

Clinical profile and outcomes of scrub typhus in patients managed at tertiary healthcare centers: A systematic review and meta-analysis

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ABSTRACT

The clinical presentation of scrub typhus is quite variable, often beginning with nonspecific symptoms such as fever, headache, myalgia, and gastrointestinal disturbances. Outcomes range from complete recovery with timely intervention to significant morbidity and mortality when diagnosis or initiation of appropriate therapy is delayed. This systematic review and meta-analysis aimed to comprehensively evaluate the clinical characteristics and outcomes of scrub typhus in patients treated in tertiary healthcare centers. A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed, Embase, Scopus, and the Cochrane Library, from inception to the most recent date available. The systematic search yielded a total of 10,839 documents from electronic databases. Following the elimination of duplicates and the evaluation of full-text publications, six studies ultimately met the inclusion criteria and were incorporated into both the qualitative and quantitative meta-analysis. All identified records were entered into reference management software, and duplicates were eliminated. Pooled prevalence estimates for clinical characteristics, complications, and outcomes were computed using a random-effects model to address inter-study variability. The I^2 statistic was employed to assess statistical heterogeneity, with elevated values indicating greater heterogeneity. Scrub typhus remains a significant cause of severe acute febrile illness among patients receiving treatment at tertiary healthcare centers in India. The disease is characterized by diverse clinical symptoms and substantial organ failure, particularly impacting the respiratory, renal, and neurological systems, resulting in high morbidity and mortality.

Keywords: Scrub typhus, clinical manifestations, clinical outcome, tertiary case hospital.

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INTRODUCTION

Orientia tsutsugamushi causes scrub typhus, a serious febrile illness that spreads via the bite of infected chigger mites. It is common in the "tsutsugamushi triangle," which includes parts of the Western Pacific, northern Australia, and South and Southeast Asia [1]. In India, scrub typhus has resurfaced as a notable public health issue in the last twenty years, significantly contributing to instances of acute undifferentiated fever, especially in the post-monsoon season [2]. The disease impacts both rural and urban populations across all age groups, with reported incidence varying significantly by geographic region due to disparities in surveillance systems, diagnostic capabilities, and clinical awareness.

The clinical manifestation of scrub typhus is markedly heterogeneous, frequently commencing with nonspecific symptoms including fever, headache, myalgia, and problems with digestion [3]. The existence of an eschar is regarded as a distinctive clinical indicator; however, its reported prevalence fluctuates significantly, and it is often absent or neglected, particularly among individuals with darker skin tones [4]. As the illness gets worse, patients may experience serious organ failure, such as acute respiratory distress syndrome, acute kidney injury, liver failure, myocarditis, shock, and central nervous system complications. These complications often require admission to tertiary healthcare centers and, in severe instances, intensive care units [5]. Outcomes vary from total recovery with prompt

treatment to considerable morbidity and mortality when diagnosis or the commencement of suitable therapy is postponed.

Numerous observational studies conducted in tertiary healthcare centers have delineated the clinical profile, laboratory anomalies, complications, and outcomes associated with scrub typhus [6-9]. These studies have consistently underscored the prevalence of multiorgan dysfunction in hospitalized patients, with mortality rates exhibiting significant variability across institutions. Variations in patient characteristics, diagnosis requirements, level of severity at presentation, the accessibility of critical care amenities, and treatment procedures have led to significant discrepancies in reported outcomes. Individual studies yield significant insights into localized disease patterns; however, their conclusions are frequently constrained by limited sample sizes and center-specific methodologies, thereby diminishing their generalization.

A handful of narrative reviews and region-specific summaries have endeavored to characterize scrub typhus in hospitalized populations [10-12]; nonetheless, a thorough systematic review with quantitative synthesis concentrating specifically on patients treated at tertiary healthcare centers is still lacking. Current reviews frequently amalgamate community-based and hospitalized cases or concentrate predominantly on diagnostic elements rather than clinical outcomes. A noteworthy systematic review conducted by Devasagayam et al [13] determined the national burden of scrub typhus in India, revealing an overall

case-fatality rate of 6.3%, which escalated to 38.9% for those patients who experienced multi-organ dysfunction syndrome. This review offered significant epidemiological insights, primarily concentrating on disease burden at the population level and encompassing diverse clinical settings, from community-based cohorts to hospitalized patients. Significantly, it did not specifically analyze clinical profiles, complication patterns, or aggregated outcomes among patients treated at tertiary healthcare centers, where severe disease and critical conditions are most commonly observed.

A focused systematic review and meta-analysis that consolidates data from tertiary healthcare settings is essential to elucidate clinically significant patterns of presentation and outcomes, ascertain the burden of severe complications, and produce evidence directly relevant to critical care decision-making. There is a clear need for a systematic synthesis of available evidence because more and more people are recognizing scrub typhus as the root cause of severe febrile illness and sepsis-like manifestations in tertiary healthcare centers and critical care settings. A meta-analytic approach facilitates the consolidation of data from various contexts, thereby yielding a more accurate assessment of clinical characteristics, complication rates, and outcomes, while simultaneously identifying areas of variability and deficiencies in knowledge. This evidence is especially pertinent for physicians operating in endemic areas, where early detection and swift intervention can markedly affect prognosis.

