



## Acute Kidney Injury Due to Rickettsial Infection - Data from a Tertiary Care Center in Southern India

### Abstract

**Background:** Scrub typhus, caused by *Orientia tsutsugamushi*, is an underdiagnosed tropical infection endemic to India, often presenting with non-specific symptoms. AKI is a serious yet potentially reversible complication that significantly impacts outcomes. This study aimed to determine the prevalence, clinical characteristics, and predictors of AKI in patients primarily diagnosed with scrub typhus at a tertiary care center in Southern India.

**Materials and Methods:** This retrospective observational study analyzed 176 adult patients with rickettsia at a tertiary care center in Karnataka from January 2021 to December 2024. Patients with co-infections were excluded. AKI was defined and staged per KDIGO criteria. Demographic, clinical, laboratory, and outcome data were assessed to identify predictors of AKI. **Results:** The prevalence of AKI was 44 (25%), with a mean age of  $37.5 \pm 16.3$  years. KDIGO categorizes AKI into Stage 1 (15.3%), Stage 2 (4.5%), and Stage 3 (5.1%); 4% required dialysis. Winter seasonality (44% cases in Dec-Feb) was noted. Independent predictors of AKI included older age (OR 3.60), male sex (OR 4.14), diabetes mellitus (OR 3.13), septic shock (OR 5.42), and Multi-organ dysfunction syndrome (MODS) (OR 52.8). Hypoalbuminemia was also associated with AKI. Overall mortality was 2.8%. **Conclusion:** AKI occurs in 1/4 of scrub typhus patients and is associated with substantial morbidity, especially among elderly males with comorbidities and systemic complications. Despite its severity, AKI in scrub typhus is often reversible with early recognition and aggressive supportive care. These findings highlight the need for heightened clinical suspicion and timely intervention in endemic settings to reduce AKI-related complications.

**Keywords:** Acute kidney injury, *Orientia tsutsugamushi*, Rickettsial infections, Scrub typhus, Tropical diseases

### Introduction

Tropical countries account for nearly 50% of the world's population, a figure projected to rise to 60% in the coming decade.<sup>1</sup> Many of these nations, especially in Southern Asia and Sub-Saharan Africa, grapple with high burdens of infectious diseases, inadequate sanitation, climate change, limited access to primary care, and poorly regulated traditional medicine. This confluence creates a distinct epidemiological landscape, contributing to a unique AKI burden associated with significant morbidity and mortality. Common tropical infections leading to AKI include diarrheal illnesses, malaria, leptospirosis, scrub typhus, dengue, and hantavirus infections.<sup>1,2</sup>

Among these, scrub typhus, caused by *Orientia tsutsugamushi*<sup>3,4</sup> and transmitted by the bite of an infected mite larva (chigger or *Leptotrombidium deliense*), poses a substantial public health threat.

An estimated 1 billion people are at risk globally,<sup>5</sup> with ~1 million annual case reports. Endemic regions include South and Southeast Asia, and parts of Latin America.<sup>6</sup> Severe disease may involve life-threatening complications such as myocarditis, meningoencephalitis, coagulopathy, Acute Respiratory distress syndrome (ARDS), AKI, and septic shock. Rickettsial-associated AKI occurs in 10-60% of patients.<sup>7-12</sup>

Rickettsial-associated AKI often goes unrecognized due to non-specific presentation, which frequently mimics other tropical diseases, making timely diagnosis challenging. This diagnostic dilemma further exacerbates morbidity and complicates patient outcomes. Underdiagnosis can lead to progression toward CKD.<sup>13,14</sup> Reported case fatality rates range from 3% to 50%.<sup>15</sup>

Despite increasing recognition of renal involvement in scrub typhus, regional data on prevalence, clinical course, and

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risk factors remain limited. In this retrospective, single-center study from a tertiary hospital in Southern India, we describe the prevalence of AKI in scrub typhus patients, along with clinical features, laboratory abnormalities, complications, and outcomes.

