



# ORIGINAL RESEARCH PAPER

## General Medicine

### STUDY OF SERUM ALBUMIN LEVEL AND ITS PROGNOSTIC SIGNIFICANCE IN SCRUB TYPHUS IN SOUTH EAST RAJASTHAN

**KEY WORDS:** Scrub typhus, Hypoalbuminemia, Eschar

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#### ABSTRACT

**Introduction:** Scrub typhus is a zoonotic bacterial infection caused by *Orientia tsutsugamushi*. It is maintained by transovarial transmission in trombiculid mites.

**Aim:** To study prognostic significance of serum albumin level in scrub typhus patients in south east Rajasthan.

**Method:** Patients with scrub typhus were divided into three groups based on serum albumin level; Group I/Normal albumin (Serum Albumin level >3.5gm/dl), Group II/Mild hypoalbuminemia (Serum Albumin level 2.5-3.5gm/dl) and Group III/Marked hypoalbuminemia (Serum Albumin level <2.5gm/dl). Patients were monitored for complication and outcome during hospital stay and data was analysed.

**Result:** A total of 114 patients were included, of which 34 patients (29.8%) were categorized in Group I, 58 patients (50.9%) in Group II and 22 patients (19.3%) in Group III. Patients in Group III had significantly higher incidence of pneumonia (59.09%,  $p = <0.0001$ ), meningo-encephalitis (13.6%,  $p = 0.0146$ ), pleural effusion (27.3%,  $p = 0.0027$ ), Acute renal failure (22.7%,  $p = 0.0294$ ) and shock (36.4%,  $p = <0.0001$ ) compare to that of Group II and Group I. Duration of hospital stay ( $p = <0.0001$ ) was significantly high in group III patients. Mortality rate was comparatively high in Group III (9.1%) as compared to Group II & I but not statistically significant ( $p = 0.0959$ ).

**Conclusion:** Patients with marked hypoalbuminemia in scrub typhus had higher incidence of complications (Pneumonia, Meningo-encephalitis, Pleural effusion, Acute renal failure, Shock), Longer hospital stay and Deaths as compared to normal albumin.

#### MATERIALS AND METHODS

This study was conducted at tertiary care hospital at Jhalawar in south east Rajasthan during July 2017 to October 2018. This is a hospital based prospective study including patients with Scrub typhus infection aged 18 years or more. A total of 114 patients were enrolled for this study after excluding patients co-infected with dengue, influenza, malaria and typhoid fever. Patients were diagnosed for Scrub typhus by ELISA IgM positive (optical density  $\geq 0.5$ ), using ELISA kit manufactured by In Bios International Inc, USA. After taking written consent, patient data including detailed history, baseline characteristics, clinical findings, hospital management, and outcomes were recorded in a pretested proforma meeting the objectives of the study. All patients underwent thorough systemic examination and laboratory investigations like CBC, LFT, RFT, X-ray chest PA View and USG abdomen.

Patients with scrub typhus were divided into three groups based on serum albumin level, Group I/Normal albumin (Serum Albumin level >3.5gm/dl), Group II/Mild hypoalbuminemia (Serum Albumin level 2.5-3.5gm/dl) and Group III/Marked hypoalbuminemia (Serum Albumin level <2.5gm/dl). Serum albumin level was measured on the day of admission.

Hypoalbuminemia, defined as a first serum albumin level < 3.5 gm/dl [5]. Acute renal failure was defined as at least 50% reduction in glomerular filtration rate (GFR) using the abbreviated modified diet in renal disease (MDRD) equation,  $GFR (ml/min/1.73m^2) = 186 \times Pcr^{-1.154} \times age^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$  [6].

Statistical analysis of data was performed by using SPSS 20.0 software.

#### RESULTS

Out of 114 patients 66 (57.9%) were females and 48 (42.1%) were males. In our study there was female preponderance with sex ratio 1.3:1. In aspect of age group 22 (19.3%) patients were between 18-29 years, 55 (48.2%) were between 30-49 years and 37 (32.5%) were 50 years or more than 50 years.

**Table 1. Distribution of study participants according to demographic data with serum albumin level.**

Gender/ Age	Group I (serum albumin >3.5 gm/dl) n=34 (29.8%)	Group II (serum albumin 2.5-3.5 gm/dl) n=58 (50.9%)	Group III (serum albumin <2.5 gm/dl) n=22 (19.3%)	Total
Female	18	35	13	66 (57.9%)
Male	16	23	9	48 (42.1%)
18-29 Years	8 (23.5%)	11 (19%)	3 (13.6%)	22 (19.3%)
30-49 Years	15 (44.1%)	31 (53.4%)	9 (40.9%)	55 (48.2%)
50 Years	11 (32.4%)	16 (27.6%)	10 (45.5%)	37 (32.5%)

Out of 114 patients majority of patients presented with complain of fever (107, 93.9%) and headache (99, 86.8%).

