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Costs & outcomes of hospitalized scrub typhus infection in a tertiary hospital in south India

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***Background & objectives*: Scrub typhus is a rickettsial infection seen along the Asian-Pacific rim and imposes a considerable burden on affected people in low- and middle-income countries. The present study was aimed to determine the direct cost of hospitalization of scrub typhus and its trend over six years.**

***Methods*: This was a retrospective, observational, hospital based study of individuals admitted to the hospital, diagnosed with scrub typhus over six years, from January 2013 to December 2018. The potential out of pocket expenditure was evaluated.**

***Results*: A total of 198 patients were included in the study. The median cost of admission (adjusted to INR 2020) for the six years (2013 to 2018) was found to be ₹ 37,026 (US $ 490) [interquartile range (IQR) 22,996-64,992]. The median cost for patients admitted to the intensive care unit (ICU) was ₹ 128,046 (US $ 1695) (IQR 71,575-201,171), while the cost for patients admitted to the ward-alone was ₹ 33,232 (US $ 440) (IQR 19,609-45,373). The multivariable analysis showed that ARDS and SOFA score were the independent predictors of ICU admission.**

***Interpretation & conclusions*: Hospitalisation for scrub typhus is associated with a substantial healthcare expense. The predictors of increased cost were the presence of acute respiratory distress syndrome (ARDS), shock, increasing sequential organ failure assessment (SOFA) score and duration of hospital stay.**

Key words Cost of illness - economic burden - India - outcomes - rickettsial infections - scrub typhus

Scrub typhus is a rickettsial infection caused by *Orientia tsutsugamushi* and is transmitted by the bite of trombiculid mite larva. This disease is seen primarily along the Asian-Pacific rim (the *tsutsugamushi* triangle) and is endemic in India, Pakistan, Japan, Taiwan, China, Korea, Malaysia, Thailand and northern Australia[1]. In India, depending on the region, the chance of scrub typhus being a cause for acute undifferentiated febrile illness ranges from 19 to 36 per cent during monsoon and cooler months of the year, between September and January[1].

[#]Equal contribution

This disease is more common in low- and middle-income countries and among daily-wage manual labourers such as farmers who have higher exposure to vegetation where the mite resides[1,2]. In India, about 55 per cent of households access the private sector for healthcare, where financing is predominantly out-of-pocket (OOP) by the citizens, constituting up to 63 per cent of the national health expenditure[3,4]. Hence, estimating the economic burden of common diseases is crucial, and to the best of our knowledge, this has not been assessed before. The rationale for this study was to ascertain the direct medical cost of scrub typhus admission to provide informed estimates for patients, hospitals and policy-makers.

The primary objective of this study was to determine the direct medical cost of hospitalization of patients affected by scrub typhus and to determine trends over six years. The secondary objectives were to describe the clinical profile, calculate the case fatality rate (CFR), determine the proportion of patients who required intensive care unit (ICU) support (in our setting) and identify the predictors of ICU care. We also wanted to ascertain the cost difference for patients admitted to the ICU and to the ward-alone.

Material & Methods

Setting: This study was conducted in the department of General Medicine, Christian Medical College and Hospital, Vellore, a 2282-bed tertiary care, referral, teaching institute in south India. It is a charitable hospital where patients are admitted in general and private wards, which have different costs for care. The general ward has common shared spaces, is cheaper and is mainly utilized by patients from the lower economic strata. However, the quality of care is same in both. For general patients, concession on the final bill is made on a case-by-case basis, after reviewing the family's socioeconomic background and paying capacity. A patient with febrile illness can enter the hospital system through the emergency department (ED) or the outpatient department (OPD). If admission is required, they are transferred to the department of general medicine and shifted to the ward. If the condition is severe, the patient can be moved from the ward or directly from ED to the intensive care unit (ICU), where physicians and intensivists jointly manage the patient.

Study design: This was a retrospective, observational study of patients admitted to the hospital with a diagnosis of scrub typhus and represents the potential OOP expenditure from a patient family perspective. The study was approved by the Institutional Review Board (IRB No. 11897, February 2019) before its commencement. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and standard guidelines for reporting cost-of-illness studies[5-7].

Participants: All patients admitted to the medicine unit with a diagnosis of scrub typhus during the study period were included. Patients with other diagnoses were excluded. In our centre, the cost of care is higher for patients admitted to private wards and those covered by insurance. Hence, such patients were excluded from the study. Data were retrieved from the electronic medical database.