## Materials and Methods

This cross-sectional observational study was conducted on adult patients diagnosed with scrub typhus at R.L Jalappa Hospital, affiliated to Sri Devaraj Urs Medical College, a tertiary care hospital in Kolar, Karnataka, India, between January 2021 and December 2024. Rickettsial infection was diagnosed based on clinical assessment, positive serology using Weil-Felix test (OX antigen subtypes: K, 2, and 19), and indirect immunofluorescent antibody assay (IFA). The study was initiated after obtaining approval from the Institutional Ethics Committee. Informed written consent was obtained from the participants. Autonomy and confidentiality were maintained. Patients with co-infection with dengue, leptospira, and malaria were excluded. Based on the study by Jayaprakash *et al.*,<sup>16</sup> in Chennai, India, the reported prevalence (p) of AKI in scrub typhus was 18.7% (36/193). Hence, with 5% margin of error (d) and a 95% confidence interval, the minimum required sample size was 106.<sup>16</sup>

Demographic details, laboratory parameters (hematological, biochemical, and coagulation profiles), treatment, and outcomes were collected from patient records. AKI was defined and staged according to the KDIGO criteria.<sup>17</sup> AKI, acute hepatitis, ARDS, pneumonia, meningitis, sepsis, and multiorgan dysfunction syndrome (MODS) were considered systemic complications. The difference was compared between patients with and without AKI, focusing on continuous data for demographic characteristics (age) and laboratory parameters. The association of clinical presentations (symptoms and signs), treatment details, and outcomes of rickettsial infection between the patients with and without AKI was also checked.

### Statistical analysis

The data entered in an Excel sheet (Microsoft Corporation, Redmont, Wahington, United States) were analyzed using IBM SPSS-Statistics for windows, 22.0 version (Released 2013; IBM Corp., Armonk, New York, United States). Continuous variables were assessed for normality using the Kolmogorov-Smirnov/Shapiro-Wilk test and visual inspection of Q-Q plots. Homogeneity of variances between groups was assessed using Levene's test. Normally distributed continuous variables were presented as mean  $\pm$  standard deviation (SD). Differences in continuous variables between patients with and without AKI were analyzed using the independent t-test.

Categorical variables were presented as frequencies and percentages. The association between categorical variables and the presence of AKI was examined using the chi-square

test or Fisher's exact test, where appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the strength of these associations

Variables that showed a significant association with AKI ( $p < 0.05$ ) were further analyzed using binary logistic regression to identify independent AKI predictors. The results of the logistic regression have been presented as adjusted odds ratios (adjusted OR) with 95% CI.

## Results

During the study, fever profile evaluation was performed for over 7000 patients, among whom 176 patients with rickettsial infection fitting the inclusion criteria were considered. Among the 176 patients included in the study, 44 (25%) developed AKI. The clinical presentation, including symptoms and signs, baseline characteristics, and laboratory parameters of the study population have been summarized in Table 1. The mean age of patients was  $37.46 \pm 16.27$  years. For the duration of hospitalization, it was  $10.54 \pm 5.68$  days. Among the 44 patients who developed AKI, all were admitted to intensive care, representing 25%

**Table 1: Baseline characteristics and laboratory serum parameters**

Parameters	n	Values	IQR
Age (years)	176	$37.46 \pm 16.27$	21.25, 50
Duration of hospitalization (days)	176	$10.54 \pm 5.68$	6, 14
Days treated in intensive care	114	$5.71 \pm 2.69$	4, 7.25
Hemoglobin (g/dL)	176	$10.62 \pm 2.10$	9, 18
White blood cells ( $\times 10^3$ /mL)	176	$15.0 \pm 8.25$	9.8, 18.56
Platelet ( $\times 10^3$ /mL)	176	$133.72 \pm 122.31$	46, 155.25
SGOT/AST (IU/L)	176	$131.96 \pm 107.49$	60, 175
SGPT/ALT (IU/L)	176	$101.98 \pm 143.47$	44, 111
Total bilirubin (mg/dL)	176	$2.48 \pm 2.49$	0.9, 2.81
Direct bilirubin (mg/dL)	176	$1.85 \pm 2.22$	0.4, 2.10
Albumin (g/dL)	176	$2.75 \pm 0.47$	2.5, 3.0
Urea (mg/dL)	176	$60.66 \pm 55.29$	24, 84
Creatinine (mg/dL)	176	$1.27 \pm 1.60$	0.6, 1.40
Sodium (mEq/L)	176	$134.13 \pm 8.22$	129, 138
Potassium (mEq/L)	176	$4.61 \pm 0.83$	4, 5.1
Ferritin <sup>a</sup> (ng/mL)	56	$579.55 \pm 434.58$	23.4, 1000
Lactate dehydrogenase <sup>a</sup> (U/L)	52	$480.50 \pm 251.41$	292.5, 569
D-dimer <sup>a</sup> (ng/mL)	35	$1836.65 \pm 2400.41$	500-2891
Calcium <sup>a</sup> (mg/dL)	26	$8.13 \pm 0.80$	7.70, 8.72
Phosphorous <sup>a</sup> (mg/dL)	39	$4.89 \pm 1.76$	3.5, 6.2
International normalised ratio <sup>a</sup>	70	$1.36 \pm 0.31$	1.20, 1.41
Activated partial thromboplastin time <sup>a</sup> (seconds)	70	$37.04 \pm 11.87$	29.20, 42.03

