

Clinico-demographic and hepatic profile as outcome predictor in scrub typhus in pediatric age group



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Submission: 14-12-2022

Revision: 28-02-2023

Publication: 01-04-2023

ABSTRACT

Background: Scrub Typhus, a Rickettsial disease is an emerging tropical disease mainly in South East Asia. Very few studies are there in pediatric age group and mainly limited to epidemiological and clinical profile only. **Aims and Objectives:** The main objective of this study is to assess different clinical, laboratory, and biochemical parameters denoting hepatic function in scrub typhus and their role in measuring final outcome and disease severity. **Materials and Methods:** This observational study included 90 children with history of febrile illness for ≥ 5 days between 1 and 12 years of age, diagnosed to be a case of scrub typhus by positive IgM ELISA test to assess the hepatic involvement by different clinical, laboratory, and radiological parameters and also to find out their role in disease severity and outcome. **Results:** Fever followed by vomiting was the most common symptoms with eschar evident in only three patients. Raised aspartate transaminase (AST) and alanine transaminase (ALT) were seen in 71.1% and 64.4%, respectively, with hypoalbuminemia in 78.9%, hepatomegaly in 47.8%, and only 2.2% had altered hepatic echotexture on ultrasonography. All of them had ALT: lactate dehydrogenase (LDH) ratio of < 5 . Shock was the most important predictor of duration of hospital stay whereas serum AST was an important predictor for final outcome and duration of hospital stay. **Conclusion:** Predominant feature of hepatic involvement in scrub typhus resembles that of anicteric hepatitis. Serum ALT: LDH ratio may be an important indicator of scrub hepatitis. Among lab parameters serum AST is the most important predictor of disease mortality and morbidity.

Key words: Scrub typhus; Mortality; Hepatic dysfunction; *Orientia tsutsugamushi*

INTRODUCTION

Scrub typhus is an emerging public health problem in the Asia-Pacific region. It is also called as Tsutsugamushi disease, caused by an arthropod borne gram negative bacillus *Orientia tsutsugamushi* and the vector of the disease is a *Leptotrombidium* mite. Socio-economic status and occupation (mainly farmers) are important risk factors and in India, rural population is predominantly affected in scrub typhus.¹ Following infected vector bite, it causes non-specific symptoms like fever (most common), rash, bite site eschar, myalgia, bodyache, headache, cough, nausea and vomiting, jaundice, pain abdomen, and body swelling.² Clinical spectrum of disease varies from mild febrile illness to multi organ dysfunction such as

hepatic derangement, acute renal failure, pneumonitis with acute respiratory distress syndrome (ARDS), myocarditis, septic shock, meningoencephalitis, and disseminated intravascular coagulation (DIC) are well-documented.³⁻⁵ Widespread damage of endothelial cells leads to release of pro-inflammatory cytokines followed by leucocytes recruitment and chemokine release,⁶ ultimately resulting in multi-organ damage.

In adult population, scrub typhus induced hepatic dysfunction is well-documented ranging from mere hepatomegaly and jaundice to even life-threatening hepatic encephalopathy. It causes intrahepatic sinusoidal endothelial vasculitis resulting in focal inflammation,

Access this article online

Website:

<http://nepjol.info/index.php/AJMS>

DOI: 10.3126/ajms.v14i4.49890

E-ISSN: 2091-0576

P-ISSN: 2467-9100

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and rarely cytopathic liver damage with increase in aminotransferases.⁷ Elevated liver transaminases along with hypoalbuminemia are important biochemical findings.⁸⁻¹⁰ Both these findings in absence of eschar have been studied as disease severity indicators.^{9,11} Despite having such importance from clinical and prognostic point of views, there are few studies concentrating upon hepatic profile of scrub typhus, especially in pediatric population.¹²

Majority of such studies are based on adult population and pediatric data on scrub typhus associated hepatic injury is scarce. Therefore, this study has been conducted to fill the gap in existing research to assess different clinico-biochemical and radiological parameters suggesting hepatic involvement in scrub typhus positive patient among pediatric population and to find out their role in assessment of disease severity and outcome.

