# Liver dysfunction in children with scrub typhus: association with severity of illness and outcome

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**Abstract**

***Background:*** Liver dysfunction is a common finding in children with scrub typhus. Adult literature has found a significant association between the extent of liver dysfunction and severity of illness and outcome. However, very few studies are available on children.

***Objectives:*** To study the extent of liver dysfunction in children with scrub typhus and its association with severity of illness and outcome.

***Method:*** It was a retrospective descriptive study conducted on children diagnosed with scrub typhus admitted to a tertiary care centre in south India from January 2016 to December 2020. Children from 1 month to 18 years of age were included. Demographic data, clinical details, laboratory parameters, course of illness and outcome data were collected and analysed.

***Results:*** Study population included 143 cases of scrub typhus. Mean age of the study population was 8.4 ± 4.4 years with a male: female ratio of 1.2:1. Fever was present in 100%, myalgia in 54.5%, decreased appetite in 54.5%, jaundice in 8.4% and hepatomegaly in 71.3% of children. Abnormal liver function tests were present in 75.5% children. Elevated aspartate transaminase (AST) was seen in 75.5%, elevated alanine transaminase (ALT) in 67.1%, hypoalbuminaemia in 47.5% and severe hypoalbuminaemia (<2.5g/dL) in 29.4%. Complications included meningitis (13.3%), shock (7.6%), meningoencephalitis (2.7%) and acute respiratory distress syndrome (2%). There were 2 (1.3%) deaths. Children with complications had higher AST ($p < 0.01$), ALT ($p = 0.018$), low serum albumin ($p<0.001$) and prolonged international normalised ratio (INR) ($p = 0.003$).

***Conclusions:*** Abnormal liver function tests were present in 75.5% of children with scrub typhus. Children with complications of scrub typhus had significantly higher median AST levels, ALT levels, low serum albumin levels and prolonged INR compared to children with no complications.

(Key words: Scrub typhus, Transaminases, Hypoalbuminaemia, Liver dysfunction, Hepatitis, Children)

**Introduction**:

Scrub typhus is one of the common causes of undifferentiated febrile illness in tropical regions. The vector for scrub typhus is chiggers or larvae of Leptotrombidium mites[1]. The diagnosis is often missed as the signs and symptoms are similar to other tropical infectious diseases especially dengue fever. Mortality rate ranges from 0-30% in untreated cases[1]. Liver dysfunction is a common finding in scrub typhus. Adult literature has found a significant association between elevated liver enzymes and hypoalbuminaemia with the severity of the illness[2]. However, very few studies are available in children.

**Objectives**

To study the spectrum of hepatic involvement in children with scrub typhus and to correlate liver dysfunction with the severity of illness and outcome.

**Method**

This was a retrospective descriptive study conducted at the department of paediatrics of a tertiary referral care centre in South India.

***Inclusion criteria:*** Children from 1 month-18 years of age diagnosed with scrub typhus and admitted during the study period of 5 years from January 2016 to December 2020. The diagnosis of scrub typhus was confirmed by IgM ELISA positivity using commercial kit (In Bios International, Inc., Seattle, WA, USA).

***Exclusion criteria:*** Children with scrub typhus who were simultaneously positive for other infections (dengue, malaria, enteric fever, hepatitis A and B, leptospirosis, blood culture positivity) and those with pre-existing liver disease which interferes with

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liver function tests (chronic active hepatitis, cirrhosis, hepatitis B, Wilson disease, thalassaemia). We also excluded those who were diagnosed as scrub typhus based only on OX-K titre in Weil Felix test as well as whose liver function test reports were not available.

Baseline demographic, clinical and laboratory information including haemogram and liver function test were documented.

- *Hepatomegaly* was considered as liver enlargement >2 cm below the right costal margin.
- *Prolonged aspartate transaminase* (AST) was defined as AST >2 times the upper limit of normal (40 IU/L).
- *Prolonged alanine transaminase* (ALT) was defined as ALT >2 times the upper limit of normal (40 IU/L).
- *Elevated serum bilirubin*: was defined as total serum bilirubin >2 mg/dl.
- *Hypoalbuminaemia:* was defined as serum albumin levels <3.4g/dL. Severe hypoalbuminaemia was considered if the serum level was <2.5g/dL[3,4].
- *Prolonged international normalized ratio* (INR) was defined as INR>1.5.

