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Original Research Article

Scrub typhus at the local hyper-endemic area, central Vietnam: epidemiology, clinical presentations, and laboratory features at admission

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ABSTRACT

Background: The objective of this study was to deacribe the epidemiological characteristics, clinical and laboratory features at admission of scrub typhus at a local hyper-endemic area-Khanh Hoa province, central Vietnam.
Methods: From August 2018 to March 2020, a hospital-based active surveillance was applied to collect suspected adult scrub typhus cases from 9 public/district hospitals. A community survey was conducted to investigate epidemiological factors. PCR and ELISA IgM tests were applied to confirm cases. Using standardized questionnaires, trained health staffs gathered demographic, clinical and laboratory data, and assessed patients' household conditions, personal behaviours/protective equipment, and vector exposure. Data was recorded using Open data kit (ODK) on Android devices and analysed with STATA version 15.
Results: Thirty-two confirmed cases were identified and analysed, with males accounting for 56.3%. Of these, 56.2% were farmers or worked in forests/mountain fields/garden. About 60% engaged in risky behaviours (urinating in the forest/near bushes/field; passing riverside; resting directly on household floor). About 96.9% lived in poor sanitation households and 60% always saw mice around their homes. Despite 72% worked in hazardous environment, only 34.4% used personal protective equipment. Common clinical symptoms beside fever included headache (84.4%), fatigue (75.0%), myalgia (68.8%), heart rate>90/min (50.0%), lymphadenopathy (34.4%). An eschar was found in 59.4%. Abnormal laboratory findings included neutrophils>70% (53.3%), lymphocytes<20% (65.6%), a neutrophils/lymphocytes ratio (<1 or >2) (60.0%), platelet<150,000/ml (56.3%), and AST/AL ≥40U/l (86.7%).
Conclusions: Comprehensive consideration of epidemiological features, clinical and laboratory examination is crucial for diagnosing scrub typhus upon admission. Clinicians in endemic areas need enhance their understanding of local scrub typhus.

Keywords: Scrub typhus, Hyper-endemic area, epidemiology, Clinical presentations, Laboratory features

INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi*, is a mite-borne zoonotic disease endemic to Asia and the Pacific. The prevalence of *Orientia tsutsugamushi* is re-emerging globally.[1,2] It threatens one billion people, and causes illness in one million each year.[2] Scrub typhus is one of the most neglected tropical diseases, a leading cause of acute undifferentiated febrile illness (AUFs) in areas of the 'tsutsugamushi triangle' countries.[3] In Vietnam, after 40 years of neglect since 1960s, scrub typhus is re-emerging and reported in 32 among 63 provinces throughout Vietnam in 2000s, with main foci in the northern part of the country.[4-7] Up to present, scrub typhus

was widely distributed in all country regions [8]. It has been confirmed as one of the most acute common AUFs, accounting for 30-50% patients with AUFs and clinically suspected rickettsiosis and 26.4% (484/1834) among AUF patients in a national surveillance.[8-10] However, due to challenges in diagnosis tests [11], all of these studies conducted at a national referral hospital or at provincial hospitals within a limited time of the project.[8] This resulted in delayed diagnosis and missing risky behaviours as well as local transmission ecology of the disease.[8,12,13] A comprehensive approach- clinical diagnosis based on considering endemic areas, risk behaviours, clinical presentations, laboratory findings, and followed by confirmed laboratory diagnosis, were recommended, and becomes more crucial due to the disease's ecological context and importance of early diagnosis and treatment in endemic areas.[3,14] We conducted this prospective analysis to describe clinical features, laboratory findings and epidemiological characteristics at admission of scrub typhus in Khanh Hoa, a local hyper endemic area in the Central Vietnam.

METHODS

Ethical approval was provided by the Scientific and Ethical Committee in Biomedical Research, Hanoi University of Public Health (No. 382/2018/YTCC-HD3 and No.329/2019/ YTCC-HD3) and by the Ethics Committee of Northwestern and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, EKNZ) (BASEC-Nr-2018-00974). All patients provided written informed consent prior to study enrolment and sample collection.

