# Rickettsial Infection amongst Febrile Illness Patient in a Tertiary Care Hospital: A Retrospective Cross-sectional Study

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## ABSTRACT

**Background**

Rickettsial infection is an emerging neglected tropical disease in the Southeast Asia. In past few years Nepal is also reporting escalating prevalence of rickettsia. The under evaluation is resulting it as undiagnosed or are simply labeled as pyrexia of unknown origin.

**Objective**

To find out the prevalence of rickettsia in a hospital setting, assess the socio-demographic and other relevant clinical features of the rickettsia patients.

**Method**

This is a hospital based retrospective cross-sectional study from October 2020 to October 2021. This study reviewed the medical records of the department.

**Result**

The study included 105 eligible patients and the prevalence rate was 4.38 per 100 patients. The mean age of the participants was 42 years, and the mean hospital stay was 3 (SD ±2.06) days. More than 55% of the participants had fever for less than or equal to 5 days and 9% had Eschar present. Vomiting, headache, and myalgia were the most common symptoms and hypertension, and diabetes were the common comorbidities. Pneumonia and the acute kidney injury were the two complications of the patients as stated in the study. The severity of the thrombocytopenia deducted from admission time to discharge, and the case fatality was 4%.

**Conclusion**

The future studies shall consider on collaborative clinical and entomological research. This would help in better understanding of the etiology of supposedly unknown febrile illness and the under-investigated field of emerging rickettsia in Nepal.

## KEY WORDS

*Eschar, Febrile illness, IgM titer, Rickettsia, Thrombocytopenia*

## INTRODUCTION

Globally, Rickettsial infections are spreading as endemic foci mostly with seasonal outbreaks.[1] These infections are reemerging as an epidemic among humans and can be fatal in nature.[2] The condition are arthropod borne in nature and are transmitted by various vectors like ticks, mites, cat fleas and sometimes by mosquitoes.[3] Rickettsia honei is responsible for most cases of spotted fever group of rickettsial infection in the South East Asian region with one complicated case reported in Nepal.[5,6] Likewise, scrub typhus is usually caused by Orientia tsutsugamushi which is transmitted by chigger mites.[1,4]

The clinical manifestations of rickettsia also differ according to the host response and geographical region and mainly shows up with mild symptoms like fever, headache, myalgia, eschar formation etc.[7,8] Several serological tools such as serological evaluation, DNA Polymerase Chain Reaction, serum immunological assay and organism isolation helps to detect this timely.[9,10]

In Nepal as well as in other South Asian countries, there has been a significant outbreak by rickettsial group of infections in recent years.[1,11] However, these infections might be under-investigated due to lack of reliable clinical evaluation and readily available diagnostic tools.

According to the epidemiology and disease control division interim Guideline on Prevention and Control of Scrub Typhus, acute undifferentiated febrile illness (AUFI) of 5 days or more with or without eschar should be suspected as a case of Rickettsial infection. (If eschar is present, fever of less than 5 days duration should be considered as scrub typhus).[12] Likewise, a “probable case” is defined as an IgM titer > 1:32 and/or a four-fold increase in titers between acute and convalescent sera; a “confirmed case of scrub typhus” is defined as O. tsutsugamushi DNA detected in eschar or whole blood samples by polymerase chain reaction (PCR), or a four-fold rise in antibody titers on acute and convalescent sera by IFA, which is the gold standard assay, or Indirect Immuno-Peroxidase (IIP) assay.[12] However, most patients presenting to hospital settings with chief complaints of fever with headache and myalgia are usually evaluated for other tropical illnesses like malaria, dengue, pneumonia and typhoid.

Thus, the study aims to find out the prevalence of rickettsia among patients presenting to the inpatient Department of Internal Medicine of Dhulikhel Hospital. The study specifically assessed the socio-demographic profile, common symptoms, thrombocytopenia and its severity, total hospital stay duration and associated comorbidities of the patients of rickettsia.