In the present study, complications of scrub typhus were defined as follows:

- *Hypotension* was defined as a systolic blood pressure below the 5th percentile for the corresponding age, sex and height.
- *Acute respiratory distress syndrome* (ARDS) was defined as per paediatric ARDS criteria[5].
- *Acute kidney injury* (AKI) was considered as per Kidney Disease Improving Global Outcomes (KDIGO) definition and classification[6].
- *Myocarditis* was diagnosed when the following conditions were observed: (i) Clinical findings consistent with left ventricular dysfunction (ii) Presence of global left ventricular wall motion abnormality on echocardiography (iii) elevated CPK-MB levels in the blood with or without electrocardiographic abnormalities.
- *Meningoencephalitis* was considered in the presence of altered sensorium along with meningeal signs and/or seizures along with positive cerebrospinal fluid findings.
- *Multiple Organ Dysfunction* (MODS): dysfunction of more than 1 organ requiring intervention to maintain homeostasis.

The extent of hepatic dysfunction was compared between children with complications and those without complications. The length of PICU stay and total duration of hospital stay were recorded. Outcome was defined in terms of mortality and survival.

***Ethical issues:*** Approval for the study was obtained from the Institutional Ethics Committee of Kasturba Medical College and Kasturba Hospital (No. IEC: 919/2020) on 08.12.2020. Being a retrospective study informed consent was not a possibility.

***Statistical analysis:*** Obtained data were analysed using the Statistical Package for Social Sciences (SPSS) version 23.0. Descriptive data were expressed as frequencies and percentages. Mean and standard deviation were computed for the variables following normal distribution curve, while median and inter-quartile range were computed for non-parametric data. Fisher exact test was used to test categorical variables. Student t-test or Mann Whitney test was used to compare mean or median value of parameter between 2 groups. p-value of <0.05 was considered statistically significant.

**Results**

A total of 188 children with scrub typhus was admitted during the study period. After excluding 45 children, the final study population included 143 children as depicted in Figure 1.

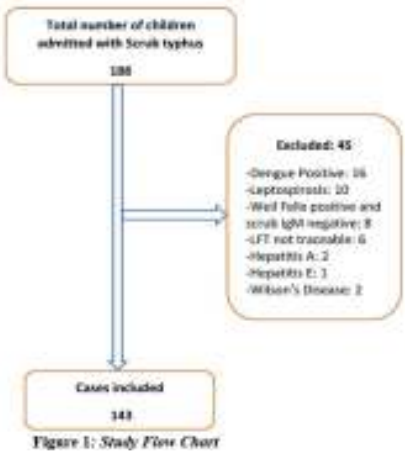


**Figure 1:** *Study Flow Chart*

The mean age of the study population was 8.4 ± 4.4 years with a range of 10 months to 18 years. The majority (66.4%) of children were in the age group of 5-10 years. There were 2 infants. Boys were more affected than girls with male-to-female ratio of 1.2:1.

Symptoms and signs of children with scrub typhus are summarised in table 1. The mean duration of illness prior to admission was 5.3±2.58 days with a range of 1-7 days. Hepatomegaly was present in 71.3% children. Maculo-papular rash involving palms and soles was observed in 20.3% children while eschar was present in 12.6% children.