Study site

Khanh Hoa is a province in South Central Vietnam, covering 5.2 km² (2011) and home to 1.2 million residents (2019). It features 200 islands and is famous for Nha Trang Bay, one of the World's Most Beautiful Bays.[15] The province has a 385 kilometer coastline and a tropical savanna climate with an average annual temperature of 27°C and rainfall of 970 mm (2017), and 2 seasons, including a dry season (from January to August) and a rainy season (from September to December).[16] The province is mostly mountainous with forests covering more than half of the total area. About 17% of the Khanh Hoa surface are used for farming, providing 4.3% of the national sugar cane and 1.7% of cashew nut production.[17]

The tropical savanna climate allows perennial grasses to grow all year long (often 3 to 6 feet high) and leads to an open shrub layer with scattered trees, suitable environment for scrub typhus transmission by chigger abundance. Khanh Hoa is recognised as endemic for scrub typhus since WWII.[16] Scrub typhus was first reported in Khanh Hoa in a retrospective study of United States Air Force personnel at Cam Ranh Bay in 1969.[18] From 2008 to 2010, 469 cases were reported in the province, and during 2013-2014, 201 of 321 suspected cases were confirmed by the Institue of Pasteur Institute (IPN).[19,20]

Study design

We conducted a hospital-based clinical active surveillance to collect all suspected cases of scrub typhus with their clinical and laboratory characteristics using case report form. A community survey was implemented to investigate epidemiological factors. Active hospital surveillance for scrub typhus was established in Khanh Hoa from 01 August 2018, to 30 March 2020, across the Khanh Hoa Hospital for Tropical Diseases and the 8 of the 9 district hospitals (Truong Sa Island district hospital due to accessibility issues).

Laboratory diagnostic assay

Diagnostic assays

Buffy coat and plasma specimens from cases were tested at IPN, using semi-nested PCR for *Orientia* spp. and using the immunoglobulin M (IgM) enzyme linked immunosorbent assay (ELISA), (Scrub Typhus Detect™ IgM ELISA, InBios International Inc., Seattle, WA, USA) for detection of antibodies to *O. tsutsugamushi* antigens.

Semi-nested PCR

An in-house semi nested PCR, validated by the qualitative SYBR green real-time PCR, for detection of partial 56-Kda outer membrane protein gene was used to identify the presence of *O. tsutsugamushi* in 28 patients with 28 buffy coat samples (3 patients did not provide buffy coat samples).[21,22] Primers used for the semi-nested PCR includes 2 forwards primers with the sequence of (F1): CAATGTCTGCRTTGTCRTTG; (F2): CCKTTTTCIGCTRGTGCGATAG and 1 reverse primer with sequence of (R): ATAGYAGGYTGAGGHGGYGTAAG. The PCR reaction mix contained 2 µl of 10X Taq buffer, 1.6 µl of MgCl2 (25mM), 0.4 µl dNTPs (20 mM), 2 µl of each primer, 0.3 µl Taq DNA Polymerase, and 29.7 µl nuclease free water (QIAGEN).

The first PCR step was performed with 2.5 µl of DNA extracted from the buffy coat or eschar. The second step was performed with 2.0 µl of the amplicon of the first PCR step. The first PCR step was performed for 1 cycle of initial polymerase activation at 94°C for 3 min; followed by 35 cycles at 94°C for 20 s, 54°C for 20 s, and 72°C for 30 s; and a final elongation step was done at 72°C for 5 min. The second PCR step was performed at 94°C for 3 min; followed by 25 cycles at 94°C for 20 s, 55°C for 20 s, and 72°C for 30 s; and a final elongation step was done at 72°C for 5 min. The PCR products were analyzed by electrophoresis on a 2% agarose gel; the products were stained with SYBR Safe and were observed under an UV trans illuminator.