Aims and objectives

1. To study the clinical, laboratory and radiological parameters in scrub typhus induced hepatic injury.
2. To find out the association of different hepatic parameters in predicting disease severity.

MATERIALS AND METHODS

This prospective observational study was conducted over 2 years, from September 1, 2019, to August 31, 2021, in a tertiary care hospital of West Bengal, India. Study protocol was approved by the Institutional Ethics Committee and informed consent was taken from the legal guardians wherever applicable and full confidentiality has been retained. The study was conducted as per Declaration of Helsinki.

Children between 1 and 12 years, admitted with acute febrile illness for ≥ 5 days and diagnosed as a case of scrub typhus, confirmed by serological test, were recruited as study population. Scrub Typhus IgM ELISA was used as a confirmatory test. This test has a good sensitivity as well as specificity of approximately 90% for detecting specific antibodies against *O. tsutsugamushi* and has been adequately validated.⁵

Children co-infected with febrile illness such as malaria, dengue, enteric fever, and viral hepatitis and those with pre-existing liver disorder were excluded from the study.

All subjects of the study population were studied in a methodical manner in a predesigned structural pro forma. Study parameters included demographic information such as age, sex, socio-economic status, and overcrowding. Detailed history of fever duration, eschar, altered sensorium, jaundice, and generalized body swelling were taken and thorough clinical examination was performed.

Laboratory investigations such as complete hemogram, liver function test, serum electrolytes were studied. Ultrasonography of whole abdomen was performed in all study subjects to look for hepatic echotexture. All the cases under study population were managed as per standard treatment protocol.

Observations were evaluated by number of patients having hepatomegaly, raised serum transaminases, hypoalbuminemia, and altered hepatic echotexture in ultrasonography.

Outcomes were measured on the basis of duration of hospital stay, need of intensive care and sequelae in the form of either discharged or death. Disease severity is measured in terms of number of death and requirement of paediatric intensive care unit (PICU) admission whereas duration of hospital stay is an important measure of disease morbidity. Statistically significant correlations were tried to establish between observations and outcome parameters.

Data of all patients were collected and compiled in Microsoft Excel 2007 sheet and statistical analysis was performed using IBM SPSS statistics version 25 for windows. All continuous variables were tested for normality and mean and standard deviation were calculated. Association by Pearson Chi-square test as well as correlations between different study variables were measured using appropriate correlation coefficient and statistical significance was defined as $P < 0.05$.

RESULTS

Out of 90 children studied, 47 (52.2%) were male and 43 (47.8%) were female with a mean age of 6.25 ± 2.76 year (mean \pm SD). Overcrowding was present in 65 (72.2%) of study subjects and majority of study subjects belonged to upper lower class (48.9%) as per modified Kuppuswamy scale (updated on 2021).¹³ Among the clinical signs and symptoms, fever was present in all study subjects with a mean duration of fever at admission was 9.1 ± 3.9 days. Vomiting was most predominant symptom seen in 42 (46.7%) children after fever whereas hepatomegaly was the most predominant clinical sign observed among 43 children (47.8%) (Table 1).

Among the laboratory parameters under liver function test, mean value of total serum protein and serum albumin were 6.2 ± 0.8 g/dL and 3.05 ± 0.58 g/dL, respectively, whereas that of total serum bilirubin was 0.4 ± 0.13 mg/dL. Among the liver enzymes, mean value of alanine transaminases (ALT), aspartate transaminases (AST), and alkaline phosphatase (ALP) was 83.6 ± 111.5 U/L, 107.5 ± 115 U/L, and 167.4 ± 106.0 U/L, respectively. Mean value of