Group III (marked hypoalbuminemia) patients had much higher incidence of abdominal pain, cough, vomiting, diarrhea, edema, altered sensorium and dyspnea.

Presence of eschar and lymphadenopathy were not significant.

**Table 2. Distribution of study participants according to presence of sign and symptoms with serum albumin level.**

	Group I (serum albumin >3.5 gm/dl) n=34 (29.8%)	Group II (serum albumin 2.5-3.5 gm/dl) n=58 (50.9%)	Group III (serum albumin <2.5 gm/dl) n=22 (19.3%)	Total	Chi square value	P value
Fever	33 (97.1%)	55 (94.8%)	19 (86.4%)	107 (93.9%)	2.843	0.2413 NS
Eschar	16 (47.1%)	21 (36.2%)	7 (31.8%)	44 (38.6%)	1.594	0.4506 NS

Chills	29 (85.3%)	47 (81.0%)	14 (63.6%)	90 (78.9%)	4.079	0.1300 NS
Abdominal pain	9 (26.5%)	13 (22.4%)	11 (50%)	33 (28.9%)	9.88	0.0071 Significant
Myalgia	24 (70.6%)	36 (62.1%)	9 (40.9%)	69 (60.5%)	5.042	0.0803 NS
Headache	30 (88.2%)	53 (91.4%)	16 (72.7%)	99 (86.8%)	4.938	0.0846 NS
Cough	11 (32.4%)	25 (43.1%)	17 (77.3%)	53 (46.5%)	1.254	0.5341 NS
Vomiting	5 (14.7%)	8 (13.8%)	9 (40.9%)	22 (19.3%)	8.186	0.0166 Significant
Diarrhea	1 (2.9%)	3 (5.2%)	6 (27.3%)	10 (8.8%)	11.793	0.0027 Significant
Edema	2 (5.9%)	7 (12.1%)	11 (50%)	20 (17.5%)	20.418	<0.0001 Significant
Altered Sensorium	0 (0%)	2 (3.4%)	4 (18.2%)	6 (5.3%)	9.859	0.0072 Significant
Skin rash	1 (2.9%)	9 (15.5%)	2 (9.1%)	12 (10.5%)	3.659	0.1604 NS
Dyspnea	4 (11.8%)	12 (20.7%)	10 (45.5%)	26 (22.8%)	8.912	0.0116 Significant
Lymphadenopathy	3 (8.8%)	8 (13.8%)	1 (4.5%)	12 (10.5%)	1.597	0.4500 NS

Shock which is defined as SBP <90 mmHg or DBP <60 mmHg (36.4%, $p<0.0001$ ) was significantly higher in Group III as compare to Group II and Group I.

On comparison of the percentage of complication in Group III with Group II and Group I. Most common complication was pneumonia (59.09%,  $p<0.0001$ ), other complications were ascites (9.1%,  $p=0.0959$ ), jaundice (22.7%,  $p=0.6218$ ), meningo-encephalitis (13.6%,  $p=0.0146$ ), pleural effusion (27.3%,  $p=0.0027$ ), cholecystitis (4.5%,  $p=0.3153$ ), Acute renal failure (22.7%,  $p=0.0294$ ), and death (9.1%,  $p=0.0959$ ).

**Table 3. Distribution And Association Of Complications And Outcomes With Serum Albumin Level In Study Participants.**

	Group I (serum albumin >3.5 gm/dl) n=34 (29.8%)	Group II (serum albumin 2.5-3.5 gm/dl) n=58 (50.9%)	Group III (serum albumin <2.5 gm/dl) n=22 (19.3%)	Total	Chi square value	P value
Shock	0 (0%)	2 (3.4%)	8 (36.4%)	10 (8.8%)	26.253	<0.0001 Significant
Pneumonia	4 (11.7%)	10 (17.2%)	13 (59.09%)	27 (23.7%)	5.179	<0.0001 Significant
Ascites	0 (0%)	1 (1.7%)	2 (9.1%)	3 (2.6%)	4.688	0.0959 NS
Jaundice	6 (17.6%)	8 (13.8%)	5 (22.7%)	19 (16.7%)	0.95	0.6218 NS
Epistaxis	1 (2.9%)	1 (1.7%)	0 (0%)	2 (1.8%)	0.671	0.7149 NS
Meningo-encephalitis	0 (0%)	1 (1.7%)	3 (13.6%)	4 (3.5%)	8.447	0.0146 Significant