The fundamental hypothesis of this study posits that scrub typhus treated at tertiary healthcare centers is linked to a significant incidence of organ dysfunction and fluctuating mortality rates, with discernible clinical characteristics and complications playing a role in negative outcomes. It is additionally posited that pooled analysis will uncover predictable trends in presentation and effects that remain obscured in individual studies.

The principal objective of this systematic review and meta-analysis was to thoroughly assess the clinical characteristics and outcomes of scrub typhus in patients treated at tertiary healthcare centers. The specific objectives were to delineate the aggregated prevalence of essential clinical characteristics and complications, evaluate significant clinical outcomes such as mortality and intensive care needs, and investigate the variability in outcomes across studies. This review aimed to offer clinically significant insights by synthesizing existing evidence to facilitate prompt detection, identification of risk factors, and effective management of scrub typhus in tertiary and critical care environments.

METHODS

Format for Reporting

This systematic review and meta-analysis were executed and reported in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. All parts of the review process were planned ahead of time, including the literature search, choosing the study, collection of data, and synthesis, to make sure that the process was clear, repeatable, and methodologically sound. The present systematic review and meta-analysis was registered in PROSPERO (ID- CRD420251266981).

Research question

The review aimed to investigate the characteristics of the disease, adverse reactions, and outcomes of scrub typhus among patients treated at tertiary healthcare centers.

The PICOS Framework

The target population comprised patients of any age identified as having scrub typhus and treated at tertiary healthcare centers. The intervention/exposure was a confirmed scrub typhus infection, validated through clinical, serological, or molecular diagnostic criteria as specified by each study. Since this review concentrated on descriptive clinical outcomes, a comparator was not required. The outcomes encompassed clinical characteristics, organ dysfunction, complications, admission to the intensive care unit,

and mortality. Observational studies, such as prospective and retrospective cohort studies and cross-sectional studies conducted in tertiary healthcare centers, were eligible for inclusion in the study designs.

Criteria for Selection

Studies were included if they presented original data regarding the clinical profile and/or outcomes of scrub typhus in patients receiving care at tertiary healthcare centers. Only studies that had been peer reviewed were taken into account. Studies published between January 2014 and January 2026 were included in the review. Case reports, case series with very small sample sizes, review articles, editorials, conference abstracts, animal studies, and studies that didn't have any extractable outcome data that could be extracted were all excluded. Studies conducted solely in primary care or community settings were excluded to ensure relevance to tertiary and critical care practice.

Search Methods

A thorough and methodical literature search was conducted across various electronic databases, such as PubMed, Embase, Scopus, and the Cochrane Library. The search strategy was improved by using Boolean operators. The following keywords and Boolean operators were used:

("scrub typhus" OR "Orientia tsutsugamushi") AND ("clinical profile" OR "clinical characteristics" OR "clinical manifestations") AND ("complications" OR "organ dysfunction") AND ("outcomes" OR "mortality" OR "ICU admission") AND ("tertiary care" OR "hospitalized patients").

Manual screening of reference lists of included studies and relevant reviews were done to find more articles that were eligible. There were no limits on the year of publication, but articles published in English language only were selected.

Data Extraction

All of the records that were found were put into reference management software, and any duplicates were taken out. Two reviewers independently evaluated titles and abstracts for eligibility, subsequently conducting a full-text review of articles deemed potentially relevant. Any disagreements were worked out through discussion, and if needed, a third reviewer was brought in to provide assistance. Two reviewers independently extracted data using a pre-designed data extraction form. The extracted variables encompassed study variables such as patient information, diagnostic specifications, clinical characteristics, laboratory results, complications, intensive care demands, and outcomes, including mortality. Any differences in the extracted data were settled by agreement.

Synthesis Methods

Quantitative synthesis was conducted when adequate homogeneity in outcome reporting was evident. Using a random-effects model to account for differences between studies, pooled prevalence estimates for clinical features, complications, and outcomes were calculated. The I^2 statistic was used to measure statistical heterogeneity, with higher values meaning more heterogeneity.

Evaluation of Bias Risk

Two reviewers used a validated tool (Newcastle–Ottawa Scale (NOS)) for observational studies to independently evaluate the methodological quality and risk of bias of the observational studies that were included [15]. The domains assessed encompassed participant selection, exposure and outcome ascertainment, study group comparability, and the sufficiency of outcome reporting. Disagreements about risk-of-bias assessment were settled through conversation.

Assessment of Certainty

A structured method was used which examined the overall certainty of the evidence for key outcomes. This method took into account study limitations, inconsistency, indirectness, imprecision, and publication bias. The strength of the evidence

was grouped so that medical professionals could understand what degree of confidence they were about the pooled estimates and conclusions from the review.

