# Clinical Features and Risk Factors for Severe Disease of Rickettsiosis: A Military Hospital-Based Study in Bangkok, Thailand

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**Background:** Rickettsiosis is Southeast Asia's third leading cause of undifferentiated fever. Due to limited epidemiological data and nonspecific symptoms, diagnosing the disease is complex, leading to treatment challenges and complications. Military personnel are at a higher risk for rickettsial exposure, and their treatment might be delayed due to military duties.
**Objectives:** The study aimed to investigate the outbreak, symptoms, and clinical manifestations of rickettsiosis, as well as the risk factors for severe disease, among patients treated at the military hospital in Bangkok, Thailand.
**Methods:** A retrospective analysis of rickettsiosis's epidemiology, symptoms, and clinical manifestations was performed. The data were collected from patient electronic medical records at Phramongkutklao Hospital from June 2009 to May 2020.
**Results:** Of 184 confirmed patients diagnosed with rickettsial infection, 12 scrub typhus, 16 murine typhus, and 156 were clinically diagnosed with rickettsiosis. Nineteen cases (10%) were grouped as severe rickettsial infection, and the other 165 (90%) were in the non-severe group. Fever, myalgia, rigor, and headache were common presentations of rickettsiosis. Alteration of consciousness and tachypnea were common in those with severe rickettsiosis group. Impaired renal function, elevated bilirubin, elevated alkaline phosphatases, aspartate aminotransferase, and alanine aminotransferase, pyuria, as well as abnormal chest radiographs, were more common findings in the severe rickettsiosis group. Additionally, the rate of ICU admission (73.7% vs. 8.5%, $p < 0.001$) and duration of hospitalization ($18.63 \pm 20$ vs. $7.42 \pm 7.58$, $p < 0.026$) were significantly higher in the severe rickettsiosis group. The mortality rate of rickettsiosis was 2.1%. Elevated bilirubin (OR = 17.93, 95% CI = 3.52-91.42, $p = 0.001$) and abnormal chest radiograph (OR = 11.73, 95% CI = 1.36-100.89, $p = 0.025$) were independently predictive for severe disease.
**Conclusion:** Murine typhus was more common in a military hospital in Bangkok and less severe than scrub typhus. Increased bilirubin levels and abnormal chest radiography with bilateral alveolar infiltration tend to predict severe rickettsial infection independently.

**Keywords:** rickettsiosis, murine typhus, scrub typhus

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## Introduction

Rickettsiosis is a disease caused by infection with the bacteria of the genus Rickettsia; it transmits to humans through bites of infected arthropod vectors such as fleas, ticks, and mites.[1] Rickettsial infections are found on every continent and throughout the year, and it is considered a significant cause of disability and death in Southeast Asia. [2-4] Based on data from untreated cases in endemic areas, mortality rates can be as high as 30-35%, according to a study from Bangladesh.[5] However, the mortality rate drops to around 5% with appropriate treatment.[5, 6] In Southeast Asia, rickettsiosis is the third leading cause of fever of unknown origin, following malaria and dengue fever.[7-9] Moreover, scrub typhus accounts for up to 33% of fever cases of unknown origin in the Thailand-Myanmar border area.[10] In Thailand, data collected between 1999 and 2014 indicated that scrub typhus was the most common cause of rickettsial diseases, accounting for up to 16% of cases, followed by murine typhus at 5%, and spotted fever group rickettsiosis.[11, 12]

The common symptoms of rickettsiosis include high-grade fever, headache, erythematous rash, blisters on the body, loss of appetite, nausea, vomiting, muscle pain, enlarged lymph nodes, and in some cases, eschars (black scabs) at the site of insect bites, typically found in skin folds such as the armpits, groin, and trunk.[9, 13, 14] Studies on patients with rickettsiosis along the Thailand-Myanmar border have identified these symptoms as indicative of the disease [Odds ratio (OR) = 21.1, 95% confidence interval (CI) = 5.4–82.4].[10] The presentation of rickettsiosis can vary from mild symptoms to severe organ failure, such as hypotension, thrombocytopenia, kidney failure, liver failure, myocarditis, meningoencephalitis, and death. [6, 14-18]

Additionally, rickettsiosis can be diagnosed through serological tests, which is the mainstay of diagnosis. Immunofluorescence assays (IFA) are currently considered the gold standard for diagnosis. However, it has limitations as it requires two separate tests spaced apart to observe changes in antibody levels (four-fold rising), and it may yield false-negative results if performed too early or after antibiotic treatment. It can also yield false-positive results in patients previously infected. [19-21] Apart from serological tests, nucleic acid amplification tests (NAATs) such as PCR are now used for diagnosis. These tests can detect the bacterium faster, eliminate the need for repeat testing, and differentiate between different strains of the bacterium causing the disease. However, NAATs are complex and not widely available.[21]