Variables: Patient information such as age, sex, state of residence, the month of admission, symptoms at presentation, site of eschar, organ system involvement at presentation, comorbidities, duration of ward and ICU stay, complications and outcome of admission were recorded. Sequential organ failure assessment (SOFA) score was calculated from laboratory data at the time of admission. The final bill reflecting the direct medical cost for each patient was retrieved from the hospital database. The costs were categorized from individual patient records as investigations, treatment, professional care and bed charges. All drugs were purchased from within the hospital. The cost of food was not included in the bill. The concession on the final bill, if given, was also accessed from the electronic medical database.

Statistical analysis: Data were analysed using STATA version 16.0 (StataCorp. 2019. College Station, Texas, USA) and R software (version 4.0.0, *https://www.R-project.org*). The normality of data was evaluated using the Kolmogorov Smirnov test and continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were presented as number and proportions. Multivariable penalized logistic regression analyses were used to identify independent risk factors associated with ICU admission due to the presence of sparse data[8]. Variables, age and SOFA score were considered continuous predictors in the model. Linearity of logits was ascertained using the Box–Tidwell procedure[9].

The determinants of the total cost of admission were evaluated using multivariable linear regression analysis in which, only variables with a significance level of <0.2 in the univariate analysis were included. To account for the skewed distribution of the total cost of admission, a natural log transformation was applied to the outcome variable. The regression estimates were then transformed back using the formula $100(e^{\beta}-1)$, allowing us to present the percentage increase in the average value of the total cost for each unit increase in the predictors[10]. Kruskal-Wallis test was used to compare the total cost among the years. All tests were two-tailed, and $P<0.05$ was considered significant.

Adjustment for inflation was made using the World Bank consumer price index for the corresponding year. All costs are presented in 2020 US $ using the average exchange rate of US $ 1 = INR (₹) 75.53[11]. The State-level incidence data and the cost of illness from this study was used to project the potential economic burden of the disease for Tamil Nadu.

Results

The total number of patients admitted from 2013 to 2018 was 8587 (Fig. 1). The number of patients with scrub typhus included in the study from these years was 73, 20, 17, 42, 32 and 14, respectively, giving a total of 198. The mean age of the participants was 48 yr ±15.9, and 64.1 per cent (n=127) were women (Supplementary Table I). The maximum number of cases were from Tamil Nadu (n=131; 66.2%), followed by Andhra Pradesh (n=63; 31.8%). The cases were clustered around August to January (Fig. 2). Almost all the patients (98%) were admitted to the ED and the rest attended the OPD.

The enzyme-linked immunosorbent assay (ELISA) test for scrub typhus was positive in 97.5 per cent of participants and 61.6 per cent had an eschar (Supplementary Table II). The eschar was most commonly identified in the inguinal region, axilla and abdomen; however, it was observed in obscure sites in a small number of cases (Supplementary Table II). Among the participants in the study, 21.2 per cent were diabetic, 14.1 per cent were hypertensive and five per cent had other chronic diseases.

The mean duration of fever before admission was 8.8±4.1 days (Supplementary Table III). The most common presenting symptoms, apart from fever, were dyspnoea, vomiting, headache, abdominal pain and altered mental state. The respiratory system was the organ system most commonly involved, and ARDS was seen in more than half of the participants. The mean SOFA score was 5.5± 2.8. ICU care was required for 18.7 per cent of the patients. The mean duration of hospital stay for patients admitted to the ward-only was 5.6±2.4 days, while those admitted to the ICU spent 6.3 ± 5.6 days in the ICU and 9.5±5.9 days in the ward. The CFR in this population was three per cent. Five patients (2.5%) developed ventilator-associated pneumonia, and there was one complication each of ICU psychosis, healthcare-associated pneumonia, catheter-associated urinary tract infection, central line-associated bloodstream infection and critical illness polyneuropathy. The multivariable analysis showed that ARDS and increasing SOFA score were the independent predictors of ICU admission (Table I; Supplementary Figs 1 and 2).

