

## ORIGINAL RESEARCH

# A retrospective study on scrub typhus-associated acute kidney injury in tertiary care hospital in central India

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## ABSTRACT

**Background:** Scrub typhus is a tropical disease caused by the rickettsial bacterium *Orientia tsutsugamushi*. It commonly affects the kidneys, and the degree of renal involvement can vary among patients; characterized by mild conditions like hematuria or proteinuria. The objective of the present study was to assess the risk factors, clinical characteristics, and laboratory parameters of patients with scrub typhus-induced acute kidney injury (AKI).

**Methods:** This was a retrospective study conducted at a tertiary care hospital in central India, for 2 years, from February 2020 to February 2022 involving patients with scrub typhus infection. The medical records of all patients who were admitted and treated for scrub typhus infection were analyzed. The patients were divided into two groups: AKI and non-AKI.

**Results:** A total of 200 patients were included in this study. There was a significant difference between the mean peak creatinine levels ( $p < 0.001$ ), the higher being in the AKI group than non-AKI group (2.8 mg/dL vs. 0.5 mg/dL). The mean duration of hospital stay was higher in AKI group than non-AKI group (9.2 days vs. 6.3 days), with a significant difference of  $p = 0.011$ . The number of patients presenting with chronic kidney disease (CKD) was higher in AKI group (12.0%) and non-AKI (6.0%),  $p = 0.007$ . The duration of hospital stays, age ( $> 65$  years), presence of CKD and lower albumin level ( $< 3.5$  g/dL) remained independent risk factors for AKI.

**Conclusion:** The presence of underlying CKD, elder age ( $> 65$  years), lower serum albumin (3.5 g/dL) level and duration of hospital stay were important risk factors to determine occurrence of AKI.

**Key words:** Acute kidney injury, multiple organ dysfunction, *Orientia tsutsugamushi*, scrub typhus

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## INTRODUCTION

Scrub typhus is a tropical disease caused by the rickettsial bacterium *Orientia tsutsugamushi*.<sup>1</sup> In recent times, the Indian sub-continent has experienced multiple epidemics of scrub typhus in the northern, eastern, and southern regions which have raised significant public health concerns.<sup>2,3</sup> Scrub typhus is frequently characterized by fever, a rash with red spots and bumps, along with a scab at the site of the mite bite. Other common symptoms include muscle pain, enlarged liver and spleen, and in severe instances, acute lung and kidney injuries, as well as dysfunction of multiple organs.<sup>4</sup> Diagnosis is achieved using a scrub typhus ELISA test,<sup>5</sup> and treatment usually involves medications like doxycycline, chloramphenicol, ciprofloxacin, and azithromycin.<sup>6</sup> Scrub typhus frequently affects the

kidneys, and the extent of renal involvement can vary. It can manifest as mild conditions such as hematuria (blood in urine) or proteinuria (presence of excess protein in urine), with an incidence of about 10-20% in cases of scrub typhus.<sup>7-9</sup> However, in some instances, it can lead to severe complications, including acute renal failure, nephrotic syndrome (characterized by excessive protein leakage in the urine),<sup>10</sup> and even end-stage renal disease, which necessitates long-term treatment like hemodialysis.<sup>11</sup> This results in prolonged hospital stays, healthcare costs, and deteriorated outcomes in patient.<sup>12</sup> In India, there has been a noticeable increase in cases of acute kidney injury (AKI), often accompanied by multiple organ dysfunction (MOD), over the past few years. These cases have been associated with scrub typhus. Reports indicate that in both the southern and

northern regions of the country, 21% to 43% of AKI cases have been linked to scrub typhus.<sup>7,13,14</sup> This highlights the significance of renal complications in scrub typhus and emphasizes the need for awareness and early detection to prevent severe outcomes. Scrub typhus is significantly underreported and often goes undiagnosed due to several reasons, mainly due to lack of awareness among healthcare providers and the general public about the disease, diagnostic tests for scrub typhus may not be readily available at peripheral medical centers, widespread use of empirical broad-spectrum antibiotics for various acute febrile illnesses can further complicate the diagnosis.<sup>15</sup> The evidence available to assess the kidney involvement in scrub typhus is inadequate. In light of this context, the present study was conducted to assess the risk factors, clinical characteristics, and laboratory parameters of patients with scrub typhus-induced AKI.