<sup>a</sup>: Data not available for the entire study population. SGOT/AST: Serum glutamate pyruvate transaminase/aspartate aminotransferase, SGPT/ALT: Serum glutamate oxaloacetate transaminase/alanine aminotransferase

of the total study population. The duration of Medical Intensive care unit/Intensive care unit (MICU)/ICU stay was  $5.71 \pm 2.69$  days. Among patients with AKI, 39 had subtype K (22.15%), five had subtype 2 (2.84%), and none had subtype 19. Among the patients with absent AKI, 113 patients had subtype K (64.2%), 8 had subtype 2 (4.54%), and 11 had subtype 19 (6.25%).

The prevalence of AKI was 25% (44/176), and the prevalence of overall complications was 81% (143/176). The distribution of AKI stages in this study, as per KDIGO guidelines, is as follows: 132 (75%) patients had no AKI, 27 (15.3%) had stage 1 AKI, eight (4.5%) had stage 2 AKI, and nine (5.1%) had stage 3 AKI. The month-wise distribution of rickettsial infection and the occurrence of AKI have been presented in Figure 1.

**Laboratory findings and univariate analysis**

Independent t-test analysis revealed significant differences in multiple continuous variables between patients with and without AKI [Table 2]. Patients who developed AKI

were older and had longer hospital stays, elevated white blood cell counts ( $20.38 \pm 10.69$  vs.  $13.21 \pm 6.36 \times 10^9/L$ ), higher total and direct bilirubin levels hyperkalemia, lower platelet counts, lower serum albumin, higher phosphorus and shorter APTT.

**Clinical associations with AKI**

Categorical analysis showed that AKI was significantly associated with age more than 50 years, male sex, diabetes mellitus, and prolonged hospitalization. Systemic complications were frequent. AKI patients had higher rates of intensive care requirement, intravenous fluid use, inotrope administration, and ventilatory support. Mortality among AKI patients was 1.13%, and dialysis was required in 2.27% of cases. The presence of rash, abdominal pain, hypoxia, hepatosplenomegaly, and uremic symptoms also demonstrated statistical significance in relation to AKI. There was no association between AKI and antigen subtypes ( $p = 0.08$ ) [Table 3].

**Multivariate predictors of AKI: Binary logistic regression**

Logistic regression analysis identified several independent AKI predictors. Age >50 years increased the odds of AKI 3.6-fold (95% CI: 1.70-7.60,  $p = 0.001$ ), and male sex increased it 4.14-fold (95% CI: 1.76-9.78,  $p = 0.001$ ). Diabetes mellitus was a significant risk factor (OR 3.13, 95% CI: 1.18-8.28,  $p = 0.021$ ). Conversely, prolonged hospitalization (OR 1.08 per day,  $p = 0.02$ ), icterus (OR 2.88), hypoxia (OR 2.33), and various acid-base abnormalities were statistically significant consequences in patients with AKI, likely representing the indicators of severe disease progression. Similarly, respiratory complications (OR 2.10), septic shock (OR 5.42), MODS (OR 52.8), the need

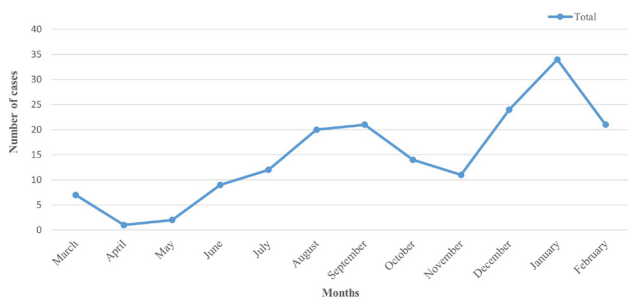


Figure 1: Seasonal trends of rickettsial infection.

Table 2: Independent t-test analysis of various parameters in rickettsial infection among patients with AKI and without AKI

