Pattern of Liver Function Test in Scrub Typhus Cases: A Hospital Based Observational Study in A Tertiary Care Center in Nepal

ABSTRACT

Background and Aim: Scrub typhus, a potentially severe but treatable infection is a major cause of acute non-malarial febrile illness in children in the rural tropics. The present study aims to explore the association between the liver function tests in the cases of scrub typhus and correlate the levels of these parameters with the severity of the scrub typhus infections, their clinical risk characteristics that may be used to forecast disease severity under routine clinical practice.

Methodology: This prospective observational study, conducted at National Medical College Teaching Hospital, a tertiary care referral teaching hospital situated in province two of Nepal over a period of 7 months (November, 2021- May 2022) enrolled 75 scrub typhus cases and their liver function tests were done following standard guidelines.

Results: There were deranged liver function tests in the participants. The mean Aspartate Transaminase, Alanine Transaminase, Total Bilirubin and Albumin were425.48 ± 505.56 U/L, 368.54 ± 402.22 U/L, 3.8 ± 3.1 mg/dL and 3.10 ± 0.8 g/dL, respectively. Most of the cases presented with hypoalbuminemia (66.7 %), cardiac dysfunction (64 %), acute kidney injury (61 %) and hepatitis (60%). About 9 % of the subjects presented as multiorgan dysfunction syndrome (MODS).

Conclusion: Scrub typhus cases presents with deranged liver function tests results and the values can be helpful in assessment of the disease severity and outcome.

Key words: Alanine Transaminase, Aspartate Transaminase, Liver Function Test, Scrub typhus

INTRODUCTION

"Scrub typhus, a potentially severe but treatable infection is a major cause of acute non-malarial febrile illness in children in the rural tropics. It is caused by the obligate intracellular bacterium Orientia tsutsugamushi".[1,2,3] "Transmission of this typhus occurs when trombiculid mites, in their larval stage, feed on humans".[4] "A report suggest that the disease is endemic over an area of at

least 13,000,000 km^2 of the Asia Pacific region although recent reports suggest it is much more widespread".[5,6]

"On particular note, hepatic dysfunction with deranged liver function test results have been occasionally reported in 77 to 96% of patients with scrub typhus in some studies with small case numbers".[7,8] "Although serum aminotransferase elevation was shown to rise to a serve level as a distinguishing parameter for scrub typhus associated with acute hepatitis A,[9] the associated factors and clinical implications of hepatic dysfunction for scrub typhus remains largely unclear". "Studies documenting the risk factors for severe scrub typhus and/or death reported somewhat similar results: mainly they include abnormal laboratory findings such as hyperbilirubinemia, hypoalbuminemia, elevated transaminase, serum creatinine levels, leukocytosis, thrombocytopenia and abnormal chest X-ray. Non-laboratory risk factors related to severity included headache, presence of eschar, and age more than 60 years".[10,11,12]

"The first ever reported case of scrub typhus in Nepal was in 1981 and a hospital-based study carried out in 2004 found 28 cases of scrub typhus among 876 enrolled febrile patients"[13]. "The finding of a recent study (2017) conducted in National Public health laboratory, Nepal reported that 40.3% of blood samples collected from patients with acute febrile illness were positive for IgM against O. tsutsugamushi". [14]

"Clinical characteristics determining the prognosis of scrub typhus severity and death have been the subject of many studies. The features may include any combinations of the following systems: respiratory system – dyspnea, crepitation, and abnormal chest findings; cardiovascular system – may be presenting with septic shock; hepatobiliary system – may have serum albumin ,<3 g/dL, bilirubin >1.5 mg/dL, and more than twofold increase in aspartate aminotransferase (AST); and kidney system – serum creatinine >1.4 mg/dL and positive urine albumin".[15,16,17,18]Early detection of these characteristics might be helpful in assisting the clinical guidelines for patient management.