Currently, there are limitations in the available data on the epidemiology and impact of rickettsiosis, and its diagnosis is still considered slow and less accurate than the actual occurrence due to the nonspecific nature of its symptoms. Additionally, some patients can recover without treatment, leading to underdiagnosis and delayed diagnosis. This results in misdiagnosis and delayed administration of appropriate antibiotics, leading to complications and increased morbidity and mortality rates. Military personnel face a higher risk of rickettsial exposure, as previously reported in an outbreak, and delayed treatment might occur due to military duties. [22]

Therefore, we studied the epidemiology of rickettsiosis in patients admitted at Phramongkutklao Hospital. The study aimed to investigate the symptoms and signs essential for diagnosing rickettsiosis and the risk of developing severe complications. Thus, it could be instrumental in the early diagnosis of the disease, prompt treatment, reduction of complications, hospitalization days, and mortality rates associated with this disease, particularly among military personnel.

## Methods

*Study design and population*

We performed a retrospective study at Phramongkutklao Hospital, a 1200-bed military teaching hospital for Phramongkutklao College of Medicine in Bangkok, Thailand. The hospital provides tertiary-level care to military personnel, their families, and civilians. The Institutional Review Board, Royal Thai Army Medical Department, approved the study (Approval number IRBRTA R080h/65). As the data were retrospective and de-identified, the Committee waived the requirement for informed consent.

Patients were eligible for inclusion in the study if they were admitted to the hospital between 1 June 2009 and 30 May 2020 with a diagnosis of rickettsiosis according to specific criteria. Patients were grouped into severe and non-severe rickettsial infections. Inclusion criteria were age 18 or older and diagnosed with rickettsiosis by clinical or serological means at positive serological titer > 1:50 IFA for scrub typhus/ murine typhus. Clinical diagnosis of rickettsiosis was defined as the patients who met all the following criteria: Presented with acute undifferentiated febrile illness (AUFI); a patient who had acute fever (≤ 14 days) without obvious organ-specific symptoms and signs of infection, for example, cellulitis, pneumonia, and acute pyelonephritis.[7] Those who had negative acute or convalescent sera of IFA for scrub typhus/ murine typhus and those with negative blood culture, and all the following laboratory (dengue NS1Ag, IgM, *Leptospira* antibody, malaria thick and thin film). Those who responded to empirical antibiotics of rickettsiosis, doxycycline, or azithromycin within 48 hours. The physician diagnosed and decided to prescribe an entire course of antibiotics, doxycycline or azithromycin, to treat rickettsiosis. Exclusion criteria were patients who were transferred to other hospitals within seven days after admission and could not follow up.

*Study procedure*

The patient's electronic medical records were reviewed for their demographic data, clinical presentation, laboratory results, and disease course in both groups during rickettsial diagnosis. Demographic data and clinical characteristics were collected, including age, sex, body weight, height, body mass index (BMI), smoking and alcohol consumption, and comorbidities. Clinical presentations were recorded, including fever, myalgia, rigor, headache, alteration of consciousness, eschar, rash, lymphadenopathy, tachycardia, tachypnea, hypotension, and hypoxia. Additionally, laboratory tests of patients were gathered, including hemoglobin, hematocrit, white blood cell count, platelet count, serum electrolytes, renal function, liver function test, white blood cell in urine, and chest radiograph. Moreover, disease courses, including ICU transfer, organ failures, duration of hospitalization, and mortality rate, were also collected. The severity of rickettsiosis was categorized using the Sepsis-related Organ Failure Assessment score or the Sequential Organ Failure Assessment score (SOFA score), a scoring tool to assess the degree of organ failure over time in groups of patients with sepsis, which was used to predict the clinical outcomes. The score was based on six scores, including the respiratory system, blood clotting ability, liver function, heart and blood vessels, central nervous system, and kidney function. Severe rickettsiosis was defined by the patient with a SOFA score greater than 6. In a previous study, the SOFA score was reported to correlate with the length of hospital stay and mortality among patients with scrub typhus.[23] The SOFA score is a standard tool routinely used to predict mortality in critically ill patients according to the clinical practice guidelines for sepsis. This practice is also followed in our institution, allowing the data to be retrievable for this retrospective study.