**Table 1:** ***Symptoms and signs of children with scrub typhus***

| Symptom | n (%) | Sign | n (%) |
|---|---|---|---|
| *Fever* | 143 (100) | Hepatomegaly | 102 (71.3) |
| *Myalgia* | 78 (54.5) | Tachycardia | 97 (67.8) |
| *Decreased appetite* | 78 (54.5) | Splenomegaly | 68 (47.6) |
| *Vomiting* | 64 (44.7) | Hepato-splenomegaly | 64 (44.7) |
| *Pain in abdomen* | 46 (32.2) | Pallor | 54 (37.8) |
| *Cough* | 38 (26.5) | Skin rash | 29 (20.3) |
| *History of tick bite* | 19 (13.3) | Oedema | 23 (16.1) |
| *Swelling of limbs* | 14 (09.8) | Eschar | 18 (12.6) |
| *Abdominal distension* | 12 (08.4) | Meningeal signs | 19 (13.3) |
| *Jaundice* | 12 (08.4) | Icterus | 12 (08.4) |
| *Hurried breathing* | 09 (06.2) | Hypotension | 12 (08.4) |
| *Altered sensorium* | 08 (05.5) | Lymphadenopathy | 11 (07.7) |
| *Seizures* | 05 (03.5) | Tachypnoea | 09 (06.3) |
| | | Ascites | 08 (05.6) |

Baseline liver function tests are summarized in table 2. Abnormal liver function tests were present in 75.5% of patients. Elevation of AST and ALT by 3 times the upper normal limit was observed in 47 (32.8%) and 25 cases (17.4%) respectively. Hypoalbuminaemia was present in 68 (47.5%) while severe hypoalbuminaemia (<2.5g/dL) was present in 42 (29.4%) children. Liver function tests normalized within 1 week of hospital stay in 56% of children, while in the remaining children normalization of LFT was documented within the next 4 weeks.

**Table 2:** ***Baseline liver function tests of children with scrub typhus***

| Parameter | Children with abnormal parameter n (%) | Median (Inter quartile range) |
|---|---|---|
| *Aspartate transaminase (IU/L)* | 108 (75.5) | 92 (56, 372) |
| *Alanine transaminase (IU/L)* | 96 (67.1) | 76 (32, 188) |
| *Total serum bilirubin (mg/dL)* | 12 (08.3) | 0.63 (0.32, 2.47) |
| *Serum albumin (g/dL)* | 68 (47.5) | 3.24 (2.14, 4.22) |
| *International normalized ratio* | 08 (95.6) | 1.02 (0.80, 1.80) |

Complications of scrub typhus were observed in 52 (36.4%) children. They included meningitis/ meningoencephalitis in 18 (12.6%), shock in 12 (8.4%), pneumonia in 9 (6.3%), ARDS in 4 (2.8%), myocarditis in 4 (2.8%), AKI in 2 (1.4%), MODS in 2 (1.4%) and purpura fulminans in 1 (0.7%).

Thirty-six (25.2%) children required admission to the paediatric intensive care unit (PICU); 12 children required inotropic support and 6 required mechanical ventilation. The mean duration of PICU stay was 4.1±2.04 days (range 1-7 days). The mean duration of hospital stay was 5.2±3.02 days (range 2-12 days).

Doxycycline was used in 95.1% of children. Chloramphenicol was used in 3.6% of children; 2 (1.4%) children were treated with azithromycin.

Mortality was observed in 2 children. Both children developed refractory shock with MODS. Both children had AST and ALT levels of >1000 IU/L, severe hypoalbuminaemia and prolonged INR.

The comparison of LFT parameters with severity of illness (between children with complications and those without complications) is shown in table 3.