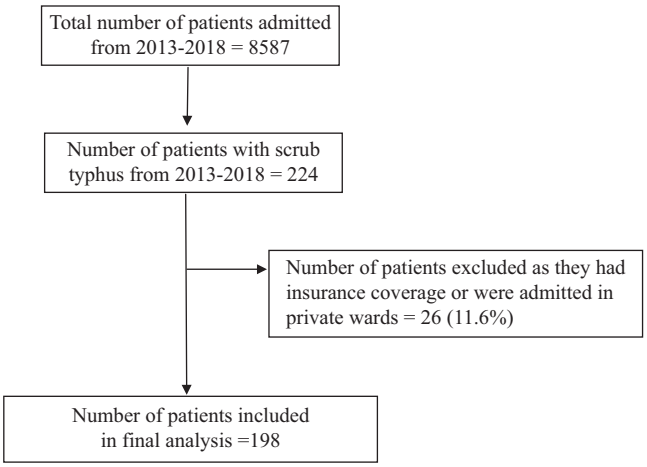

Fig. 1. STROBE diagram.

The median cost of admission across the six years was ₹ 37,026 (US $ 490) (IQR 22,996-64,992) (Table II). The median cost for ICU-admitted patients was ₹ 128,046 (US $ 1695) (IQR 71,575-201,171), and for patients admitted to ward-only, it was ₹ 33,232 (US $ 440) (IQR 19,609-45,373). Since the costs were right-skewed, we report the median costs in Table II. Here, the main cost of care is attributed to treatment costs (and investigations) for ICU patients and bed charge and professional care fees for the ward-only patients. The year-wise median costs are given in Table III. After adjusting for inflation, there was a significant difference in median cost across the years, with the highest median cost being noted for the year 2017. One third of all the patients admitted (32.8%) received a concession on their bill amount. The average concession ratio (concession amount/total bill amount)

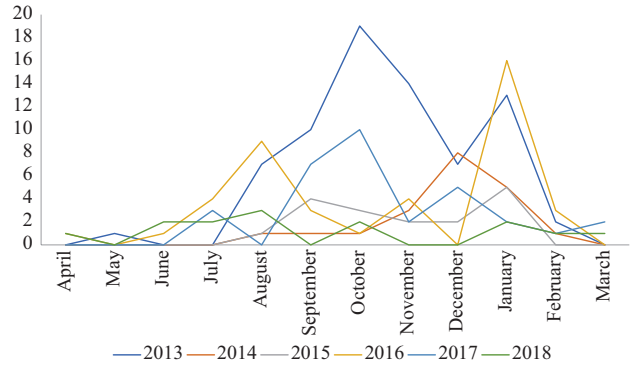

Fig. 2. Monthly distribution of cases of scrub typhus.

Table I. Multivariable regression analysis (penalised logistic regression) results for intensive care unit requirement

Variables	Multivariable analysis		
	Odds ratio	95 per cent CI	*P*
Dyspnoea			
No	Reference		
Yes	1.24	0.51-3.03	0.639
Decreased alertness			
No	Reference		
Yes	1.72	0.51-5.8	0.384
ARDS			
No	Reference		
Yes	41.92	2.43-722.08	0.01
Shock			
No	Reference		
Yes	1.2	0.39-3.72	0.756
Age	1.01	0.98-1.04	0.444
SOFA score	1.34	1.11-1.61	0.002

SOFA, sequential organ failure assessment; CI, confidence interval; ARDS, acute respiratory distress syndrome

was 27.4 per cent among those who received concession. The predictors of increased cost were the presence of ARDS, shock, increasing SOFA score and the duration of hospital stay (Table IV; Supplementary Fig. 3). Concession costs were not included in the analysis.

Discussion

Scrub typhus is a disease that is common in developing countries where OOP healthcare payments are high. Since low-income, daily-wage earning manual labourers are the most susceptible population, a severe illness can result in catastrophic health expenditure for the household[12]. In several parts of the world, scrub typhus is seen as a neglected or resurgent disease, and hence, the economic impact has not been systematically assessed. In India, scrub typhus has been reported predominantly in the central and southern regions with a seasonal clustering during monsoon and winter months of September to January, which was reflected in our study[13]. It is a common cause of undifferentiated fever with a seroprevalence of 15-60.2 per cent, depending on the region[14]. The seroprevalence of scrub typhus in the area where our centre is located was 31.8 per cent, according to a study published in 2017[15].