	n	Without AKI	With AKI	p-value
Age (years)	176	34.50 ± 15.65	46.36 ± 14.96	< 0.05
Duration of hospitalization (days)	176	9.84 ± 5.10	12.63 ± 6.78	0.015
Intensive care treatment (days)	114	5.38 ± 2.82	6.22 ± 2.42	0.105
White blood cells (×10 <sup>3</sup> /mL)	176	13.21 ± 6.36	20.38 ± 10.69	< 0.05
Platelet (×10 <sup>3</sup> /mL)	176	145.94 ± 128.10	97.06 ± 95.17	0.021
SGOT/AST (IU/L)	176	125.73 ± 113.06	150.65 ± 87.20	0.184
SGPT/ALT (IU/L)	176	102.71 ± 158.28	99.81 ± 86.29	0.908
Total bilirubin (mg/dL)	176	1.85 ± 1.95	4.40 ± 2.95	< 0.05
Direct bilirubin (mg/dL)	176	1.34 ± 1.74	3.37 ± 2.76	< 0.05
Albumin (g/dL)	176	2.84 ± 0.45	2.47 ± 0.45	< 0.05
Sodium (mEq/L)	176	133.31 ± 7.28	136.59 ± 10.27	0.055
Potassium (mEq/L)	176	4.39 ± 0.65	5.26 ± 0.95	< 0.05
Ferritin <sup>a</sup> (ng/mL)	56	513.96 ± 421.45	730.02 ± 439.09	0.08
Lactate dehydrogenase <sup>a</sup> (U/L)	52	467.69 ± 247.32	509.31 ± 266.29	0.58
D-dimer <sup>a</sup> (ng/mL)	35	1970.45 ± 2709.51	1544.72 ± 1602.70	0.63
Calcium <sup>a</sup> (mg/dL)	26	8.32 ± 0.60	7.70 ± 1.05	0.06
Phosphorous <sup>a</sup> (mg/dL)	39	4.02 ± 0.49	5.42 ± 2.05	0.003
International normalized ratio <sup>a</sup>	70	1.37 ± 0.24	1.35 ± 0.39	0.73
Activated partial thromboplastin time <sup>a</sup> (seconds)	70	39.36 ± 10.31	33.56 ± 13.33	0.044

<sup>a</sup>: Data not available for the entire study population. SGOT/AST: Serum glutamate pyruvate transaminase/aspartate aminotransferase, SGPT/ALT: Serum glutamate oxaloacetate transaminase/alanine aminotransferase

**Table 3: Association between various parameters in rickettsial infection among patients with AKI and without AKI**

Parameters	Without AKI	With AKI	p value
Demographic details			
Age			
<50	109 (61.9)	25 (14.2)	0.001
>50	23 (13.06)	19 (10.79)	
Sex			
Male	58 (32.9)	33 (18.75)	< 0.05
Female	74 (42.04)	11 (6.25)	
Diabetes mellitus			
No	118 (67.04)	27 (15.34)	< 0.05
Yes	14 (7.95)	17 (9.65)	
Days of hospitalization			
<7	42 (23.8)	13 (7.38)	0.048
>7	60 (34.09)	13 (7.38)	
>14	30 (17.04)	18 (10.22)	
Required intensive care admission			
No	63 (35.79)	0	< 0.05
Yes	69 (39.2)	44 (25)	
Symptoms			
Chills and Rigor			
No	4 (2.27)	5 (2.84)	0.03
Yes	128 (72.72)	39 (22.15)	
Rash			
No	85 (48.29)	40 (22.72)	0.001
Yes	47 (26.7)	4 (2.27)	
Abdominal pain			
No	105 (59.65)	41 (23.29)	0.03
Yes	27 (15.34)	3 (1.7)	
Signs			
Icterus			
No	109 (61.93)	22 (12.5)	< 0.05
Yes	23 (13.06)	22 (12.5)	
Hypoxia (arterial saturation < 90%)			
No	110 (62.5)	30 (17.04)	0.031
Yes	22 (12.5)	14 (7.95)	
Hepatomegaly			
No	110 (62.5)	44 (25)	0.004
Yes	22 (12.5)	0	
Hepatosplenomegaly			
No	116 (65.90)	44 (25)	0.015
Yes	16 (9.09)	0	
Arterial blood gas analysis <sup>a</sup>			
Normal	21 (15.55)	2 (1.48)	-
Respiratory alkalosis	51 (37.77)	15 (11.11)	
Respiratory acidosis	5 (3.7)	5 (3.7)	
Metabolic alkalosis	5 (3.7)	4 (2.96)	
Metabolic acidosis	13 (9.62)	14 (10.37)	
Outcomes			
Presence of systemic complications			
No	33 (18.75)	0	< 0.05
Yes	99 (56.25)	44 (25)	

