

Clinical Heterogeneity of Scrub Typhus: Identification of Distinct Phenotypes via Cluster Analysis

Xiaoyan Du

The Affiliated Guangdong Second Provincial General Hospital of Jinan University

Fangfang Wei

The Sixth Affiliated Hospital, Sun Yat-sen University

Yangjian Pan

The Affiliated Guangdong Second Provincial General Hospital of Jinan University

Zhijun Qin

The Affiliated Guangdong Second Provincial General Hospital of Jinan University

Qian Wang

wangq@gdph.org.cn

Guangdong Academy of Medical Sciences, Southern Medical University

Research Article

Keywords: Scrub Typhus, Clinical phenotypes, Cluster analysis, Heterogeneity, Infectious disease, Atypical presentation

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10893486/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective

Scrub typhus, an acute infectious disease caused by *Orientia tsutsugamushi*, is clinically recognized for its diverse and non-specific symptomatology, which often complicates diagnosis and timely management. While heterogeneity in presentation is commonly observed, it has not been systematically categorized using a data-driven approach. This study aimed to identify distinct clinical phenotypes among scrub typhus patients based on presenting symptoms and signs, and to evaluate their association with prognosis.

Methods

We conducted the first known application of cluster analysis to classify scrub typhus clinical presentations. We conducted a retrospective analysis of 64 patients with confirmed scrub typhus admitted to Guangdong Second Provincial General Hospital between January 2018 and December 2021. An unsupervised hierarchical agglomerative clustering algorithm was employed to group patients based on ten symptom/sign variables. The optimal number of clusters was determined using the elbow method and silhouette coefficient. Comparative analyses (Chi-square/Fisher's exact and Mann-Whitney U tests) were performed to assess differences in demographic and clinical variables between the derived clusters.

Results

Two distinct clinical clusters were identified. Cluster 1 (Typical Polysymptomatic Group, $n = 43$, 67.2%) was characterized by a high prevalence of classic presentations, including sore throat (37.2%), headache (81.4%), and lymphadenopathy (90.7%). In contrast, Cluster 2 (Atypical Severe-Prone Group, $n = 21$, 32.8%) exhibited a paradoxical pattern: despite significantly lower rates of sore throat (0%) and lymphadenopathy (0%), this group showed higher frequencies of dyspnea (38.1%), confusion (14.3%), and high fever (85.7%). Crucially, clinical treatment failure was significantly more common in Cluster 2 (28.6%) compared to Cluster 1 (0%) ($p < 0.001$). Smoking history was more prevalent in Cluster 1 ($p = 0.02$), but this was interpreted as a potential sex-related confounder rather than an independent risk factor. No statistically significant differences were found between clusters for sex, age, comorbidities, or most laboratory parameters.

Conclusions

This study empirically demonstrates that scrub typhus presents as two distinct phenotypes. Clinicians should be alerted that the absence of classic local signs (eschar or lymphadenopathy) does not preclude

severe disease; rather, the atypical cluster carries a higher risk of respiratory distress, neurological involvement, and poor therapeutic response. Cluster analysis provides a valuable framework for early bedside risk stratification, particularly in endemic regions.

Introduction

Scrub typhus, also called tsutsugamushi disease, is an acute natural pathogenic infectious disease caused by the mite-borne obligate intracellular bacterium *Orientia tsutsugamushi* belonging to the family Rickettsiaceae and transmitted by larval forms of *Leptotrombidium* mites called chiggers[1]. The disease is endemic in Southeast Asia, the Pacific Islands, and Northern Australia, named 'tsutsugamushi triangle' [2]. A high disease burden in southern China, especially in Guangdong, Yunnan, and Fujian provinces, with cases reported annually despite the recent COVID-19 pandemic [3].