Being an acute febrile illness, all the patients in our study were from the neighbouring region, and 98 per cent were admitted through the ED. There were more women in our study than others, which could be due to 'mite islands' and the fact that women perform household chores, laundry and farm work around scrub vegetation in rural India[14].

At presentation, all patients had fever, 43 per cent had dyspnoea, 22 per cent had vomiting, 15 per cent had headache and 11 per cent had abdominal pain. An eschar was noted in 61.6 per cent of the participants. The clinical profile of scrub typhus can be varied, with odd neurological, acute abdominal presentations or severe sepsis, among others[14]. The rate of detecting an eschar is variable and requires a thorough physical examination because, in 55 per cent of patients, the eschar can be beneath the regular clothing or at concealed sites[16]. However, the absence of an eschar does not rule out the disease, and commercially available immunochromatographic tests have a pooled sensitivity and specificity of 66 and 92 per cent, respectively[17]. In our study, the ELISA was positive in 97.5 per cent of the cases. Currently, the management of scrub typhus is using azithromycin or doxycycline, with appropriate supportive care[18]. There is a role for broad-spectrum antibiotics if the patient is in a multiorgan dysfunction state, and the aetiology is undetermined at presentation[19]. The disease has an excellent response to early, appropriate antibiotic treatment and CFRs vary from 0 to 70 per cent in countries with a median CFR of six per cent[1]. The predictors of mortality have been ARDS, acute kidney injury, age being above 65 yr, hyperbilirubinaemia, duration of fever, higher APACHE-II score, metabolic acidosis, altered sensorium and shock[20-23]. As noted in the multivariable analysis, SOFA score and ARDS were factors associated with the requirement of ICU admission for treatment. Delay in the diagnosis

Table II. Cost of admission and their components

Category	Currency	Median (IQR)		
		Overall	Patients who required ICU care	Patients with only ward care
Total bill	INR (₹)	37,026 (22,996-64,992)	128,046 (71,575-201,171)	33,232 (19,609-45,373)
	US$	490 (304-860)	1695 (948-2663)	440 (260-601)
Tests	₹	11,872 (6516-20,700)	22,138 (19,103-34,502)	10,097 (5660-16,474)
	US $	157 (86-274)	293 (253-457)	134 (75-218)
Treatment	₹	10,899 (4584-24,107)	53,402 (32,100-85,040)	9021 (3990-14,115)
	US $	144 (61-319)	707 (425-1126)	119 (53-187)
Bed charge and fees	₹	11,143 (8333-15,729)	47,093 (27,055-76,667)	9958 (8028-12,489)
	US $	148 (110-208)	624 (358-1015)	132 (106-165)
Tests breakdown				
Investigations	₹	10,925 (5729-17,671)	20,971 (17,464-32,102)	8746 (5097-15,040)
	US $	145 (76-234)	278 (231-425)	116 (67-199)
Radiology	₹	656 (254-2164)	1884 (863-2972)	274 (243-1473)
	US $	9 (3-29)	25 (11-39)	4 (3-20)
Treatment breakdown				
Medication (pharmacy)	₹	8661 (4315-15,276)	30,865 (19,980-51,535)	6455 (3608-11,550)
	US $	115 (57-202)	409 (265-682)	85 (48-153)
Oxygen	₹	4660 (2304-10,881)	11,979 (8658-21,151)	3526 (1441-5795)
	US $	62 (31-144)	159 (115-280)	47 (19-77)
Ventilator	₹	3174 (1330-6659)	6590 (4290-8787)	1875 (979-3099)
	US $	42 (18-88)	87 (57-116)	25 (13-41)
Bed charge and fees breakdown				
Ward bed charge	₹	5433 (4158-7510)	4082 (2818-5764)	5764 (4639-7636)
	US $	72 (55-99)	54 (37-76)	76 (61-101)
ICU bed charge	₹	28,726 (13,583-51,322)	28,726 (13,583-51,322)	-
	US $	380 (180-679)	380 (180-679)	-
Professional fee	₹	4273 (3368-5816)	10,408 (7396-14,801)	4083 (3333-4831)
	US $	57 (45-77)	138 (98-196)	54 (44-64)

All costs are adjusted for inflation with 2020 as the reference fiscal year. ICU, intensive care unit; IQR, interquartile range

and institution of appropriate antibiotics can lead to progressive multiorgan dysfunction and higher mortality, hence the need for prompt recognition and treatment of this disease.