## METHODS

This is a hospital-based retrospective cross-sectional study conducted at Dhulikhel Hospital, Kathmandu University Hospital from October, 2020 to October, 2021. The study reviewed the medical records of the inpatient of the internal medicine department of Dhulikhel Hospital. The patients whose age was 16 years and above were included in the study. Also, the study included the patients with acute undifferentiated febrile illness of less than to more than five days, with or without eschar formation.

As per the record/registration of the internal medicine department of Dhulikhel Hospital, the total number of admitted patients from October, 2020 to October, 2021 AD. was 2396. The study included all the eligible Rickettsia patients from the study period. The eligible Rickettsia patients were those presented with fever, myalgia, headache, conjunctival injection, nausea and vomiting.[12] The symptoms depend on severity of disease with features of neurological and respiratory distress in severe cases. The study also included laboratory findings from the patient records, and majority of the tests were conducted in laboratories of Dhulikhel Hospital. In the laboratory findings, the platelets were expressed in uL. The platelets value was further categorized as mild, moderate, and severe. The platelets count above 150,000 were considered normal, 100,000 to 150,000 as mild, 100,000 to 50,000 as moderate and below 50,000 as severe thrombocytopenia.

The study developed a proforma based on previous study to collect the required data from the hospital records. The data were entered in the Open data kit software and later exported to STATA 13 for further data cleaning, analysis and other management. The Kathmandu University School of Medical Sciecnes -Institutional Review Committee (KUSMS-IRC) approval number: 10/22 approved the ethical aspects to conduct the study.

The data analyzed in STATA 13 were expressed as descriptive statistics such as frequencies, percentages, average/mean, and standard deviation.

## RESULTS

This study included 105 eligible Rickettsia patients admitted in the internal medicine department of Dhulikhel Hospital during the study period. Since, the total number of the admitted patient in the Internal medicine department was 2396, the prevalence of the Rickettsia patients was 4.38 per 100 patients. The socio-demographic and clinical characteristics of the patients with their relative frequencies are illustrated in the tables below.

This study summarizes the socio demographic characteristics of the rickettsia patients admitted in the internal medicine department of Dhulikhel Hospital. The mean age of the patients was 42 (standard deviation [SD] ±16.7) years. The minimum and maximum age of the patients in the study was 17 and 85 years respectively. The patient included in the study were more female (57.1%) than male (42.8%). More than 60% of the participants belonged to Kavre

**Table 1. Socio-demographic information of the rickettsia patients**

| Variables (n=105) | n | % |
|---|---|---|
| Age in years [Mean, (SD), (Min, Max)] | [42, (±16.7), (17,85)] | |
| Hospital stay in days [Mean, (SD), (Min, Max)] | [3, (±2.06), (1,9)] | |
| **Sex** | | |
| Male | 45 | 42.8 |
| Female | 60 | 57.1 |
| **Address** | | |
| Kavre | 64 | 60.9 |
| Sindhupalchowk | 11 | 10.5 |
| Bhaktapur | 6 | 5.7 |
| Sindhuli | 7 | 6.7 |
| Ramechhap | 5 | 4.7 |
| Dolakha | 2 | 1.9 |
| Other districts* | 10 | 9.5 |
| **Ethnicity** | | |
| Brahmin | 29 | 27.6 |
| Chhetri | 18 | 17.1 |
| Janjati | 24 | 22.9 |
| Dalit | 7 | 6.7 |
| Tamang | 27 | 25.7 |

*Other districts included Bhojpur, Birgunj, Dang, Dhankuta, Kathmandu, Lalitpur, Lamjung, Sunsari

