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Original Article

Clinical manifestations and treatment outcomes of scrub typhus in a rural health care facility on the Thailand-Myanmar border

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Abstract

Introduction: Scrub typhus is endemic in rural Southeast Asia. The district of Umphang in northwestern Thailand is a prototype environment for this disease. We report the clinical manifestations and outcomes of patients diagnosed with scrub typhus in this area.

Methodology: Patients diagnosed with scrub typhus between 2011 and 2014 were analyzed. Diagnosis was based on clinical symptoms in conjunction with a positive rapid test or a pathognomonic eschar lesion.

Results: A total of 857 patients were included, of which 488 were adults and 369 were children. Most patients (728; 84.9%) were included via a positive serology on rapid test, 86 patients (10.0%) had eschar only, and 43 patients (5.0%) had both sero-confirmation and presence of eschar. The most common symptom was fever (93.8%), followed by headache (48.1%) and cough (33.1%). Eschars were reported in 129 patients, with a significantly higher percentage in children ($p < 0.001$), and a different anatomical distribution was found when adults and children were compared. Common complications were elevated transaminases, acute kidney injury, and pneumonia. Most patients recovered from the disease.

Conclusions: Scrub typhus in Umphang district is common. Patients can present with a variety of clinical symptoms, regardless of the presence of fever. Standard treatment led to a favorable outcome in most patients.

Key words: scrub typhus; eschar; resource-limited; clinical manifestations.

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Introduction

Scrub typhus is an acute febrile illness caused by the obligatory intracellular bacteria *Orientia tsutsugamushi*. It is endemic in an area described as the "tsutsugamushi triangle" that covers large parts of Asia and the Western Pacific region [1]. Umphang, the southernmost district of the Thai province Tak, is situated at the Thai-Myanmar border and lies near the center point of this triangle. Transmission occurs through the bite of an infected mite of the genus *Leptotrombidium* [2]. As these mites can be found in many different types of vegetation (*e.g.*, forests, rice paddies, or plantations), farmers and people who engage in outdoor activities have a higher risk of contracting scrub typhus [3-5]. Umphang district is dominated by untouched nature, farmland, and mountainous terrain; more than 90% of the registered population lives in a non-urban environment, and the majority of Umphang's population is engaged in the farming industry. Hence, the demography and surrounding environment make Umphang district an ideal setting for scrub typhus. Umphang district harbors many unregistered people, such as refugees, migrant workers, and descendants from hill tribes, entailing a complicated humanitarian situation. Umphang Hospital is the focal point in the region for people, both Thais and immigrants from neighboring countries or refugee camps, who require medical attention.

Patients infected with *O. tsutsugamushi* can present with a wide variety of symptoms; thus, diagnosis solely based on clinical findings is difficult [6,7]. However, a valuable clue for diagnosis is an eschar lesion, a skin lesion that can develop at the inoculation site where the mite bit its host. These lesions do not develop in every patient [6]; therefore, laboratory-based tools are needed to confirm diagnosis, especially if eschars are absent. Currently, the serologic gold standard is the indirect fluorescent antibody (IFA) test, a quantitative test that detects antibodies against *Orientia* species [8]. Alternatives include other serologic tests or molecular

tests. However, many of these tests are expensive, require a high level of expertise, or they have limitations in early or late stages of the disease [9]. Empiric treatment is often chosen if a patient has a potential *O. tsutsugamushi* infection, as many primary healthcare facilities in rural settings do not have access to or lack resources to afford these laboratory-based tools, or if patients cannot comply with follow-up visits. These diagnostic limitations could mean that scrub typhus is potentially one of the most underreported causes of acute febrile illness in endemic areas and accountable for a large proportion of acute undifferentiated febrile illnesses [4,10,11].

The aim of this study was to describe the clinical manifestations of patients diagnosed with scrub typhus in a resource-limited but endemic area and to assess the treatment outcome. Due to lack of recommended diagnostic options and the heterogeneous population, the results also reflect the daily challenges encountered by the healthcare personnel at Umphang Hospital.

Methodology

This retrospective study was conducted at Umphang Hospital at the Thai-Myanmar border. Hospital records of in- and outpatients who were diagnosed with scrub typhus between 2011 and 2014 were reviewed. The only laboratory-based test available at Umphang Hospital is a qualitative immunochromatographic rapid test (SD BIOLINE Tsutsugamushi Assay, Standard Diagnostics, Inc., Yongin, South Korea) that detects antibodies of the IgM, IgG, and IgA classes. Therefore, inclusion criteria were clinical symptoms in conjunction with either a positive rapid test or a pathognomonic eschar lesion.