A study done in 2020 in India by Gaba et al. concluded that "renal and liver dysfunctions are common in scrub typhus, and their occurrence adversely affects the outcome". "They stated that liver enzyme ALT was higher and albumin was lower in the mortality group but without statistical significance".[19]

"Another study in India in 2019 stated that liver function abnormalities are most common among various laboratory abnormalities. Elevation of ALT, AST and ALP are in favor of scrub typhus in suspicious cases. Fifty nine of 71 subjects (83.1%) had some degree of hepatic enzyme derangement".[20]

Although documented few studies have been reported previously, the data of scrub typhus in correlation with the laboratory findings is scarce. Therefore, this hospital-based study conducted in Parsa district of province two of Nepal, to study the clinico-laboratory profile and outcome of scrub typhus cases will have some informative prospect in understanding the disease. The present study aims to explore the abnormal liver function tests in the cases of scrub typhus and their clinical risk characteristics that may be used to forecast disease severity under routine clinical practice. The findings of this study may be incorporated into clinical evaluation, awareness, and prevention of disease complications, which may reduce case fatality.

METHODOLOGY

This prospective hospital based observational study conducted at National Medical College Teaching Hospital (NMCTH), a tertiary care referral teaching hospital situated in province two of Nepal over a period of 7 months (November, 2021- May 2022) enrolled 75 scrub typhus subjects.

All scrub positive cases with fever diagnosed in the OPDs and indoor unit of Department of Medicine and Pediatrics and Emergency unit were included in the study.

Common infectious conditions such as that could clinically mimic scrub typhus were ruled out by performing the following tests: peripheral smear and rapid antigen test for malaria, dengue (NS1 antigen and IgM antibody) test, urine and blood cultures as per clinical aspect. Serological diagnosis for scrub typhus was done by IgM ELISA test (In BiOS International, Inc. Seattle USA). The parameters for Liver Function Tests (LFT) were performed in AU480 Beckman Coulter, California following the standard recommended guidelines in Central Laboratory of NMCTH.

Patients with fever and scrub IgM positive between 10 to 60 years and Nepali citizens were enrolled in the study. Patients with fever but negative for scrub, those with co-existing drug dependence or psychiatric illness, tuberculosis or under ATT, pregnancy and any chronic illness and disorder were excluded from the study.

Data were collected, entered using Microsoft Excel and analyzed using Statistical Package of Social Sciences (SPSS) version 11.5. Descriptive statistics was used to express demographic data. Bivariate analysis between groups was done using Chi-square for categorical data. For parametric variables, independent t-test for continuous data and Pearson correlation coefficient were used to assess the relation between quantitative variables. For non-parametric variables, Mann Whitney U test and Spearman correlation were used. Level of significance of 5%, i.e., 95% confidence interval was considered. Statistical significance was considered at $p \leq 0.05$.

RESULTS AND DISCUSSION

There were total of 75 participants presenting with fever and scrub positive serological test results were enrolled in this study. The maximum participants were from 19-40 years of age group, 40% (n=30) and male participant were 60% (n=45) and female were 40% (n=30). Majority of the participants were from Bara and Rauthat, 33 % each (n=25 each) followed by Bara (n=20, 27%) and Sarlahi (n=5, 7%).

Fever with more than 5 days were presented by 44 participants with lymphadenopathy in 51 participants (68%). The hepatomegaly (51%) and splenomegaly (37%) were seen. Jaundice was the presenting features in 53% of the cases. The other clinical manifestations are as mentioned in table number 1.

Table 1: Clinical manifestations of the participants

Clinical Manifestation	Frequency (N)	Percentage (%)
Fever	75	100
< 5 days	31	41.33
>5 days	44	59.67
Headache	54	72
Myalgia	60	80
Vomiting	50	66.67
Lymphadenopathy	51	68
Nausea	45	60
Pain Abdomen	49	65.33
Hepatomegaly	38	50.67
Jaundice	40	53.33

Splenomegaly	28	37.33
Shortness of breath	20	26.67
Altered Sensorium	14	18.67
Rashes	8	10.67
Seizures	10	13.33

There were deranged liver function tests in the participants. The mean Aspartate Transaminase (AST), Alanine Transaminase (ALT), Total Bilirubin and Albumin were425.48 ± 505.56 U/L, 368.54 ± 402.22 U/L, 3.8 ± 3.1 mg/dL and 3.10 ± 0.8 g/dL, respectively. The platelets counts were also low with the mean value of 135000.21 ± 109000.98 (cells/mm3). Other biochemical and hematological parameters are as mentioned in table number 2.