In the Indian context, almost 55 per cent of healthcare is delivered by the private sector, where there is wide variability in cost and quality[3]. Considering the prevalence of this disease and how eminently treatable it is, we need data that reflect the costs for the perspective of the patient and for hospitals. This study is from an OOP direct medical cost from the payer perspective. The cost of hospitalized services in our tertiary care teaching hospital could give a reference to the economic burden of this disease. The direct medical cost was over three times for the ICU patients in comparison to the ward-only care. These patients had a median ICU stay of nine days. The major contributor to the total expense was treatment charges for those admitted to the ICU and bed charge and professional care fees for the ward only patients. These inflation-adjusted median costs varied across the years between ₹ 28,480 and 62,385, which could be due to differences in the severity of the clinical profiles or treatment regimens during the years (Supplementary Table IV). Putting the costs into context, the average inflation-adjusted total direct medical cost

Table III. Year-wise total median cost after adjustment for inflation*

Year	Currency	Median (IQR)		
		Overall cost	Cost for patients who required ICU care	Cost for patients with only ward care
2013	₹	28,480 (18,501-52,276)	105,043 (70,742-132,234)	22,997 (17,255-41,170)
	US $	377 (245-692)	1391 (937-1751)	304 (228-545)
2014	₹	49,909 (31,934-83,488)	74,409 (57,404-193,920)	37603 (30,273-64,725)
	US $	661 (423-1105)	985 (760-2567)	498 (401-857)
2015	₹	35,939 (31,552-66,952)	162,246 (54,447-334,048)	33,483 (30,959-37,392)
	US $	476 (418-886)	2148 (721-4423)	443 (410-495)
2016	₹	39,983 (24,261-54,504)	175,876 (159,465-195,305)	33,873 (22,544-44,975)
	US $	529 (321-722)	2329 (2111-2586)	448 (298-595)
2017	₹	62,385 (32,847-91,817)	156,774 (96,556-202,789)	44,249 (28,581-69,561)
	USD	826 (435-1216)	2076 (1278-2685)	586 (378-921)
2018	₹	35,266 (29,976-47,474)	200,376 (70,926-329,826)	34,865 (27,504-38,003)
	US $	467 (397-629)	2653 (939-4367)	462 (364-503)

*Adjusted for inflation with 2020 as the reference fiscal year. ICU, intensive care unit; IQR, interquartile range

(₹ 41,994) was about 22 per cent of the state GDP per capita of Tamil Nadu for 2020 (₹ 193,964)[24].

Assuming an annual incidence of hospitalized scrub typhus infections as 0.4 per 1000 population, for an adult population of the state of Tamil Nadu in India with about 53 million (70% of 72 million), with 52 per cent living in rural areas, there would be about 10,483 infections each year. Since our institute is a referral tertiary care centre, we assume that the median cost in other hospitals would be 30 per cent lower due to admission of less severe cases and higher in corporate hospitals with fewer admissions. A projection, using a gamma distribution of costs, for the state of Tamil Nadu, the total annual direct medical costs of hospitalization would be about ₹ 640 million. The state would bear about 40 per cent of this cost in the public sector, where there is no charge to patients. In many centres, scrub typhus fever goes undiagnosed as an undifferentiated febrile illness; hence, this cost may not be apparent under a diagnosis. Given the high impact of undiagnosed or untreated scrub typhus in terms of cost and disease burden, strong and continuous collaboration between the public, physicians and microbiologists is required to build up a robust system to handle scrub typhus infections. It may be worthwhile for the states and union government to recognize rickettsial infections as a priority disease with a proven and effective treatment, when treated early and appropriately, failing which, there could be higher morbidity and costs for patients and health departments. Moreover, a national programme focusing on the prevention and appropriate treatment of acute undifferentiated febrile illnesses, including rickettsial infections, can help in a significant reduction of disease burden as well as overall cost.

