



# Risk Factors for Mechanical Ventilation in Patients with Scrub Typhus Admitted to Intensive Care Unit at a University Hospital

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**Background:** The purpose of this study was to evaluate the risk factors for mechanical ventilation in the patients with scrub typhus admitted to intensive care unit (ICU) at a university hospital.

**Methods:** We retrospectively selected and analyzed clinical data from the medical records of 70 patients (32 men, 38 women) admitted to the ICU with scrub typhus between 2004 and 2014. The patients had a mean±standard deviation age of 71.2±11.1 years and were evaluated in two groups: those who had been treated with mechanical ventilation (the MV group, n=19) and those who had not (the non-MV group, n=51). Mean ages of the MV group and the non-MV group were 71.2±8.3 years and 71.2±11.1 years, respectively.

**Results:** Significant differences between the two groups were observed with respect to acute respiratory failure (p=0.008), Acute Physiology and Chronic Health Evaluation (APACHE) II score (p=0.015), Sequential Organ Failure Assessment (SOFA) score (p=0.013), death (p=0.014), and ICU duration (p<0.01). Multivariate analysis indicated that the following factors were significantly associated with mechanical ventilation: acute respiratory failure (p=0.011), SOFA score (p=0.005), APACHE II score (p=0.011), platelet count (p=0.009), and lactate dehydrogenase (LDH) (p=0.011).

**Conclusion:** Thus, five factors—acute respiratory failure, SOFA score, APACHE II score, platelet count, and LDH—can be the meaningful indicators for mechanical ventilation for the patients with scrub typhus admitted to ICU.

**Keywords:** Scrub Typhus; Mechanical Ventilations; Intensive Care Units; APACHE; Blood Platelets; Lactate Dehydrogenase

## Introduction

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*. It is endemic to the 'tsutsugamushi triangle,' which areas of South East Asia, the Indian subcontinent, Sri Lanka, Indian Ocean islands, Papua New Guinea, and North Queensland<sup>1,2</sup>. It is characterized by fever, headache, mental confusion, a macular rash, and an eschar. The majority of patients can recover with early diagnosis and proper management.

But, in spite of the availability of treatment such as doxycycline, scrub typhus with severe complication is still regarded as a fatal disease. As previous reports<sup>3-5</sup>, the mortality rate of scrub typhus ranges from 16.7% to 30% in Southeast Asia. Severe complications can be manifested by acute respiratory distress syndrome, encephalitis, interstitial pneumonia, myocarditis, acute renal failure, and acute hepatic failure<sup>6</sup>. In case

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of accompanying acute respiratory failure, the patients have to admit to intensive care unit (ICU) and should be treated with mechanical ventilation. The prognostic risk factors for mechanical ventilation in those patients may provide a timely initiation of appropriate therapy, reduce a respiratory arrest and the mortality rate of scrub typhus.

To our knowledge, there has been few study on the risk factors for mechanical ventilation in patients with scrub typhus. Therefore, we conducted this study to evaluate the risk factors for mechanical ventilation in the patients with scrub typhus admitted to ICU at a university hospital for the last 10 years.

## Materials and Methods

### 1. Study population and data collection

We retrospectively analyzed data of 70 patients who were consecutively admitted to ICU of Eulji University Hospital, Daejeon, Republic of Korea and diagnosed with scrub typhus between May 2004 and December 2014. The diagnosis of scrub typhus was based on the World Health Organization's criteria<sup>7</sup>. When an immunofluorescent antibody assay (IFA) titer against *O. tsutsugamushi* increased more than four times or an indirect IFA IgM titer against *O. tsutsugamushi* to  $\geq 1:80$ , scrub typhus was confirmed.

The following data were collected from medical records: age, gender, vital signs, months at admission, reasons for ICU admission, comorbidities, symptoms, and laboratory findings at admission, transfusion, inotropic agent, eschar, death, cause of death, total duration of hospitalization, duration of ICU stay, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) score.