The primary outcome was to evaluate rickettsiosis's epidemiology, scrub typhus clinical manifestations, and risk factors for severe disease. The secondary outcome was to evaluate complications, hospitalization duration, and rickettsial infection mortality rate.

*Statistical analysis*

In a previous study, the prevalence of severe rickettsiosis was 11%. [6] With 80% power and a two-sided alpha level of 0.05, this study needed at least 134 participants with rickettsiosis. Data were de-identified, entered into an electronic database, and analyzed using statistical software (STATA version 18.0). For continuous data such as age, vital signs, and laboratory test results for both severe and non-severe rickettsiosis groups, the data were calculated as mean ± SD, median, and interquartile range. The data were also analyzed using the Mann-Whitney U and Unpaired t-test for non-normal and normal distribution. Calculate frequency and percentage for categorical data such as gender, comorbidities, and symptoms or clinical manifestations of rickett-

siosis, and compare these between the severe and non-severe rickettsiosis groups using the Chi-square test. Interpret all data to identify variables associated with severe rickettsiosis using univariate analysis. Variables selection for multivariate analysis was based on the results. Logistic regression analysis was used to determine the relationship between selected variables and the occurrence of severe rickettsiosis. The significance level for all statistical tests was $p < 0.05$.

## Results

One hundred eighty-six patients met the inclusion criteria, with two medical records unavailable due to missing data. None of the patients were excluded according to the exclusion criteria. Among these 184 patients, 28 were serologically positive for rickettsial infection: 12 cases were positive for scrub typhus (6.5%), and 16 cases (8.6%) were positive for murine typhus. The remaining 156 cases were reviewed, confirming a clinical diagnosis of rickettsial infection as the final diagnosis. (**Figure 1**). Among the participants, 19 cases had a SOFA score of more than 6, identified as the severe rickettsiosis group (10%), while the other 165 cases (90%) were classified as the non-severe rickettsiosis group.

In the severe rickettsiosis group, three cases (3/19, 15.8%) were IFA positive for scrub typhus, two (2/19, 10.5%) were positive for murine typhus, and 14 (73.7%) were serologically negative for rickettsial infection. In the non-severe group, nine cases (5.5%) were positive for scrub typhus, 14 cases (8.5%) were positive for murine typhus, and 142 (86.1%) were serologically negative for rickettsial infection.