## METHODS

### Study design

This was a retrospective study conducted at tertiary care center in central India for 2 years, from February 2020 to February 2022 involving patients with scrub typhus infection. The medical records of all patients who were admitted and treated for scrub typhus infection were analyzed. The patients were divided into two groups: AKI and non-AKI.

### Eligibility criteria

The patients with diagnosis of scrub typhus infection of either sex, and age group  $\geq 18$  years were included in this study. The patients with concurrent dengue, malaria, leptospirosis, enteric fever, viral hepatitis, or known preexisting liver or kidney disease were excluded from the study.

### Data collection

The demographic characteristics of the patients were recorded. The clinical findings such as fever, myalgia, and gastrointestinal symptoms were recorded. The laboratory results of hemoglobin, blood urea, serum creatinine, serum electrolytes, serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and serum albumin levels were evaluated. Scrub typhus infection was diagnosed by enzyme-linked immunosorbent assay (ELISA) technique (In Bios Scrub Typhus Detect I g M ELISA kit), and the test was performed according to the manufacturer's instructions.

### Endpoints

The primary endpoint of the present study was to assess the risk factors, clinical characteristics, and laboratory parameters of AKI in scrub typhus patients.

## Statistical analysis

All the quantitative variables in the present study such as age and sex distribution of patient are expressed in terms of frequency and percentage. Data analysis was performed by using SPSS (Statistical package for social sciences) version 20. The parameters including serum creatinine, hemoglobin, platelet counts, serum bilirubin, AST, ALT, serum albumin, and total days of hospitalization of each group were compared for statistical significance. Similarly, parameters such as age, hypertension, diabetes mellitus, bilirubin, AST, ALT were compared between AKI and "no AKI" groups for statistical significance.

## RESULTS

**Demographic characteristics and laboratory parameters of patients** A total of 200 patients were included in this study. The mean age of the patients was 47.2 years. The number of male patients was higher than the female patients (62.5 vs. 37.5). The laboratory parameters at baseline were as follows; the mean hemoglobin was 10.8 g/dL, the mean AST levels were 139.0 IU/L, the mean ALT was 128.0 IU/L, and the mean peak serum creatinine was 1.3 mg/dL. The mean duration of hospital stay was 6.5 years. These demographic and laboratory parameters are summarized in Table 1. Comparison of laboratory parameters between groups On comparison between both the groups, the mean age was higher in AKI group when compared with non-AKI group (46.2 years vs. 39.2 years). There was a significant difference between the mean peak creatinine levels ( $p < 0.001$ ), the higher being in the AKI group than non-AKI group (2.8 mg/dL vs. 0.5 mg/dL). The mean bilirubin levels were higher in AKI group (2.0 mg/dL) than non-AKI group (0.6 mg/dL), with a significant difference of  $p < 0.001$ . The mean AST levels were higher in AKI group than non-AKI group, (245.0 U/L vs. 110.2 U/L) with a significant difference of  $p = 0.003$ . The mean duration of hospital stay was higher in AKI group than non-AKI group (9.2 days vs. 6.3 days), with a significant difference of  $p = 0.011$ . These observations were summarized in Table 2. Comparison of clinical findings between groups The proportion of patients presenting with hypertension was higher in the AKI group than non-AKI group (22.0% vs. 17.5%), with a significant difference of  $p = 0.003$ . There was a significant difference ( $p = 0.020$ ) in the number of patients presenting with DM in AKI (15.0%) than non-AKI (13.0%). The number of patients presenting with CKD was higher in AKI group (12.0%) and non-AKI (6.0%),  $p = 0.007$ . These comparisons were summarized in Table 3. Risk factors for the development of the scrub typhus associated AKI From univariate analysis, it was seen that duration of hospital stay, age ( $> 65$  years), the presence of DM, HTN and CKD, and lower albumin ( $< 3.5$  g/dL) and hemoglobin levels were significant predictors of AKI. From the multivariate analysis, duration of hospital stays, age ( $> 65$  years), presence

of CKD and lower albumin level (<3.5 g/dL) is summarized in Table 4. remained independent risk factors for AKI. This data