### 2. Definitions

In this study, we divided study patients into the following two groups: the mechanical ventilation group (MV group) and the non-mechanical ventilation group (non-MV group). We considered mechanical ventilation if patients were treated with mechanical ventilation, whether the time of diagnosis was before or after mechanical ventilation. Sepsis was defined by the present of both infection and systemic inflammatory response syndrome (SIRS). SIRS was considered if patients fulfilled at least two of the following criteria: body temperature  $<36^{\circ}\text{C}$  or  $>38^{\circ}\text{C}$ , heart rate  $>90$  beats per minute, respiratory rate  $>20$  breaths per minute, leukocyte count  $<4,000$  or  $>12,000$  cells/ $\mu\text{L}$  or the presence of more than 10% band forms. Neurologic problem was defined by the presence of central nervous system (CNS) related symptoms such as confusion, seizure, or coma. Acute respiratory failure was defined not only by the result that hypoxemia, hypercapnia, or

both cannot be maintained within normal ranges, but also by the presence of symptoms and signs resulted in the need for mechanical ventilation, pneumonia, pleural effusion, pulmonary edema, or acute respiratory distress syndrome. Cardiac problem was defined by the presence of symptoms and signs result in pericardial effusion, ischemic heart failure, and arrhythmia such as atrial fibrillation, ventricular tachycardia, and complete atrioventricular block. Acute renal failure was defined as at least 50% reduction in glomerular filtration rate using the abbreviated modified diet in renal disease equation.

### 3. Statistical analysis

Continuous variables were compared using the two-tailed Student's t test. Categorical data were analyzed using the chi-square test. Factors associated with mechanical ventilation were analyzed by binary linear regression models. Univariate binary logistic regression analysis was done. Then, multivariate analysis was done with the significant factors in the univariate analysis. Results were reported as mean $\pm$ standard deviation or number (%). Data was collected in Microsoft EXCEL (Microsoft Excel 2007; Microsoft Corp., Seattle, WA, USA) and all statistical analysis were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). All p-values were 2-tailed and statistical significance was considered when p-value was less than 0.05.

### 4. Ethics statement

This study was conducted in compliance with the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Eulji University Hospital (IRB File No. EMC 2014-08-007). Informed consent was waived by the board.

## Results

### 1. Clinical features of the patients with scrub typhus admitted to ICU

A total of 70 patients, 32 (45.7%) were males, 15 (21.4%) had rash, 35 (50.0%) had eschar, and seven (10%) were dead. The mean age of patients was  $71.2\pm 11.1$  years (Table 1). The antibiotic treatment between 69 patients and one non-mechanical ventilation patient were doxycycline and flumoxef plus clarithromycin, respectively. The most common reasons of the patients admitted to ICU were acute respiratory failure in MV group and sepsis in non-MV group. Statistically significant differences were observed in acute respiratory failure between the two groups ( $p=0.008$ ). Clinical features were analyzed between MV group and non-MV group (Table 1). The mean of peak airway pressure, positive end-expiratory pressure,

**Table 1.** Clinical characteristics of patients with scrub typhus, according to treatment with or without mechanical ventilation

Characteristic	Total (n=70)	Mechanical ventilation		p-value ( $\chi^2$ test)
		Yes (n=19)	No (n=51)	
Age, yr	71.2±11.1	71.2±8.3	71.2±11	0.990*
Male	32 (45.7)	10 (52.6)	22 (43.1)	0.592
Reasons for ICU admission				
Acute respiratory failure	16 (22.9)	9 (47.4)	7 (13.7)	0.008 <sup>†</sup>
Neurologic problem	21 (30.0)	4 (21.1)	17 (33.3)	0.390
Sepsis	22 (31.4)	3 (15.8)	19 (37.3)	0.146
Cardiac problem	7 (10.0)	3 (15.8)	4 (7.8)	0.379
Gastrointestinal bleeding	3 (4.3)	0	3 (5.9)	0.557
Acute renal failure	1 (1.4)	0	1 (2.0)	1.000
Comorbidity <sup>‡</sup>				
None	22	7 (36.8)	15 (29.4)	0.573
Hypertension	32	8 (42.1)	24 (47.1)	0.791
Diabetes mellitus	19	5 (26.3)	14 (27.5)	1.000
Cerebrovascular disease	7	1 (5.3)	6 (11.8)	0.665
Chronic liver disease	4	1 (5.3)	3 (5.9)	1.000
COPD	3	1 (5.3)	2 (3.9)	1.000
Old pulmonary tuberculosis	2	1 (5.3)	1 (2.0)	0.472
PF ratio of acute respiratory failure	160.2±120.6	134.5±114.5	193.3±128.9	0.351*
Rash	15 (21.4)	1 (5.3)	14 (27.5)	0.053
Eschar	35 (50.0)	8 (42.1)	27 (52.9)	0.592
Transfusion	11 (15.7)	5 (26.3)	6 (11.8)	0.140
Inotropic agent	18 (25.7)	5 (26.3)	13 (25.5)	1.000
APACHE II score	14.9±4.8	17.3±4.7	14.1±4.6	0.015* <sup>†</sup>
SOFA score	6.0±2.7	7.3±2.9	5.5±2.4	0.013* <sup>†</sup>
Death	7 (10.0)	5 (26.3)	2 (3.9)	0.014 <sup>†</sup>
Cause of death				
Respiratory failure	4 (5.7)	3 (15.8)	1 (2.0)	0.058
Cardiac arrest	2 (2.9)	1 (5.3)	1 (2.0)	0.472
Multi-organ failure	1 (1.4)	1 (5.3)	0	0.271