On analyzing the cases where cost was high, we noted that five per cent had a nosocomial complication such as ventilator-associated and healthcare-associated pneumonia, central line-associated bloodstream infection, catheter-associated urinary tract infection, ICU psychosis and critical illness polyneuropathy. In this group, the median total cost was ₹ 173,890, and the median length of stay was 12 days. Since ARDS was a significant complication of scrub typhus, the utilization of supplemental oxygen and portable chest X-ray imaging was significant. Unsurprisingly, the presence of ARDS was a predictor of increased cost. The pharmacy costs were also high, considering the fact that doxycycline and azithromycin are relatively inexpensive antibiotics. In our analysis, we found in addition that 39.9 per cent (79 patients) of patients received an empiric beta lactam-beta lactamase inhibitor and 14.6 per cent (29 patients) received carbapenem antibiotic at admission. Around 55 per cent received additional Gram-negative treatment even though there was an eschar diagnosis at admission. The present study was conducted in a referral centre with a higher degree of morbidity as evidenced by the higher SOFA score and ICU admissions. This could explain the high prevalence of broad-spectrum antibiotic usage. Antibiotics for the Gram-negative cover should be de-escalated to provide targeted therapy if blood cultures are positive and should be discontinued as soon as

Table IV. Univariate and multivariable linear regression analysis of predictors of the total cost

Variables	Univariate analysis			Multivariable analysis[#]		
	Per cent increase in total cost	95 per cent CI for per cent increase in total cost	*P*	Per cent increase in total cost	95 per cent CI for per cent increase in total cost	*P*
Year of admission	7.20	0.63-14.21	0.031	12.75	8.58-17.09	<0.001
Gender						
Male	11.91	−11.36-41.3	0.342	-	-	-
Female	Reference					
Dyspnoea						
Yes	20.22	−3.97-50.5	0.108	−0.92	−13.92-14.04	0.896
No	Reference			Reference		
Decreased alertness						
Yes	106.73	44.58-195.6	<0.001	9.03	−15.49-40.68	0.504
No	Reference			Reference		
Seizure						
Yes	69.45	−23.34-274.57	0.191	53.37	−4.09-145.25	0.074
No	Reference			Reference		
Abdominal pain						
Yes	−2.99	−32.09-38.58	0.867	-	-	-
No	Reference					
Jaundice						
Yes	53.39	−30.69-239.47	0.289	-	-	-
No	Reference					
Diabetes mellitus						
Yes	10.34	−16.09-45.09	0.479	-	-	-
No	Reference					
Hypertension						
Yes	22.31	−11.20-68.48	0.216	-	-	-
No	Reference					
Bronchial asthma						
Yes	2.11	−50.02-108.6	0.954	-	-	-
No	Reference					
Ischemic heart disease						
Yes	36.06	−45.59-240.23	0.508	-	-	-
No	Reference					
Chronic obstructive pulmonary disease						
Yes	127.96	−25.24-595.08	0.147	−43.18	−70.88-10.87	0.097
No	Reference			Reference		
Hypothyroidism						
Yes	−24.81	−84.52-265.29	0.722	-	-	-
No	Reference					
Epilepsy						
Yes	−8.52	−63.45-128.97	0.848	-	-	-

Contd...

Variables	Univariate analysis			Multivariable analysis[#]		
	Per cent increase in total cost	95 per cent CI for per cent increase in total cost	*P*	Per cent increase in total cost	95 per cent CI for per cent increase in total cost	*P*
No	Reference					
Chronic liver disease						
Yes	25.9	−74.25-515.47	0.775	-	-	-
No	Reference					
Acute respiratory distress syndrome						
Yes	76.16	42.69-117.48	<0.001	23.83	6.52-43.95	0.006
No	Reference			Reference		
Gastrointestinal symptoms[*]						
Yes	44.03	6.26-95.22	0.019	13.75	−5.04-36.25	0.161
No	Reference			Reference		
Cardiovascular system dysfunction						
Yes	54.73	−6.91-157.19	0.092	−1.41	−26.38-32.02	0.924
No	Reference			Reference		
Shock						
Yes	75.69	28.64-139.95	<0.001	21.86	−0.03-48.54	0.050
No	Reference			Reference		
Renal failure						
Yes	44.22	8.69-91.37	0.011	4.94	−11.46-24.37	0.577
No	Reference			Reference		
CNS dysfunction						
Yes	67.31	22.88-127.79	0.001	16.99	−6.08-45.72	0.160
No	Reference			Reference		
Age	1.10	0.41-1.80	0.002	0.27	−0.14-0.69	0.188
SOFA score	12.73	8.69-16.92	<0.001	7.16	4.26-10.14	<0.001
Duration of hospital stay	17.58	15.17-20.03	<0.001	14.87	12.81-16.97	<0.001

