Clinical manifestation, laboratory characteristics and predictors of severity in scrub typhus patients hospitalized in 103 Military Hospital and 108 Military Central Hospital

Nguyen Dang Manh*, Pham Van Chung** **108 Military Central Hospital, **Navy Hospital*

Summary

Objective: To investigate clinical manifestation, laboratory characteristics and predictors of severity in scrub typhus patients hospitalized in 103 Military Hospital and 108 Military Central Hospital. *Subject and method:* This was a descriptive study on 50 cases of scrub typhus confirmed by dot-ELISA or PCR hospitalized in 103 Military Hospital and 108 Military Central Hospital. *Result and conclusion:* There were 62% male and 38% female in our study. Patients in urban and non-urban accounted for 36% and 64%, respectively. The majority of patients had fever, headache and myalgia (> 96%) followed by eschar 70%, congested skin 60%, lymphadenopathy 44%, cough 42%, crackle 36%, dyspnea 22%. Thrombocytopenia and elevated liver enzyme accounted for 70% and more than 88, respectively. 100% patients had elevated PCT ($\bar{X} \pm$ SD 2.396 ± 2.119ng/ml). Lung involvements on chest X-ray: Patchy opacity 8.7%, unilateral infiltrate 10.9%, bilateral infiltrate 8.7%. Pleural effusion and serous fluid on ultrasound were 30.8% and 33.3% respectively. Complications included respiratory failure 12%, septic shock 8%, and meningoencephalitis 8%, acute kidney injury 8%. Factors such as shortness of breath (OR = 6.6), respiratory rate ≥ 22 cycles/minutes (OR = 8.16), moist rale (OR = 14.25), increased PCT (AUC = 0.75), diffuse infiltration on X-rays (OR = 18), pleural fluid on ultrasound (OR = 5.17), have associated with the life-threatening complications (p<0.05).

Keywords: Scrub typhus, clinical manifestation, complications, factors of severity.

1. Background

Scrub typhus is caused by *Orientia tsutsugamushi*, an obligatory intracellular Gram (-) bacterium, belonging to the family Rickettsiaceae. This is zonooses and tick-borne disease transmitted to humans through an intermediate vector called the larvae. The disease is endemic in many countries in the Asia and Pacific belt (Tsutsugamushi triangle) [1] with estimately 1 billion people in the epidemic area are at risk of infection and millions of new cases occur each year [1]. The mortality rate is as high as 60% in the era without specific antibiotics [2].

The earliest reports of scrub typhus cases in Vietnam can be dated back to the 1960s during the Vietnam War. Recent studies of scrub typhus in North Vietnam demonstrated that the cumulative incidence of scrub typhus was about 1.1% among the general population [3], and ~3.5% among patients admitted to hospitals [4]. In the National Hospital for Tropical Diseases, scrub typhus accounted for one third of acute undifferentiated fevers with the mortality rate of 5.4% between 2015 and 2017 [5].

Correspondence to: Nguyen Dang Manh - Institute of Clinical Infectious Diseases, 108 Military Central Hospital
Email: drmanha4b108@gmail.com.

It is challenging to diagnosis scrub typhus because the clinical manifestations are vary and consist of nonspecific symptoms: Fever, headache, and myalgias with or without nausea, vomiting, and cough. The classical symptoms such as rash; eschar or lymphadenopathy are not always presented. Some patients develop complications such as ARDS; meningoencephalitis, acute kidney injury; septic shock [6]. Therefore, it is easy lead to misdiagnosis or omission of diagnosis, accompanied by complications and higher mortality.

An in-depth understanding of clinical, paraclinical features and prognostic factors of the disease caused by *O. tsutsugamushi* will help clinicians promptly diagnose with appropriate treatment, minimize complications and improve outcome of patients. Based on the aforementioned conditions, we implemented this project to investigate clinical manifestation, laboratory characteristics and predictors of severity in scrub typhus patients hospitalized in 103 Military Hospital and 108 Military Central Hospital.