ELISA assays

The Scrub Typhus Detect IgM ELISA (part no. 500242, Lot no. XM5033; InBios International Inc., Seattle, WA, USA) was used for IgM detection all 31 serum samples of patients enrolled from 2018-2019. This ELISA uses recombinant p56kD type specific antigens of *Orientia tsutsugamushi* Karp, Kato, Gilliam, and TA716 strains. The manufacturer's methods were followed exactly. All sera were tested at a 1:100 dilution and absorbance was determined at 450 nm (OD@450 nm) using a microplate reader to give a final optical density (OD) result. The OD cut-off applied was 1.00 with a sensitivity of 91.5% and specificity of 90.9% for admission samples to confirm cases among suspected scrub typhus infection, as reported previously.[23,24]

Case definitions and selection criteria

Suspected scrub typhus

Patients with age≥16 years old those with acute fever (axillary temperature ≥37.5°C) and having had at least one of the following twelve secondary findings: eschar, nonspecific skin rash, headache, myalgia, retro-orbital pain, congestion of the conjunctival blood vessels, tinnitus, lymphadenopathy (regional/body), hepatomegaly, splenomegaly, dry cough, dyspnoea without upper respiratory tract discharge were included.

Patients diagnosed/co-infected with malaria (confirmed by Giemsa thin film), dengue fever (confirmed by NS1), measles, influenza, bacterial pneumonia, and urinary tract infections were excluded.

Confirmed acute cases

Scrub typhus

Patients with a positive PCR result (buffy coat or eschar swab specimens) or positive IgM ELISA result [optical density (OD) of≥1.0] for *O.tsutsugamushi* by the IPN reference laboratory, in Vietnam.

Data collections

All clinical diagnoses and laboratory investigations during hospitalization admission were made by trained local physicians and laboratory staffs following suspected acute scrub typhus case definition. All patients satisfying criteria were asked for their informed consent to be enrolled. Demographic, clinical and laboratory data was collected with standardized questionnaires by trained health staffs. Blood specimens were collected from all enrolled patients at admission [each 2 tubes, with and without Ethylenediaminetetraacetic acid (EDTA)]. Using EDTA blood samples, buffy coat and plasma centrifugation (616 *g* during 15 min) was conducted within 24 hours by trained technicians and stored at 2-8ºC in the hospital laboratories, before transfer weekly without thawing in ice boxes to IPN, for PCR and enzyme-linked immunosorbent assay (ELISA).[21] All samples were labelled with the subject's unique identification number (ID) and preserved in -20℃ freezer at the Department of Microbiology and Immunology, IPN until further processing.

The risk factor survey used a questionnaire based on landscape determinant framework of disease transmission.[35] The development process and structure of the questionnaire was presented at.[25] Participants were visited and asked about five key areas: i) socio-economic status, ii) behaviours related to land/sand/soil/grass/bushes and their personal protective equipments (PPE), iii) species' habitat connections, vi) land use, and v) vector contact. The questionnaire had 96 questions based a "daily-life" assessment approach, and took about 40 minutes to complete (30 minutes for questions and 10 minutes for environment observation checklist). Interviews were conducted within 30 days after laboratory confirmation by data collectors from the Department of Epidemiology, IPN. A data supervisor checked total numbers and content of all collected paper forms daily, and incomplete forms were completed by collectors or after re-contacting participants.

Data were entered using a short form built in Open Data Kit (ODK) on Android devices (Samsung table), before uploading at http://sg.smap.com.au/.[26]

Statistical analysis

Categorical variables were summarized as frequencies and percentages were used to describe of clinical/laboratory characteristics and risk factor features. Continuous variables were summarized as median (IRQ), mean and standard deviation. STATA version 15 (Stata Corp LP, College Station, TX) was used for statistical analysis.

