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, **i**ncreasing 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[3] and **mortality rate varies widely from 0-70%.**[4-6] Scrub typhus was first reported in Nepal in early 1981[7] 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 support[11,16] and up to 64 % require invasive ventilation for respiratory support.[11,12,16] 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

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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 analysiswere 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 more than 11000/mm³ (31, 72.1%); platelets count less than 100000/mm³ (38, 88.4%); total protein level less than 6 gm/dl (32, 74.4%); and albumin level less than 3.5 gm/dl (37, 86.0%). Just above half of the patients had bilirubin level more than 1.5 mg/dl. Similarly, three-fifths of patients had transaminase level more than 120 IU/l and serum creatinine level more than 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(%)**
[a]Age in years		42.7(16.8)
Sex (female)		31(72.1)
Duration of fever	< 7 days	24(55.8)
	7-14 days	18(41.9)
	15-21 days	1(2.3)
[b]Duration of ventilation use in hours (n=42)		53(101)
[b]Number of vasopressor use		1(1)
[b]Duration of vasopressor use in hours (n=38)		48(79.5)
Haemoglobin level (< 12 mg/dl)		40(93.0)
WBC count (>11000/mm³)		31(72.1)
Platelets count (<100000/mm³)		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)
GI bleeding		1(2.3)
Pneumonia		5(11.6)
Myocarditis		5(11.6)
Outcomes	Recovered	19(44.2)
	Death	24(55.8)

[a]mean(SD); [b]median(IQR)

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.
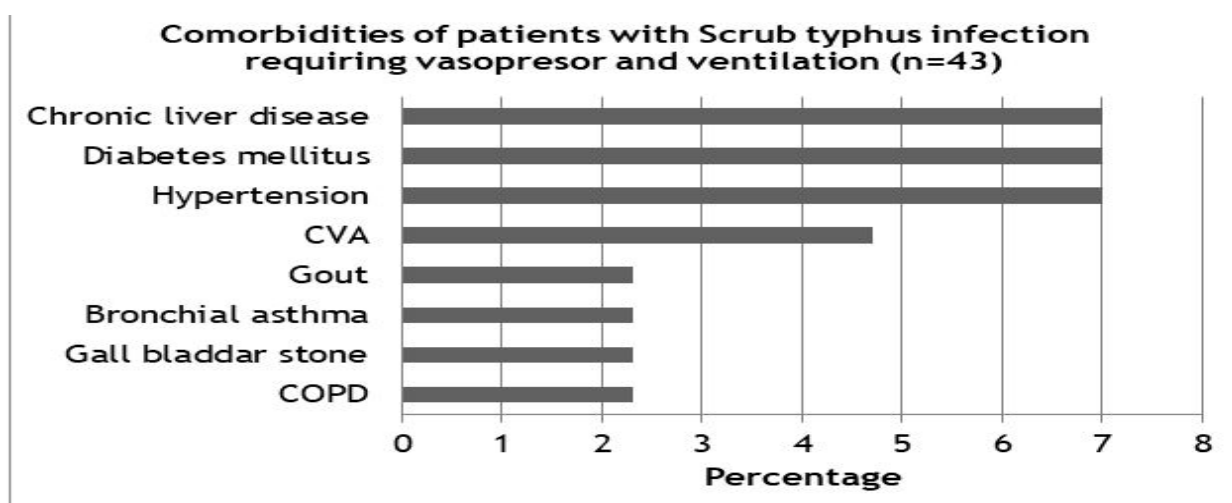
Figure 1. Co-morbidities of patients with Scrub typhus infection requiring vasopressor and ventilator support.

