border: predictive factors of rickettsioses. *Southeast Asian J Trop Med Public Health* 2004;**35**:657—63.
9. Wang CC, Liu SF, Liu JW, Chung YH, Su MC, Lin MC. Acute respiratory distress syndrome in scrub typhus. *Am J Trop Med Hyg* 2007;**76**:1148—52.
10. Tsay RW, Chang FY. Serious complications in scrub typhus. *J Microbiol Immunol Infect* 1998;**31**:240—4.
11. Wu KM, Wu ZW, Peng GQ, Wu JL, Lee SY. Radiologic pulmonary findings, clinical manifestations and serious complications in scrub typhus: experiences from a teaching hospital in eastern Taiwan. *Int J Gerontol* 2009;**3**:223—32.
12. Chang K, Chen YS, Lee NY, Lee HC, Lin CY, Tsai JJ, et al. Murine typhus in southern Taiwan between 1992 and 2009. *Am J Trop Med Hyg* 2012;**87**:141—7.
13. Chang K, Lee NY, Chen YH, Lee HC, Lu PL, Chang CM, et al. Acute Q fever in southern Taiwan: atypical manifestations of hyperbilirubinemia and prolonged fever. *Diagn Microbiol Infect Dis* 2008;**60**:211—6.
14. Lee MS, Hwang KP, Chen TC, Lu PL, Chen TP. Clinical characteristic of dengue and dengue hemorrhagic fever in a medical center of southern Taiwan during the 2002 epidemic. *J Microbiol Immunol Infect* 2006;**39**:121—9.
15. Lai CH, Huang CK, Chen YH, Chang LL, Weng HC, Lin JN, et al. Epidemiology of acute Q fever, scrub typhus, and murine

typhus, and identification of their clinical characteristics compared to patients with acute febrile illness in southern Taiwan. *J Formos Med Assoc* 2009;**108**:367—76.
16. Lee HC, Ko WC, Lee HL, Chen HY. Clinical manifestations and complications of rickettsiosis in southern Taiwan. *J Formos Med Assoc* 2002;**101**:385—92.
17. Hung MN, Chou YF, Chen MJ, Hou MY, Lin PS, Lin CC, et al. Q fever outbreak in a small village, Taiwan. *Jpn J Infect Dis* 2010;**63**:212—3.
18. Aronoff DM, Watt G. Prevalence of relative bradycardia in *Orientia tsutsugamushi* infection. *Am J Trop Med Hyg* 2003;**68**:477—9.
19. Chang K, Lu PL, Ko WC, Tsai JJ, Tsai WH, Chen CD, et al. Dengue fever scoring system: new strategy for the early detection of acute dengue virus infection in Taiwan. *J Formos Med Assoc* 2009;**108**:879—85.
20. Chen HL, Chen HY, Wu YC, Horng CB. Q fever in Taiwan. *Zhonghua Yi Xue Za Zhi (Taipei)* 1994;**54**:1—6.
21. Chen HL, Chen HY, Horng CB. Surveillance of scrub typhus in Taiwan. *Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi* 1993;**26**:166—70.
22. Hernandez Cabrera M, Angel-Moreno A, Santana E, Bolanos M, Frances A, Martin-Sanchez MS, et al. Murine typhus with renal involvement in Canary Islands, Spain. *Emerg Infect Dis* 2004;**10**:740—3.
23. Parola P, Socolovschi C, Jeanjean L, Bitam I, Fournier PE, Sotto A, et al. Warmer weather linked to tick attack and emergence of severe rickettsioses. *PLoS Negl Trop Dis* 2008;**2**:e338.
24. Chen SC, Liao CM, Chio CP, Chou HH, You SH, Cheng YH. Lagged temperature effect with mosquito transmission potential explains dengue variability in southern Taiwan: insights from a statistical analysis. *Sci Total Environ* 2010;**408**:4069—75.
25. Wu PC, Lay JG, Guo HR, Lin CY, Lung SC, Su HJ. Higher temperature and urbanization affect the spatial patterns of dengue fever transmission in subtropical Taiwan. *Sci Total Environ* 2009;**407**:2224—33.
26. Kim DM, Kim SW, Choi SH, Yun NR. Clinical and laboratory findings associated with severe scrub typhus. *BMC Infect Dis* 2010;**10**:108.
27. Ogawa M, Hagiwara T, Kishimoto T, Shiga S, Yoshida Y, Furuya Y, et al. Scrub typhus in Japan: epidemiology and clinical features of cases reported in 1998. *Am J Trop Med Hyg* 2002;**67**:162—5.
28. Sonthayanon P, Chierakul W, Wuthiekanun V, Phimda K, Pukrittayakamee S, Day NP, et al. Association of high *Orientia tsutsugamushi* DNA loads with disease of greater severity in adults with scrub typhus. *J Clin Microbiol* 2009;**47**:430—4.
29. Dumler JS, Taylor JP, Walker DH. Clinical and laboratory features of murine typhus in south Texas, 1980 through 1987. *JAMA* 1991;**266**:1365—70.
30. Whiteford SF, Taylor JP, Dumler JS. Clinical, laboratory, and epidemiologic features of murine typhus in 97 Texas children. *Arch Pediatr Adolesc Med* 2001;**155**:396—400.
31. Ergas D, Keysari A, Edelstein V, Sthoeger ZM. Acute Q fever in Israel: clinical and laboratory study of 100 hospitalized patients. *Isr Med Assoc J* 2006;**8**:337—41.
32. Raoult D, Tissot-Dupont H, Foucault C, Gouvernet J, Fournier PE, Bernit E, et al. Q fever 1985-1998. Clinical and epidemiologic features of 1,383 infections. *Medicine (Baltimore)* 2000;**79**:109—23.
33. Tissot Dupont H, Raoult D, Brouqui P, Janbon F, Peyramond D, Weiller PJ, et al. Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. *Am J Med* 1992;**93**:427—34.
34. Leone M, Honstettre A, Lepidi H, Capo C, Bayard F, Raoult D, et al. Effect of sex on *Coxiella burnetii* infection: protective role of 17 beta-estradiol. *J Infect Dis* 2004;**189**:339—45.
35. van der Hoek W, Hunink J, Vellema P, Droogers P. Q fever in The Netherlands: the role of local environmental conditions. *Int J Environ Health Res* 2011;**21**:441—51.
36. Horta MC, Ogrzewalska M, Azevedo MC, Costa FB, Ferreira F, Labruna MB. Rickettsia felis in Ctenocephalides felis felis from five geographic regions of Brazil. *Am J Trop Med Hyg* 2014;**91**:96—100.
37. Guerrant RL, Walker DH, Peter F, Weller PF. *Tropical infectious diseases principals, pathogens, & practice*, vol. 1. Philadelphia: Churchill Livingstone; 1999.
38. Chang CC, Lin PS, Hou MY, Lin CC, Hung MN, Wu TM, et al. Identification of risk factors of *Coxiella burnetii* (Q fever) infection in veterinary-associated populations in southern Taiwan. *Zoonoses Public Health* 2010;**57**:e95—101.
39. de Rooij MM, Schimmer B, Versteeg B, Schneeberger P, Berends BR, Heederik D, et al. Risk factors of *Coxiella burnetii* (Q fever) seropositivity in veterinary medicine students. *PLoS One* 2012;**7**:e32108.
40. Lee YS, Wang PH, Tseng SJ, Ko CF, Teng HJ. Epidemiology of scrub typhus in eastern Taiwan, 2000—2004. *Jpn J Infect Dis* 2006;**59**:235—8.