Values are presented as mean±standard deviation or number (%).

\*Student's t test. <sup>†</sup>p<0.05. <sup>‡</sup>The total number of comorbidities may be more than 70, because the parameters are overlapped.

ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; PF: the ratio of arterial oxygen partial pressure to fractional inspired oxygen; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

fraction of inspired oxygen (FiO<sub>2</sub>), and tidal volume in MV group were 14.6±3.2 mm Hg, 5.6±3.8 mm Hg, 71.6±21.2%, and 437.4±68.7 mL, respectively. There were statistically significant differences in APACHE II score (p=0.015), and death (p=0.014) between two groups. In comparison of laboratory features between two groups, there was no statistically significant difference (Table 2).

## 2. Factors associated with mechanical ventilation in the patients with scrub typhus admitted to ICU

We analyzed factors associated with mechanical ventilation in the patients with scrub typhus admitted to ICU. In univariate analysis, acute respiratory failure at admission to ICU (p=0.005), APACHE II score (p=0.017), SOFA score (p=0.020),

**Table 2.** Laboratory features of patients with scrub typhus, according to treatment with or without mechanical ventilation

Laboratory test	Total (n=70)	Mechanical ventilation		p-value (t test)
		Yes (n=19)	No (n=51)	
C-Reactive protein, mg/dL	14.0±6.9	17.3±10.1	12.8±9.3	0.082
White blood cell count, ×10 <sup>3</sup> /μL	12.6±11.1	17.2±19.3	10.9±4.9	0.178
Platelet count, ×10 <sup>3</sup> /μL	168.2±101.7	207.2±139.0	153.1±80.7	0.128
Thrombocytopenia	18 (25.7)	6 (31.6)	12 (23.5)	0.545*
AST, IU/L	118.5±176.8	107.6±96.3	122.5±199.4	0.765
ALT, IU/L	63.5±50.1	66.6±61.9	62.3±45.6	0.775
Total bilirubin, mg/dL	1.2±1.8	1.1±1.1	1.3±2.0	0.812
GGTP, IU/L	97.4±108.7	93.1±74.1	98.9±119.3	0.848
ALP, IU/L	134.9±87.2	152.3±103.5	128.4±80.5	0.312
Albumin, g/dL	3.0±0.5	3.0±0.6	3.0±0.4	0.844
Protein, g/dL	6.2±0.7	6.4±0.7	6.1±0.7	0.255
LDH, IU/L	1,033.5±999.7	1,516.2±1,785.2	863.1±403.0	0.142
Calcium, mg/dL	8.2±0.7	8.2±0.6	8.1±0.7	0.533
Phosphorus, mg/dL	3.2±1.2	3.0±0.9	3.3±1.3	0.420
BUN, mg/dL	29.2±18.9	26.3±14.6	30.2±20.3	0.439
Creatinine, mg/dL	1.3±0.8	1.2±0.5	0.3±0.9	0.484
Sodium, mEq/L	134.1±6.1	133.7±7.7	134.3±5.4	0.679
Potassium, mEq/L	3.9±0.6	3.8±0.6	3.9±0.5	0.834
Uric acid, IU/L	5.4±2.6	5.5 ±2.2	5.4±2.7	0.926
INR	1.2±0.1	1.2±0.1	1.2±0.1	0.363
Prothrombin time, sec	14.8±1.3	14.9±1.4	14.7±1.2	0.484

Values are presented as mean±standard deviation or number (%).