Pleural effusion	1 (2.9%)	3 (5.2%)	6 (27.3%)	10 (8.8%)	11.793	0.0027 Significant
Cholecystitis	1 (2.9%)	0 (0%)	1 (4.5%)	2 (1.8%)	2.308	0.3153 NS
Acute renal failure	1 (2.9%)	4 (6.9%)	5 (22.7%)	10 (8.80%)	7.053	0.0294 Significant
Death	0 (0%)	1 (1.7%)	2 (9.1%)	3 (2.6%)	4.688	0.0959 NS

**Table 4. Distribution of study participants according length of hospital stay with serum albumin level.**

Duration of hospital stay	Group I (serum albumin >3.5 gm/dl) n=34 (29.8%)	Group II (serum albumin 2.5-3.5 gm/dl) n=58 (50.9%)	Group III (serum albumin <2.5 gm/dl) n=22 (19.3%)	Total	Chi square value	P value
1-3 days	20 (58.8%)	19 (32.8%)	3 (13.6%)	42 (36.8%)	25.8	<0.0001 Significant
4-7 days	13 (38.3%)	32 (55.1%)	9 (40.9%)	54 (47.4%)		
>7 days	1 (2.9%)	7 (12.1%)	10 (45.5%)	18 (15.8%)		

58.8% patient in Group I discharged within 1 to 3 days while 45.5% patients in Group III stayed more than 7 days in hospital ( $p<0.0001$ )

## DISCUSSION

The mechanism of hypoalbuminemia in acute infectious diseases is known to be due to poor oral intake of protein, decreased synthesis of protein from the liver, increased catabolism of proteins and increased metabolism of albumin due to the vascular leakage of serum proteins due to increased vascular permeability [7]. Pathologic finding in scrub typhus is a focal & disseminated vasculitis due to macrophage activation and the secretion of cytokines leads to destruction of endothelial cell lining of the small vessels which is manifested as perivascular infiltrations of leukocytes [8,9]. Pathology of scrub typhus due to affinity of agent to endothelial cells of small blood vessels evoke vascular inflammation which leads to microthrombi and haemorrhage in lymph nodes and spleen [10]. Vasculitis & perivasculitis in scrub typhus may involve multiple organ systems like lung, brain, kidney, gastrointestinal tract, liver, spleen and lymph node [11,12].

The pulmonary manifestations of scrub typhus vary from mild atypical pneumonia to very serious adult respiratory distress syndrome include varying degrees of bronchitis and interstitial pneumonitis [13]. Interstitial pneumonitis frequently occurs in patients with scrub typhus and such patients had higher incidences of hypoxia, hypotension, severe thrombocytopenia and hypoalbuminemia. Interstitial pneumonitis in scrub typhus is closely associated with severity in scrub typhus [14]. Scrub typhus patients with abnormal CXR findings had a higher rate of serious complications including pneumonitis, septic shock, acute respiratory distress syndrome, meningitis/meningoencephalitis, CHF, severe jaundice, acute renal failure, acute pancreatitis and peptic ulcer compared with patients with negative CXR results [15].

The renal pathology usually shows characteristic acute diffuse glomerulonephritis, focal interstitial lesions, cloudy swelling of the tubular epithelium and occasional evidence of severe vascular damage [16]. Acute renal failure in patients with scrub typhus is caused by acute tubular necrosis due to the direct invasion of Orientia tsutsugamushi, which is confirmed by renal biopsy with Immunohistochemistry staining and electron microscopy [17].

Gastrointestinal symptoms and signs of scrub typhus were vomiting, diarrhoea, jaundice and abdominal pain frequently reported [18]. Scrub typhus induced hepatitis causes mild portal inflammation and intra hepatic sinusoidal endothelial vasculitis which leads to increased serum AST and ALT [19].

CNS involvement is another complication of scrub typhus. It ranges from aseptic meningitis to frank meningoencephalitis. Meningoencephalitis is a constant autopsy finding in fatal cases of scrub typhus [20]. Patients with septic shock in scrub typhus had multiple organ failure: respiratory failure and DIC being predominant, followed by renal and hepatic involvement [21].

## CONCLUSION

Scrub typhus patients with marked hypoalbuminemia had higher incidence of complication most likely pneumonia than the patients with mild hypoalbuminemia and normoalbuminemia, length of hospital stay was significantly longer in marked hypoalbuminemia and mortality rate high in marked hypoalbuminemia patients as compared to mild hypoalbuminemia and normoalbuminemia patients.