[*]Gastrointestinal symptoms refers to nausea, vomiting, diarrhoea and/or abdominal pain; [#]Goodness-of-fit indicators for the multivariable linear regression model: R^2-0.7304; adjusted R^2-0.7098. Note 1: linear regression was done based on log-transformed total cost adjusted for inflation with 2020 as outcome; Note 2: variables that were significant at $P<0.20$ in the univariate analysis were considered in the multivariable linear regression model; Note 3: per cent increase in total cost and 95 per cent CI are back-transformed values. CNS, central nervous system; CI, confidence interval; SOFA, sequential organ failure assessment

possible if blood cultures are negative or a diagnosis of scrub typhus is confirmed. Appropriate antimicrobial stewardship may help in this regard. Further cost appropriation analysis regarding the appropriateness of investigations would be feasible in prospective studies.

This study, however, has certain limitations. The study was conducted in a non-profit, charitable, teaching, tertiary care, referral centre, and therefore, the costs may not be directly generalizable to cover other situations. Here, we present the price of care due to fees and charges of services that are levied to patients (which includes profits for the hospital) and not the actual 'bottom-up cost' incurred to provide care. Hence, this must be considered while interpreting the values and may represent variation between centres. The appendix of the unit costs and the compartmentalization of costs could provide a framework to make the costs comparable in context. The study was conducted at a tertiary care hospital and biases the study population toward sick patients who may have been referred from other centres. Furthermore, patients from private wards and those covered by health insurance were not included in the study. Therefore, we leave to the readers' discretion, the extent to which these inferences can be

applied to their patient population and geographical location, relying on their personal experience and prudence. This is a partial economic evaluation, and in this retrospective study, we were not able to gauge indirect costs and the costs incurred after the patients were discharged from the hospital but continued as outpatients. It would be valuable to know how the household arranged to meet these high expenses and the long-term effects of hospitalization on the family's socio-economic situation. Even though mortality is also an outcome for scrub typhus infection, we were not able to elucidate the predictors of mortality, as the number of deaths due to scrub typhus in our study was only six (3%).

In conclusion, scrub typhus is a common cause of undifferentiated acute febrile illness in south India and is commonly seen from August to January. The common presenting symptoms are dyspnoea, ARDS, vomiting, headache, abdominal pain and altered mental state. Despite referral bias, the overall mortality was three per cent. The median ICU cost (₹ 128,046) was almost four times the cost for ward-only care (₹ 33,232), and this was a significant OOP expenditure for the average Indian household. Further studies to streamline costs could help in optimizing care for this eminently treatable disease.

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***Conflicts of Interest*:** None.

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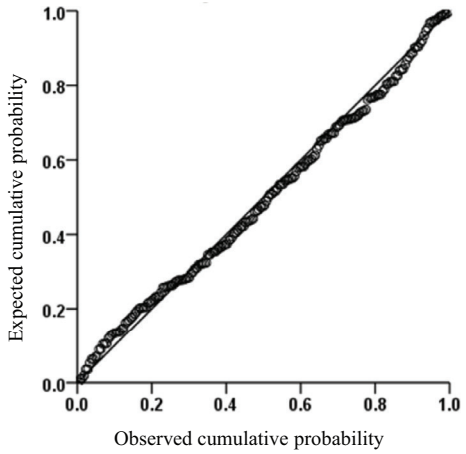
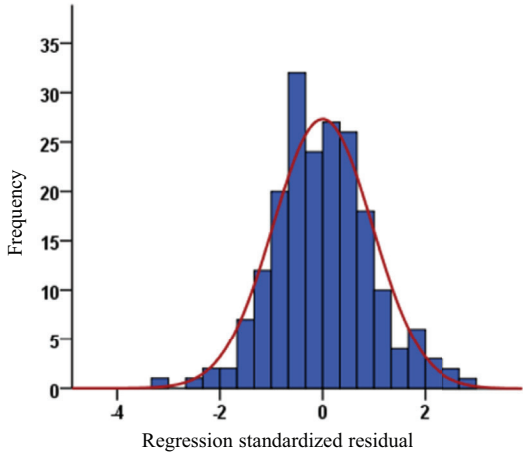
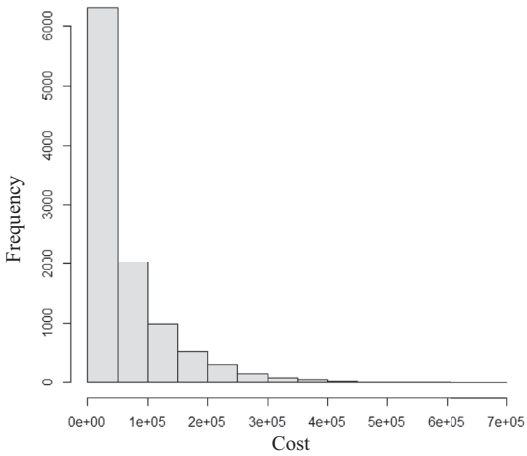