Study Selection:

The systematic search produced a total of 10,839 records from electronic databases. After getting rid of duplicates, the titles and abstracts were checked for relevance. Then, 15 full-text articles were looked at to see if they met the requirements. Studies lacking extractable data on the clinical features or outcomes of scrub typhus treated at tertiary healthcare centers were excluded. Ultimately, six studies satisfied the inclusion criteria and were integrated into both the qualitative and quantitative meta-analysis (figure 1).

General Traits of the Studies Included

The studies included were observational in nature and primarily carried out in tertiary care hospitals throughout India. There were both prospective and retrospective cohorts. Sample sizes exhibited considerable variability, spanning from diminutive single-center cohorts to extensive hospital-based series. The diagnosis of scrub typhus was determined through an amalgamation of clinical manifestations, serological assays, and/or molecular techniques, as delineated by specific studies. Most studies involved adult patients, with hospitalized cohorts exhibiting moderate to severe disease, including individuals necessitating intensive care support. The outcomes reported from all studies included signs and symptoms, major organ failure and death during hospitalization.

The study populations were primarily composed of adults, with mean or median ages spanning from the third to the fifth decade of life. Most studies found that women were slightly more likely than men to be involved. All studies were conducted in tertiary healthcare centers, indicating a population with moderate to severe disease necessitating hospitalization and specialized care.

Clinical Characteristics and Outcomes of Scrub Typhus

People often reported that they had serious problems. Acute respiratory distress syndrome and acute kidney injury were often noted, although their reported prevalence varied significantly among studies. Several cohorts exhibited central nervous system involvement, characterized by meningoencephalitis and altered sensorium. Multiorgan dysfunction syndrome was documented in extensive tertiary care studies and constituted a major factor in disease severity.

Admission to intensive care or critical care units varied, indicating disparities in disease severity, institutional admission criteria, and reporting methodologies. Mortality rates varied from 0% to 13.6%, with increased fatalities noted in studies indicating a higher prevalence of organ dysfunction.

Results of Meta-analysis

A meta-analysis of significant clinical manifestations (Table 3) revealed that fever was the most commonly reported symptom, with a combined prevalence of 84.3% (Table 3). However, significant heterogeneity was noted among studies, with some indicating fever in all enrolled patients, implying discrepancies in case definitions or selection criteria. The average length of fever across all studies was 9.23 days, which shows that the febrile course was longer even though the patients were treated in the hospital (Table 3 and figure 2).

RESULT

Eschar, a classic sign of scrub typhus, was found in about 28.1% of the patients. The significant disparity in reported prevalence among studies underscores disparities in clinical examination, record keeping practices, or characteristics of the patient (Table 3 and figure 3). ARDS was seen in 21.4% of patients with severe complications, showing how much scrub typhus affects the lungs in people who are in the hospital. Approximately one in five patients developed ARDS, but the wide confidence interval and high heterogeneity suggest that the true prevalence may vary considerably across different settings or patient population (Table 3 and figure 4). Nearly a quarter of patients experience AKI with a pooled prevalence of 24.8%, though the extreme variability between studies indicates potential differences in AKI definitions, severity, or patient characteristics (Table 3 and figure 5).

An analysis of mortality showed that the overall pooled mortality rate was 8.2%. The absolute mortality rate seemed low, but there was a lot of variation between studies (Table 3 and figure 6). This suggests that factors like severity of the disease during initial diagnosis, how long it took to reach a diagnosis, other health problems, and the accessibility of intensive care facilities could affect the results.

Evaluation of Bias Risk

Studies exhibiting diminished bias risk were distinguished by rigorous case definitions, representative tertiary-care populations, and thorough outcome evaluation. Conversely, studies exhibiting moderate to high bias risk frequently failed to account for potential confounders, featured smaller sample sizes, or offered insufficient reporting of outcomes pertinent to disease severity and prognosis. No study was excluded solely due to risk of bias; however, these evaluations were taken into account when analyzing pooled estimates.

Assessment of Certainty

The level of certainty in the evidence for important outcomes varied from low to moderate. The main things that affected certainty were high statistical heterogeneity, different definitions of outcomes, and the design of observational studies. The pooled estimates offer significant insights into disease patterns; however, the extensive prediction intervals suggest that results must be interpreted with caution, especially when generalizing findings to diverse clinical contexts.

Synthesis of Findings

This meta-analysis shows that scrub typhus treated at tertiary healthcare centers is linked to an abundance of systemic problems, especially problems with breathing and kidney function. Fever is still the most common symptom that people present with, but how common and how long it lasts can vary substantially. The low pooled mortality rate must be understood in light of the significant variability between studies, which highlights the importance of early diagnosis, prompt antimicrobial treatment, and supportive critical care in enhancing outcomes. The findings collectively underscore scrub typhus as a clinically relevant etiology of severe febrile illness necessitating tertiary-level intervention in endemic areas.