prothrombin time and INR was 13.9 ± 1.7 s and 1.4 ± 0.16 , respectively, and that of serum lactate dehydrogenase (LDH) was 863.9 ± 370.0 U/L (Table 2). All the study subjects had ALT: LDH ratio of < 5 . Total 53 (58.9%) children had a AST: ALT ratio of >1 whereas 37 (41.1%) patients had AST: ALT ratio of ≤ 1 . Four children had raised bilirubin level of >1 mg/dL whereas raised AST, ALT, and serum ALP were seen in 64 (71.1%), 58 (64.4%) and 3 (3.3%) children, respectively, as per age specific cut off value.² Hypoalbuminemia was seen in 71 children (78.9%) whereas elevated prothrombin time and raised serum LDH were seen in 53 (58.9%) and 87 (96.7%) children, respectively.

Among the radiological parameters, 43 (47.8%) study subjects had hepatomegaly and only two children (2.2%) had altered hepatic echotexture on ultrasonography. Among the outcome parameters, 16 (17.8%) patients required PICU admission and the mean duration of hospital stay was 8.1 ± 3.1 days. Six patients (6.7%) died in due course of hospital stay.

Among the clinical parameters, jaundice, drowsiness, and shock had significant association with final outcome (either death or discharged); whereas as per requirement of PICU admission is considered, it had significant association with presence of body swelling, vomiting, jaundice,

drowsiness, and shock. Correlation study between clinical parameters and duration of hospital stay showed shock was the most important predictor of duration of hospital stay (correlation coefficient 0.455, $P < 0.001$). Among the other clinical parameters, body swelling, icterus, drowsiness and vomiting had a significant positive correlation with duration of hospital stay (Table 3). Among laboratory parameters, raised serum AST and ALT were the most significant predictors of final outcome. However, serum ALT, AST, and LDH had significant positive correlation with PICU admission. On the other hand, serum albumin had significant negative correlation with requirement of PICU admission (Table 3).

Among the two radiological parameters studied, presence of hepatomegaly on USG had significant association with final outcome and requirement of PICU admission by Pearson Chi-square test, whereas presence of altered hepatic echotexture had significant association with PICU admission. However, correlation study (point biserial correlation) between radiological parameters and duration of hospital stay revealed significant positive correlation between presence of hepatomegaly on USG and duration of hospital stay (Table 3).

DISCUSSION

The recent increase in prevalence of scrub typhus in different parts of India is a matter of concern.¹ This prospective observational study included 1–12 years of age group children tested positive for scrub typhus IgM ELISA. Scrub typhus is caused by *O. tsutsugamushi*, an obligate intracellular organism. It gets transmitted by the bite of an infected Trombiculid mite larva. Children usually exposed to the larval mites when they get involved in outdoor games or harvesting activities.⁵ The inoculation period of scrub typhus is 10–12 days in human.⁸

In this study, mean age of the index population was 6.6 years, exactly same as the only pediatric study available

Table 1: Clinical characteristics profile of children with scrub typhus (n=90)

Signs and symptoms	No of cases (percentage)
Fever	90 (100)
Hepatomegaly	43 (47.8)
Vomiting	42 (46.7)
Drowsiness	30 (33.3)
Anorexia	28 (31.1)
Pain abdomen	24 (26.7)
Body swelling	19 (21.1)
Shock	8 (8.9)
Icterus	7 (7.8)
Bleeding	4 (4.4)
Eschar	3 (3.3)

Table 2: Statistical data of different laboratory parameters among the study subjects (n=90)

Laboratory parameter (unit)	Statistical data			
	Mean \pm SD	Minimum	Maximum	Abnormalities, n (%)
Total serum protein (g/dL)	6.2 \pm 0.8	4.4	7.6	
Serum albumin (g/dL)	3.05 \pm 0.58	2.0	5.2	71 (78.9)
ALT (U/L)	83.6 \pm 111.5	15.0	970.0	58 (64.4)
AST (U/L)	107.5 \pm 115	19	754	64 (71.1)
ALP (U/L)	167.4 \pm 106.0	48	770	3 (3.3)
Total serum bilirubin (mg/dL)	0.4 \pm 0.13	0.1	15.1	4 (4.4)
Prothrombin time (sec)	13.9 \pm 1.7	12	23	53 (58.9)
INR	1.4 \pm 0.16	1	2	53 (58.9)
LDH (U/L)	863.9 \pm 370.0	106	3089	87 (96.7)