Scrub typhus is characterized by the formation of eschar or ulcer at the bite site, high fever, rash, lymphadenopathy, hepatosplenomegaly, and a decrease in the number of peripheral blood leukocytes. Clinically, scrub typhus presents a diagnostic challenge due to its non-specific early manifestations, which often mimic viral infections, malaria, or bacterial sepsis [4]. While fever, headache, myalgia, and cough are common, the disease can occasionally be complicated by life-threatening conditions including myocarditis, pneumonia, acute kidney injury (AKI), meningoencephalitis, and multi-organ dysfunction syndrome (MODS), and if not treated in time, the mortality rate can be as high as 45% [5]. However, early diagnosis and timely antibiotic therapy (e.g., doxycycline) significantly reduce complications and mortality[4].

Despite the well-recognized clinical diversity, few studies have systematically classified these heterogeneous presentations. Previous research has primarily focused on laboratory parameters or individual risk factors for severe disease [6, 7], rather than employing a holistic, symptom-driven approach. Cluster analysis, an unsupervised machine learning technique, has been successfully used in other medical fields to identify symptom patterns and refine phenotypic diagnostic criteria[8], but its application to scrub typhus remains scarce[9].

In this study, we innovatively applied cluster analysis to identify subgroups of scrub typhus patients based on their presenting symptom profiles. We further examined whether these derived clusters differed with respect to demographics, comorbidities, and most importantly, clinical prognosis. We aimed to provide clinicians with an intuitive, bedside-available tool for early recognition of potentially severe cases.

Methods

Study Design and Subjects

This was a retrospective observational study conducted at Guangdong Second Provincial General Hospital. We included all patients with a confirmed diagnosis of scrub typhus who were admitted

between January 1, 2018, and December 31, 2021, and who fulfilled the following inclusion criteria, based on established guidelines[10, 11] :

☒Epidemiological history: Travel to an endemic area within three weeks prior to onset, with a history of outdoor activities (such as field work, camping, sitting or sleeping on grass);

☒Clinical manifestations: Fever, eschar/ulcer, rash, superficial lymphadenopathy, or hepatosplenomegaly;

☒Laboratory confirmation: "Technical Guidelines for the Prevention and Control of Tsutsugamushi Disease (Trial)" states that a Weil-Felix agglutination titer $\geq 1:160$ (or specific antibody titer $\geq 1:320$ to *Proteus* OX-K antigen) and/or a positive ELISA for *O. tsutsugamushi*-specific IgM (titer $\geq 1:80$).

A total of 64 patients with complete baseline data were included in the final analysis. After diagnosis, all patients received standard antibiotic therapy (doxycycline) and symptomatic supportive care. This retrospective study was approved by the Institutional Ethics Committee of Guangdong Second Provincial General Hospital (Approval No. : 2024-KY-KZ-418-01, Date: December 26, 2024), and obtained ethical approval with a waiver of informed consent. All data were anonymized prior to analysis.

Data Collection

We extracted the following data from electronic medical records:

- **Demographics:** Sex, age.
- **Clinical symptoms and signs:** Dyspnea, sore throat, abdominal symptoms (nausea/vomiting/diarrhea/pain), headache, rash, eschar/ulcers, altered consciousness, lymphadenopathy, high fever (defined as body temperature $\geq 39^{\circ}\text{C}$), and cough.
- **Comorbidities and lifestyle:** Hypertension, diabetes, smoking history, and alcohol consumption (defined as active use within the past year).
- **Laboratory tests:** White blood cell count (WBC), hemoglobin (HGB), red blood cell count (RBC), platelet count (PLT), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), uric acid (UA), creatinine (CREA), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), glucose (Glu), triglycerides (TG), and total cholesterol (CHO).
- **Clinical outcomes:** Complications (pneumonia, liver injury, kidney injury, myocardial injury) and clinical efficacy (effective vs. ineffective, based on fever resolution and symptom improvement within 72 hours of doxycycline treatment).

Selection of Variables for Cluster Analysis

Ten clinically relevant dichotomous variables representing the most common symptoms and signs in scrub typhus were selected for clustering: dyspnea, sore throat, abdominal symptoms, headache, rash, eschar/ulcers, altered consciousness, lymphadenopathy, high fever, and cough.