Table 2: Results of laboratory parameters in the participants

Parameters	**Mean ± SD**
Total Leukocyte Count (TLC) cells/mm3	10200.28 ± 6523.48
Platelets (cells/mm3)	135000.21 ± 109000.98
Bilirubin (mg/dL)	
Total	3.8 ± 3.1
Direct	2.4 ± 2.22
Aspartate Transaminase (U/L) (AST)	425.48 ± 505.56
Alanine Transaminase (U/L) (ALT)	368.54 ± 402.22
Serum Albumin (gm/dL)	3.10 ± 0.8
Prothrombin Time (PT) (secs)	17.2 ± 3.8
International Normalized Ratio (INR)	1.32 ± 0.4
Urea (mg/dL)	48.5 ± 40.10
Creatinine (mg/dL)	1.45 ± 0.88

Hypoalbuminemia (67%) was the main complications in the participants followed by cardiac dysfunction (myocarditis) in 64%. There were the complications of kidney injury, hepatitis and MODS as mentioned in the table 3 below.

Table 3: Complications of scrub typhus in participants

Complications of the scrub typhus	**Frequency (N)**	**Percentage (%)**
Cardiac Dysfunction (myocarditis)	48	64

Hypoalbuminemia	50	66.7
Severe thrombocytopenia (<50,000/mm3)	12	9
Acute kidney injury	46	61
Hepatitis	45	60
Multi organ dysfunction syndrome (MODS)	7	9.3

There was a total of 9 mortality (12%) cases with 7 cases with MODS as complication and 2 cases of myocarditis.

Table 4: Liver function test and platelets in different ranges in participants

Liver Function Test Parameters	Frequency (N)	Percentage (%)
AST (U/L)		
0 – 40	25	35.7
41 – 80	10	14.3
81 - 120	20	28.6
> 120	15	21.4
ALT (U/L)		
0 – 45	25	35.7
46 – 90	10	14.3
91 - 135	20	28.6
> 136	15	21.4
ALP (U/L)		
< 100	40	57.1
100 - 260	30	42.9
> 260	10	14.3
Total Bilirubin (mg/dL)		
< 1	15	21.4
1 - 1.5	15	21.4
1.6 – 3	25	35.7
3 - 4.9	10	14.3
>5	10	14.3
Albumin (gm/dL)		
> 3.5	25	35.7
2.5 - 3.4	40	57.1
< 2.5	10	14.3
Hematological Parameters	N	%
Total Platelets		
10000–50000	9	12
50001–100000	14	18.7
100001–150000	17	22.7
150001–333000	35	46.6

A report published in 1995 by Yang et al. from a study in Taipei states that hepatic dysfunction occurred in 77% (36/47) of patients. The percentage of abnormality was 74.5% for AST, 74.5% for ALT, 57.4% for ALP and 44.7% for serum bilirubin. Six patients presented with a picture of true hepatitis similar to acute viral hepatitis. The results suggests that hepatocellular damage does occur in scrub typhus, and is perhaps, more common than previously realized. The results are also in accordance with the findings of our study.[8]

A study done in 2006 in South India by Vargheseet al. reported that "Transaminase elevation (>twice normal) was present in 90% and was significantly (P=0.004) more common in those with scrub typhus. The combination of elevated transaminases, thrombocytopenia and leukocytosis, the specificity and positive predictive value are about 80%. Case fatality rate was 14% similar to the result of our study. Univariate analysis dictated that hyperbilirubinemia (>1.5mg%) has a RR of 9 (95% CI=1.48-58.5) and higher creatinine level (>1.4 mg%) had a RR of 43.99 (95% CI=3.65-530.5) for death. Increased creatinine level was found to be an independent predictor of mortality (P=0.02). The reports provide are in accordance with the results of our study".[18]

