Outcome Predictors in Scrub Typhus Requiring Ventilator and Vasopressor Support

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ABSTRACT

Background: Age and serum creatinine are known to be predictors of mortality in scrub typhus patients admitted in intensive care unit. This study aimed to explore the factors predicting mortality in patients with scrub typhus requiring both ventilator and vasopressor support in our set up.

Methods: A retrospective analysis of 43 patients with scrub typhus (ELISA IgM positive, optical density ≥0.5) admitted in Medical Intensive Care Unit of Chitwan Medical College Teaching Hospital between April 2016 to September 2017 was performed considering recovery or death (poor outcome) as outcome measurement. Potential variables (p<0.25) from bivariate analysis were used to perform a multivariate logistic regression analysis (p<0.10) to predict mortality.

Results: The mortality rate was 56% (24/43). Acute respiratory distress syndrome and shock were observed in all 43 patients. The median (IQR) duration of ventilation use and vasopressor use was 53(101) hours and 48(79.5) hours, respectively. On bivariate analysis, an independent and statistically significant association of mortality with age in years (p=0.039), number of vasopressor use (p<0.001) and serum creatinine more than 1.4 mg/dl (p=0.012) was observed and on multivariate regression analysis, these variables were also the predictors of mortality (age in years: p=0.011, \( \beta = 0.115, OR=1.211, 95\% CI=1.027-1.225 \); number of vasopressor use: p=0.009, \( \beta = 3.705, OR=40.647, 95\% CI=2.532-652.425 \); serum creatinine more than 1.4 mg/dl: p=0.046, \( \beta = -2.205, OR=0.110, 95\% CI=0.013-0.961 \) ).

Conclusions: In scrub typhus with ARDS and septic shock, increasing age and serum creatinine, and requiring more than one vasopressor to maintain blood pressure are at increased risk of mortality.

Keywords: Mortality; predictors; scrub typhus; shock.

INTRODUCTION

Scrub typhus, an infectious disease caused by gram-negative obligatory intracellular bacillus Orientia tsutsugamushi is a serious public health issue.1,2 Approximately one million individuals are infected annually with this infection and mortality rate varies widely from 0-70%.4,5 Scrub typhus was first reported in Nepal in early 19817 and it was confirmed as having magnitude of fatal outbreaks in August 2015.8 The reported fatality case of scrub typhus in Nepal ranges from 1.7% to 7.92%.8-10 Scrub typhus can cause several complications including multiorgan failure.11-15 Approximately a quarter of patients require vasopressor support13,15 and up to 64 % require invasive ventilation for respiratory support.13,15 Studies have reported the clinical profile and outcomes of patients requiring intensive care admission.12,17 However, data are scarce in predicting outcome of patients requiring both ventilator and vasopressor support. This study aimed to find predictors of mortality in patients with scrub typhus requiring both ventilatory and vasopressor support.

METHODS

This was a retrospective study among patients with scrub typhus requiring both ventilator and vasopressor support at Medical Intensive Care Unit (ICU) of Chitwan Medical College Teaching Hospital, Chitwan, Nepal. Email: adhikari00@gmail.com, Phone: +9779851069976.
Medical College between April 2016 to September 2017. The ethical approval of this study was obtained from Institutional Review Committee of this institution. Nursing census was used for patient’s identification. Patients aged ≥16 years with serum scrub typhus IgM (ELISA) positive (optical density ≥0.5 using ELISA kit manufactured by InBios International Inc. USA) and requiring both ventilator and vasopressor support were included in this study. Co-infected patients with dengue, influenza, malaria, leptospirosis, typhoid fever and other causes requiring ventilator support and vasopressor were excluded. Patient’s medical records and electronic data base were used for retrieving socio-demographic information, clinical information, laboratory information and complication. The outcomes were categorized as recovered or death.

Statistical analysis was performed by using IBM SPSS version 20 (IBM Corporation, Armonk, NY, USA). All the variables were subjected to univariate analysis. Normality test of numeric variables were confirmed using Shapiro-Wilk test. The comparison of proportion of categorical variables with respect to outcome measures (recovered/death) was performed using various kinds of Chi-square tests depending upon their number of categories while the comparison of central tendency and dispersion for the same was performed using Student’s t-test or Mann-Whitney test whichever was applicable. Variables with p<0.25 from bivariate analysis were subjected to multiple logistic regression analysis (p<0.10) to determine the predictors of mortality for patients requiring both ventilator and vasopressor supports considering p<0.05 as statistically significant.