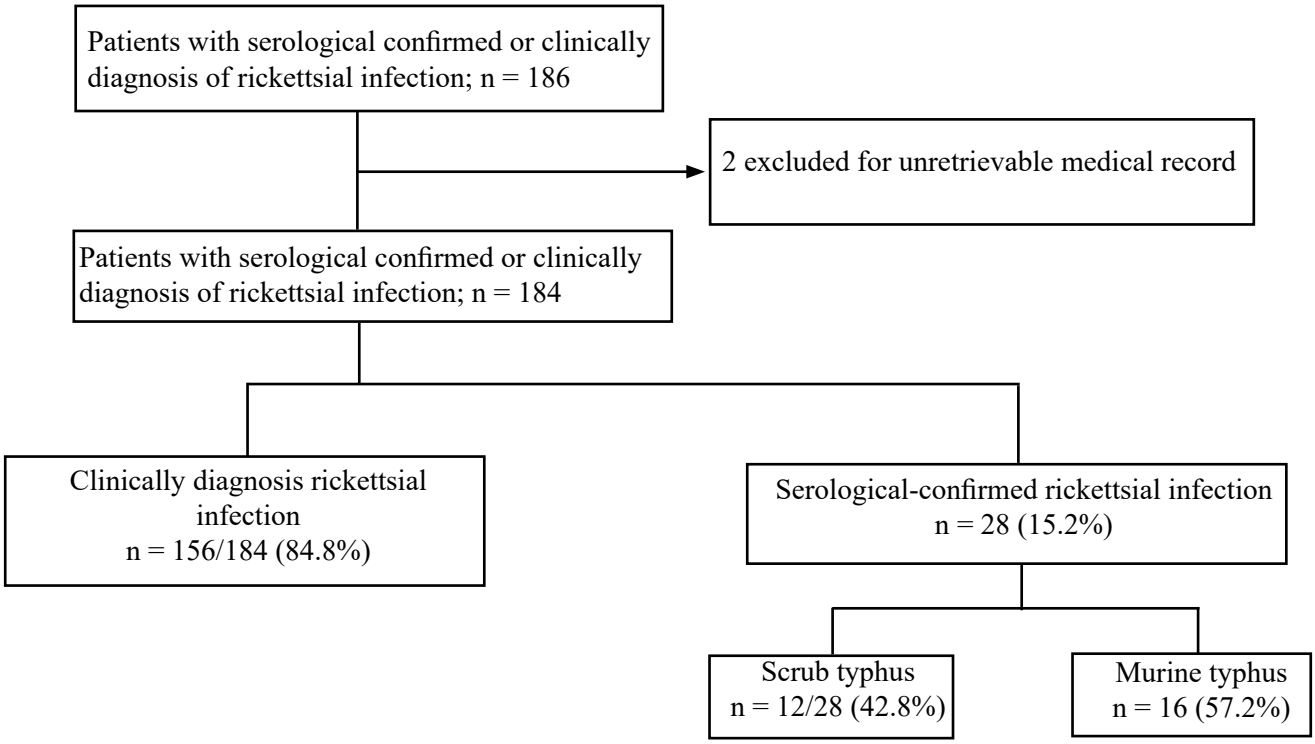


Figure 1. Enrollment diagram of participants

*Baseline characteristics*

**Table 1.** shows that the mean age of the study patients was 47.87 ± 18.45; 120 (65.2%) were men. Demographic data and clinical characteristics, including age, sex, body weight, height, BMI, smoking, and alcohol consumption, as well as comorbidities, were not significant differences between the two groups.

*Symptoms and signs*

All cases presented with acute undifferentiated febrile illness, with 130 out of 135 cases (96%) having fever (Table 2); myalgia, rigor, and headache were common presentations in both groups. Alteration of consciousness was more common in those with severe rickettsiosis than in those with non-severe rickettsial infection [6/19 (31.6%) vs.

**Table 1.** Baseline characteristics among severe rickettsiosis and non-severe rickettsiosis group

| Characteristics | Total (n=184) | Severe rickettsiosis (n=19) | Non-severe Rickettsiosis (n=165) | *p*-value |
|---|---|---|---|---|
| **Age (years)** | 47.87 ± 18.45 | 51.21 ± 17.94 | 47.48 ± 18.53 | 0.406 |
| **Sex** | | | | |
| Male | 120 (65.2%) | 15 (78.9%) | 105 (63.6%) | 0.185 |
| Female | 64 (34.8%) | 4 (21.1%) | 60 (36.4%) | |
| **Body weight (kg.)** | 63.76 ± 10.56 | 62.26 ± 11.67 | 63.93 ± 10.45 | 0.517 |
| **Height (cm.)** | 165.58 ± 8.14 | 166.58 ± 9.83 | 165.47 ± 7.95 | 0.574 |
| **BMI (kg/m2)** | 23.1 ± 3.01 | 22.16 ± 2.67 | 23.21 ± 3.03 | 0.152 |
| **Smoking** | 49 (26.6%) | 8 (42.1%) | 41 (24.8%) | 0.107 |
| **Alcohol consumption** | 50 (27.2%) | 8 (42.1%) | 42 (25.5%) | 0.122 |
| **Underlying disease** | | | | |
| Diabetes mellitus | 26 (14.1%) | 2 (10.5%) | 24 (14.5%) | 0.634 |
| Coronary artery disase | 15 (8.2%) | 2 (10.5%) | 13 (7.9%) | 0.69 |
| Chronic lung disease | 2 (1.1%) | 0 (0%) | 2 (1.2%) | 0.629 |
| Cirrhosis | 3 (1.6%) | 1 (5.3%) | 2 (1.2%) | 0.187 |
| Chronic kidney disease | 4 (2.2%) | 1 (5.3%) | 3 (1.8%) | 0.33 |
| Hypertension | 35 (19%) | 4 (21.1%) | 31 (18.8%) | 0.812 |
| Dyslipidemia | 29 (15.8%) | 3 (15.8%) | 26 (15.8%) | 0.997 |
| Congestive heart failure | 1 (0.5%) | 0 (0%) | 1 (0.6%) | 0.734 |
| **Other comorbidities** | 35 (19%) | 4 (21.1%) | 31 (18.8%) | 0.812 |

3/165 (1.8%), $p < 0.001$]. Other symptoms, such as rash, lymphadenopathy, and eschar, were less frequent in all groups. The rash was commonly found in the non-severe group; however, there was no statistically significant difference in this study [1/19 (5.3%) vs. 16/165 (9.7%), $p = 0.527$]. Eschar was identified in only one severe rickettsial infection and had a positive IFA result for scrub typhus. All cases with lymphadenopathy (n=4) were identified in the non-severe rickettsial infection group. One of them was serologically positive for murine typhus, while the others were clinically diagnosed patients. Tachypnea was more common in severe rickettsiosis than in non-severe rickettsiosis [11/19 (31.6%) vs. 6/165 (1.8%), $p < 0.001$].