Statistical Analysis

Considering the exploratory nature of this study and the limited sample size ($n = 64$), which could cause instability in parametric latent class models, we adopted a hierarchical agglomerative clustering approach. This distance-based algorithm does not assume a specific data distribution and is more tolerant to small sample sizes in exploratory contexts.

Specifically, we standardized the ten binary symptom variables and calculated the similarity between patients using the Euclidean distance. Clusters were aggregated using Ward's linkage method (minimum variance criterion). The optimal number of clusters was determined by comprehensively evaluating the elbow method (plotting the within-cluster sum of squares) and the silhouette coefficient, combined with clinical interpretability.

After cluster assignment, to compare differences in demographic characteristics, laboratory parameters, and clinical outcomes between the two groups. Categorical variables were compared using the Chi-square test or Fisher's exact test (when any expected cell count was < 5). Continuous variables (presented as mean $\pm$ SD) were compared using the Mann-Whitney U test due to the non-normal distribution of most laboratory parameters.

All tests were two-sided, and a p -value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria) with the *factoextra* package for clustering visualization. As this was an exploratory cluster analysis rather than a confirmatory causal inference study, no multivariable adjustment for confounders was performed in the primary analysis.

Results

Baseline characteristics of the total cohort

A total of 64 patients were enrolled in the study. Baseline demographic and clinical characteristics of the participants are presented in Table 1. The mean age was 53.25 ± 13.56 years, and males accounted for 50% of the study population, indicating balanced sex distribution. Eschar or ulcers were identified in 93.8% (60/64) of patients, confirming the high diagnostic suspicion in this cohort.

Table 1. Demographic and clinical characteristics of the total cohort and by clusters

Variables	Total cohort (n=64)	Cluster 1 (n=43)	Cluster 2 (n=21)	p-value
Subjects n(%)	64(100)	43(67.2)	21(32.8)	
Males n (%)	32 (50.0)	24 (55.8)	8 (38.1)	0.14
Age (years, mean±SD)	53.25±13.56	52.65±13.49	54.48±13.95	0.62
Comorbidities				
hypertension	5	2	3	0.20
diabetes	3	2	1	0.70
smoking	14	13 (92.9%)	1 (7.1%)	0.02
Alcohol consumption	7	5	2	0.58
Laboratory tests				
WBC(×10 ⁹ /L)	7.82±3.60	8.19±3.47	7.06±3.83	0.26
HGB(g/L)	125.89±18.02	127.21±18.52	123.19±17.08	0.40
RBC(×10 ¹² /L)	4.33±0.64	4.39±0.64	4.22±0.63	0.33
PLT(×10 ⁹ /L)	128.66±71.10	128.35±59.91	129.29±91.56	0.96
ALB(g/L)	32.27±6.09	31.38±5.60	34.05±6.77	0.10
ALT(U/L)	102.94±72.51	105.67±74.77	97.33±69.07	0.67
AST(U/L)	108.27±89.33	110.07±93.02	104.57±83.34	0.82
GGT(U/L)	109.50±160.0	119.37±185.87	87.16±73.36	0.47
UA(μmol/L)	262.89±100.13	257.40±94.21	273.86±112.69	0.54
CREA(μmol/L)	98.52±74.87	97.33±61.92	100.95±97.95	0.86
CK(U/L)	297.92±775.30	207.90±221.69	482.45±1319.62	0.37
CK-MB(U/L)	11.12±13.86	9.56±7.75	14.31±21.54	0.35
Glu(mmol/L)	6.39±2.44	5.97±1.76	7.28±3.38	0.05
TG(mmol/L)	2.26±1.32	2.13±1.05	2.54±1.78	0.29
CHO(mmol/L)	3.45±0.96	3.33±0.96	3.73±0.92	0.15

Abbreviations: WBC, white blood cell; HGB, hemoglobin; RBC, red blood cell; PLT, platelet; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase;

GGT, gamma-glutamyl transferase; UA, uric acid; CREA, creatinine; CK, creatine kinase; CK-MB, creatine kinase isoenzyme; Glu, glucose; TG, triglycerides; CHO, total cholesterol. Data are presented as mean $\pm$ SD unless otherwise stated.