Table 1. General characteristics of the studies included

Author (Year)	Study design	Study setting	Geographic location	Study period	Sample size (n)	Age (years)	Sex distribution	Diagnostic method
Varghese et al., 2014[16]	Retrospective observational	Tertiary care teaching hospital	Tamil Nadu (South India)	2005–2010	623	Mean 45 ± 15	M 48%, F 52%	IgM ELISA ± PCR
Sharma et al., 2016 [6]	Prospective observational	Tertiary care referral centre	Chandigarh (North India)	2013–2014	228	Median 35 (IQR 24.5–48.5)	M 48.7%, F 51.3%	IgM ELISA ± PCR
Kamath et al., 2022 [17]	Retrospective observational	Tertiary care hospital	Jharkhand (East India)	2019–2021	42	Mean 18.4 ± 17.6	M 38.1%, F 61.9%	IgM ELISA / Weil–Felix
Verma et al., 2021 [18]	Prospective observational	Tertiary care hospital	Uttar Pradesh (North India)	2019–2020	52	Mean 35.2 ± 16.9	M 46.2%, F 53.8%	IgM ELISA
Mandal et al., 2023 [19]	Cross-sectional observational	Government tertiary care hospital	West Bengal (East India)	NR	35	NR (14–70)	M 42.9%, F 57.1%	IgM ELISA
Bhowmik et al., 2024 [20]	Cross-sectional observational	Tertiary care medical college	West Bengal (East India)	2020–2021	154	Mean 36.7 ± 18.9	M 40.3%, F 59.7%	IgM ELISA

Table 2. Clinical Profile and Outcome of Scrub Typhus in the studies included

Author (Year)	Fever (%)	Mean fever duration (days)	Eschar (%)	ARDS (%)	AKI (%)	CNS involvement (%)	MODS (%)	ICU/CCU admission (%)	Mortality (%)
Varghese et al., 2014[16]	100	9.6 ± 4.8	43.5	33.7	32.0	26.0	34.0	29.5 (ventilated)	9.0
Sharma et al., 2016 [6]	85.0	NR	14.0	25.0	32.0	7.0	20.0	NR	13.6
Kamath et al., 2022 [17]	71.4	9.5 ± 4.6	38.1	16.7	0.0	21.4	NR	57.2	0.0
Verma et al., 2021 [18]	100	9.6 ± 2.0	21.2	19.2	23.1	47.0	NR	NR	NR
Mandal et al., 2023 [19]	100	NR	34.3	NR	NR	NR	NR	NR	NR
Bhowmik et al., 2024 [20]	100	NR	13.0	7.8	57.1	NR	NR	NR	6.5

Table 3. Summary of all outcomes

Outcome	Pooled Estimate	95% CI	I ² (%)	Studies (n)
ARDS	21.4%	8.9% to 33.9%	96.2	5
AKI	24.8%	12.2% to 37.4%	98.3	6
Eschar	28.1%	18.6% to 37.7%	98.1	6
Mortality	8.2%	3.7% to 12.7%	92.7	4
Fever	84.3%	63.4% to 105.2%*	99.6	5
Fever Duration	9.23 days	8.45 to 10.01 days	73.5	3

Table 4. Risk of bias assessment of included studies

Study	Selection (4)	Comparability (2)	Outcome (3)	Total score (/9)	Overall risk of bias
Varghese et al., 2014[16]	★★★★	★★	★★★	9	Low
Sharma et al., 2016 [6]	★★★★	★★	★★★	8	Low
Kamath et al., 2022 [17]	★★★★	★☆	★★★	7	Moderate
Verma et al., 2021 [18]	★★★☆	★☆	★★★	7	Moderate
Mandal et al., 2023 [19]	★★★☆	★☆	★★★	7	Moderate
Bhowmik et al., 2024 [20]	★★★☆	☆☆	★★★	4	High