RESULTS

The mean ± SD age of patients was 42.7± 16.8 years. Of the 43 patients, 31 (72.1%) were females. Twenty-four (55.8%) patients had fever for less than seven days. The median (IQR) duration of ventilation use and vasopressor use was 53(101) hours and 48(79.5) hours, respectively. Similarly, the median (IQR) number of vasopressor use was 1(1). Majority of patients had hemoglobin level less than 12 mg/dl (40, 93%); WBC count >11000/mm$^3$ (31, 72.1%); platelets count <100000/mm$^3$ (38, 88.4%); total protein level <6 gm/dl (32, 74.4%); and albumin level <3.5 gm/dl (37, 86.0%). Just above half of the patients had bilirubin level >1.5 mg/dl. Similarly, three-fifths of patients had transaminase level >120 IU/l and serum creatinine level >1.4 mg/dl. Five (11.6%) patients required dialysis due to acute kidney injury. All the patients with scrub typhus requiring ventilatory and vasopressor support had ARDS and shock. Meningoencephalitis (6, 14%) was the most common complication, followed by pneumonia (5, 11.6%) and myocarditis (5, 11.6%) (Table 1).

### Table 1. Baseline characteristics (n=43).

| Characteristics | N(%) |
|-----------------|------|
| Age in years    | 42.7(16.8) |
| Sex (female)    | 31(72.1) |
| Duration of fever |   |
| 7-14 days      | 18(41.9) |
| 15-21 days     | 1(2.3) |
| Duration of ventilation use in hours (n=42) | 53(101) |
| Number of vasopressor use | 1(1) |
| Duration of vasopressor use in hours (n=38) | 48(79.5) |
| Haemoglobin level (< 12 mg/dl) | 40(93.0) |
| WBC count (>11000/mm$^3$) | 31(72.1) |
| Platelets count (<100000/mm$^3$) | 38(88.4) |
| Bilirubin level (>1.5 mg/dl) | 22(51.2) |
| Total Protein level (< 6 gm/dl) | 32(74.4) |
| Albumin level (< 3.5 gm/dl) | 37(86.0) |
| Transaminase level (> 120 IU/l) | 26(60.5) |
| Serum creatinine level (>1.4 mg/dl) | 26(60.5) |
| AKI requiring dialysis | 5(11.6) |
| ARDS            | 43(100.0) |
| Shock           | 43(100.0) |
| Meningoencephalitis | 6(14.0) |
| Gl bleeding     | 1(2.3) |
| Pneumonia       | 5(11.6) |
| Myocarditis     | 5(11.6) |
| Outcomes        |          |
| Recovered       | 19(44.2) |
| Death           | 24(55.8) |

Chronic liver disease, diabetes and hypertension were most common co-morbidities in this study. Details of other co-morbidities have been mentioned in figure 1.

Most common signs and symptoms documented in this study were fever, abdominal and shortness of breath. Details of other signs and symptoms have been illustrated in Figure 2.
Figure 1. Co-morbidities of patients with Scrub typhus infection requiring vasopressor and ventilator support.
COPD: Chronic Obstructive Pulmonary Disease; CVA: Cardiovascular Accident

Figure 2. Signs and symptoms of patients with Scrub typhus requiring vasopressor and ventilation support.

Bivariate analysis demonstrated that age in years (p=0.039); number of vasopressor use (p=<0.001); and serum creatinine (>1.4 mg/dl) (p=0.012) were associated with mortality (Table 2). The model shows that age, number of vasopressors use and serum creatinine level (>1.4 mg/dl) are the statistically significant predictors of mortality of such patients. It depicts that one year increase in age increases the odds of mortality of by 1.121 times (p=0.011; 95% CI=1.027 to 1.225) and addition of one vasopressor increases the odds of mortality by 40.647 times (p=0.009; 96% CI=2.532 to 652.425). However, those with serum creatinine less than 1.4 mg/dl have 0.110 times lower odds of mortality compared to those with serum creatinine level more than 1.4 mg/dl (p=0.046; 95% CI=0.013 to 0.961).

Table 3 shows the model for predicting mortality of ICU patients with scrub typhus who were under ventilation and vasopressor support. The model was developed from multivariable logistic regression analysis of explanatory variables (p<0.25 from Table 2) namely age in years, number of vasopressor use, duration of fever, serum creatinine level (>1.4 mg/dl) and meningoencephalitis.
Table 2. Bivariate analysis of baseline characteristics according to outcome measures in patients with scrub typhus under ventilation and vasopressor (n=43).