Identification of two distinct clusters

The hierarchical clustering algorithm, validated by the elbow method and silhouette coefficient, consistently supported a two-cluster solution.

Cluster 1 (Typical Polysymptomatic Group, n=43, 67.2%): This group exhibited a higher probability of presenting with "classic" scrub typhus symptoms, including sore throat (37.2%), headache (81.4%), and superficial lymphadenopathy (90.7%).

Cluster 2 (Atypical Severe-Prone Group, n=21, 32.8%): Paradoxically, this group was characterized by an absence of localizing signs (sore throat 0%, lymphadenopathy 0%) but exhibited higher frequencies of systemic and severe manifestations, including dyspnea (38.1%), altered consciousness (14.3%), and high fever (85.7%).

Table 2 presents the prevalence of all 10 symptoms across the two clusters, and Figure 1 visualizes the contrasting probability profiles.

Table 2. Symptoms and signs in the total cohort and by clusters

Variables	Total cohort (n=64)	Cluster 1 (n=43)	Cluster 2 (n=21)	p-value
Dyspnea	16 (25.0%)	8 (18.6%)	8 (38.1%)	0.13
Sore throat	16 (25.0%)	16 (37.2%)	0 (0%)	0.001
Abdominal symptoms	17 (26.6%)	12 (27.9%)	5 (23.8%)	0.77
Headache	40 (62.5%)	35 (81.4%)	5 (23.8%)	<0.001
Altered consciousness	5 (7.8%)	2 (4.7%)	3 (14.3%)	0.32
Cough	17 (26.6%)	13 (30.2%)	4 (19.0%)	0.39
High fever	46 (71.9%)	28 (65.1%)	18 (85.7%)	0.14
Rash	13 (20.3%)	11 (25.6%)	2 (9.5%)	0.19
Lymphadenopathy	39 (60.9%)	39 (90.7%)	0 (0%)	<0.001
Eschar/ulcers	60 (93.8%)	42 (97.7%)	18 (85.7%)	0.10

Differences in demographics and clinical outcomes

As shown in Table 1, there were no statistically significant differences between the two clusters regarding age, sex, underlying comorbidities, alcohol consumption, or routine laboratory parameters.

Smoking history was significantly more prevalent in Cluster 1 (13/14 smokers, 92.9%) compared to Cluster 2 (1/14 smokers, 7.1%; $p=0.02$). However, given the male predominance in Cluster 1 and the lack of difference in pneumonia rates between the groups, we interpret this as a potential sex-related behavioral confounder rather than an independent clinical predictor.

Clinical prognosis is detailed in Table 3. Most importantly, clinical efficacy differed significantly between the clusters ($p<0.001$). All patients (100%) in Cluster 1 responded well to doxycycline treatment, whereas the treatment failure rate in Cluster 2 was 28.6% (6/21 patients). Although complications such as liver injury were common in both groups, no statistically significant differences were observed in the rates of pneumonia, liver injury, kidney injury, or myocardial injury between the two clusters.

Table 3. Clinical prognosis by clusters

Variables	Cluster 1 (n=43)	Cluster 2 (n=21)	p-value
Clinical efficacy (Effective)	43 (100%)	15 (71.4%)	<0.001
Pneumonia	25 (58.1%)	10 (47.6%)	0.59
Liver injury	36 (83.7%)	16 (76.2%)	0.51
Kidney injury	3 (7.0%)	1 (4.8%)	1.00
Myocardial injury	10 (23.3%)	9 (42.9%)	0.15

Discussion

Scrub typhus is a vector-borne zoonotic infection and is one of the commonest rickettsial infections worldwide. Over one million new infections are detected annually, and an estimated one billion people globally are at risk[5]. Up to now, however, there is still no reliable and effective human vaccine against tsutsugamushi disease, which will pose a significant threat to public health[9]. Without appropriate treatment, the case fatality rate varies from 30% to 45%[5]. With early diagnosis and treatment, these complications and mortality rates can be considerably reduced[12].