**Table 2. Clinical information of the patient admitted in the internal medicine department of Dhulikhel Hospital**

| Variables (n=105) | N | % |
|---|---|---|
| **Fever** | | |
| More than 5 days | 47 | 44.8 |
| Less than or for 5 days | 58 | 55.2 |
| **Eschar present** | | |
| Yes | 9 | 8.6 |
| No | 96 | 91.4 |
| **History/Complaints** | | |
| Vomiting | 54 | 51.5 |
| Headache | 49 | 46.7 |
| Conjunctival Injection | 40 | 38.1 |
| Myalgia and Generalized weakness | 34 | 32.4 |
| Cough | 31 | 29.5 |
| Rash | 22 | 21.0 |
| Abdominal pain | 19 | 18.1 |
| Shortness of breath | 18 | 17.1 |
| Lower limb Swelling | 11 | 10.5 |
| Burning micturition | 10 | 9.5 |
| Loose stool | 9 | 8.6 |
| Polyarthraigia | 8 | 7.6 |
| Other history* | 18 | 17.4 |
| **Comorbidity** | | |
| Yes | 19 | 18.1 |
| No | 86 | 81.9 |
| **Comorbidities (n=19)** | | |
| Hypertension | 7 | 36.8 |
| Diabetes Mellitus | 6 | 31.6 |
| Chronic obstructive pulmonary disease | 3 | 15.8 |
| Chronic kidney disease | 1 | 5.3 |
| Chronic liver disease | 1 | 5.3 |
| Congestive cardiac failure | 1 | 5.3 |
| Other comorbidity (Gullian Barre Syndrome, Panic disorder, Benign prostatic hyperplasia) | 4 | 21.1 |
| **Complication (n=101)** | | |
| Pneumonia | 7 | 6.7 |
| Acute kidney injury (AKI) | 4 | 3.8 |
| **Platelets (Thrombocytopenia)** | | |
| Platelets in admission [Mean, (SD), (Min, Max)] | [119393.3, (±81591.6), (14000, 576000)] | |
| Platelets in discharge/after death [Mean, (SD), (Min, Max)] | [137781, (±70605.4), (20000, 513000)] | |
| **Thrombocytopenia severity** | | |
| **During Admission** | | |
| Normal | 43 | 41.0 |
| Mild | 18 | 17.1 |
| Moderate | 35 | 33.3 |
| Severe | 9 | 8.6 |
| **During Discharge/death** | | |
| Normal | 40 | 38.1 |
| Mild | 35 | 33.3 |
| Moderate | 25 | 23.8 |
| Severe | 5 | 4.8 |
| **IgM Titer** | | |
| Positive | 22 | 20.9 |
| Negative | 83 | 79.1 |
| **Outcome of the patient** | | |
| Normal discharge | 101 | 96.2 |
| Expired ** | 4 | 3.8 |

***Other history:** altered sensorium, blurred vision, constipation, loss of consciousness, nasal bleeding, neck stiffness, confusion, palpitation, seizures, photophobia, runny nose, and dysphagia
****Immediate death causes:** Septic shock, Cardiopulmonary arrest

district of Nepal, however the participants were from several parts of Nepal. In this study, the cases were mostly from Brahmin, Tamang and Janjati ethnicity.

The mean hospital stay days was 3 (SD ±2.06) days with 1 and 9 days as the minimum and maximum days respectively.

This study demonstrates the clinical features of the patients admitted in the internal medicine department of DH. More than half (58%) of the participants had fever for less than or equal to five days while remaining has fever for more than five days and about 9% had the Eschar present. Regarding the sign and symptoms, just above half (52%) of the participants had vomiting, about 47% had headache, 38% had conjunctival injection, 32% had myalgia and generalized weakness, 29% had cough, 21% had rashes,

18% had abdominal pain, 17% had shortness of breath, 11% had lower limb swelling, 10% had burning micturition, 8% had loose stool, 8% had polyarthraigia and 17% had other history such as altered sensorium, blurred vision, constipation, loss of consciousness, nasal bleeding, neck stiffness, confusion, palpitation, seizures, photophobia, runny nose, and dysphagia.