Limitation of our study is outcomes of albumin administration had not evaluated.

## REFERENCES

- Harrison's Principles of internal medicine 19th Edition; Part 8 Infectious Diseases; Rickettsial Disease 2015; 211:1159
- Kelly DJ, Fuerst PA, Ching WM, Richards AL (2009) Scrub typhus: the geographic distribution of phenotypic and genotypic variants of *Orientia tsutsugamushi*. Clin Infect Dis 48 Suppl 3:203-230.
- Carratala J, Roson B, Fernandez-Sabe N, Shaw E, del Rio O, Rivera A: Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. Eur J Clin Microbiol Infect Dis 2003, 22:151-157.
- Kim YO, Jeon HK, Cho SG, Yoon SA, Son HS, Oh SH, et al. The role of hypoalbuminemia as a marker of the severity of disease in patients with tsutsugamushi disease. Korean J Internal Med. 2000;59:516-521
- Herrmann FR, Safran C, Levkoff SE, Minaker KL. Serum albumin level on admission as a predictor of death, length of stay, and readmission. Arch Intern Med. 1992;152(1):125-130.
- Manjunath G, Sarnak MJ, Levey AS: Prediction equations to estimate glomerular filtration rate: An update. Curr Opin Nephrol Hypertens. 2001,10:785-792.
- Kim YO, Yoon SA, Ku YM, Yang CW, Kim YS, Kim SY, Choi EJ, Chang YS, Bang BK: Serum albumin level correlates with disease severity in patients with hemorrhagic fever with renal syndrome. J Korean Med Sci. 2003,18:696-700.
- Kim SJ, Chung IK, Chung IS, Song DH, Park SH, Kim HS, Lee MH: The clinical significance of upper gastrointestinal endoscopy in gastrointestinal vasculitis related to scrub typhus. Endoscopy 2000,32:950-955.
- Seong SY, Choi MS, Kim IS: *Orientia tsutsugamushi* infection: Overview and immune responses. Microbes Infect 2001, 3:11-21.
- Hwang TS, Chu YC, Kim YB, Lim BU, Kang JS: Pathologic study of mice infected with rickettsia tsutsugamushi r19 strain. J Korean Med Sci 1993,8:437-445.
- Sirisanthana V, Puthanakit T, Sirisanthana T: Epidemiologic, clinical and laboratory features of scrub typhus in thirty thai children. Pediatr Infect Dis J 2003, 22:341-345.
- Chi WC, Huang JJ, Sung JM, Lan RR, Ko WC, Chen FF: Scrub typhus associated with multiorgan failure: A case report. Scand J Infect Dis 1997,29:634-635.
- Chayakul P, Panich V, Silpapojakul K. Scrub typhus pneumonitis: an entity which is frequently missed. Q J Med 1988; 68: 595-602.
- Song SW, Kim KT, Ku YM, Park SH, Kim YS, Lee DG, Yoon SA, Kim YO: Clinical role of interstitial pneumonia in patients with scrub typhus: A possible marker of disease severity. J Korean Med Sci 2004, 19:668-673.
- Wu KM, Wu ZW, Peng ZQ, Wu JL, Lee SY: Radiologic pulmonary findings, clinical manifestations and serious complications in scrub typhus: Experiences from a teaching hospital in eastern Taiwan. INT J Gerontol. 2009;3:223-32.
- Allen AC, Spitz S. A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases. Am J Pathol 1945; 21: 603-8.
- Kim DM, Kang DW, Kim JO, Chung JH, Kim HL, Park CY, Lim SC: Acute renal failure due to acute tubular necrosis caused by direct invasion of *Orientia tsutsugamushi*. J Clin Microbiol 2008, 46:1548-1550.
- Thu A, Supanaranond W, Phumiratanaprapin W, Phonrat B, Chinprasatsak S, Ratanajaratroj N : Gastrointestinal manifestations of septic patients with scrub typhus in Maharat Nakhon Ratchasima Hospital. Southeast Asian J Trop Med Public Health. 2004; 35(4):845-51.
- Chung JH, Lim SC, Yun NR, Shin SH, Kim CM, Kim DM. Scrub typhus hepatitis confirmed by immunohistochemical staining. World J Gastroenterol 2012; 18(36): 5138-5141
- Pai H, Sohn S, Seong Y, et al. Central nervous system involvement in patients with scrub typhus. Clin Infect Dis 1997; 24: 436-40.
- 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, 33:780-786