LDH: Lactate dehydrogenase, ALT: Alanine transaminases, AST: Aspartate transaminases, ALP: Alkaline phosphatase

Table 3: Association and correlation between clinical parameters, liver function tests and ultrasonographic findings of liver with final outcome, PICU admission, and duration of hospital stay among study subjects (n=90)

Variables	Final outcome*		PICU admission needed		Duration of hospital stay	
	Degree of association	P-value	Degree of association	P-value	Correlation coefficient	P-value
Clinical parameters						
Body swelling	3.221 [¥]	0.073	9.751 [¥]	0.002	0.086 [€]	0.420
Pain abdomen	0.329 [¥]	0.566	0.209 [¥]	0.648	0.454 [€]	<0.001
Vomiting	3.473 [¥]	0.062	6.277 [¥]	0.012	0.140 [€]	0.188
Anorexia	1.070 [¥]	0.301	1.450 [¥]	0.228	0.391 [€]	<0.001
Jaundice	5.853 [¥]	0.016	8.047 [¥]	0.005	0.319 [€]	0.002
Drowsiness	7.232 [¥]	0.007	10.984 [¥]	0.001	0.042 [€]	0.691
Bleeding	0.299 [¥]	0.585	2.973 [¥]	0.085	0.455 [€]	<0.001
Shock	13.416 [¥]	<0.001	19.679 [¥]	<0.001	0.325 [€]	0.002
Biochemical parameters (LFT)						
Serum albumin	0.178 [€]	0.093	-0.302 [€]	0.004	-0.241 [£]	0.022
ALT	-0.334 [€]	0.001	0.414 [€]	<0.001	0.380 [€]	<0.001
AST	-0.385 [€]	<0.001	0.489 [€]	<0.001	0.723 [£]	<0.001
LDH	-0.063 [€]	0.553	0.241 [€]	0.022	0.410 [€]	<0.001
PT	-0.012	0.687	0.068 [€]	0.750	0.019 [£]	0.312
Ultrasonographic findings of liver						
Hepatomegaly	7.027 [¥]	0.007	12.306 [¥]	<0.001	0.354 [€]	0.001
Altered echotexture	0.146 [¥]	0.702	9.460 [¥]	0.002	0.179 [€]	0.091

¥ represents Chi-square (X²) values. € indicates point biserial correlation coefficient is used here, which is a type of Pearson correlation used when one variable is continuous and other variable is categorical but of dichotomous pattern. £ denotes spearman's rho correlation. * Final outcome was described in the form of either discharged or death in study subjects, PT: Prothrombin time, LDH: Lactate dehydrogenase, ALT: Alanine transaminases, AST: Aspartate transaminases, ALP: Alkaline phosphatase

describing hepatic profile in scrub typhus.^{9,12} This incidence is higher in older population as they indulge more in outdoor activities compared to younger. Males were predominantly involved in this study similar to other studies in Indian subcontinent.^{9,10,12,14} Overcrowding was an important factor associated with severe disease outcome, comparable to other adult studies.¹⁵ But in pediatric population, the role of overcrowding due to urbanization of rural areas and occupational risk factors needs to be explored.¹⁴

Fever was most predominant symptom involving 100% study cohort like other similar studies on pediatric population.^{3,5,8,10} Average duration of fever in most studies reported were 7–14 days, similar to our finding of 9.1 (±3.9) days.^{5,9} Lack of response of broad spectrum first line antibiotics may contribute to this observation. Therefore, any patient with febrile illness for ≥5 days, non-responsive to empirical antibiotic therapy with or without liver dysfunction should be investigated for scrub typhus. Eschar, a pathognomonic clinical finding, was found in only 3 cases in our study, due to cutaneous variation of immunity as well as dark complexion of skin among Indian population, which is evident in other study also.^{5,10,16}