As a novel approach with the potential to refine phenotypic diagnostic criteria, cluster analysis has been used in other medical conditions to identify symptom patterns and clinical phenotypes[8]. A recent study using cluster analysis identified to analyze the incidence of scrub typhus in Yunnan, sixteen municipalities infected were classified into three groups numbered in sequence[9]. In a systematic review of the burden of scrub typhus in India by Devasagayam et al., some of the common presenting symptoms of confirmed cases in the descending order were fever (34.7%), eschar (22.1%), headache (18.2%), nausea/vomiting (17.1%), abdominal pain (10.5%), breathlessness (10.4%), and cough (10.4%) [13]. Thus, we including dyspnea, sore throat, abdominal symptoms, headache, rash, eschar or ulcers, altered consciousness, lymph node enlargement, high fever, cough in the cluster analysis.

To the best of our knowledge, this is the first study to apply cluster analysis to systematically categorize the clinical heterogeneity of scrub typhus. Our data-driven approach successfully identified two distinct phenotypic subgroups, revealing a critical clinical paradox: patients with absent typical local signs (sore throat and lymphadenopathy) may paradoxically face a higher risk of severe systemic complications and treatment failure. This finding has immediate implications for clinical practice, especially in endemic regions.

The most noteworthy and clinically meaningful finding of the present study is the characterization of Cluster 2 (Atypical Severe-Prone Group). It might be intuitively presumed that patients presenting with fewer symptoms experience a milder clinical course. However, our data challenge this conventional assumption. Although Cluster 2 patients exhibited zero incidence of sore throat and lymphadenopathy—classic diagnostic hallmarks of scrub typhus for clinical recognition—they experienced significantly higher rates of dyspnea (38.1%) and altered consciousness (14.3%) compared to Cluster 1. More importantly, the treatment failure rate in this atypical group was alarmingly high at 28.6%, while the polysymptomatic Cluster 1 had a 100% response rate to doxycycline.

This paradoxical presentation likely accounts for the frequent missed or delayed diagnosis of scrub typhus. Clinicians typically rely on the classic triad of ‘fever, eschar, and lymphadenopathy’ to raise early clinical suspicion [10]. However, Cluster 2 patients lack the latter two components, making them easily misdiagnosed as viral pneumonia, primary encephalitis, or undifferentiated sepsis, thereby delaying the administration of life-saving doxycycline[12, 14]. Our findings provide strong evidence that in endemic areas, the absence of eschar or lymphadenopathy should not reassure clinicians that the disease will follow a mild clinical course. Instead, any acute febrile illness accompanied by unexplained respiratory distress or neurological symptoms should promptly raise the index of suspicion for scrub typhus, and empirical anti-rickettsial therapy should be strongly considered, as delays drastically increase mortality [5].

Regarding the significant association between smoking history and Cluster 1 ($p=0.02$), this finding should be interpreted with caution. While statistically significant, the small number of smokers ($n=14$) and the higher proportion of males in Cluster 1 (55.8% vs. 38.1%) suggest that this association is likely confounded by gender-related lifestyle factors rather than representing an independent protective or risk

factor for a specific phenotype. This inference is supported by the absence of any clinically meaningful difference in pneumonia incidence between the two clusters (58.1% vs. 47.6%, $p=0.59$), which would be expected if smoking primarily drove pulmonary involvement. This aligns with a previous study by Kim et al. which found that smoking was not an independent risk factor for acute ischemic stroke in scrub typhus patients [15].

Numerous studies have described the clinical symptoms of scrub typhus[4, 14], however, few studies have explored the prognostic value of clinical manifestations. Our study builds upon and extends previous clinical observations. While prior investigations have identified age-specific predictors (e.g., dyspnea and bilirubin in the elderly)[16] and routine laboratory markers, such as blood platelets[6, 7], our approach offers a holistic, multivariate, "bedside" perspective. The symptom clusters we identified do not necessarily replace laboratory risk stratification but rather complement it, providing immediate risk cues at the point of first patient contact, even before blood test results are available. The high prevalence of eschar in our cohort (over 90%) is notable and higher than in some other reports (ranging from 9.5% to 55%) [13, 17]. This likely reflects a selection bias at our center, where clinicians have high awareness and actively search for eschars in concealed areas, leading to earlier diagnosis and hospitalization. It also underscores the fact that while eschar is pathognomonic, its absence is diagnostically silent but prognostically treacherous.