contd.,

**Table 3: Continued**

Respiratory system complication (pneumonia/acute respiratory distress syndrome)				
No	97 (55.11)	25 (14.2)	0.038	
Yes	35 (19.88)	19 (10.79)		
Acute hepatitis				
No	121 (68.7)	35 (19.88)	0.028	
Yes	11 (6.25)	9 (5.11)		
Septic shock				
No	85 (48.29)	11 (6.25)	< 0.05	
Yes	47 (26.7)	33 (18.75)		
Multiorgan dysfunction syndrome				
No	120 (68.18)	7 (3.97)	< 0.05	
Yes	12 (6.81)	37 (21.02)		
Management				
Intravenous fluids				
No	11 (6.25)	0	0.048	
Yes	121 (68.75)	44 (25)		
Intravenous ceftriaxone and oral doxycycline				
No	66 (37.5)	31 (17.6)	0.018	
Yes	66 (37.5)	13 (7.38)		
Need for higher antibiotics				
No	77 (43.75)	18 (10.22)	0.045	
Yes	55 (31.25)	26 (14.77)		
Need for inotropes				
No	80 (45.45)	18 (10.22)	0.023	
Yes	53 (30.11)	26 (14.77)		
Trial of NIV or NIV ever required				
No	70 (39.77)	10 (5.68)	< 0.05	
Yes	62 (35.22)	34 (19.31)		
Need for invasive ventilation (MV)				
No	110 (62.5)	28 (15.9)	0.006	
Yes	22 (12.5)	16 (9.09)		
Albumin infusion				
No	132 (75)	42 (23.86)	0.014	
Yes	0	2 (1.13)		

<sup>a</sup>: Data not available for the entire study population. AKI: Acute kidney injury, NIV: Non-invasive ventilation, MV: Mechanical ventilation

for higher antibiotics (OR 2.02), inotropes (OR 2.02), and NIV (OR 2.99) or MV (OR 2.85) primarily reflected critical illness often accompanying or following AKI.

### Discussion

We present data from 176 patients who tested positive for typhus in our hospital over 4 years from 2021 to 2024. We did not have facilities for ELISA or PCR testing for *Orientia tsusugamushi* and hence relied on Weil-Felix and IFA for confirmation.

Fever was universal (100%), associated with chills in 95% of patients, cough in 50%, nausea and vomiting in 44%, and dysuria in 23%; however, a skin eschar was seen in only

1%. This could be because eschars are difficult to identify in dark-skinned individuals. Other studies have reported an increasing incidence coinciding with the rainy season, where warm, humid conditions facilitate the proliferation of the mite vectors. However, we found that more cases occurred in the winter months from November to January.

Various previous studies [Supplementary Table 4] have reported AKI incidence in the range of 6.6-45%.<sup>7,10,11,16-36</sup> In our study, the incidence was 25%, with most patients in KDIGO stages 1 and 2. Dialysis was necessary only in 4% of patients. When patients with AKI were compared to those without, we found that older age, male sex, longer duration of hospitalization, leucocytosis, thrombocytopenia, hypotension, ARDS, and increased liver enzymes predicted a higher risk of AKI. These findings are similar to those of other published literature.<sup>7,10,17,18</sup> Thrombocytopenia and the need for intensive care (ICU) support are significant predictors of AKI in scrub typhus. In our AKI cohort, >50% of the study population proportion (61.5%) had thrombocytopenia, and a substantial number required ICU support (25%).

Furthermore, AKI was a risk factor for mortality. The mortality rate in our study was 2.8% as compared with that of 0.8-27.5% in other studies.<sup>7-11</sup> In our study, older age, longer duration of hospital stays, severity of leukocytosis, thrombocytopenia, AKI, hypoalbuminemia, and hepatic dysfunction were associated with mortality. Moreover, mortality was linked to the comorbidities (ARDS, encephalopathy, and multiorgan failure) and the requirement for intensive care unit support.

AKI associated with scrub typhus infection is not as rare as previously assumed. Our study from a semi-rural tertiary center adds to the evidence of published literature on AKI in scrub typhus, which is an emerging epidemic in India. Prompt intensive management is the mainstay for these cases of complicated scrub typhus to prevent severe morbidity or mortality. It is important to consider the possibility of scrub typhus when patients present with fever and varying degrees of AKI along with a history of environmental exposure in an area where scrub typhus is endemic. Prompt diagnosis and the use of appropriate antibiotics can alter the clinical course of the disease and prevent the development of serious or fatal complications. The limitation of our study was that this was a retrospective single-center study, and the results cannot be generalized to larger studies of scrub typhus-associated AKI.

We show that AKI associated with scrub typhus had serious disease with a high incidence of severe manifestations, complications, and mortality. Enhanced awareness of this entity is paramount, as early identification and treatment of risk factors have the potential to significantly reduce the prevalence of AKI and its associated morbidity and mortality.

**Conflicts of interest:** There are no conflicts of interest.

*The authors declare that no generative AI or AI-assisted tools were used in drafting, editing, or preparing this manuscript.*

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