RESULTS

This study represents the first of its kind to identify common clinical, laboratory, and risk factors associated with scrub typhus in a local hyper-endemic area of Vietnam. The study flow chart is shown in Figure 1. A total of 114 suspected acute scrub typhus cases were initially enrolled to the study. Blood specimens at admission were collected from 114 suspected cases. Buffy coats were collected from 104 suspects. Forty-five of the 114 suspects were positive with PCR buffy coat and/or ELISA IgM at admission, accounting for approximately 39.5% of the total suspects. After exclusion of one positive due to living outside the study area and 12 positive because clinical data could not be collected due to COVID-19, we included epidemiological characteristics, clinical and laboratory data of 32 confirmed cases in the study analyses.

The demographic features of the patients are given in Table 1. The majority of patients were farmers (43.8%), with some working in forests/mountain fields (9.4%) or garden (3.1%). 'Other' occupations included travelers, factory workers, nurses, freelancers, businessmen, housewives, teachers, construction workers, hotel receptionists

(43.8%). The cases were found in all age groups and resided in Khanh Hoa. About 12.5% patients and 6.3% of their family member had history of scrub typhus within 2 years prior to the study.

Table 2 presents the ecological and behavioral risk factors among 32 scrub typhus cases. Most patients (84.4%) reported common risk behaviors associated with field work, including exposure to forest/vegetable garden/field/fruit/industrial garden. However, 15.6% reported other activities such as travelling or working in construction sites. About 60% had all three risk behaviours such as urinating in forest/near bushes/field, regularly passing riverside, sitting/laying/taking a nap directly on household floor. Almost all patients (96.9%) lived in households with poor sanitation/conditions (bushes within 5 meters, a mud yard/house floor, drainage on yard), and about 60% always observed mice around home. About 72% worked in risky workplace environment (in/close to forest, in/close to hilly field, near water bodies within 100 meters/bushes within 10 meters) within 3 week prior to fever onset, however only 34.4% used PPE. The clinical and laboratory features of the patients are given in Table 3. Of note, the findings revealed that even at the primary care level, about 37.5% of patients were referred from other clinics and 25% of those took more than 10 days after the onset of fever to reach a hospital (days of fever on admission: a median of 6 days, and an interquartile range of 4-10 days).

Patients presented throughout the year, though incidence was highest in the winter months (Figure 2). This peak coincided with farming activities and the period leading up to the Lunar New year (Tet in Vietnam). Many people aimed to increase their earnings in preparation for the New Year festival. As the results, participation in short-term hiring jobs nature-related surged, including loading wood onto truck, driving wood truck, loading fruits and sugarcane, and working in mountain fields.

Regarding the clinical aspect, the most common clinical features, other than fever, were headache (84.4%, 27/32), fatigue (75.0%, 24/32), myalgia (68.8%, 22/32), heart rate >90/min (50.0%, 16/32), rigors/chills (37.5%, 12/32), regional lymphadenopathy (>1 cm) (34.4%, 11/32), dry cough (25.8%, 8/32) and retro-orbital pain (21.9%, 7/32). No hemorrhagic signs or skin hemorrhage was reported. Gastrointestinal findings and clinical severity were found in 28.1% (9/32) and 31.2% (10/32), respectively. An eschar was found in 59.4% (19/32) of cases.

About laboratory indicators, abnormal findings in blood test reported includes neutrophils >70% (53.3%, 16/30), lymphocytes <20% (65.6%, 21/32), neutrophils /lymphocytes ratio (<1 or >2) (90.0%, 27/30), platelet <150,000/ml (56.3%, 18/32), and AST and/or ALT ≥40 U/l (86.7%, 13/15).

Table 1: Demographic characteristics of scrub typhus patients at admission (n=32).