*Laboratory and radiological findings*

The mean hemoglobin level and hematocrit level were lower in the severe rickettsiosis group (10.92 ± 2.41 vs. 12.33 ± 2.19, $p = 0.009$) and (32.74 ± 7.26 vs. 37.55 ± 6.38, $p = 0.002$), respectively. The two groups had no statistically significant differences in white blood cell count, platelet count, serum sodium, serum potassium, international normalized ratio (INR) level, and activated partial thromboplastin time (APTT). However, impaired renal function, elevated bilirubin, elevated alkaline phosphatases, aspartate aminotransferase, and alanine aminotransferase, pyuria, as well as abnormal chest radiographs, were more common findings in severe rickettsiosis than in non-severe rickettsiosis (**Table 2**).

*Management and course of illness*

The treatment of rickettsiosis in this study mainly comprised doxycycline (89.1%), followed by azithromycin (10.9%). The use of azithromycin was significantly higher among the severe rickettsiosis group (57.9% vs. 15.53%; $p < 0.001$). According to the complications of the rickettsial disease, there was a significantly higher

rate of complications in severe rickettsiosis than in non-severe rickettsiosis, including respiratory failure, shock, renal failure, encephalopathy, heart failure, and liver failure (**Table 2**). One hundred four patients received an antibiotic with anti-rickettsial activity at presentation (104/184, 56%). However, the two groups had no statistically significant duration difference before proper antibiotic administration ($p = 0.944$). Additionally, the rate of ICU admission [14/19 (73.7%) vs. 14/165 (8.5%), $p < 0.001$] and duration of hospitalization [18.63 ± 20 vs. 7.42 ± 7.58, $p < 0.026$] were higher in severe rickettsiosis. Four deaths were recorded in this study (4/184, 2.1%). All of them belonged to the severe rickettsiosis group, and one had a positive serological result for scrub typhus. Three out of four cases resulted in death from septic shock with multiorgan failure within one week of admission. The other case resulted in death from a hospital-acquired multidrug-resistant gram-negative infection 45 days after admission.

*Prediction of severe disease*

Several variables were statistically significant in univariate analysis for predicting severe rickettsiosis among the populations. However, using multivariate analysis, elevated bilirubin (OR= 17.93, 95% CI 3.52-91.42, $p = 0.001$) and abnormal chest radiograph (bilateral alveolar infiltration) (OR = 11.73, 95% CI = 1.36-100.89, $p = 0.025$] were independently predictive for severe disease (**Table 3**).

**Table 2.** Clinical and laboratory findings among severe rickettsiosis and non-severe rickettsiosis group.

| Clinical and laboratory findings | Total (n=184) | Severe rickettsiosis (n=19) | Non-severe Rickettsiosis (n=165) | *p*-value |
|---|---|---|---|---|
| **Clinical manifestations and physical examinations** | | | | |
| Fever* | 121 (65.8%) | 13 (68.4%) | 108 (65.5%) | 0.796 |
| Myalgia | 143 (77.7%) | 16 (84.2%) | 127 (77%) | 0.473 |
| Rigor | 93 (50.5%) | 10 (52.6%) | 83 (50.3%) | 0.848 |
| Headache | 58 (31.5%) | 9 (47.4%) | 49 (29.7%) | 0.116 |
| Alteration of consciousness | 9 (4.9%) | 6 (31.6%) | 3 (1.8%) | <0.001* |
| Rash | 17 (9.2%) | 1 (5.3%) | 16 (9.7%) | 0.527 |
| Eschar | 1 (0.5%) | 1 (5.3%) | 0 (0%) | 0.003* |
| Lymphadenopathy | 4 (2.2%) | 0 (0%) | 4 (2.4%) | 0.493 |
| Tachycardia* | 72 (39.1%) | 10 (52.6%) | 62 (37.6%) | 0.203 |
| Tachypnea* | 17 (9.2%) | 11 (57.9%) | 6 (3.6%) | <0.001* |
| Mean arterial pressure | 85.32 ± 15.28 | 67.81 ± 23.96 | 87.34 ± 12.57 | 0.002* |
| **Laboratory investigations** | | | | |
| Hemoglobin (g/dL) | 12.18 ± 2.24 | 10.92 ± 2.41 | 12.33 ± 2.19 | 0.009* |
| Hematocrit (%) | 37.05 ± 6.62 | 32.74 ± 7.26 | 37.55 ± 6.38 | 0.002* |
| White blood count /μL | 10313.7 ± 11749.26 | 12384.21 ± 6020.08 | 10075.27 ± 12227.29 | 0.419 |
| Platelet count /μL | 204298.91 ± 123826.04 | 163210.53 ± 141335.13 | 209030.3 ± 121238.2 | 0.127 |
| Serum sodium (mEq/L) | 134.99 ± 5.66 | 137.05 ± 11.93 | 134.76 ± 4.43 | 0.416 |
| Serum potassium (mEq/L) | 3.62 ± 0.5 | 3.64 ± 0.77 | 3.62 ± 0.46 | 0.914 |
| Serum creatinine (mg/dL) | 1.37 ± 1.65 | 3.55 ± 3.37 | 1.12 ± 1.08 | 0.006* |
| Total bilirubin (mg/dL) | 1.32 ± 2.01 | 4.17 ± 3.47 | 0.99 ± 1.47 | 0.001* |