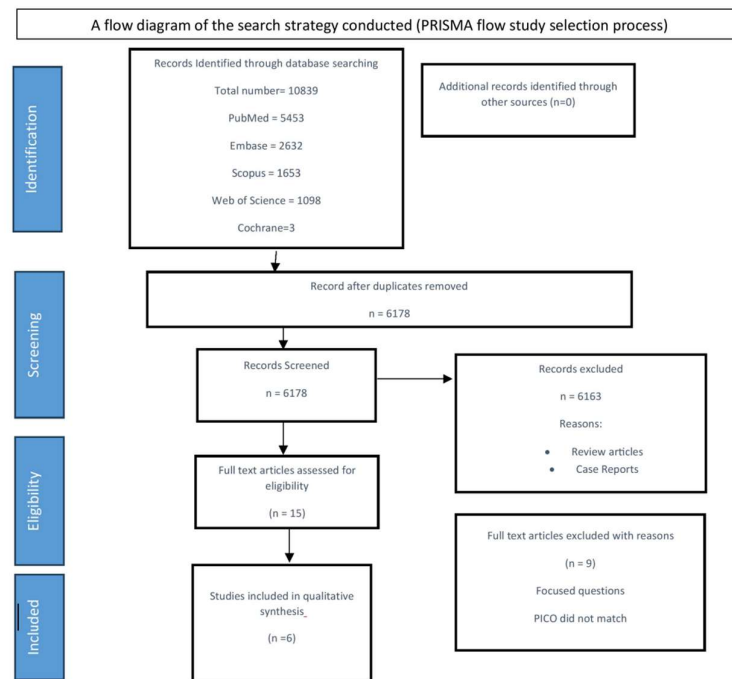


Figure 1 PRISMA chart

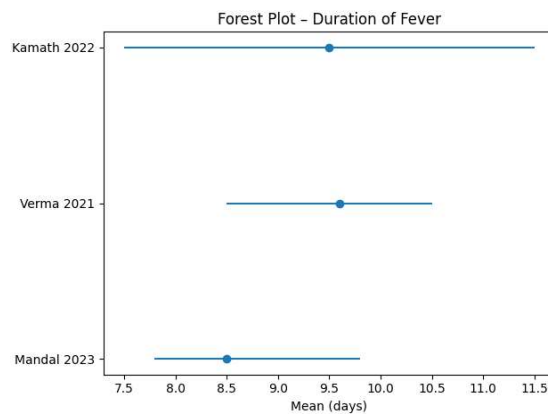


Figure 2 Forest plot- Duration of fever

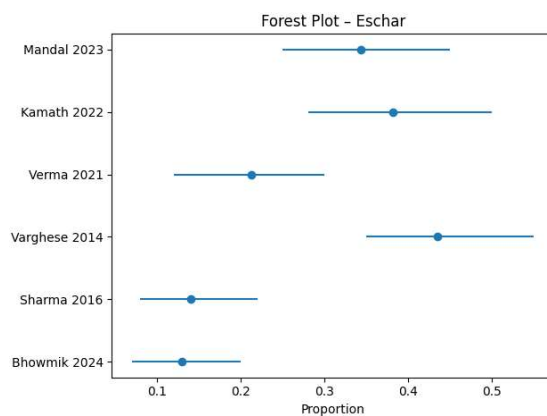


Figure 3 Forest plot- Eschar

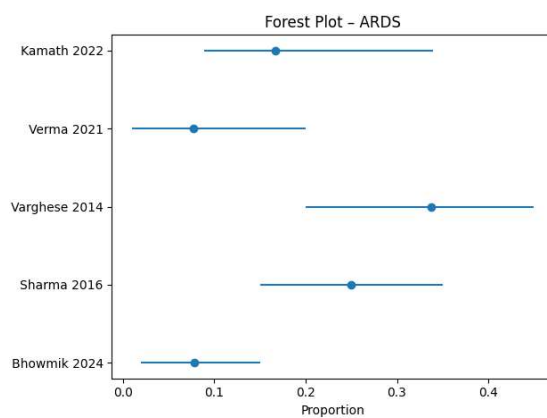


Figure 4 Forest plot- ARDS

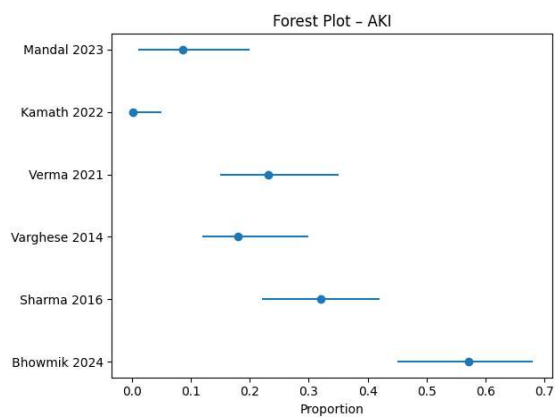


Figure 5 Forest plot- AKI

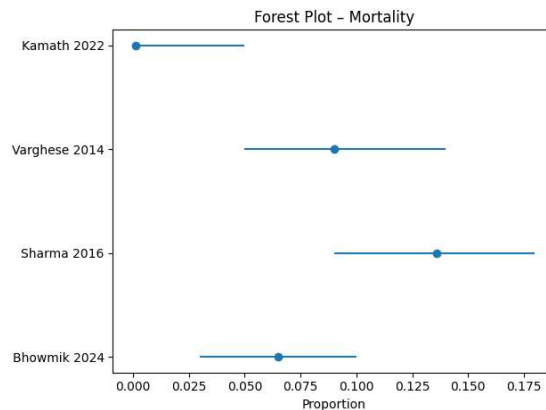


Figure 6 Forest plot- Mortality

DISCUSSION

Scrub typhus is a zoonotic infection transmitted by vectors and ranks among the most prevalent rickettsial infections globally. The disease is common in South Asia, Southeast Asia, East Asia, the Pacific Islands, and Northern Australia, which is known as the "tsutsugamushi triangle" [21]. There have also been reports of cases from Chile, Peru, Africa, and the Arabian Peninsula. In India, cases have reemerged in recent years across various states [22]. Immunological methods used to look at strain DNA show that the Karp strain is responsible for about 50% of all cases in areas where the disease is common, such as South Asia [23].