Variables	N	%
Age group (years)		
≤30	8	25.0
31-40	6	18.8
41-50	10	31.3
≥51	8	25.0
Sex		
Male	18	56.3
Female	14	43.8
Ethical group		
Kinh	29	90.6
Others	3	9.4
Education		
Illiteracy	2	6.5
Primary school	11	35.5
Secondary school	8	25.8
High school	8	25.8
University and higher	2	6.5
Occupation		
Farmer	14	43.8
Working in forests/ mountain fields	3	9.4
Gardening, growing vegetables	1	3.1
Others (traveller, factory workers, nurse, freelancers, business man, housewife, teacher, construction workers, hotel receptionist)	14	43.8
History of scrub typhus		
Participants got scrub typhus within 2 years prior to the study	4	12.5
Family members got scrub typhus within 2 years prior to study	2	6.3

Table 2: Ecological and behaviour risk factors among scrub typhus in Khanh Hoa, Vietnam, August 2018-March 2020 (n=32).

Variables	N	%
Field work group		
Work in forest/hilly field and others	18	56.25
Work in vegetable garden and others	5	15.63
Work in sugarcane/crop/rice field and others	3	9.38
Work in fruit/industrial tree garden and others	1	3.13
No work related to the work in field/garden (travellers, work in a construction place)	5	15.63
Use of Personal Protective Equipment in the field*	11	34.4
Urinating in the forest/near bushes/field	17/27	63.0
Passing regularly at the riverside	19	59.4
Sitting/laying/take a nap directly on the household floor	21	65.6
Always observing mice around home	19	59.4
Households with poor sanitation/conditions**	31	96.9
Workplace environment with risk**	23	71.9

*-Use of personal protective equipment (PPE) in the field" meant that the person used all 5 PPEs (socks, boots, long/extra shirt, long/extra trousers, and gloves) with a minimum frequency of 5/10 times when working in the field, **- Household (HH) with poor sanitation/conditions", the binary composite variable, was generated as HH with at least one of following characteristics: bushes within 5 meters, a mud yard, a mud house floor, or drainage on yard; ***-workplace environment with risk" were defined as HH or workplace surrounded by at least one of four natural characteristics: in/close to forest, in/close to hilly field, near water bodies within 100 meters or bushes within 10 m.

Table 3: Clinical and laboratory characteristics of scrub typhus patients at admission in Khanh Hoa, Vietnam, August 2018-March 2020 (n=32).

Variables	N	%/IQR
History		
Referral, N (%)	12	37.5
Days of fever on admission (≥37.5°C), median (IQR)#	6	4-10 (min 0 max 16)
Clinical presentation at admission		
Symptoms		
Headache, N (%)	27	84.4
Myalgia, N (%)	22	68.8
Retro-orbital pain, N (%)	7	21.9
Rigors/chills, N (%)	12	37.5
Dry cough, N (%)	8	25.8
Abdominal pain, N (%)	3	9.4
Diarrhea (at least 3 days), N (%)	3	9.4
Physical signs		
Body temperature ≥38°C, N (%)	21	65.3
Heart rate>90/min, N (%)	16	50.0
Respiratory rate>22/min, N (%)	4	12.5
Hypotension, N (%)	3	9.4
Eschar, N (%)	19	59.4
Rash, N (%)	3	9.4
Hemorrhagic signs (Petechial hemorrhage (epistaxis, bleeding gums, organs), skin hemorrhage, N (%)	0	0.0
Regional lymphadenopathy (>1 cm), N (%)	11	34.4
Hepatomegaly and/or splenomegaly, N (%)	1	3.2
Pharyngo-laryngitis, N (%)	1	3.2
Documented dyspnoea, N (%)	2	6.5
Lung crepitation, N (%)	5	16.3
Fatigue, N (%)	24	75
Malaise, N (%)	0	0.0
Nausea, N (%)	5	15.6

Continued.