Supplementary Fig. 1. P-P plot of residuals.



Supplementary Fig. 2. Histogram for the residuals.



Supplementary Fig. 3. Histogram of the generated cost data for Tamil Nadu. Sum of the generated cost=644,935,023.

Supplementary Table I. Demographic details

Parameter	n=198, n (%)
Female sex	127 (64.1)
Age (SD)	48±15.9
Geographic distribution	
Tamil Nadu	131 (66.2)
Andhra Pradesh	63 (31.8)
Bihar	2 (1)
West Bengal	2 (1)
Monthly distribution of cases	
January	43 (21.7)
February	8 (4)
March	3 (1.5)
April	2 (1)
May	1 (0.5)
June	3 (1.5)
July	9 (4.5)
August	21 (10.6)
September	25 (12.6)
October	36 (18.2)
November	25 (12.6)
December	22 (11.1)
Portal of entry to the hospital	
Emergency department	194 (98)
Outpatient department	4 (2)

Supplementary Table II. Diagnostic details

Parameter	n (%)
ELISA	193 (97.5)
Eschar	122 (61.6)
Eschar distribution	
Side	
Right	58 (29.3)
Left	43 (21.7)
Midline	16 (8.1)
Not mentioned	4 (2)
Site	
Inguinal	24 (12.1)
Axilla	16 (8.1)
Abdomen	12 (6.1)
Neck	9 (4.5)
Thigh	11 (5.6)
Back	4 (2)
Infra-mammary	6 (3)
Scrotum	6 (3)
Shoulder	6 (3)
Breast	5 (2.5)
Chest	4 (2)
Not mentioned	4 (2)
Penis	2 (1)
Ear	2 (1)
Gluteal	2 (1)
Others	9 (4.5)

ELISA, enzyme-linked immunosorbent assay

Supplementary Table III. Clinical features and outcome

Characteristic	n (%)
Symptoms at presentation	
Fever	198 (100)
Duration of fever (days)	Mean: 8.8±4.1 10 (median)
Dyspnoea	86 (43.4)
Vomiting	44 (22.2)
Headache	30 (15.2)
Altered sensorium	20 (10.1)
Seizure	4 (2)
Diarrhoeal	12 (6.1)
Abdominal pain	22 (11.1)
Jaundice	4 (2)
Organ system involvement at presentation	
Pulmonary	109 (55.1)
Gastrointestinal	31 (15.7)
Cardiovascular system	10 (5.1)
Shock	28 (14.1)
Renal failure	37 (18.7)
CNS dysfunction	29 (14.6)
SOFA score	Mean: 5.51±2.8 5 (median)
Patients who required ICU care	37 (18.7)
Duration of hospital day	Mean: 6.4±3.65 (median)
Duration of ward stay	Mean: 5.2±2.8 5 (median)
Duration of ICU stay	Mean: 1.2±3.4 0 (median)
Mortality	6 (3)

SOFA, sequential organ failure assessment; ICU, intensive care unit; SD, standard deviation; CNS, central nervous system

Supplementary Table IV. Kruskal–Wallis test for comparing cost between years

Year of admission	Median (IQR)	*P*
2013	28,480 (18,501-52,276)	0.005*
2014	49,909 (31,934-83,488)	
2015	35,939 (31,552-66,952)	
2016	39,983 (24,261-54,504)	
2017	62,385 (32,847-91,817)	
2018	35,266 (29,976-47,474)	

*Kruskal–Wallis *P* value; Total cost is adjusted for inflation with 2020. IQR, interquartile range