\*χ<sup>2</sup> test.

AST: aspartate aminotransferase; ALT: alanine transaminase; GGTP: γ-glutamyl transpeptidase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; INR: international normalized ratio.

platelet count (p=0.058), and lactate dehydrogenase (LDH) (p=0.074) were statistically significant factors (Table 3). In multivariate analysis, acute respiratory failure at admission to ICU (odds ratio [OR], 6.289; 95% confidence interval [CI], 1.517–26.071; p=0.011), SOFA score (OR, 1.453; 95% CI, 1.119–1.888; p=0.005), APACHE II score (OR, 1.187; 95% CI, 1.040–1.353; p=0.011), platelet count (OR, 1.010; 95% CI, 1.002–1.017; p=0.009), and LDH (OR, 1.002; 95% CI, 1.000–1.003; p=0.011) were independent significant factors associated with mechanical ventilation in the patients with scrub typhus admitted to ICU (Table 3).

### 3. Various periods and chronological orders of the patients with scrub typhus admitted to ICU between mechanical ventilation and non-mechanical ventilation

We analyzed various periods of the patients with scrub

typhus between MV group and non-MV group. There was statistically significant differences in the duration of ICU stay between two groups (p=0.028). However, there were no statistically significant differences in the duration of hospitalization, and doxycycline treatment before admitting to ICU between two groups (Table 4).

## Discussion

In this study, the mortality rate of patients with scrub typhus admitted to ICU was 10.0%. As previous reports performed in ICU<sup>3-5</sup>, the mortality rate of scrub typhus ranges from 16.7% to 30% in Southeast Asia. The mortality rate of ICU in our study was lower than that of previous reports<sup>3-5</sup>; however, the reason was not understood exactly. We found that the patients with mechanical ventilation represented 27.1% of all patients with scrub typhus admitted to ICU. Acute respiratory failure was

**Table 3.** Factors associated with mechanical ventilation in patients with scrub typhus: results of univariate and multivariate logistic regression analysis

Factor	Odds ratio	95% Confidence interval	p-value
Univariate analysis			
Acute respiratory failure	-	-	0.005*
APACHE II score	-	-	0.017*
SOFA score	-	-	0.020*
Platelet	-	-	0.058*
Lactate dehydrogenase	-	-	0.074*
Multivariate analysis			
Acute respiratory failure	6.289	1.517–26.071	0.011 <sup>†</sup>
SOFA score	1.453	1.119–1.888	0.005 <sup>†</sup>
APACHE II score	1.187	1.040–1.353	0.011 <sup>†</sup>
Platelets	1.010	1.002–1.017	0.009 <sup>†</sup>
Lactate dehydrogenase	1.002	1.000–1.003	0.011 <sup>†</sup>

\*p<0.1. <sup>†</sup>p<0.05.

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

**Table 4.** Mean±standard deviation days in hospital, in intensive care unit, and on doxycycline therapy for patients with scrub typhus, according to treatment with or without mechanical ventilation

Period, day	Total (n=70)	Mechanical ventilation		p-value (t test)
		Yes (n= 19)	No (n=51)	
Hospital stay	18.6±27.4	20.9±15.4	17.7±30.8	0.666
ICU stay	5.0±7.0	10.0±11.4	3.3±3.0	0.028*
Doxycycline therapy <sup>Total</sup>	11.2±4.6	9.9±4.9	11.6±4.4	0.162
Doxycycline therapy <sup>Pre-ICU</sup>	1.5±1.5 (n=52)	1.2±0.6 (n=13)	1.6±1.7 (n=39)	0.465
Doxycycline therapy <sup>Pre-MV</sup>	-	2.6±1.2 (n=7)	-	-

\*p&lt;0.05. Student's t test.

ICU: intensive care unit; Doxycycline therapy<sup>Total</sup>: period of doxycycline therapy during hospitalization; Doxycycline therapy<sup>Pre-ICU</sup>: period of doxycycline therapy before admitting to ICU; Doxycycline therapy<sup>Pre-MV</sup>: period of doxycycline therapy before mechanical ventilation.

the most common reason of ICU admission in MV group (47.4%). The mortality rate of MV group and non-MV group were 26.3% and 3.9%, respectively. The results of the present study revealed that the factors leading patients with scrub typhus to mechanical ventilation were acute respiratory failure, SOFA score, APACHE II score, platelet count, and LDH. By logistic regression analysis, they were defined as significant variables associated with mechanical ventilation.