Variables	N	%/IQR
Vomiting, N (%)	2	6.5
Lung crepitation and/or documented dyspnoea, N (%)	5	16.3
Gastrointestinal findings, N (%)[##]	9	28.1
Clinical severity, N (%)[###]	10	31.2
Laboratory findings [^]		
WBC>12,000/ml	5	15.6
NEU≥70%	16/30	53.3
Lymphocytes < 20%	21	65.6
N/L Ratio (neutrophils/lymphocytes) (<1 or >2)	27/30	90.0
Hematocrit < 30%	1/31	3.2
RBC (<3.8 or >5.1)	5	15.6
PLT <150,000/ml	18	56.3
HGB <10.0 g/dl)	1/30	3.3
AST and/or ALT ≥40 U/l (n, %)	13/15	86.7

[#]-Fever: tympanic temperature >37.5˚C measured by axillary method, #- Clinical presentation,[##] -gastrointestinal findings: at least one of abdominal pain, vomiting, nausea, jaundice, hepatomegaly, splenomegaly, [###] - clinical severity- at least one of these: intubation; respiratory rate >30/min; pulse >100/min; systolic blood pressure<90 mmHg or >160 mmHg, or diastolic blood pressure <60 mmHg; [^]- WBC: white blood cell, NEU: neutrophil; RBC: red blood cell; PLT: platelet; HGB: hemoglobin; AST- aspartate aminotransferase; ALT- alanine aminotransferase.

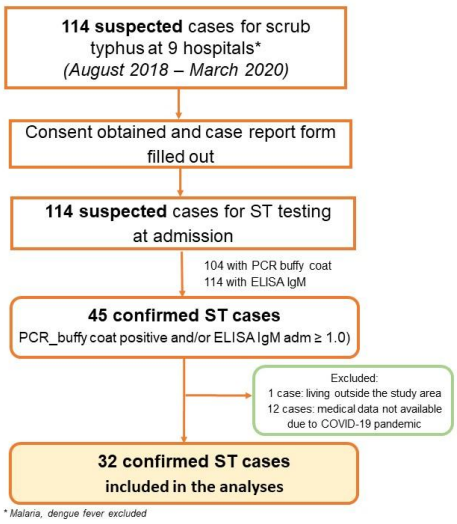

Figure 1: Study overview and flow chart for enrolment of suspected scrub typhus cases in Khanh Hoa.

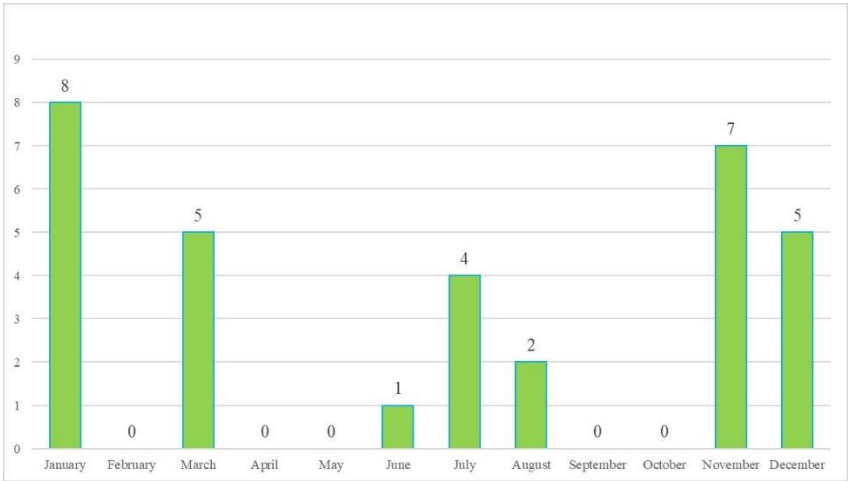

Figure 2: Frequency of scrub typhus cases per month from August 2018 to March 2020 in Khanh Hoa Vietnam.