**Table 2.** Clinical and laboratory findings among severe rickettsiosis and non-severe rickettsiosis group. (Cont.)

| Clinical and laboratory findings | Total (n=184) | Severe rickettsiosis (n=19) | Non-severe Rickettsiosis (n=165) | *p*-value |
|---|---|---|---|---|
| Alkaline phosphatases (IU/L) | 127.72 ± 123.02 | 163.63 ± 70.48 | 123.58 ± 127.18 | 0.180 |
| Aspartate aminotransferase (IU/L) | 121.16 ± 386.53 | 483.32 ± 1101.14 | 79.45 ± 129.18 | 0.128 |
| Alanine aminotransferase (IU/L) | 110.42 ± 295.77 | 399.11 ± 816.02 | 77.18 ± 117.32 | 0.103 |
| INR | 1.15 ± 0.23 | 1.27 ± 0.3 | 1.11 ± 0.17 | 0.052 |
| APTT | 30.71 ± 7.96 | 33.44 ± 10.89 | 29.5 ± 6.05 | 0.100 |
| Pyuria* | 27 (14.7%) | 8 (42.1%) | 19 (11.5%) | <0.001* |
| **Complications** | | | | |
| Elevated bilirubin level* | 29 (15.8%) | 15 (78.98%) | 14 (8.5%) | <0.001* |
| Elevated Alkaline phosphatases level* | 72 (39.1%) | 16 (84.2%) | 56 (33.9%) | <0.001* |
| Elevated Aspartate aminotransferase level* | 82 (44.6%) | 16 (84.2%) | 66 (40%) | <0.001* |
| Elevated Aspartate aminotransferase level* | 86 (46.7%) | 17 (89.5%) | 69 (41.8%) | <0.001* |
| Acute renal failure* | 19 (10.3%) | 9 (47.4%) | 10 (6.1%) | <0.001* |
| Mechanical ventilator | 20 (10.9%) | 11 (57.9%) | 9 (5.5%) | <0.001* |
| Vasopressor therapy | 27 (14.7%) | 16 (84.2%) | 11 (6.7%) | <0.001* |
| Renal replacement therapy | 14 (7.6%) | 10 (52.6%) | 4 (2.4%) | <0.001* |
| Encephalopathy | 8 (4.3%) | 6 (31.6%) | 2 (1.2%) | <0.001* |
| Heart failure | 18 (9.8%) | 10 (52.6%) | 8 (4.8%) | <0.001* |
| Liver failure | 10 (5.4%) | 6 (31.6%) | 4 (2.4%) | <0.001* |
| **Radiographic findings** | | | | |
| Normal findings | 167 (90.8%) | 10 (52.6%) | 157 (95.2%) | <0.001* |
| Bilateral interstitial infiltration | 6 (3.3%) | 2 (10.5%) | 4 (2.4%) | |
| Bilateral alveolar infiltration | 11 (6%) | 7 (36.8%) | 4 (2.4%) | |
| **Treatment** | | | | |
| Duration before proper antibiotics administration | 0.92 ± 1.53 | 0.95 ± 1.75 | 0.92 ± 1.51 | 0.944 |
| Definite antibiotics | | | | |
| Doxycycline | 164 (89.1) | 8 (42.1) | 156 (84.47) | <0.001* |
| Azithromycin | 20 (10.9) | 11 (57.9) | 9 (15.53) | |
| **Treatment outcomes** | | | | |
| ICU admission/ transfer | 28 (15.2%) | 14 (73.7%) | 14 (8.5%) | <0.001* |
| Length of hospitalization | 8.58 ± 10.13 | 18.63 ± 20 | 7.42 ± 7.58 | 0.026* |