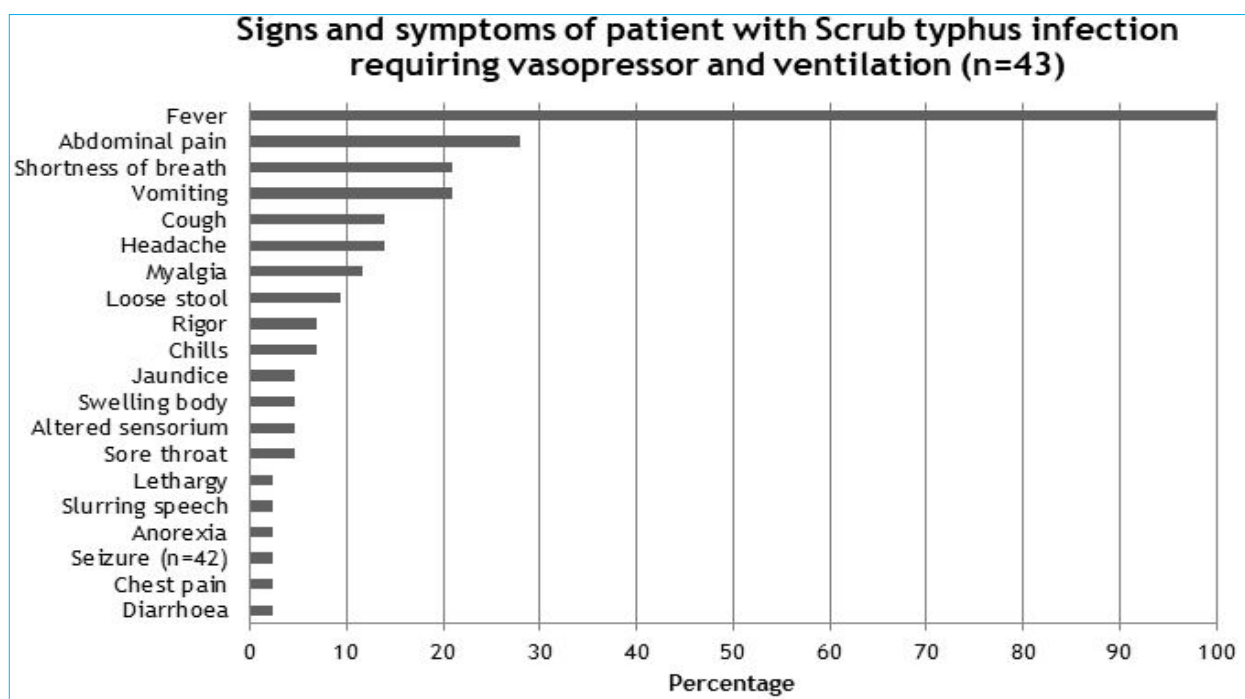COPD: Chronic Obstructive Pulmonary Disease; CVA: Cardiovascular Accident

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).

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.

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 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
		Recovered n(%)	Death n(%)	
[a]Age in years		36.8(15.9)	47.4(16.4)	0.039*
Sex (female)		15(48.4)	16(51.6)	0.583
Duration of fever (days)	<7 days	8(33.3)	16(66.7)	0.154
	7-14 days	10(55.6)	8(44.4)	
	15-21 days	1(100.0)	0	
[b]Duration of ventilation use in hours (n=42)		80(102)	36(104)	0.418
[b]Number of vasopressor use		1(0.00)	2(2)	<0.001**
[b]Duration of vasopressor in hours (n=38)		72(70)	40(105)	0.460
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
GI 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

[a]mean(SD) using student t-test; [b]median(IQR) using Mann-Whitney U test; n(%) using Chi-square test

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

Variables	β (SE)	P-value	Odds ratio	95% CI	
				Lower	Upper
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[6] and 33.3% in treated patients.[4] In this study, the overall mortality was 55.8% which is higher than the mortality in treated patients.[4] 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.[12, 15-19] 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 gm/dl, and albumin level < 3.5 gm/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) [19], WBC count (>11000 per mm^3)[5,19,20] platelets count (<100000/mm^3)[5,19,21,23] albumin level (< 3.5 gm/dl)[20] and bilirubin level (>1.5 mg/dl)[5], and their influence on mortality were inconsistent.[5, 11,15,16,18,21,22] Elevated serum creatinine was one of the well-known predictors for mortality in scrub typhus.[5,11,17,18,20-23] 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 hypotension requiring vasoactive agents as an independent predictor of mortality.[11,16] 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.[24] More than a fifth of patients had pneumonia. Meningeoencephalitis, myocarditis, GI bleeding and arrhythmia 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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