**Table 3:** ***Liver function tests in scrub typhus children with and without complications***

| Parameter | With complications *(n=52)* | Without complications *(n=91)* | Odds ratio [95% CI] | p value |
|---|---|---|---|---|
| Elevated aspartate transaminase (n=108)<br>Median aspartate transaminase (IQR) IU/L | 48<br>135 (85.2, 272.4) | 60<br>67 (42, 123) | 6.12 [1.97, 25.56] | **<0.01***<br>**<0.01#** |
| Elevated alanine transaminase (n=96)<br>Median alanine transaminase (IQR) IU/L | 44<br>104 (52.2, 118.4) | 52<br>56 (37.4, 92.6) | 4.08 [1.65, 11.21] | **0.0008***<br>**0.018**[#] |
| Elevated total serum bilirubin (n=12)<br>Median total serum bilirubin (IQR) IU/L | 10<br>0.73 (0.32,4.95) | 2<br>0.44 (0.28,1.49) | 10.41 [2.08, 12.46] | **0.007***<br>0.1[#] |
| Hypoalbuminemia (n=68)<br>Mean serum albumin ±SD<br>Range (g/dL) | 42<br>2.28±0.74<br>1.6-3.5 | 26<br>3.26±0.61<br>2.3-4.5 | 10.2 [4.32, 26.62] | **<0.001***<br>**<0.001**[$] |
| Prolonged INR (n=8)<br>Mean INR (±SD)<br>Range | 7<br>1.09 ± 0.51<br>1.4-3.5 | 1<br>1 ± 0.4<br>1.9-4.2 | 13.7 [1.68, 63.56] | **0.003***<br>0.3[$] |

*CI: confidence interval; *Fisher's exact test; [#]Mann-Whitney U test, [$]Student-T test INR: International normalized ratio*

Mann-Whitney U test was used to analyse data for AST and ALT levels as the values were not normally distributed. It was found that elevated AST and ALT levels, hypoalbuminaemia and prolonged INR were associated with increased risk of complications and this was statistically significant. Odds ratio for complications were 6.12, 4.18, 10.2 and 13.7 respectively. The average value (mean/median) of LFT parameters were compared between the 2 groups. It was found that children with complications had higher median AST ($p<0.01$), ALT levels ($p=0.018$), low serum albumin levels ($p<0.001$) and prolonged INR ($p=0.003$). All children with severe hypoalbuminaemia (n=42) were in the complications group. However, the association of mean total serum bilirubin levels with complications was not significant ($p = 0.1$).

## Discussion

Scrub typhus is a recognized cause of acute liver failure related to tropical infectious disease. Other tropical infectious diseases related to hepatic dysfunction include malaria, dengue fever, leptospirosis, typhoid and tuberculosis. Most of these illnesses initially present with undifferentiated fever (often >5 days). Though skin rash and eschar are specific for scrub typhus, their prevalence varies from 7-97%[7]. Weil Felix test is a nonspecific test for the diagnosis of scrub typhus. In the present study we included children with positive IgM Scrub Typhus ELISA test. Though indirect immunofluorescent antibody (IFA) test is the gold standard, it is expensive and not easily available[7,8].

Risk factors reported to be associated with severe illness in scrub typhus include malnutrition, anaemia, dyspnoea at admission, leucocytosis, high C-reactive protein and elevated hepatic transaminases[8]. Very few studies are available in children regarding liver dysfunction and the spectrum of liver involvement in scrub typhus[9-11]. The prevalence of hepatic dysfunction in scrub typhus varies from 70-90%[9]. The spectrum of liver involvement includes hepatomegaly, jaundice, elevated transaminases, hypoalbuminaemia and coagulopathy[10]. In a study by Chanta C, *et al*[11] in Thailand, it was found that increased AST, ALT, and hypoalbuminaemia were associated with the severity of illness. Authors also concluded that raised AST can be used to diagnose scrub typhus if serological tests are not easily available.

The main pathology in scrub typhus is vasculitis that is secondary to infiltration of the endothelial lining of the vessels. Scrub typhus infiltrates the endothelial cells and initiates the release of pro-inflammatory cytokines like TNFα and CXCL8 (IL-8), which further leads to recruitment of leucocytes and chemokines leading to microvascular injury in liver, brain, lungs, kidneys leading to multi-organ dysfunction[12].

The prevalence of hepatomegaly varies in different studies. Studies by Pathak S, *et al*[13], in central Nepal and Balaji J, *et al*[14] in south India showed hepatomegaly in 47% and 62% respectively. In current study, hepatomegaly was noted in 71.3% of cases. Previous studies have demonstrated that the prevalence of serum aminotransferase elevation ranges from 34% to 96%[14,15]. In the study by Su TH, *et al*[15], serum aminotransferase elevation predicted the diagnosis of scrub typhus, especially in those patients without eschar. The median AST level of children in the present study was 92 [56, 372] IU/L [Q1, Q3] which itself is >2 times the upper limit.