The excellent response to doxycycline in Cluster 1 reinforces the standard treatment protocol. However, the poor response in Cluster 2 suggests that delayed diagnosis leading to more advanced tissue injury at treatment initiation, rather than antibiotic resistance, is the likely culprit. This highlights that therapeutic efficacy in scrub typhus is time-dependent [12].

Our research findings hold clinical significance in two key aspects. Firstly, they indicate that scrub typhus is prevalent in Guangdong and should be considered in the differential diagnosis of patients presenting with acute febrile illnesses accompanied by dyspnea and confusion. When examining such patients, conducting a thorough search for an eschar, particularly in hidden areas, is crucial as it can be a diagnostic indicator. However, it is important to note that the absence of an eschar does not rule out scrub typhus, so clinicians should not exclude this diagnosis solely based on the lack of an eschar. Secondly, our findings highlight the need for clinicians in endemic areas to develop a greater awareness of scrub typhus. This awareness is essential for the early detection of the disease and the prevention of complications. If there is a high index of suspicion, empirical therapy with doxycycline should be initiated promptly as it may prove to be lifesaving.

Limitations

This study has several limitations. First, the relatively small sample size ($n=64$) and single-center design restrict the generalizability of the results and the stability of the clustering solution. As an exploratory pilot study, our results require independent validation in larger, multi-center cohorts. Second, the retrospective design inherently carries potential information bias, as symptoms were extracted from clinical records rather than standardized prospective questionnaires. Third, we did not perform genotypic

analysis of *O. tsutsugamushi* strains, which may influence clinical presentation and severity[1]. Fourth, due to limited events, we could not perform multivariable logistic regression to assess the independent prognostic value of the clusters, and we refrained from such analysis to avoid overfitting. Fifth, the smoking analysis is limited by small event numbers and potential confounding, as discussed.

Conclusions

In conclusion, this study empirically validates the clinical heterogeneity of scrub typhus through the identification of two distinct phenotypic clusters. The "Atypical Severe-Prone" cluster, despite lacking classic local signs, presents a higher risk of respiratory and neurological complications and poorer treatment response. We propose that clinicians in endemic zones maintain a high index of suspicion for scrub typhus based on systemic symptom constellations alone, rather than waiting for the classic triad. Future large-scale prospective studies are warranted to validate these subtypes, explore underlying genetic differences[18], and assess potential differences in optimal therapeutic strategies tailored to these distinct clinical phenotypes.

Abbreviations

AKI	
Acute kidney injury	
ALB	
Albumin	
ALT	
Alanine aminotransferase	
AST	
Aspartate aminotransferase	
CHO	
Total cholesterol	
CK	
Creatine kinase	
CK-MB	
Creatine kinase isoenzyme	
CREA	
Creatinine	
ELISA	
Enzyme-linked immunosorbent assay	
GGT	
Gamma-glutamyl transferase	
Glu	
Glucose	
HGB	

Hemoglobin
MODS
Multi-organ dysfunction syndrome
PLT
Platelet
RBC
Red blood cell
TG
Triglycerides
UA
Uric acid
WBC
White blood cell

Declarations

Conflict of Interests

The authors declare no competing interests.

Ethical Approval Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the Guangdong Second Provincial General Hospital (Approval No.: 2024-KY-KZ-418-01, Date:December 26,2024).

All personal identifiers were removed to ensure confidentiality.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to institutional privacy policies but are available from the corresponding author on reasonable request.

Authors' Contribution

Qian Wang conceived and designed the study. Xiaoyan Du, Fangfang Wei, Yangjian Pan, Zhijun Qin and Qian Wang collected data and analyzed the data. Qian Wang, Fangfang Wei and Xiaoyan Du wrote the paper. All authors reviewed and approved the final version. Xiaoyan Du and Fangfang Wei contributed equally to this study.