A study of seasonal distribution revealed an elevated incidence from October to December. Islam et al.[23] and Ngulani et al.[24] also saw the same things in their studies in Eastern India. Nonetheless, the peak incidence of cases occurred from July to October (during the monsoon) in the study conducted by Gurung et al. [25] from Sikkim and in another study by Sharma et al. from Darjeeling [26].

This systematic review and meta-analysis offer an extensive synthesis of the clinical characteristics and outcomes of scrub typhus in patients treated at tertiary healthcare centers in India. The results conclude that scrub typhus continues to be a significant cause of severe acute febrile illness necessitating hospitalization, accompanied by substantial organ dysfunction and quantifiable mortality. The broad clinical spectrum noted in various studies underscores the erratic progression of the disease and the difficulties encountered in prompt diagnosis and identification of risk factors in standard clinical practice.

Fever was the most frequently mentioned manifesting symptom in all included (100%) studies, indicating its role as the most common clinical indicator of scrub typhus. The prevalence of eschar, however, varied significantly across studies [7,8]. This variability has been extensively documented in prior Indian and Asian literature and is likely due to variations in clinical awareness, anatomical distribution of eschars, pigmentation of the skin, and unreliable documentation [9,10]. Multiple preceding studies have underscored that dependence on eschar for diagnosis may be deceptive, as its absence does not rule out scrub typhus [4,6]. The current findings corroborate this observation and underscore the necessity for clinicians to sustain diagnostic suspicion, even in the absence of classical signs.

The significant complications noted in this review align with earlier hospital-based studies characterizing scrub typhus as a systemic vasculitic disorder with multisystem involvement [22,27]. In a systematic review conducted by Devasagayam et al. [14] on the burden of scrub typhus in India, the prevalent symptoms in confirmed cases, listed in descending order, were fever (34.7%), eschar (22.1%), headache (18.2%), nausea/vomiting (17.1%), abdominal pain (10.5%), breathlessness (10.4%), cough (10.4%), jaundice (5.6%), and

seizure (2.7%). Respiratory complications, especially acute respiratory distress syndrome, were commonly reported among cohorts. Previous single-center studies from India have identified pulmonary involvement as a prevalent cause of clinical deterioration, frequently requiring mechanical ventilation. The aggregated estimates in this review reinforce these findings and validate that respiratory failure continues to be a principal factor influencing severity in tertiary care environments.

Renal involvement, evidenced by acute kidney injury, was another significant finding. Prior research has indicated fluctuating rates of AKI was due to variations in diagnostic criteria, patient baseline characteristics, and the timing of hospital admission [28]. The aggregated results of this review indicate that renal dysfunction is a prevalent and clinically relevant complication among hospitalized scrub typhus patients. The proposed underlying mechanisms in previous literature such as endothelial injury, hypoperfusion, rhabdomyolysis, and sepsis-related renal injury likely collectively contribute to this presentation [29].

Several studies included in the review reported neurological manifestations, such as altered sensorium and meningoencephalitis [6,16-18]. Previous systematic review by Alam et al [30] have consistently identified central nervous system involvement as an indicator of severe disease and unfavorable prognosis. This synthesis corroborates previous findings, illustrating that neurological complications constitute a significant aspect of scrub typhus-related morbidity in tertiary care populations.

The mortality estimations in this review align with those reported in earlier Indian studies, yet exhibit significant variability between studies. A systematic review by Taylor et al [31] has indicated mortality rates varying from low single-digit percentages to significantly elevated rates in patients exhibiting multiorgan dysfunction. Following the systematic review by Devasagayam et al.,[14] which indicated an overall case-fatality rate of 6.3%, with significantly elevated mortality in patients exhibiting multiorgan dysfunction, our findings similarly reveal a considerable incidence of systemic complications and significant clinical mortality. The differences in mortality rates between studies are probably due to disease severity, time of diagnosis, presence of co-morbidities and availability of critical care support.

This study enhances previous systematic reviews by concentrating on hospitalized patients treated at tertiary care centers and by quantitatively summarizing clinically significant outcomes. Prior reviews frequently amalgamated community-based and hospital-based populations or prioritized epidemiological burden over in-hospital clinical outcomes. In contrast, this review offers aggregated estimates of significant complications and outcomes that are directly relevant to inpatient

and critical care decision-making. Furthermore, the incorporation of more recent studies facilitates the examination of emerging trends in disease identification and treatment, which may partially elucidate the comparatively reduced mortality rates observed in certain contemporary cohorts.

Previous systematic reviews and extensive narrative reviews of scrub typhus have documented comparable degrees of heterogeneity [14,30,31]. This variability is probably caused by differences in the way studies are set up, the way diseases spread in different areas, the criteria used to diagnose them, the severity levels that lead to hospitalization, and the way results are reported. This heterogeneity does not undermine the validity of the findings; rather, it illustrates the genuine diversity of scrub typhus manifestations and healthcare delivery throughout India. Being open about this variability and reporting it clearly makes the results easier to understand.