A study by Jim et al. done in 2009 in Eastern Taiwan, "145 patients fulfilled the diagnostic criteria for scrub typhus, of whom 106 (73%) were adults and 39 (27%) were children. The study reported the most common clinical manifestations of pediatric scrub typhus were fever (*n* = 39; 100%), cough (*n* = 28; 72%), anorexia (72%), eschar (69%), chill (67%) and lymphadenopathy (64%). The complications were hepatic dysfunction (77%) and pneumonitis (54%). The results are also in accordance with our study but done in pediatric age group only".[15]

A study in 2009 by Lee et al. however showed the mortality rate of only 6.1 % as compared to our 12%. This may be due to their highly facilitated medical intervention. The study reports that 297 scrub typhus patients analyzed that multivariate logistic regression analysis revealed absence of eschar, event of intensive care unit admission and higher APACHE II score were independent predictive variables.[16]

A study done in 2011 in South Korea by Lee et al., reported that fever and headache were significantly more common in patients with scrub typhus. At presentation, ALT level ≥ 500 U/L was observed in 1% of scrub typhus patients. A bilirubin level ≥ 1.3 mg/dL was observed in

16.8% of scrub typhus patients. Fever, headache, rash, and eschar were findings that indicate scrub typhus. The deranged ALT and bilirubin levels were found in less number of scrub cases as compared to our study. This may be due to the early diagnosis and treatment in country like South Korea.[9]

A recent study done in 2020 in India by Gaba et al., reported that "bilirubin and AST were found to be higher in mortality group with statistical significance ($p < 0.05$). ALT was higher and albumin was lower in the mortality group but without statistical significance. About 90.9% of the participants had liver dysfunction and one patient had acute liver failure. All the pregnant patients had fetal loss".[19]

Another study conducted "in 2019 in India also reports about elevation of AST, ALT and ALP are in favor of scrub typhus in suspicious cases. Liver function abnormalities are most common among various laboratory abnormalities. Out of 71 patients diagnosed in 1 year, fifty nine of 71 (83.1%) had some degree of hepatic enzyme derangement. Mild AST elevation was seen in 22 patients (40-80 UL), moderate elevation (81-120 UL) in 18 patients and >3 times elevation was seen in 20 patients. ALT elevation was seen in 59 patients, < 2 times in 26 patients, < 3 times in 20 patients, and >3 times in 13 patients. Serum ALP elevation was seen in 45 patients, < 2 times in 32 patients, < 3 times in 4 patients, and >3 times in 9 patients. Bilirubin elevation was seen in 41 patients, 12 patients had >3 times. Hypoalbuminemia was seen in 90.1% patients, among them severe hypoalbuminemia (<2.5g/dL) was seen in (47.9%) patients. One observation in our study was 90% patients had hypoalbuminemia and 50% had severe hypoalbuminemia".[20]

LIMITATIONS

The study included a small number of participants of scrub typhus. More explanatory and precise result would be generated in case of larger sample size.

CONCLUSION

Scrub typhus, an endemic should be considered for every febrile cases regardless of the typical presenting features and liver function tests with other laboratory markers can be done for

assessment and prognosis of the scrub typhus. Hypoalbuminemia, myocarditis and acute kidney injury are complications that needs to be taken in consideration that can be very much helpful in case management and prevention of mortality.

Ethical Approval and Consent

Written consent in understandable language were obtained and ethical clearance was taken from the institutional Review Committee (IRC) of NMCTH (Ref. F-NMC/540/078/079).

REFERENCES

1. Mayxay M, Castonguay-Vanier J, Chansamouth V, et al. Causes of non-malarial fever in Laos: a prospective study. Lancet Glob Health 2013; 1: e46–54.

2. Chheng K, Carter MJ, Emary K, et al. A prospective study of the causes of febrile illness requiring hospitalization in children in Cambodia. PLoS One 2013; 8: e60634.