Funding Source

This work was supported by the National Natural Science Foundation of China (NNSF) (No. 72374085 to Qian Wang).

Acknowledgements

Not applicable.

References

1. Kamath SD, Kumari S, Sunder A. A Study of the Profile of Scrub Typhus in a Tertiary Care Hospital in Jharkhand: An Underestimated Problem. *Cureus*. 2022;14:e26503. <https://doi.org/10.7759/cureus.26503>.
2. Varghese GM, Janardhanan J, Trowbridge P, Peter JV, Prakash JAJ, Sathyendra S, et al. Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome. *Int J Infect Dis*. 2013;17:e981–987. <https://doi.org/10.1016/j.ijid.2013.05.017>.
3. Yue Y, Ren D, Liu X, Wang Y, Liu Q, Li G. Spatio-temporal patterns of scrub typhus in mainland China, 2006–2017. *PLoS Negl Trop Dis*. 2019;13:e0007916. <https://doi.org/10.1371/journal.pntd.0007916>.
4. Le Van N, Pham Van C, Nguyen Dang M, Dao Van T, Le T, Do Q, Vu Hoang H, et al. Clinical Features, Laboratory Characteristics and Prognostic Factors of Severity in Patients with Rickettsiaceae at Two Military Hospitals, Northern Vietnam. *Infect Drug Resist*. 2020;13:2129–38. <https://doi.org/10.2147/IDR.S253540>.
5. Chrispal A, Boorugu H, Gopinath KG, Prakash JAJ, Chandy S, Abraham OC, et al. Scrub typhus: an unrecognized threat in South India – clinical profile and predictors of mortality. *Trop Doct*. 2010;40:129–33. <https://doi.org/10.1258/td.2010.090452>.
6. Chen H, Ning Z, Qiu Y, Liao Y, Chang H, Ai Y, et al. Elevated levels of von Willebrand factor and high mobility group box 1 (HMGB1) are associated with disease severity and clinical outcome of scrub typhus. *Int J Infect Dis*. 2017;61:114–20. <https://doi.org/10.1016/j.ijid.2017.06.015>.
7. He S, Ge L, Jin Y, Huang A. [Clinical analysis of scrub typhus-associated hemophagocytic syndrome]. *Zhonghua Er Ke Za Zhi*. 2014;52:683–7.
8. Miaskowski C, Aouizerat BE, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. *J Natl Cancer Inst Monogr*. 2007;39–46. <https://doi.org/10.1093/jncimonographs/lgm003>.
9. Peng P-Y, Xu L, Wang G-X, He W-Y, Yan T-L, Guo X-G. Epidemiological characteristics and spatiotemporal patterns of scrub typhus in Yunnan Province from 2006 to 2017. *Sci Rep*. 2022;12:2985. <https://doi.org/10.1038/s41598-022-07082-x>.
10. Lim H-K, Wang J-MS, Typhus. Seven-Year Experience and Literature Review. *J Acute Med*. 2018;8:99–108. [https://doi.org/10.6705/j.jacme.201809_8\(3\).0003](https://doi.org/10.6705/j.jacme.201809_8(3).0003).