* Fever: body temperature > 38°C, tachycardia; heart rate > 100/min, tachypnea; respiratory rate > 22/min, acute renal failure; increase serum creatine ≥ 0.3 mg/dl within 48 hours or ≥ 1.5 times baseline within the prior seven days, elevated bilirubin; serum total bilirubin > 2 mg/dL, elevated alkaline phosphatases; serum alkaline phosphatases > 105 IU/L, elevated aspartate aminotransferase; serum aspartate aminotransferase > 50 IU/L, elevated alanine aminotransferase; serum Alanine aminotransferase > 50 IU/L, pyuria; white blood cells in urine > 5 cells

**Table 3.** Univariate and multivariate analysis of factors associated with severe rickettsiosis

| Risk factors for severe rickettsioses | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95%CI) | *p*-value | Adjusted OR (95%CI) | *p*-value |
| **Alteration of consciousness** | 24.92 (5.58, 111.32) | <0.001* | 10.95 (0.43, 281.75) | 0.149 |
| **Acute renal failure** | 13.95 (4.62, 42.1) | <0.001* | 7.02 (0.98, 50.13) | 0.052 |
| **Elevated bilirubin level** | 40.45 (11.81, 138.57) | <0.001* | 17.93 (3.52, 91.42) | 0.001* |
| **Elevated Alkaline phosphatase level*** ** | 10.38 (2.9, 37.13) | <0.001* | 3.1 (0.51, 18.73) | 0.218 |
| **Abnormal CXR** | | | | |
| **Bilateral interstitial infiltration** | 7.9 (1.3, 48.1) | 0.026* | 3.84 (0.27, 54.87) | 0.321 |
| **Bilateral alveolar infiltration** | 27.5 (6.9, 109.7) | <0.001* | 11.73 (1.36, 100.89) | 0.025* |

## Discussion

This study demonstrated that rickettsial diseases in the military hospital in Bangkok represent a predominance of murine typhus and a lower prevalence of scrub typhus. Out of 1,120 patients with suspected rickettsial disease, 186 cases were diagnosed with rickettsial infection, both clinically (156 cases, 84%) and serologically, with scrub typhus (12 cases, 6.5%) and murine typhus (16 cases, 8.6%). This finding is consistent with the previous study conducted in a civilian hospital, which demonstrated that in the urban area of Bangkok, murine typhus was more common than scrub typhus.[7] Nineteen cases were identified as the severe rickettsiosis group, while the other 165 cases were classified as the non-severe rickettsiosis group, showing that 10% of rickettsial disease cases developed severe symptoms. The prevalence of severe rickettsiosis disease was comparable in previous studies in Australia, which account for 11% of severe disease.[6] Moreover, the study showed that confirmed murine typhus infection was more common in non-severe cases than scrub typhus.

This study emphasized the difficulties of diagnosing rickettsial infection. The clinical manifestations of rickettsial diseases could vary from mild self-limiting illness to life-threatening multiorgan failure. Based on patients' medical records in this series, the common presentations in all groups were fever, myalgia, rigor, and headache, which were nonspecific symptoms. Other symptoms, such as rash, lymphadenopathy, and eschar, were less frequent in all groups. Tachypnea and alteration of consciousness were statistically significant in severe cases. From a laboratory finding perspective, impaired renal function, elevated bilirubin, elevated alkaline phosphatases, aspartate aminotransferase, and alanine aminotransferase, pyuria, as well as abnormal chest radiographs, were significantly statistically found in severe cases. Moreover, according to multivariate analysis, increased bilirubin and abnormal chest radiography with bilateral alveolar infiltration were independent variables that could predict severe rickettsiosis. Previous studies in China also described elevated bilirubin as a predictor of severe rickettsiosis, similar to our result. [24] As well as the study in Korea revealed pulmonary involvement and pulmonary complications of severe rickettsiosis, described as predictors for prolonged hospitalization.[25] Several risk factors were described for severe rickettsiosis, including acute kidney injury, absence of skin rash or eschar, high white blood cell count, alteration of consciousness, and hypoalbuminemia, which were not statistically significant in our study.[24-26] These findings represent multiorgan involvement by rickettsial infection, leading to complications and severe disease.