The direct cytotoxic effect versus immune mediated damage in the aetiopathogenesis of liver cell injury has been debated. *O. tsutsugamushi* has been visualized in infected hepatocytes through electron microscope[16]. It is believed that it's the triad of host immune reaction, organism load, and virulence plays important role in hepatic dysfunction.

Few studies have demonstrated the elevation of total bilirubin as a common marker of hepatocellular dysfunction in scrub typhus. In the present study, serum bilirubin was elevated in only 8.3% of the study population and there was no statistical significance in the difference between mean TSB levels between the 2 groups. In other studies,

elevated total serum bilirubin ranged from 7.4% to 19.7%[16,17].

Hypoalbuminaemia was found to be significantly associated with an increased risk of complications in the present study which was comparable to previous studies[19]. Children with complications were observed to have low mean serum albumin (2.28±0.74 vs. 3.26±0.61) and this was statistically significant ($p<0.001$). It was also observed that all children with severe hypoalbuminaemia were present in the complication group. Though we found prolonged INR in 8 children, none of them had significant bleeding manifestations.

Doxycycline is the mainstay of treatment for scrub typhus. Recommended dose is 4-4.5mg/kg/day in 2 divided doses for >40kg body weight for 7-10days[20]. In severe cases IV doxycycline can be used. Azithromycin is an effective alternative. In the current study azithromycin was used in 2 children under 2 years of age, where doxycycline is relatively contraindicated.

**Conclusions**

Abnormal liver function tests were present in 75.5% of children with scrub typhus. Children with complications of scrub typhus had significantly higher median AST levels, ALT levels, low serum albumin levels and prolonged INR compared to children with no complications.

**References**


1. Rathi N, Kulkarni A, Yewale V; For Indian Academy of Pediatrics Guidelines on Rickettsial Diseases in Children Committee. IAP Guidelines on Rickettsial Diseases in Children. *Indian Pediatrics* 2017; **54**(3): 223-9. https://doi.org/10.1007/s13312-017-1035-0 PMid: 28361787

2. Taylor AJ, Paris DH, Newton PN. A systematic review of mortality from untreated scrub typhus (Orientia tsutsugamushi). *PLoS Neglected Tropical Diseases* 2015; **9**(8): e0003971. https://doi.org/10.1371/journal.pntd.0003971 PMid: 26274584 PMCid: PMC4537241

3. Kim MH, Kim SH, Choi JH, Wie SH. Clinical and laboratory predictors associated with complicated scrub typhus. *Infection and Chemotherapy* 2019; **51**(2): 161-70. https://doi.org/10.3947/ic.2019.51.2.161 PMid: 31270995 PMCid: PMC6609747

4. Sivaprakasam E, Rajan M, Pasupathy U, Ravichandran L. Clinical characteristics and predictors of severity of paediatric scrub typhus in a tertiary level hospital in South India. *Archives of Pediatric Infectious Diseases* 2020; **8**(1): e92752. https://doi.org/10.5812/pedinfect.92752

5. Orloff KE, Turner DA, Rehder KJ. The current state of paediatric acute respiratory distress syndrome. *Pediatric Allergy, Immunology and Pulmonology* 2019; **32**(2): 35-44. https://doi.org/10.1089/ped.2019.0999 PMid: 31236307 PMCid: PMC6589490

6. Sethi SK, Bunchman T, Chakraborty R, Raina R. Paediatric acute kidney injury: new advances in the last decade. *Kidney Research and Clinical Practice* 2021; **40**(1): 40-51. https://doi.org/10.23876/j.krcp.20.074 PMid: 33663033 PMCid: PMC8041642

7. Palanivel S, Nedunchelian K, Poovazhagi V, Raghunadan R, Ramachandran P. Clinical profile of scrub typhus in children. *Indian Journal of Pediatrics* 2012; **79**(11): 1459-62. https://doi.org/10.1007/s12098-012-0721-0 PMid: 22374234