Nearly 18% of the participants were comorbid and among those who were having comorbidity, 37% had hypertension, 32% had diabetes mellitus, 16% had chronic obstructive pulmonary disease, 10% had benign prostatic hyperplasia, 5% had chronic liver disease, 5% had chronic kidney disease, 5% had congestive cardiac failure, and 21% had other comorbidities such as Gullian Barre syndrome. In this study population, about 7% had pneumonia and 4% had acute kidney injury (AKI) that has been considered as the complications present in the rickettsia patients of the study.

The mean platelets that study population had during the admission and discharge was 119393.3 (SD ±81591.6) and 137781 (SD ±70605.4) respectively. During admission, 41% had normal platelets counts and the thrombocytopenia severity was distributed as 17% had mild, 33% had moderate and 9% had severe severity. In this study, about 59% of the patient had thrombocytopenia during their admission. In the same way, during discharge, 38% had normal platelets counts, about 33.3% reported mild, 24% reported moderate and 5% reported severe severity of the thrombocytopenia. The two of the severe thrombocytopenia cases during discharge were those cases who got discharge on request.

Also, the study reported about 21% with positive IgM titer and 79% with negative IgM titer. In this study, more than 96% participants got discharged and about 4% of the participants expired during the medical treatment. The major immediate causes of death were septic shock and cardiopulmonary arrest.

## DISCUSSION

Rickettsial infection might not even be a part of diagnosis of exclusion. Sometimes this delay in diagnosis can lead to complications like meningoencephalitis, neurological deficit, acute respiratory distress syndrome, acute kidney injury etc.[13,14] A prompt diagnostic evaluation by use of real time quantitative PCR and serological evaluation can help prevent these complications. This study will therefore be an aid to clinicians, who should be ruling out rickettsial infection in any patient presenting to their department with fever and other associated symptoms and also contributes to reduce the burden of rickettsial diseases that go undiagnosed and/or are under-investigated.

The findings of this study with 105 eligible Rickettsia patients assessed the socio demographic and other relevant clinical features of those who were admitted in the internal medicine department of Dhulikhel Hospital from October 2020 to October 2021.

The study showed about 4.38 per 100 patients' prevalence among 105 Rickettsia patients. The incidence of scrub typhus in Nepal was 1271 cases in the year 2019 as reported.[15] The study showed that 21% of the Ricketsia patients had positive titer indicative of scrub typhus. This study reports 3 days of total hospital admission in average and the incubation period was 6-21 days. The patients may not have presented themselves in the hospital during the diagnosis period of the scrub typhus, so the presentation might have been too early or too late for the diagnosis. And some may have done their investigation in different institution and the reports could not be included in their clinical records. The poor health infrastructure and inadequate diagnostic facilities may have underreported the existing cases and the varieties of the cases. A study conducted in Dhulikhel Hospital earlier and Kathmandu valley reported similar prevalence of the Scrub typhus.[16,17] However, the studies had some differences in duration, sample size and the types of departments the patient were examined. Also, the changes in the living standard and the lifestyle might have contributed to the increasing number of cases in Nepal.[18]

The mean age of the Rickettsia patients in our study was 42 years (SD ±16.7) and study had more female participants than male i.e about 58%. A study held in several districts of Nepal showed less mean age group of the Rickettsia patients.[1,19] The other studies held in Nepal gave consistent proportion in the distribution of the male and female proportion for this disease.[17] Some studies also have highlighted the higher number of female having infected with scrub typhus during the outbreaks, as such female members might have been exposed to outdoor activities for their daily chores.[1] A study in India, South Korea and China also reported greater incidence among the female.[20-22] More than 64% of the Ricketssia patients were from Kavre district and this could be because the location of the hospital is the same district and this district covers huge geographical area as well. Also, due to less accessibility, the patients from other districts might not seek health services unless they have the severe health issues. The patients included in this study also belonged to other nearby districts as well.