Clinically significant icterus was present in only 7.8% cases with average bilirubin level 0.4±0.13 mg/dL in our study.¹¹ Interestingly, some pediatric studies have reported jaundice in as high as 30.7% cases.^{10,14} Although very common in acute viral hepatitis, jaundice is not a common finding in scrub typhus, hence appropriately termed as anicteric

hepatitis. Absence of direct cytotoxic liver injury, unlike viral hepatitis, may attribute to such observation in different studies.^{5,8,17} Hepatic dysfunction and complications sometimes are often missed in early stage of the disease due to non-specific symptoms and absence of jaundice.

As a part of liver function test, elevation of serum AST and ALT is found almost in every study on hepatic dysfunction of scrub typhus similar to our study.^{5,10,12,18} Due to less cytopathic liver damage, the degree of elevation of serum transaminases are generally less than five folds of normal value unlike acute viral hepatitis, where it may increase up to ten folds.¹⁸ Average serum AST value is more than ALT in the index cohort.^{5,8} Serum AST is a non-liver specific enzyme, which co-exists in cardiac muscles and RBCs; hence, it rises more than ALT in scrub typhus indicates multiple organ involvements, that carries a poorer prognosis.

Systemic dissemination of bacteria from the sites of inoculation is followed by inflammation of the endothelial cells. Consequent vasculitic injury resulting in organ dysfunctions is hypothesized as the mechanism of multisystem involvement in scrub typhus.¹⁹ In liver, scrub typhus causes intrahepatic sinusoidal endothelial vasculitis resulting in focal inflammation in mild cases. Granulomatous hepatitis is the most frequent histopathological finding of liver in different studies.²⁰ Although acute liver failure and fulminant hepatitis is rare in scrub typhus, one case report in a 73-year-old woman with acute liver failure in

scrub typhus displayed necrosis and fatty degeneration of hepatocytes and presence of fibrin thrombi in the hepatic sinusoids suggesting micro vascular injury due to DIC.²¹

Hypoalbuminemia is also an important finding indicating hepatic dysfunction due to both synthetic function defect and endothelial leakiness.^{5,8,10,14,18} Similarly, serum LDH is also elevated in scrub typhus which is present in 96.7% of patients in our study, probably due to multiorgan involvement. Serum LDH has not been separately studied in any pediatric study on scrub typhus till date. Only some adult studies²² have found that ALT: LDH ratio is <5 has diagnostic role in scrub typhus. Such finding is consistent to all the participants of our study cohort. This ALT: LDH ratio, as a differentiator between scrub hepatitis and viral hepatitis, requires extensive study for validation on pediatric population and opens scope of future research in this cause.

In our study, 16 out of 90 patients (17.8%) required PICU admission due to myocarditis, shock, acute meningoencephalitis, DIC and multiorgan dysfunction syndrome (MODS). Median duration of hospital stay was 7 days. Death occurred in 6 children (6.7%) and 50% were due to MODS, similar to finding by Nallasamy et al.⁹ Despite the severity of illness and high risk of multiorgan dysfunction, early treatment with Doxycycline had shown favorable outcome in children.⁵ Drowsiness in patients as a part of CNS involvement results from direct CNS infection (meningitis or encephalitis) to other systemic factors such as hypoxia (due to pulmonary edema), renal failure (due to vascular permeability or direct tubular damage), and hepatic dysfunction (hepatic encephalopathy). Presence of drowsiness has significant association with mortality as well as requirement of PICU support in our study similar to other study.⁹ Apart from CNS involvement, presence of jaundice and shock has significant association with final outcome, corroborative to other study conducted by Sivaprakasam et al.¹¹ The presence of edema either due to hypoalbuminemia or increased capillary permeability may complicate myocarditis and acute renal failure and results in prolonged hospital stay and requirement of intensive care support which is evident in this study. Presences of vomiting and shock have shown association with requirement of intensive care. Presence of shock which requires prolonged inotropes and antibiotic (due to superadded sepsis) support increases the duration of hospital stay and it is the most important predictor of duration of hospital stay.