8. Narayanasamy DK, Arun Babu T, Vijayadevagaran V, Kittu D, Ananthakrishnan S. Predictors of severity in paediatric scrub typhus. *Indian Journal of Pediatrics* 2018; **85**(8): 613-7. https://doi.org/10.1007/s12098-018-2612-5 PMid: 29368107

9. Park MJ, Lee HS, Shim SG, Kim SH. Scrub typhus associated hepatic dysfunction and abdominal CT findings. *Pakistan Journal of Medical Sciences* 2015; **31**(2): 295-9. https://doi.org/10.12669/pjms.312.6386

10. Kanno A, Yamada M, Murakami K, Torinuki W. Liver involvement in Tsutsugamushi disease. *Tohoku Journal of Experimental Medicine* 1996; **179**(3): 213-7. https://doi.org/10.1620/tjem.179.213 PMid: 8888510

11. Chanta C, Triratanapa K, Ratanasirichup P, Mahaprom W. Hepatic dysfunction in

paediatric scrub typhus: role of liver function test in diagnosis and marker of disease severity. *Journal of the Medical Association of Thailand*. 2007; **90**(11): 2366-2369.

12. Rathi P, Siddiqui KA, Shah P. Scrub typhus-related hepatotoxicity: The Indian scenario. *Tropical Doctor* 2021; **51**(2): 228-31. https://doi.org/10.1177/0049475521991353 PMid: 33612084

13. Pathak S, Chaudhary N, Dhakal P, Shakya D, Dhungel P, Neupane G. *et al.* Clinical profile, complications and outcome of scrub typhus in children: A hospital based observational study in central Nepal. *PLoS One* 2019; **14**(8): e0220905. https://doi.org/10.1371/journal.pone.0220905 PMid: 31408484 PMCid: PMC6692021

14. Balaji J, Punitha P, Babu BR, Kumaravel KS. A study on clinical profile, complications and outcome of scrub typhus in south Indian children. *International Journal of Contemporary Pediatrics* 2017; **4**: 848- 52. https://doi.org/10.18203/23493291.ijcp20171593

15. Su TH, Liu CJ, Shu PY, Fu YH, Chang CH, Jao P, *et al.* Associated factors and clinical implications of serum aminotransferase elevation in scrub typhus. *Jiurnal of Microbiology, Immunology and Infection* 2016; **49**(6): 941-6. https://doi.org/10.1016/j.jmii.2014.10.005 PMid: 25556044

16. Pongponratn E, Maneerat Y, Chaisri U, Wilairatna P, Punpoowong B, Veeriyavejakul P, et al. Electron-microscopic examination of Rickettsia tsutsugamushi-infected human liver. *Tropical Medicine and International Health*. 1998; **3**(3): 242-8. https://doi.org/10.1046/j.13653156.1998.00231.x PMid: 9593364

17. Ganesh R, Suresh N, Pratyusha LL, Janakiraman L, Manickam M, Andal A. Clinical profile and outcome of children with scrub typhus from Chennai, South India. *European Journal of Pediatrics* 2018; **177**(6): 887-90. https://doi.org/10.1007/s00431-018-3143-9 PMid: 29637374

18. Rathi NB, Rathi AN, Goodman MH, Aghai ZH. Rickettsial diseases in central India: proposed clinical scoring system for early detection of spotted fever. *Indian Pediatrics* 2011; **48**(11): 867-72. https://doi.org/10.1007/s13312-011-0141-7 PMid: 21555807

19. Lee CS, Min IS, Hwang JH, Kwon KS, Lee HB. Clinical significance of hypoalbuminemia in outcome of patients with scrub typhus. *BMC Infectious Diseases* 2010; **10**: 216. https://doi.org/10.1186/1471-2334-10-216 PMid: 20646323 PMCid: PMC2919547

20. Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR guidelines for diagnosis & management of Rickettsial diseases in India. *Indian Journal of Medical Research* 2015; **141**(4): 417- 22. https://doi.org/10.4103/0971-5916.159279 PMid: 26112842 PMCid: PMC4510721