2. Subject and method

2.1. Subject

50 patients were diagnosed with scrub typhus at 103 Military Hospital and 108 Military Central Hospital from January 2014 to June 2019.

Inclusion criteria: According to scrub typhus case definition of the US Centers for Disease Control (CDC) 2016 [7]. Rapid test or PCR was used to confirm cases.

Exclusion criteria: Patients did not have enough research data and patients had evidence of infection with other acute fever organisms were excluded out of our study.

2.2. Method

Study design

This was a cross-sectional study. Eligible participants were performed clinical examination and investigations that consist of routine tests and recorded in a standard questionnaire form. Thereafter, the clinical presentation laboratory results were determined in each group of patients based on these above data.

Sample size and method of sample selection

A sample size of convenience was used. All eligible participants in the period from 01/2014 to 06/2019 were included in this study.

Research variables

Demographic features, background pathologies, clinical and laboratory characteristics, life-threatening complications (ARDS according to Berlin 2002 criteria, septic shock according to Sepsis 3, Meningoencephalitis according to European consensus, acute kidney injury (AKI) according to KDIGO 2012).

Data collection methods

An identical medical record form was used for documenting obtained data consisting of both clinical and paraclinical manifestations.

Division of the research group

The uncomplicated group and the group had at least 1 of 4 aforementioned life-threatening complications.

Statistics

Use SPSS 22.0 software with the following algorithms: Calculate the average; ratio %; rate comparison; compare mean values with squared test or Fisher's exact test; univariate analysis of logistics regression model; Application of ROC curves in assessing the value of several quantitative variables has significant prognosis for complications of the disease.

3. Result

3.1. Baseline characteristics of the study population

Table 1. Demographic profile

	Cases	Percentages
Male	31/50	62
Female	19/50	38
Urban	18/50	36
Non-urban	32/50	64
Mean of ages	***52.1 ± 17.9***	

Males with scrub typhus accounted for 62% and females were 38%, the average age of research respondents was 52.1 ± 17.9 years. The proportion of patients living in urban areas was 36%, non-urban area accounted for 64%.

3.2. Clinical features of patients with scrub typhus

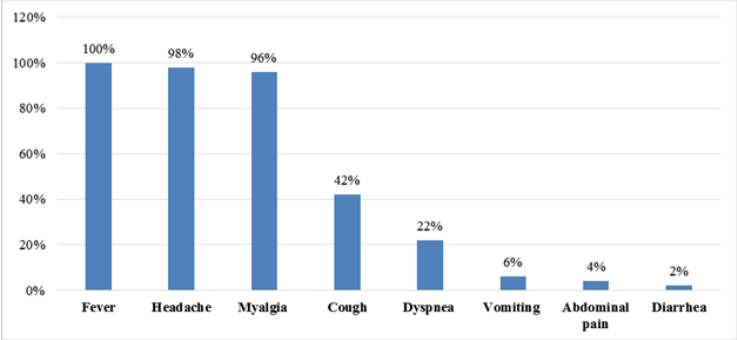

Figure 1. Acute symptoms at disease onset

Figure 1 shown that the most clinical symptoms such as fever, headache, and myalgia accounted for over 96%, following by cough (42%), dyspnea (22%), abdominal pain 4% and diarrhea 2%.

Table 2. Physical symptoms during hospitalization

	Cases	Percentages
Congested skin/ eyes	30/50	60
Maculopapular rash	10/50	20
Eschar	35/50	70
Lymphadenopathy	22/50	44
Liver enlarged	5/50	10
Respiratory rate > 25	3/50	6
Crackles	18/50	36
Mean duration of fever (day)	12.7 ± 5.1	

Skin - mucosal lesions, endothelial sagging system involvements were quite common in the study group with eschar rate of 70%, skin - conjunctival congestion 60%, lymphadenopathy 44%. Lung damage (crackles) accounted for 36% of patients with 6% of patients had respiratory rate > 25 cycle/min.