From a clinical standpoint, the results highlight the significance of prompt identification and methodical assessment for organ dysfunction in patients with probable scrub typhus. The consistent link between adverse outcomes and issues with the lungs, kidneys, and nervous system shows how important it is to make prompt care and have a team of specialists work together in tertiary centers. These findings are consistent with current guidelines that promote early antimicrobial treatment and robust supportive care to avert the advancement to multiorgan failure [32].

The risk-of-bias assessment indicated that the majority of studies were of low to moderate quality, aligning with the observational characteristics of scrub typhus research undertaken in tertiary care environments. More extensive cohort studies with well-defined diagnostic criteria and systematic outcome reporting demonstrated a reduced risk of bias and significantly enhanced the pooled estimates.

Studies that were thought to have a moderate risk of bias usually didn't take into account important confounding factors like the severity of the disease at the start, other health problems, or delays in getting treatment. This limitation might help explain why the reported complication rates and outcomes were so different from each other. The single study deemed high risk of bias had a small sample size and limited outcome reporting, which diminishes the significance of its findings in quantitative synthesis [20].

This review has certain strengths, such as that it focuses on tertiary care populations, follows the PRISMA method, and brings together clinically important outcomes. Nonetheless, it is imperative to recognize specific limitations. The dependence on observational studies restricts causal inference, and the varying presentation of outcomes curtailed the extent of quantitative synthesis. A lot of differences between studies could make pooled estimates less accurate, and it couldn't be accounted for unmeasured confounders.

Future research ought to concentrate on prospective, multicenter studies employing established diagnostic and outcome definitions to facilitate more rigorous comparisons. The creation of approved severity assessment tools and predictive models could enhance the early identification of high-risk patients and facilitate the utilization of resources in tertiary and critical care environments.

CONCLUSION

This systematic review and meta-analysis show that scrub typhus is still a major cause of severe acute febrile illness in patients treated at tertiary healthcare centers in India. The disease is marked by varied clinical manifestations and a considerable burden of organ dysfunction, especially affecting the respiratory, renal, and neurological systems, leading to significant morbidity and mortality. The results show that patients who seek treatment in tertiary healthcare facilities are often a high-risk group with advanced disease who need more intensive supportive care.

Enhancing clinical awareness in endemic areas and implementing standardized diagnostic and management protocols at the tertiary

care level may mitigate disease-related complications and fatalities. To improve the quality of evidence and inform optimal care strategies for severe scrub typhus, additional prospective, multicenter studies with standardized outcome reporting are necessary.

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REFERENCE

- Rapsang AG, Bhattacharyya P (2013) Scrub typhus. *Indian J Anaesth* 57:127–134. <https://doi.org/10.4103/0019-5049.111835>
- Sivarajan S, Shivalli S, Bhuyan D, Mawlong M, Barman R (2016) Clinical and paraclinical profile, and predictors of outcome in 90 cases of scrub typhus, Meghalaya, India. *Infect Dis Poverty* 5:91. <https://doi.org/10.1186/s40249-016-0186-x>
- Peter JV, Sudarsan TI, Prakash JA, Varghese GM (2015) Severe scrub typhus infection: clinical features, diagnostic challenges and management. *World J Crit Care Med* 4:244–250. <https://doi.org/10.5492/wjccm.v4.i3.244>
- Prakash JAJ (2017) Scrub typhus: risks, diagnostic issues, and management challenges. *Res Rep Trop Med* 8:73–83. <https://doi.org/10.2147/RRTM.S105602>
- Park BD, Faubel S (2021) Acute kidney injury and acute respiratory distress syndrome. *Crit Care Clin* 37:835–849. <https://doi.org/10.1016/j.ccc.2021.05.007>
- Sharma N, Biswal M, Kumar A, Zaman K, Jain S, Bhalla A (2016) Scrub typhus in a tertiary care hospital in North India. *Am J Trop Med Hyg* 95:447–451. <https://doi.org/10.4269/ajtmh.16-0086>
- Takhar RP, Bunkar ML, Arya S, Mirdha N, Mohd A (2017) Scrub typhus: a prospective observational study during an outbreak in Rajasthan, India. *Natl Med J India* 30:69–72
- Premraj SS, Mayilananthi K, Krishnan D, Padmanabhan K, Rajasekaran D (2018) Clinical profile and risk factors associated with severe scrub typhus infection among non-ICU patients in semi-urban South India. *J Vector Borne Dis* 55:47–51. <https://doi.org/10.4103/0972-9062.234626>
- Sinha P, Gupta S, Dawra R, Rijhawan P (2014) Recent outbreak of scrub typhus in North Western part of India. *Indian J Med Microbiol* 32:247–250. <https://doi.org/10.4103/0255-0857.136552>
- Kore VB, Mahajan SM (2022) Recent threat of scrub typhus in India: a narrative review. *Cureus* 14:e30092. <https://doi.org/10.7759/cureus.30092>
- Chakraborty S, Sarma N (2017) Scrub typhus: an emerging threat. *Indian J Dermatol* 62:478–485. https://doi.org/10.4103/ijid.IJD_388_17
- Richards AL, Jiang J (2020) Scrub typhus: historic perspective and current status of the worldwide presence of *Orientia* species. *Trop Med Infect Dis* 5:49. <https://doi.org/10.3390/tropicalmed5020049>
- Devasagayam E, Dayanand D, Kundu D, Kamath MS, Kirubakaran R, Varghese GM (2021) The burden of scrub typhus in India: a systematic review. *PLoS Negl Trop Dis* 15:e0009619. <https://doi.org/10.1371/journal.pntd.0009619>
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lala MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. <https://doi.org/10.1136/bmj.n71>
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al (2011) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute, Ottawa
- Varghese GM, Trowbridge P, Janardhanan J et al (2014) Clinical profile and improving mortality trend of scrub typhus in South