DISCUSSION

With tropical savanna climates, rainy seasons with high humidity occurred between June and December in Khanh Hoa. In this current study, we noted some seasonal variation. The scrub typhus season approximately lasted from July to March, with a peak from November to January. Scrub typhus occurred sporadically between seasons. These data was in-line with other reports, with higher number of case in rainy season in other areas with tropical savanna climates.[27-29]. Furthermore, we observed that the rise in human activities in the hazardous environment zones, motivated by the pursuit of higher earnings in preparation for the Lunar new year/tet festival by January, also increased the risk of scrub typhus exposure.

About half of the patients were farmers or worked in forests/mountain fields/gardening (56.2%) while 43.8% had various occupations such as travellers, nurses, housewives, teachers, hotel receptionist. These aligns with other reports indicated that 'non-famer' comprised 40-50% of infected cases.[8,30,31] This study highlights that daily activities in endemic areas like Khanh Hoa contributed more to risk of scrub typhus than primary occupation. About 60% engaged risky behaviours such as urinating near bushes, regularly passing riversides, and resting directly on household floor, and nearly all (96.9%) lived in poor sanitation household. While 71.9% worked in high-risk environment, only 34.4% used of PPE. Many patients, regardless of their occupations (nurses or hotel receptionists) mowed grass for their family's livestock in their day-off. Housewives reported that they picked up firewood or planted vegetation in river streams for family meals, while a teacher watered flowers at home. Therefore, it is important to investigate patients' risky behaviours to assess the risk of scrub typhus, rather than focusing solely on their occupations or their 'famer' label.[25] Other studies confirmed that household/environmental factors were common features among cases and significant high-risk factors for scrub typhus in endemic areas.[32-36]

The clinical features of scrub typhus are often nonspecific due to disseminated vasculitis. The common presentations included fever, headache, myalgia, fatigue, rigors/chills, rash, pneumonia, hepatitis.[30,37] Characteristic signs included eschar and swollen lymph nodes.[8,12,13,30,37,38] A high proportion of patients (85-97.3%) presenting with a visible eschar must be interpreted in the context of using this finding as part of the inclusion criteria and depended on study site endemicity and study design.[37-41] In this study, other than fever, we adjusted suspected case definition to use eschar as one of twelve secondary findings, resulting in 59.4% of confirmed cases having eschar, compared to 93.1% in the 2013-2014 cohort on the same area.[37] Of noted, relying mainly on eschar can lead to miss scrub typhus cases and underestimated incidence in areas with low eschar presenation, such as children in Thailand (7%), adults in India (0.2%), patients aged 13 years or older in another province in Vietnam (18.2%), or getting difficulties in finding eschar on patients' body.[11,42,43]

Laboratory indicators in patients with scrub typhus mainly have an increased neutrophil count, though the WBC count remains in the normal range.[31,37,44-46] In this current study we found that abnormal N/L ratio (<1 or >2) occurred among 90% (27/30) of scrub typhus infection, indicating a reverse severe situation/severe inflammation among scrub typhus patients.[47] A study by Chatterjee et al in India found that the presence of body temperature >40^{0}C and absolute neutrophil to lymphocyte ratio >2 increases the probability of suffering from scrub typhus by 25 and 10 folds, respectively.[48] Rath et al also confirmed that the neutrophil/lymphocyte ratio was the most important predictor for differentiating the scrub and nonscrub cases in a study of the scrub typhus encephalitis assessment tool validation.[43]

Limitations

Our study had some limitations, including the small number of patients due to the COVID-19 pandemic in 2020 in Vietnam. However, we do attach weight to its clinical implications in view of this AUF illness diagnosis in the local endemic areas. Being conducted in Khanh Hoa province with a tropical savanna climate, our study may not be representative of the pattern of disease in the northern provinces of Vietnam where the climate is humid subtropical or southern provinces where the climate is tropical.

CONCLUSION

In conclusion, a comprehensive and careful examination of epidemiology features, as well as clinical and laboratory characteristics, is important for diagnosing scrub typhus at the admission. Clinicians in endemic areas need to strengthen their understanding of scrub typhus as it relates to the local endemic context.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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