3.3. Laboratory characteristics of patients with scrub typhus

Table 3. Test results

Variables		Cases	Percentages
Platelet (G/L)	Platelet < 50	7	14
	50 ≤ Platelet < 100	11	22
	100 ≤ Platelet < 150	17	34
Leukocytes (G/L)	Leukocytes < 4	1/50	2
	Leukocytes > 10	24/50	48

PCT	0.05 ≤ PCT < 2	14/26	53.8
	2 ≤ PCT ≤ 10	10/26	38.5
	PCT > 10	2/26	7.7
Liver enzyme	AST > 40	46/50	92
	ALT > 40	44/50	88

Thrombocytopenia and increased liver enzymes were common in the study group, with 70% and > 88% respectively. There were 48% of patients had an increase in white blood cell count and 100% had an increase in PCT > 0.05ng/ml with $\overline{X} \pm$ SD: 2.396 ± 2.119ng/ml.

Table 4. Image diagnostic results

Variables		Cases	Percentages
Chest X-ray	Patchy opacity	4/46	8.7
	Unilateral infiltrate	5/46	10.9
	Bilateral infiltrate	4/46	8.7
	Pleural effusion	9/46	19.6
Ultrasound	Pleural effusion	12/39	30.8
	Visceral fluid	13/39	33.3

Lung damage on chest X-ray were: Patchy opacity 8.7%, unilateral infiltration 10.9%, bilateral infiltrate 8.7%, pleural effusion 9.6%. Manifestations of pleural effusion and serous fluid on ultrasound were quite common with the rates of 30.8% and 33.3%, respectively.

3.4. Life-threatening complications in the pathological process and some prognostic factors

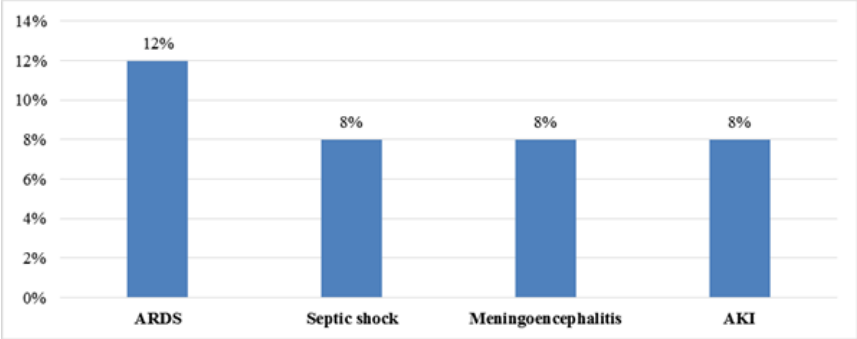

Figure 2. Complications during the pathological process

Patients with scrub typhus in the study group had ARDS, septic shock, meningoencephalitis, AKI at the rate of 12%, 8%, 8% and 8% respectively.

Table 5. Some prognostic factors

Variables	Non-complications	Complications*	p
Age ≥ 60	14/39	4/11	1*
Male	23/39	8/11	0.498
Dyspnea	4/39	7/11	<0.001
Respiratory rate > 22	5/39	6/11	0.008
Vomiting	3/39	3/11	0.050
Eschar	28/39	5/11	0.994
Moist rale	1/39	3/11	0.012

Hematocrit	0.392 ± 0.046	0.352 ± 0.066	0.009
Hb	131.06 ± 16.97	116.23 ± 23.74	0.008
Leukocytosis	20/39	9/11	0.008
PCT	1.32 ± 1.08	3.23 ± 3.05	0.013
Bilirubin	14.40 ± 11.15	24.17 ± 23.63	0.033
AST ≥ 200UI/l	8/39	7/11	0.01
Bilateral infiltrate on X-ray	1/39	3/11	0.013
Pleural effusion on ultrasound	9/39	6/11	0.002

**Included: ARDS, septic shock, meningoencephalitis, AKI.*

There were statistically significant differences between the 2 groups for factors such as: Dyspnea, increased breathing rate, vomiting, moist rale, hematocrit, anemia, leukocytosis, increased PCT, increased bilirubin, bilateral infiltrate, pleural fluid on ultrasound.