Among the biochemical parameters, both serum AST and ALT are significant indicators of disease severity, though serum AST has shown better correlation in terms of disease prognostication. This suggests multisystem involvement in scrub typhus as elevation of serum AST is not specific to

liver cell damage. Unlike transaminases, serum LDH has no significant correlation with final outcome. Presence of hypoalbuminemia prolongs duration of hospital stay and has significant association with requirement of PICU admission. Other pediatric studies^{9,11} supports this observation, probably due to delay in recovery by complicating myocarditis and acute renal failure as well as ARDS.

In our study, ultrasonography of abdomen revealed, presence of hepatomegaly in 47.8% and altered hepatic echotexture in only 2.2% patients. Although alteration of hepatic echotexture is very rare in scrub typhus, it showed significant association with PICU admission however this finding should be implicated cautiously as the numbers of patients having altered hepatic echotexture are very sparse. However, hepatomegaly has significant association with final outcome and PICU admission. Though our observation is consistent with study on adult patients by Pathania et al.,²³ any pediatric study has not reported radiological profile of liver in scrub typhus till date.

Hepatic dysfunction in scrub typhus is common, but often missed due to lack of specific symptoms and late presentation. Despite this, hepatic profile is a potential indicator in disease severity and outcome assessment. However, only few studies on pediatric population have concentrated on this domain, especially its role in outcome assessment. Therefore, our study will open the new horizon in research of this tropical disease among pediatric age group and make a robust knowledge to the budding pediatric intensivists.

Limitations of the study

The study was done in a single center so hospital based bias could not be ruled out as well as small sample size was also a constraint in the study. Relationship between therapeutic management and its relation to outcome and severity could not be addressed here. We concentrated on clinical, biochemical and radiological parameters related to hepatic involvement in scrub typhus in our study. Histopathological findings by liver biopsy were not studied as it is not the standard of care, unless clinically indicated.

CONCLUSION

Scrub typhus, a Rickettsial disease caused by *O. tsutsugamushi* is predominantly seen in overcrowded places and in those with poor socio-economic status. Although scrub typhus can cause multisystem involvement, hepatic dysfunction in any forms such as clinical, biochemical, or radiological is an important aspect of disease severity. While fever is the most predominant symptom in scrub typhus, the

predominant feature of hepatic involvement in scrub typhus resembles that of anicteric hepatitis. ALT: LDH ratio may be a diagnostic indicator in scrub typhus with ratio <5 may be suggestive of scrub infection. Among the laboratory parameters in liver function test, raised serum AST is the most important indicator of disease mortality as well morbidity in scrub typhus. Although hepatomegaly detected on USG has significant association with final outcome of disease as well as significant correlation with duration of hospital stay, presence of altered hepatic echotexture on USG which is present in very less number of patients has no such significant association with final outcome or correlation with duration of hospital stay.

ACKNOWLEDGMENTS

The authors are thankful to all members of the nursing staffs and residents of department of Pediatrics.

The author(s) did not receive any financial support for the research, authorship, and/or publication of this article.

ETHICAL APPROVAL/PATIENT CONSENT

Informed consent in written form has been taken from parents or local guardians of all the patients before disclosing their medical data. The study was approved by institutional ethical committee.

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TK- Designed study, managed patients, data collection, prepared first draft of manuscript; **RP-** Designed study, reviewed the literature, and manuscript preparation; **MM-** Concept, interpretation of data, review of manuscript; **SS-** Reviewed literature, revised manuscript, statistical analysis, and interpretation.

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Source of Support: Nil, **Conflicts of Interest:** None declared.