Demographic and clinical characteristics of patients, including clinical symptoms, physical examination, co-infections, and complications were retrieved from medical records. For hospitalized patients, fever clearance time (FCT) was recorded. FCT was defined as the time from the start of an appropriate antibiotic therapy to the first instance when a body temperature of 37.5°C or lower was recorded and remained below that level continuously for 48 hours. Complications were defined either by elevation of laboratory parameters above the reference level, or by physician diagnosis according to the patients' discharge summary. Antibiotic treatment related to scrub typhus and outcomes were also recorded. Disease outcome and complications were not analyzed in cases with unclear outcome (*i.e.*, patients without follow-up who were lost to follow-up, or who left against advice).

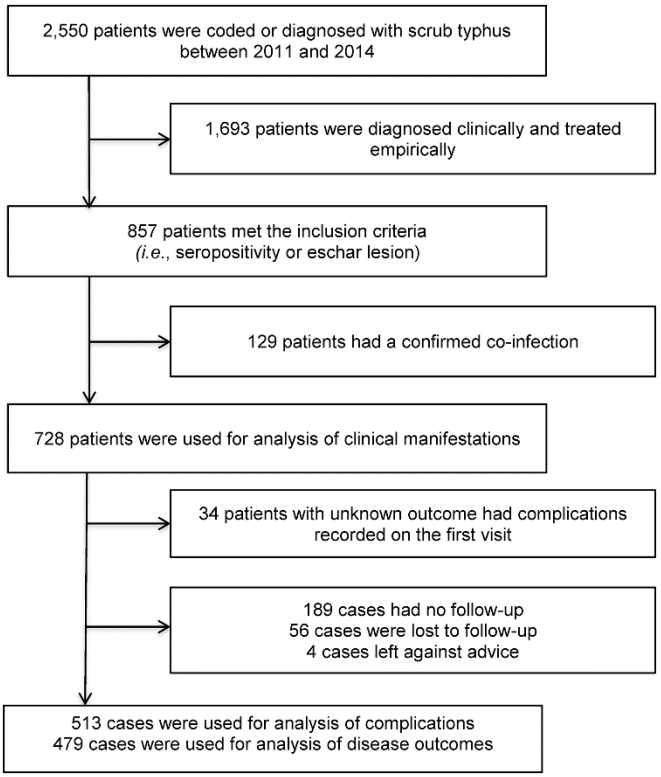
Clinical manifestations and treatment response may differ between adults and children; therefore, clinical manifestations were described and compared between the two groups. Children were defined as participants under 15 years of age. Chi-square or Fisher's exact tests were used for comparison of categorical data. The Mann-Whitney U test was used for comparison of continuous data with non-normal distribution, such as duration of symptoms and FCT. The analyses were performed using SPSS software, version 20 (IBM, Armonk, USA).

The protocol of this retrospective study was reviewed and approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University.

Results

In the period between 2011 and 2014, 2,550 patients were diagnosed with or coded as having scrub typhus at Umphang Hospital. Patients included in this analysis are shown in Figure 1. Most patients were diagnosed clinically, without sero-confirmation or a visible eschar lesion, and could therefore not be included in this study. A total of 857 patients met the inclusion criteria mentioned above. About 43.1% (n = 369) of patients were children under 15 years of age. Most patients (n = 728; 84.9%) were included via sero-confirmation only,

Figure 1. Cases for analysis of manifestations, complications, and disease outcomes.



while 86 (10.0%) of all cases had an eschar lesion and 43 (5.0%) had both (*i.e.*, seropositivity and eschar lesion). Diagnostic confirmation of scrub typhus was different between adults and children, as children were significantly more likely to be diagnosed based on the presence of an eschar lesion. Details of the inclusion process are shown in supplementary figure 1. Overall, the youngest patient was an infant under one year of age, while the oldest was 88 years of age. Of the 488 patients who were categorized as adults, 44.7% were farmers, followed by a heterogenic group classified as laborers (25.2%).

The median duration of symptoms, which was identical with the duration of fever in most cases, was 5 days (interquartile range [IQR]: 3–7) and did not differ significantly between adults and children (p = 0.499). Clinical symptoms of children and adults are compared and summarized in Table 1.