Table 6. Results of univariate logistic regression analysis of some predictive variables

Variables	Non-complications	Complications*	p	OR
Dyspnea	4/39	7/11	0.012	6.6
Respiratory rate > 22	5/39	6/11	0.007	8.16
Moist rale	1/39	3/11	0.029	14.25
Leukocytosis	20/39	9	0.074	3.83
AST ≥ 200	8/39	7/11	0.01	6.78
Bilateral infiltrate on X-ray	1/39	3/11	0.019	18
Pleural effusion on ultrasound	9/39	6/11	0.04	5.71

Among the aforementioned factors, the variables: Diffuse infiltrates on lung X-ray, moist rale, rapid breathing ≥ 22 cycle/min, dyspnea, pleural fluid on ultrasound, increased AST ≥ 200 had high OR with $p<0.05$.

Table 7. The reliability of some prognostic factors

Variables	AUC
Hematocrit	0.40
Hb	0.43
PCT	0.75
Bilirubin	0.67

The PCT value was able to distinguish between the two groups with quite high reliability (the area under the ROC curve was 0.75).

4. Discussion

In our study, men with scrub typhus accounted for 62%, higher than females 38%, the mean age of research respondents was 52.1 ± 17.9 years. This result was similar to Hamaguchi [4]. However, in Nguyen Vu Trung's research group, the incidence of men and women was similar [5].

The proportion of patients living in urban areas accounted for 36%, less than patients living in rural

and mountainous areas 64%. This result is similar to that of Nguyen Vu Trung [5] and the epidemiological results of other large studies, confirming that there is more scrub typhus cases in rural areas with a higher incidence of disease in farmers.

Clinical characteristics

During the disease onset, fever, headache, and myalgia accounted for over 96%. Respiratory symptoms were quite common (cough 42%, shortness of breath 22%). This result was similar to Nguyen Vu Trung, but the digestive symptoms in our study group was < 6%, less common than the results of Nguyen Vu Trung's research [5].

Skin - mucosal lesions, endothelial sagging system involvements were quite common in the study group with eschar rate of 70%, skin - conjunctival congestion 60%, and lymphadenopathy 44%. It is noteworthy that the proportion of patients with eschar was higher than that of Hamaguchi (64.9%) [4] and Nguyen Vu Trung (50%), this may be due to the differences in selection of subjects where the other authors selected higher ranges of patients than our study. According to the literature, the eschars caused by larvae bite are a typical manifestation of the scrub typhus; however, the detection of these eschars should be very meticulous and require a high degree of alertness in the search for lesions, even in private areas. In addition, if the author only relied on the eschar, the majority of the authors ignore up to 50% of cases.

The average duration of fever in our research group was 12.7 ± 5.1 (days), this result was similar to that of Nguyen Vu Trung [5], this prolonged fever is a sign to think about scrub typhus in the differential diagnosis, provoke thorough examination in order to detect eschar and appoint appropriate diagnostic test. Lung damage (crackles rale) accounted for 36% of patients with 6% of patients with breathing rate > 25 cycle/min. This is related to common respiratory complications in patients with scrub typhus. The proportion of patients with lung lesions in our study was lower than that of Hamaguchi (43.8%) [4] and equivalent to Nguyen Vu Trung (32.5%) [5].

Laboratory characteristics

Thrombocytopenia increased liver enzymes were common manifestations in the study group with rates of 70% and > 88%, respectively. This result is similar to the research of Nguyen Vu Trung 2019 and Hamaguchi 2003, showing that these are common laboratory abnormalities in patients with scrub typhus. Therefore, in the guidelines for diagnosis and treatment of vector-borne diseases, CDC has included these two criteria above into one of the criteria for cases suspected of scrub typhus.