This study indicated that more patients belonged to Brahmin (28%), Tamang (26%) and Janajati (23%) ethnicity of Nepal. Another study in Nepal reported more Janajati which is also consistent with this study reporting Janajatis and Tamangs ethnic groups.[1]

The study reported very less i.e. about 9% had Eschar present and more than half of the patients had fever less than or for 5 days. Among the clinical manifestations, fever has been reported to long last for about 14 days.[12] Other studies reported Eschar presence similar to this study, resulting that the presence of Eschar should be

considered for the Scrub typhus.[23,24] Eschar formation in the initial stages are painless, non-itchy and are located in the body sites which are not visible directly. Thus, due to such tendency the presence of Eschar reporting is usually underreported.

Majority of the patients in this study had vomiting (52%), headache (47%) and conjunctival injection (38%) as the clinical history. These are also commonly reported clinical symptoms of the Rickettsia in the study. Other studies reported of headache, cough, abdominal pain, arthralgia, myalgia, rash and diarrhea as the common symptoms.[23,24]

Among 18% of the comorbid patients, majority of them had hypertension (37%) and diabetes (32%). The hypertension is escalating in young adults and the reported mean age of this study population is young adult. Other studies also reported some comorbidities such as chronic cardiovascular diseases, chronic lung diseases, chronic renal diseases, active malignancy and diabetes mellitus.[25] This study reported pneumonia and acute kidney injury as some of the complication that few patients had.

This study demonstrated about 59% of patient with thrombocytopenia while a study in India in a small sample size showed only 47% of the rickettsial cases with thrombocytopenia.[26] Moreover, this study also categorized the thrombocytopenia severity resulting in 17%, 33% and 9% of mild, moderate and severe thrombocytopenia respectively. Also, the thrombocytopenia severity declined and improved from the time of admission to the discharge.

Among the 105 patients, about 4% of the participant's outcome was death and the major immediate causes of the death were septic shock and cardiopulmonary arrest. The deceased had complication concluding that the deceased might have been presented in the hospital in the later stages when the complications took place already. A study in Nepal that was held during the outbreak reported reduction in the case fatality rate of the Rickettsia from 6% to approximately 1% from 2015 to 2017 respectively.[1] The case fatality rate is not consistent throughout the year and differs seasonally. With the advent of the disease control programs, the case fatality may not rise, but other immediate causes of the cases can be fatal. The case-fatality rate of other studies mentioned for untreated classic cases was 7% which is similar to this study. However, the fatal cases in this study were all hospital admitted cases, so may or may not have received complete medical treatment.[27] All the expired cases had negative IgM titre, as the presentation of the cases may not be in the time of the diagnosis as Scrub typhus IgM is diagnosed and test positive only within 5-7 days from the appearance of the symptoms.[12]

This study has been conducted under several limitations. Firstly, this is a retrospective cross-sectional study and may need further measures to generalize its findings to wider population. Secondly, the study is limited to inpatient internal medicine department of only one tertiary care hospital and future studies may be more representative and comprehensive. The study was also limited to the information available in the medical records, thus other studies can do the prospective and follow up studies to obtain required information through additional variables. The study can also be extended in the community settings so that future outbreak control measures can be controlled through routine recording and surveillance. The study is limited to a single year which was also the post COVID year in Nepal, and due to this many cases might have been under reported, thus future studies may consider including several years and all the seasons for the comprehensive report.

## CONCLUSION

The study reported 4.38 per 100 patients' prevalence of Scrub typhus among 105 Rickettsia patients. Most of the Rickettsia patients were female and belonged to the Tamang and Brahmin Ethnic groups. In the Rickettsial patients, nine percent had Eschar and the most common symptom was fever for less than or for five days, majorly complained of vomiting and had hypertension as comorbidity. The clinical as well as community-based interventions should emphasis on majorly affected social groups. Adapting proper measures of the comprehensive study, the future study should consider collaborative clinical and entomological research for the better understanding of the etiology of unknown febrile illness and the under-investigated field of emerging rickettsioses in Nepal and Asian region.

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