3. Brown GW, Shirai A, Jegathesan M, et al. Febrile illness in Malaysia—an analysis of 1629 hospitalized patients. Am J Trop Med Hyg 1984; 33:311–5.

4. Lewthwaite R. Scrub-typhus: a disease of man transmitted by mites. Br Med Bull 1945; 3:227.

5. Jiang J, Richards A. Scrub typhus: no longer restricted to the Tsutsugamushi triangle. Trop Med Infect Dis 2018; 3:11.

6. Kelly DJ, Fuerst PA, Ching WM, Richards AL. Scrub typhus: the geographic distribution of phenotypic and genotypic variants of Orientia tsutsugamushi. Clin Infect Dis 2009; 48(Suppl 3): S203–30.

7. Hu ML, Liu JW, Wu KL, Lu SN, Chiou SS, Kuo CH, et al. short report: abnormal liver function in scrub typhus. Am J Trop Med Hyg 2005; 73:667e8.

8. Yang CH, Hsu GJ, Peng MY, Young TG. Hepatic dysfunction in scrub typhus. J Formos Med Assoc 1995; 94:101e5.

9. Lee J, Kim DM, Yun NR, Byeon YM, Kim YD, Park CG, et al. A comparative study of hepatitis caused by scrub typhus and viral hepatitis A in South Korea. Am J Trop Med Hyg 2011;85: 873e7.

10. Lee CS, Hwang JH, Lee HB, Kwon KS. Risk factors leading to fatal outcome in scrub typhus patients. Am J Trop Med Hyg. 2009;81(3): 484–488

11. Varghese GM, Abraham OC, Mathai D, et al. Scrub typhus among hospitalized patients with febrile illness in South India: magnitude and clinical predictors. J Infect. 2006;52(1):56–60.

12. Kim DM, Kim SW, Choi SH, Yun NR. Clinical and laboratory findings associated with severe scrub typhus. BMC Infect Dis. 2010; 10:108.

13. Murdoch DR, Woods CW, Zimmerman MD, Dull PM, Belbase RH, Keenan AJ, et al. The etiology of febrile illness in adults presenting to Patan hospital in Kathmandu, Nepal. Am J Trop Med Hyg. 2004 Jun; 70(6):670–5. PMID: 15211012

14. Upadhyaya BP, Shakya G, Adhikari S, Rijal N, Acharya J, Maharjan L, et al. Scrub Typhus: An Emerging Neglected Tropical Disease in Nepal. J Nepal Health Res Counc. 2016 May; 14(33):122–7. PMID: 27885295

15. Jim WT, Chiu NC, Chan WT, et al. Clinical manifestations, laboratory findings and complications of pediatric scrub typhus in eastern Taiwan. *Pediatr Neonatol*. 2009;50(3):96–101.

16. Lee CS, Hwang JH, Lee HB, Kwon KS. Risk factors leading to fatal outcome in scrub typhus patients. *Am J Trop Med Hyg*. 2009;81(3): 484–488.

17. Thap LC, Supanaranond W, Treeprasertsuk S, Kitvatanachai S, Chinprasatsak S, Phonrat B. Septic shock secondary to scrub typhus: characteristics and complications. *Southeast Asian J Trop Med Public Health*. 2002;33(4):780–786.

18. Varghese GM, Abraham OC, Mathai D, et al. Scrub typhus among hospitalized patients with febrile illness in South India: magnitude and clinical predictors. *J Infect.* 2006;52(1):56–60.

19. Gaba S, Gaba N, Gupta M, et al. Hepatic and Renal Profile of Scrub Typhus Patients at a Tertiary Care Center in India. Cureus. 2020: 12(5): e7925. doi:10.7759/cureus.7925

20. Subbalaxmi MVS, Reddy KRM, Prasad KK, Laxmi V. Liver Function Test Abnormalities in Scrub Typhus. *International Journal of Scientific Research*. 2019; 8(3): Print ISSN No 2277 – 8179.