**Table : 1 Demographic characteristics and laboratory parameters of patients**

Parameter	No. of patients (n=200)
Age (years)	47.2 (1.7)
Sex, n (%)	
Male	125 (62.5)
Female	75 (37.5)
Hemoglobin (g/dL)	10.8 (1.5)
Platelet count (lakh cells/mm <sup>3</sup> )	1.5 (0.3)
Serum bilirubin (mg/dL)	1.0 (0.5)
AST (IU/L)	139.0 (251.0)
ALT (IU/L)	128.0 (305.0)
Serum creatinine, presenting (mg/dL)	0.7 (0.6)
Serum creatinine, peak (mg/dL)	1.3 (1.1)
Serum albumin (g/dL)	3.1 (0.4)
Na <sup>+</sup> (mmol/L)	130.0 (4.4)
K <sup>+</sup> (mmol)	3.2 (0.4)
HCO <sup>3-</sup>	6.5 (4.2)
Mean duration of hospital stays (days)	6.5 (4.2)
Data given as mean (SD), unless otherwise specified. AST, aspartate transaminase; ALT, alanine transaminase; Na <sup>+</sup> , sodium; K <sup>+</sup> , potassium	

**Table: 2 Comparison of laboratory parameters between groups**

Parameters	AKI group (n=100)	Non-AKI group (n=100)	p-value
Age (years)	46.2 (14.2)	39.2 (11.2)	0.080
Peak creatinine (mg/dL)	2.8 (1.5)	0.5 (0.1)	<0.001
Bilirubin (mg/dL)	2.0 (2.4)	0.6 (0.4)	<0.001
AST (U/L)	245.0 (411.2)	110.2 (188.3)	0.003
ALT (U/L)	172.4 (50)	118.2 (345.3)	0.341
Hemoglobin (g/dL)	12.0 (1.8)	11.8 (1.5)	0.488
Serum albumin (g/L)	2.7 (0.2)	3.5 (0.2)	0.003
Mean duration of hospital stays (days)	9.2 (6.3)	6.3 (4.2)	0.011
Data given as mean (SD). AKI, acute kidney injury; AST, aspartate transaminase; ALT, alanine transaminase			

**Table: 3 Comparison of clinical findings between groups**

Parameter	Total (n=200)	AKI group (n=100)	No AKI group (n=100)	p-value
Fever	188 (94.0)	96 (48.0)	92 (46.0)	0.281
Myalgia	114 (57.0)	46 (23.0)	68 (34.0)	0.344
HTN	79 (39.5)	44 (22.0)	35 (17.5)	0.003
DM	56 (28.0)	30 (15.0)	26 (13.0)	0.020
CKD	36 (18.0)	24 (12.0)	12 (6.0)	0.007
Shock	19 (9.5)	10 (5.0)	9 (4.5)	0.085
Data given as n (%). AKI, acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension				

**Table: 4 Risk factors for the development of the scrub typhus associated AKI**

Risk factors	Univariate analysis		Multivariate analysis	
	p-value	OR (95% CI)	p-value	OR (95% CI)
Age (>65 years)	<0.001	2.095 (1.034 to 3.097)	<0.001	1.876 (1.130 to 3.020)
HTN	0.003	2.109 (1.902 to 3.145)	0.201	1.324 (0.791 to 2.435)
DM	0.009	2.123 (1.124 to 3.189)	0.176	1.498 (0.811 to 2.798)
CKD	0.003	2.901 (1.817 to 4.090)	0.011	3.245 (1.205 to 9.512)
Albumin (<3.5 g/dL)	0.010	2.101 (1.211 to 3.191)	0.003	2.090 (1.324 to 3.207)
Hemoglobin	0.048	1.324 (1.023 to 2.341)	0.671	0.890 (0.611 to 1.412)
Duration of hospital stay (days)	0.029	1.402 (1.092 to 2.341)	0.040	1.621 (1.011 to 2.387)
AKI, acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension				