Regarding to inflammatory maker, the results of Table 3 showed that in the study group, 48% of patients had an increase in white blood cell count and 100% patients had PCT increased > 0.05ng/ml with $\bar{X} \pm$ SD of 2.396 ± 2.119ng/ml. Although the PCT level is rarely mentioned in other studies in Vietnam, our results are consistent with Nguyen Vu Trung's finding, confirming that PCT increase is a common manifestation of scrub typhus.

Lung damage on chest X-ray of scrub typhus patients were: Patchy opacity (8.7%), unilateral infiltration (10.9%), bilateral infiltrate (8.7%), Pleural effusion (19.6%). Manifestations of pleural effusion and serous fluid on ultrasound are quite common with the rates of 30.8% and 33.3%, respectively. Chest X-ray descriptions are rarely mentioned in domestic studies about scrub typhus, however they have been mentioned in many studies by foreign authors [8]. This may be due to the lack of interest in collecting diagnostic data, and the domestic image diagnostic descriptions may not be as detailed as those of foreign authors, so the value of the features lesions on diagnostic images were limited.

Prognostic factors for life-threatening complications

The life-threatening complications in scrub typhus are following the microvascular damage caused by the ability to invade and damage vascular endothelial cells. The severity of the disease depends not only on host factors but also on pathogens such as different *O. tsutsugamushi* strains with different virulences. Patients with scrub typhus in the research group had a life-threatening complication rate of 22%, in which respiratory failure, septic shock, encephalitis - meningitis, acute renal injury (AKI) were 12% and 8%, 8%, 8% respectively. The proportion of patients with severe complications in our study was lower than that of Nguyen Vu Trung with the complication rate up to 61.7%. This difference is due to differences in the criteria of complication between 2 studies. However, some complications have similar results such as acute kidney damage, septic shock [5].

In the Chi-square test and T-test (Table 5), there was a statistically significant difference between the two groups of uncomplicated and complicated patients, on factors such as: Shortness of breath, increased respiratory rate, moist rale, vomiting, mean of hematocrit, anemia, leukocytosis, increased PCT, increased bilirubin, diffuse infiltrates on X-ray, pleural effusion on ultrasound. This result was similar to that of Nguyen Vu Trung's research, but the author also mentioned other prognosis factors related to age group (above and below 60 years old), eschar, subcutaneous - mucosa hemorrhage, edema [5].

On univariate logistic regression analysis: Among the aforementioned factors, the variables such as diffuse infiltrates on lung X-ray, moist rale, rapid breathing ≥ 22 cycle/min, dyspnea, pleural fluid on ultrasound, increased AST ≥ 200 had high OR with $p<0.05$.

Table 7 showed the reliability of some factors in prognosis of complications in the research group, in which PCT values was capable of distinguishing between the two groups with high reliability (area under the ROC curve is 0.75). At the PCT cutoff point > 4.4ng/ml, the specificity of PCT in predicting severe complications is 94.4%, however the sensitivity at this cutoff is only 37.5%. Therefore, PCT values should be combined with other variables to predict the likelihood of complications in scrub typhus patients.

5. Conclusion

Scrub typhus patients in our study was more common in men and in rural areas.

Clinical manifestations: The majority of patients had fever, headache, and myalgia following by eschar, skin-conjunctival congestion, and lymphadenopathy. Respiratory symptoms were also common.

Common laboratory features: PCT increased by > 0.05ng/ml, thrombocytopenia and elevated liver enzyme.

Complications: Scrub typhus had wide range of complications: Respiratory failure; septic shock; encephalitis - meningitis; acute kidney injury.

Severe prognostic factors: Dyspnea (OR = 6.6), tachypnea ≥ 22 cycles/minute (OR = 8.16), moist rale (OR = 14.25), increased PCT (AUC = 0.75)), diffuse infiltrates on chest X-ray (OR = 18), pleural effusion on ultrasound (OR = 5.17).

References