In this study, the treatment for rickettsiosis consisted mainly of doxycycline and azithromycin. Doxycycline was used as the first-line therapy, adhering to standard recommendations. Although azithromycin was recommended as an alternative agent for rickettsiosis treatment, it was more commonly used in the severe group due to being the only anti-rickettsial drug avail-

able in Thailand in the intravenous formulation. The complications and outcomes associated with rickettsial disease in severe rickettsiosis have a significantly higher rate of complications, including respiratory failure, shock, renal failure, encephalopathy, heart failure, and liver failure. Furthermore, the rate of ICU admission and duration of hospitalization were notably higher in severe rickettsiosis cases. Additionally, many patients received antibiotics with anti-rickettsial activity upon presentation. However, there was no statistically significant difference in the duration before proper antibiotics were administered between the severe and non-severe groups. There were four deaths recorded in the study, all of which were in the severe rickettsial infection group, with one of them having a positive serological result for scrub typhus. This study found murine typhus more common than scrub typhus during the study period. However, scrub typhus tends to have a more severe clinical phenotype. For example, it was more common in the severe infection group and was associated with one of the death cases. The mortality rate of rickettsiosis in this present study was 2.17%, comparable to other cohorts, with scrub typhus and murine typhus being the predominant rickettsial diseases.[27] However, compared to a study in a civilian hospital in Thailand, where the overall mortality rate for scrub typhus was 6%, the mortality rate in the present study was relatively lower. [28] This observation might be attributed to the previous study consisting only of scrub typhus cases, where the disease was more severe than murine typhus, as well as a high proportion of elderly patients (age >65 years) and comorbid diseases, particularly among the fatal cases. The rickettsiosis patients in the military hospital cohort represent active military personnel who are younger and have fewer comorbidities.

Although rickettsial infections are considered neglected due to their nonspecific clinical manifestations and laboratory findings, a notable number of cases during the ten years were clinically diagnosed with rickettsial infection and response to antibiotics. Nevertheless, serology remains the gold standard for diagnosing rickettsial infection nowadays. In this study, only 28 cases were confirmed using serology tests for rickettsial infection due to early blood testing, not routinely performed convalescent serum IFA tests for murine and scrub typhus, and blood samples taken after antibiotic administration. Since antibodies may not be detected in the acute phase of rickettsial illness, follow-up serological tests should be conducted to detect rickettsial antibodies, with a four-fold rise as the standard diagnosis. Encouraging specimen collection at the appropriate timing and enhancing the practice of sending convalescent sera for IFA testing to compare with acute sera could benefit the definite diagnosis of rickettsiosis.

This study constituted a large cohort of rickettsiosis cases gathered from 10 years of treatment experiences at a Thai military university hospital. However, it encountered several limitations. Firstly, due to its retrospective nature, these included incomplete data regarding clinical manifestations, laboratory findings, and under-reported or difficult handwriting. Secondly, the positive rate of serum IFA was limited; thus, the diagnosis might not definitively confirm rickettsiosis.

Nonetheless, among the clinically diagnosed group, we excluded other tropical infectious diseases that mimicked rickettsiosis and relied on the response to anti-rickettsiosis treatment for presumptive diagnosis. This reflects routine clinical practice, where rickettsial serology is often undetected in the early phase of the disease. Therefore, empirical anti-rickettsiosis treatment should be promptly administered when rickettsiosis is suspected, and clinical response is usually dramatic. Furthermore, as a tertiary care unit, the severity of the disease might have been overestimated. Additionally, this study was based on experience from a single center where almost all cases were scrub typhus and murine typhus. Therefore, the less generalizable findings should be carefully evaluated and compared with other cohorts. A prospective multicenter study employing appropriate and well-controlled laboratory investigations, particularly regarding timing and comparing acute and convalescent sera for IFA in Rickettsiosis, should be pursued for further investigation.

## Conclusion

Murine typhus was more common in a military hospital in Bangkok and less severe than scrub typhus. Increased bilirubin levels and abnormal chest radiography with bilateral alveolar infiltration independently predict severe rickettsial infection.

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## Competing interests

The authors declare no existing or potential conflict of interest relevant to this work.

## Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

## Author contributions

Conceptualization, PO, WN, method, PO, WN; data collection, PO, WN; formal analysis, PO, WN; writing—original draft preparation, PO, WN, supervision, WN; project administration, PO, WN All authors contributed to manuscript writing and revision and agreed to submit the manuscript for publication. All authors meet the ICMJE authorship criteria.

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