## DISCUSSION

Scrub typhus is an infectious disease caused by the gram-negative intracellular bacillus *Orientia tsutsugamushi*. This disease is transmitted by the bite of larval trombiculid mites, which are commonly found in semi-arid tropical areas characterized by high temperatures and high humidity. These mites act as vectors, facilitating the spread of the disease to humans and other hosts.<sup>16</sup> In addition to the vector bite, scrub typhus presents with various clinical features. Symptoms like fever, myalgia (muscle pain), and gastrointestinal symptoms typically manifest in the second week after being bitten by the vector. In more severe cases, complications can arise, such as multi-organ failure, where multiple organs in the body may be affected simultaneously. Prompt recognition and early medical intervention are crucial to managing these complications effectively.<sup>17,18</sup> The development of AKI and renal complications in scrub typhus is considered to have various contributing factors. The potential mechanisms leading to kidney

failure encompass prerenal failure, septic shock, rhabdomyolysis, vasculitis, acute interstitial nephritis, and direct invasion of the kidney tissues by the bacterium *O. tsutsugamushi*.<sup>1</sup> In this study, the mean age was 47.2 years which was similar to the mean age of 45.7 years observed in a study by Jayaprakash et al. Among the presenting symptoms, fever was present in almost all the cases (94.0%), followed by myalgia (57.0%), hypertension (39.5%), and diabetes mellitus (28.0%). This was consistent in multiple studies where fever was present in almost all the cases.<sup>19,20</sup> Hypoalbuminemia is frequently observed in individuals suffering from Rickettsial infection due to the release of albumin from the blood vessels into the surrounding tissues caused by vascular damage.<sup>21</sup> This was also observed in this present study where the hypoalbuminemia was recognized as an independent risk factor in scrub induced. In a review, elevated levels of AST were found in 63% to 97% of the patients, while raised ALT levels were observed in 45% to 96% of them.<sup>22</sup> This was also observed in a

study by Prakash et al. where the median ALT levels were 88.5 IU/L and median AST levels were 174 IU/L.<sup>21</sup> In a study by Hwang K et al. elder age, the presence of DM, HTN and CKD, and lower albumin and hemoglobin levels were significant predictors of AKI.<sup>1</sup> These results were also consistent in this study as well where the duration of hospital stay, age (>65 years), the presence of DM, HTN and CKD, and lower albumin (<3.5 g/d L) and hemoglobin levels were recognized as significant predictors of AKI.<sup>24-26</sup> Earlier studies did not establish CKD as a risk factor for AKI or mortality. However, a study by Hwang K et al. demonstrated CKD as an important determinant of AKI.<sup>1</sup> This was also consistent with the present study. There have been limited reports on the prognosis of AKI linked to scrub typhus. However, if a patient survives AKI, the renal prognosis is generally favorable.<sup>1</sup> Limitations This study had several notable limitations. Firstly, its retrospective design could have introduced biases and limitations in data collection and analysis. Moreover, since the study relied on medical records, the ability to explore other potential causes of AKI was restricted, as well as the measurement of urine volume, possibly leading to an underestimation of AKI incidence. Furthermore, being a single-center study, the results might have been influenced by the specific characteristics of that particular facility. Patients had relatively similar laboratory values, were predominantly treated at the same center, and diagnosed using the same criteria and treatment protocols. While this aspect offers consistency in data, it also limits the findings to other healthcare settings. This study indicates that there have been improved outcomes concerning renal involvement and mortality, which is supported by a recent study group. The improvement can be attributed to increased awareness among physicians about this tropical infectious disease, the use of empirical antibiotics like doxycycline and azithromycin at the primary health-care level, early referral of patients, and enhanced intensive care measures.

## CONCLUSION

Based on the current findings, it appears that several factors play a crucial role in determining the occurrence of AKI. These factors include underlying CKD, advanced age, lower levels of serum albumin, and the duration of hospital stay. It remains essential to explore whether early detection and timely treatment in patients exhibiting these risk factors can effectively reduce the incidence and severity of AKI. Further investigation in this regard is warranted.

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