There were a few reports of clinical features, laboratory findings, and risk factors leading to fatal outcome associated with severe scrub typhus<sup>2,6,8,9</sup>. However, to our knowledge, there was few report of risk factors leading to mechanical ventilation in patients with scrub typhus admitted to ICU.

Previous studies<sup>2,6,8,9</sup> have reported that the risk factors for severe scrub typhus were age ≥60 years, CNS dysfunction, white blood cell (WBC) counts >10,000/μL, total bilirubin >2

mg/dL, albumin ≤3.0 g/dL, creatinine ≥2 mg/dL, APACHE II score, and SOFA score. In our study, the population, patients with scrub typhus admitted to ICU, fulfilled the results of previous studies as showing that age was 71.2±11.1 years, WBC counts was 12,600/μL, and albumin was 3.0±0.5 g/dL. But, the parameters of CNS dysfunction, total bilirubin, and creatinine were different from previous studies (Tables 1, 2)<sup>2,6,8,9</sup>.

In multivariate analysis, the parameters which can be the meaningful indicators of mechanical ventilation for the patients with scrub typhus admitted to the ICU were SOFA score (p=0.005), platelet count (p=0.009), acute respiratory failure (p=0.011), LDH (p=0.011), and APACHE II score (p=0.011).

It was surprising to find that LDH was significantly associated with mechanical ventilation for patients with scrub typhus admitted to ICU by multivariate analysis. LDH has been one of medical significant indicators, because it is extensively found

in body tissues, such as heart muscle and blood cells. Because it is released during tissue damage, it can be a marker of injuries and disease. Ogawa et al.<sup>10</sup> reported that elevated levels of LDH was observed in 91%. Tachibana et al.<sup>11</sup> reported that severe type scrub typhus seemed to have the higher mean value of LDH. Venkategowda et al.<sup>12</sup> reported that increase LDH was statistically significant ( $p < 0.0001$ ) in scrub typhus patients group with acute respiratory distress syndrome. In our study, the mean levels of LDH were 1,516.2 IU/L in MV group, and 863.1 IU/L in non-MV group (Table 2). So, the levels of LDH can be the one of meaningful indicators of mechanical ventilation for the patients with scrub typhus admitted to ICU.

The association between acute respiratory failure and mechanical ventilation are not surprising. The patients with scrub typhus admitted to ICU should be carefully monitored, and the intensivists should prepare to mechanical ventilation, if they initially had complication of acute respiratory failure.

Griffith et al.<sup>8</sup> reported that APACHE II scores were significantly higher ( $p = 0.007$ ) in patients with scrub typhus who needed invasive mechanical ventilation ( $21.32 \pm 8.6$ ) when compared with those requiring non-invasive ventilation ( $16.63 \pm 7.24$ ). In our study, it is different from point of view that we compared APACHE II scores between MV group and non-MV group ( $p = 0.015$ ).

There was statistically significant differences in the duration of ICU stay between MV group and non-MV group in our study ( $p = 0.028$ ) (Table 4). However, in case of MV group, the duration of ICU stay included the duration of mechanical ventilation. So, when the duration of only non-mechanical ventilation between two groups was analyzed, we found that significant differences were not observed ( $p = 0.782$ ).

There are few limitations in this study. First, our study was retrospectively designed from a single medical center, such as the bias in selection of patient or mechanical ventilation. So, the results of our study may not be extrapolated as general. Second, specific circumstance of our institution and geographic distribution of *O. tsutsugamushi* might affect clinical feature, laboratory, and treatment of scrub typhus. Third, we could not analyze the difference in virulence according to genotypes of *O. tsutsugamushi*. As previous report<sup>13</sup>, genotypes may be related to the virulence of scrub typhus in patients with scrub typhus admitted to ICU. So, we thought that the genotypes would be one of risk factors to increase the admission of ICU, acute respiratory failure, and mechanical ventilation. Therefore, prospectively designed, a large number of patients, and multi-center studies should be performed to overcome these limitations.

In conclusion, we found that acute respiratory failure, SOFA score, APACHE II score, platelet count, and LDH can be the meaningful indicators of mechanical ventilation for the patients with scrub typhus admitted to ICU.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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