- India. *Int J Infect Dis* 23:39–43. <https://doi.org/10.1016/j.ijid.2014.02.009>
- Kamath SD, Kumari S, Sunder A (2022) A study of the profile of scrub typhus in a tertiary care hospital in Jharkhand: an underestimated problem. *Cureus* 14:e26503. <https://doi.org/10.7759/cureus.26503>
- Verma SK, Gupta KK, Arya RK et al (2021) Clinical and biochemical profile of scrub typhus patients at a tertiary care hospital in Northern India. *J Family Med Prim Care* 10:1459–1465. https://doi.org/10.4103/jfmpe.jfmpe_1162_20
- Mandal R, Banerjee SG, Sinha A, Bandyopadhyay U, Sinha A (2023) Study of clinical and biochemical profile of scrub typhus in a tertiary care hospital of West Bengal. *Asian J Med Sci* 14:93–98. <https://doi.org/10.71152/ajms.v14i7.3702>
- Bhowmik KK, Sarkar A, Chakrabarti A, Mukhopadhyay N, Paul A (2024) Clinical and investigative profile of scrub typhus patients at a tertiary care center in Southern West Bengal, India. *Asian J Med Sci* 15:118–125. <https://doi.org/10.3126/ajms.v15i2.58401>
- Mahajan SK, Rolain JM, Kashyap R et al (2006) Scrub typhus in Himalayas. *Emerg Infect Dis* 12:1590–1592. <https://doi.org/10.3201/eid1210.051697>
- Varghese GM, Abraham OC, Mathai D et al (2006) Scrub typhus among hospitalised patients with febrile illness in South India: magnitude and clinical predictors. *J Infect* 52:56–60. <https://doi.org/10.1016/j.jinf.2005.02.001>
- Islam A, Saha R, Roy A (2021) Scrub typhus – a threatening scenario in North Bengal. *J Evid Based Med Healthc* 8:3417–3422
- Ngulani KS, Kakati S, Hussain S, Singh MU, Kaguilan K (2019) Outbreak of scrub typhus in Manipur: experience at a tertiary care hospital. *IOSR J Dent Med Sci* 18:33–38
- Gurung S, Pradhan J, Bhutia PY (2013) Outbreak of scrub typhus in the North East Himalayan region–Sikkim: an emerging threat. *Indian J Med Microbiol* 31:72–74. <https://doi.org/10.4103/0255-0857.108729>
- Sharma PK, Ramakrishnan R, Hutin YJ et al (2009) Scrub typhus in Darjeeling, India: opportunities for simple, practical prevention measures. *Trans R Soc Trop Med Hyg* 103:1153–1158. <https://doi.org/10.1016/j.trstmh.2009.02.006>
- Loomba V, Mani A, John M, Oberoi A (2014) Scrub typhus in Punjab: an acute febrile illness with multisystem involvement. *Trop Doct* 44:152–155. <https://doi.org/10.1177/0049475514522226>
- Esposito P, Cappadona F, Marengo M et al (2024) Recognition patterns of acute kidney injury in hospitalized patients. *Clin Kidney J* 17:sfae231. <https://doi.org/10.1093/ckj/sfae231>
- Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA (2019) Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 96:1083–1099. <https://doi.org/10.1016/j.kint.2019.05.026>
- Alam AM, Gillespie CS, Goodall J et al (2022) Neurological manifestations of scrub typhus infection: a systematic review and meta-analysis of clinical features and case fatality. *PLoS Negl Trop Dis* 16:e0010952. <https://doi.org/10.1371/journal.pntd.0010952>
- Taylor AJ, Paris DH, Newton PN (2015) A systematic review of mortality from untreated scrub typhus (*Orientia tsutsugamushi*). *PLoS Negl Trop Dis* 9:e0003971. <https://doi.org/10.1371/journal.pntd.0003971>
- Joannidis M, Forni LG, Klein SJ et al (2020) Lung–kidney interactions in critically ill patients: consensus report of the ADQI 21 workgroup. *Intensive Care Med* 46:654–672. <https://doi.org/10.1007/s00134-019-05869-7>