| Characteristics                      | Outcome                  | P-value | Odds ratio |
|--------------------------------------|--------------------------|---------|------------|
|                                      | Recovered n(%)           | Death n(%) |            |
|                                      | 36.8(15.9)               | 47.4(16.4) | 0.039*     |
| Age in years (years)                 | 15(48.4)                 | 16(51.6) | 0.583      |
| <7 days                              | 8(33.3)                  | 16(66.7) |            |
| 7-14 days                            | 10(55.6)                 | 8(44.4)  | 0.154      |
| 15-21 days                           | 1(100.0)                 | 0        |            |
| Duration of fever (days)             |                         |          |            |
| Hemoglobin level (<12 mg/dl)         | 18(45.0)                 | 22(55.0) | 1.000      |
| WBC count (>11000 per mm$^3$)        | 13(41.9)                 | 18(58.1) | 0.892      |
| Platelets count (<100000 per mm$^3$)| 17(44.7)                 | 21(55.3) | 1.000      |
| Bilirubin level (>1.5 mg/dl)         | 8(36.4)                  | 14(63.6) | 0.453      |
| Total protein level (<6 g/dl)        | 13(40.6)                 | 19(59.4) | 0.495      |
| Albumin level (>3.5 g/dl)            | 16(43.2)                 | 21(56.8) | 1.000      |
| Transaminase level (>120 IU/l)       | 13(50.0)                 | 13(50.0) | 0.525      |
| Serum creatinine level (>1.4 mg/dl)  | 7(26.9)                  | 19(73.1) | 0.012*     |
| AKI requiring dialysis               | 1(20.0)                  | 4(80.0)  | 0.363      |
| Meningoencephalitis                  | 1(16.7)                  | 5(83.3)  | 0.205      |
| G1 bleeding                          | 0                       | 1(100.0) | 1.000      |
| Pneumonia                            | 2(40.0)                  | 3(60.0)  | 1.000      |
| Myocarditis                          | 1(20.0)                  | 4(80.0)  | 0.363      |

Table 3. Regression model for predicting mortality of ICU patients with Scrub typhus under ventilation and vasopressor (n=43).

| Variables                      | $B$ (SE) | P-value | Odds ratio |
|--------------------------------|----------|---------|------------|
| Age in years                   | 0.115(0.045) | 0.011 | 1.121 | 1.027 | 1.225 |
| Number of vasopressor use      | 3.705(1.416) | 0.009 | 40.647 | 2.532 | 652.425 |
| Serum creatinine level (>1.4 mg/dl) | -2.205(1.105) | 0.046 | 0.110 | 0.013 | 0.961 |

Model $x^2= 34.582$ (p<0.001), -2Log likelihood=24.446, Cox & Snell $R^2=0.553$, Nagelkerke $R^2=0.740$, Hosmer and Lemeshow p=0.378

DISCUSSION

Scrub typhus is a potentially serious infection with mortality up to 70% in untreated patients and 33.3% in treated patients. In this study, the overall mortality was 55.8% which is higher than the mortality in treated patients. This may be primarily due to study in patients already with organs failure requiring ventilator and vasopressor support.

Association between increasing age of patients with scrub typhus infection to mortality has been inconsistent. This study found that in both bivariate and multivariate analysis, one year increase in age increased the odds of mortality by 1.121 times (p=0.011; 95% CI=1.027 to 1.225). We also found hemoglobin level < 12 mg/dl, WBC count (>11000 per mm$^3$), platelets count <100000/mm$^3$, total protein level < 6 g/dl, and albumin level < 3.5 g/dl in majority of the patients. Similarly, bilirubin level >1.5 mg/dl were documented in more than half of patients while transaminases level > 120 IU/l in three-fifths patients. But, none of the aforementioned laboratory
parameters were associated with poor outcome. Findings of other studies in different parameters like hemoglobin level (< 10 mg/dl), WBC count (>11000 per mm³), platelets count (<100000/mm³), albumin level (< 3.5 gm/dl) and bilirubin level (>1.5 mg/dl), and their influence on mortality were inconsistent. Elevated serum creatinine was one of the well-known predictors for mortality in scrub typhus. However, different studies considered different cutoff value while doing analysis. We used serum creatinine >1.4 mg/dl as a cutoff for analysis and found that those with serum creatinine level less than 1.4 mg/dl have 0.110 times lower odds of mortality compared to those with serum creatinine of more than 1.4 mg/dl (p=0.046; 95% CI=0.013 to 0.961). Some patients needed more than one vasopressor for optimization of blood pressure. Noradrenaline was the drug used in all patients requiring vasopressor support. Vasopressin and adrenaline were first and second add on vasopressors respectively. This study found addition of one vasopressor increased the odds of mortality by 40.647 times (p=0.009; 96% CI=2.532 to 652.425) which was an independent predictor for mortality. Other studies also reported hypertension requiring vasoactive agents as an independent predictor of mortality. Some patients required dialysis as renal replacement therapy, however, this was not associated with increased mortality. In sharp contrast to this, need for dialysis was reported as an independent predictor for mortality in previous study. More than a fifth of patients had pneumonia. Meningoencephalitis, myocarditis, GI bleeding and arhythmia were also documented in our study. However, these complications were not associated with the adverse outcomes in present study probably due to small sample size.

**CONCLUSIONS**

The factors predicting mortality of Nepalese patients with scrub typhus admitted to ICU and requiring both ventilatory and vasopressor support at CMCTH are increasing age, requirement of more than one vasopressors to maintain perfusion and higher serum creatinine. Larger prospective study is required to find out other clinical and laboratory parameters to identify other possible adverse prognostic factors.

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