11. Kannan K, John R, Kundu D, Dayanand D, Abhilash KPP, Mathuram AJ, et al. Performance of molecular and serologic tests for the diagnosis of scrub typhus. *PLoS Negl Trop Dis*. 2020;14:e0008747. <https://doi.org/10.1371/journal.pntd.0008747>.
12. Mokta J, Ranjan A, Mokta K. Early Clinical Suspicion and Early Use of Doxycycline Reduces Scrub Typhus Associated Complications. *J Assoc Physicians India*. 2019;67:26–7.
13. Devasagayam E, Dayanand D, Kundu D, Kamath MS, Kirubakaran R, Varghese GM. The burden of scrub typhus in India: A systematic review. *PLoS Negl Trop Dis*. 2021;15:e0009619. <https://doi.org/10.1371/journal.pntd.0009619>.
14. Guan X-G, Wei Y-H, Jiang B-G, Zhou S-X, Zhang A-R, Lu Q-B, et al. Clinical characteristics and risk factors for severe scrub typhus in pediatric and elderly patients. *PLoS Negl Trop Dis*. 2022;16:e0010357. <https://doi.org/10.1371/journal.pntd.0010357>.
15. Kim D, Cho YH, Bong JB, Kim YS, Shin B-S, Kang HG. Acute ischemic stroke in Tsutsugamushi: understanding the underlying mechanisms and risk factors. *BMC Neurol*. 2024;24:42. <https://doi.org/10.1186/s12883-024-03534-1>.
16. He J, Ma Q, Teng Z, Zhou J, Zhao N, Liang W, et al. Epidemiological and clinical characteristics of scrub typhus in Guizhou Province, China: An outbreak study of scrub typhus. *PLoS Negl Trop Dis*. 2024;18:e0011963. <https://doi.org/10.1371/journal.pntd.0011963>.
17. Kim D-M, Kim SW, Choi S-H, Yun NR. Clinical and laboratory findings associated with severe scrub typhus. *BMC Infect Dis*. 2010;10:108. <https://doi.org/10.1186/1471-2334-10-108>.
18. Geissen E-M, Hasenauer J, Radde NE. Inference of finite mixture models and the effect of binning. *Stat Appl Genet Mol Biol*. 2019;18. <https://doi.org/10.1515/sagmb-2018-0035>.

Figures

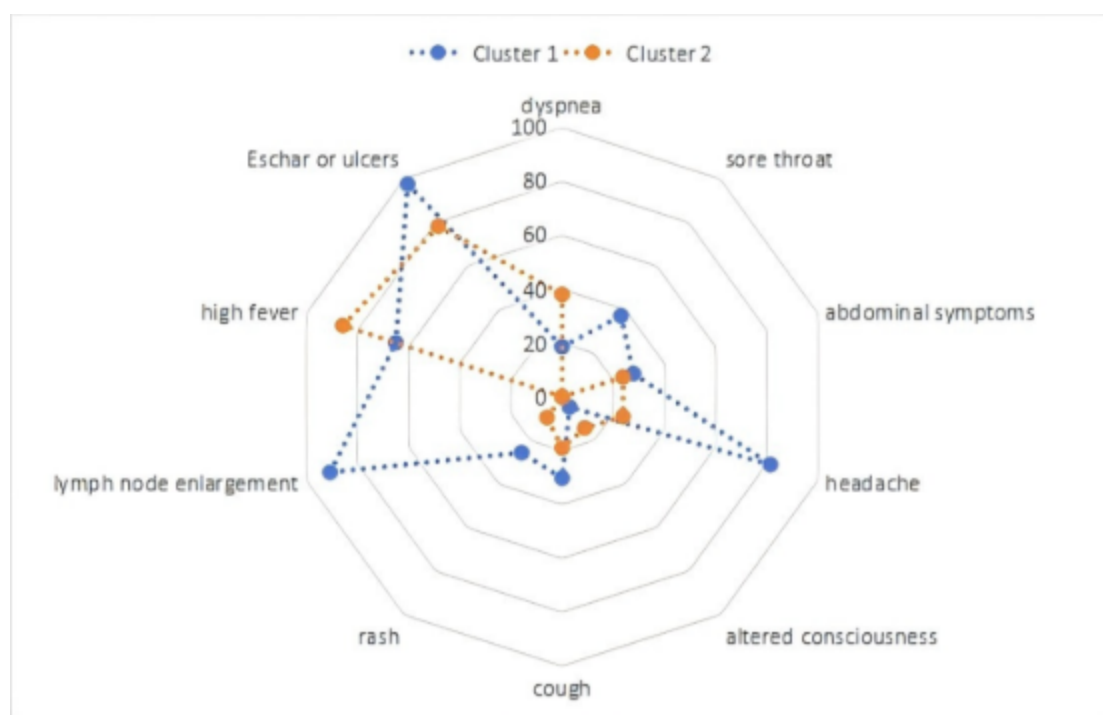


Figure 1

Probability of having each symptom within Cluster 1 and Cluster 2