In total, 93.8% patients complained of fever; fever was the most common symptom on presentation, with a significantly higher percentage in children than adults (99.7% vs. 89.6%, p < 0.001). Headache, the second-most prevalent symptom, was described in 48.1% of cases, but adults were more commonly affected (53.1% vs. 41.2%, p = 0.002).

Other symptoms that were found to be significantly different between adults and children included chills, myalgia, dyspnea, abdominal pain, dizziness, and dysuria; these findings were more common in adults, while skin rash, cough, and runny nose were more frequently observed in children.

Table 1. Symptoms and complaints on presentation.

	N (%) of cases (n = 728)		P value
	Adults (n = 422)	Children (n = 306)	
Fever	378 (89.6)	305 (99.7)	< 0.001
Headache	224 (53.1)	126 (41.2)	0.002
Chills/rigor	90 (21.3)	31 (10.1)	< 0.001
Myalgia	151 (35.8)	16 (5.2)	< 0.001
Skin rash	32 (7.6)	53 (17.3)	< 0.001
Nausea	85 (20.1)	47 (15.4)	0.098
Vomiting	116 (27.5)	99 (32.4)	0.156
Diarrhea	36 (8.5)	23 (7.5)	0.621
Dyspnea	39 (9.2)	12 (3.9)	0.006
Cough	115 (27.3)	126 (41.4)	< 0.001
Abdominal pain	98 (23.2)	41 (13.4)	0.001
Loss of appetite	95 (22.5)	85 (27.8)	0.104
Fatigue	54 (12.8)	34 (11.1)	0.491
Sore throat	35 (8.3)	26 (8.5)	0.922
Runny nose	36 (8.5)	67 (21.9)	< 0.001
Seizure	11 (2.6)	4 (1.3)	0.223
Alteration of consciousness	7 (1.7)	5 (1.6)	0.979
Dizziness	17 (4.0)	0	< 0.001
Dysuria	22 (5.2)	4 (1.3)	0.005
Eschar [a]	38/107 (36)	91/144 (63)	< 0.001

Table 2. Eschar distribution comparison between adults and children.

	N (%) of cases (n = 128)	
	Children (n = 90)*	Adults (n = 38)
Genitals	26 (28.9)	5 (13.2)
Axilla	15 (16.7)	3 (7.9)
Groin/inguinal	13 (14.4)	3 (7.9)
Trunk front	12 (13.3)	11 (28.9)
Buttocks/anus	8 (8.9)	0
Legs	6 (6.7)	5 (13.2)
Head	3 (3.3)	1 (2.6)
Neck	3 (3.3)	2 (5.3)
Trunk back	3 (3.3)	2 (5.3)
Arms	1 (1.1)	6 (15.8)

* Excluding one case, whose anatomical location of eschar was not recorded.

Table 3. Complications among patients.

	N (%) of cases (n =5 13)		P value
	Adults (n = 303)	Children (n = 210)	
Complications	161 (53.1)	80 (38.1)	0.001
Pneumonia	30 (9.9)	33 (15.7)	0.049
Jaundice	36 (11.9)	5 (2.4)	< 0.001
Meningo-encephalitis	4 (1.3)	8 (3.8)	0.079
GI bleeding	16 (5.3)	8 (3.8)	0.438
Elevated liver enzymes	74 (24.4)	29 (13.8)	0.003
Elevated kidney function tests	58 (19.1)	6 (2.9)	< 0.001
Shock	37 (12.2)	6 (2.9)	< 0.001
Seizure/convulsion	9 (3.0)	3 (1.4)	0.375
Acute renal failure	8 (2.6)	0	0.024
Acute hepatic failure	1 (0.3)	0	1
Pregnancy (n = 28)			
Preterm labor/contraction	6 (21.4)	0	NA
Abortion/DFIU	6 (21.4)		

NS: not significant; NA: not available; GI: gastrointestinal; DFIU: dead fetus *in utero*.

Eschar lesions were significantly more often seen in children than adults (24.6% and 7.8%, respectively), and a different anatomical distribution was found when adults and children were compared (Table 2). In adults, eschars were most commonly found at the front trunk, whereas in children, the genital region was the most prevalent place of finding.

Information about complications was available for 303 adults and 210 children. Patients who did not come back for a follow-up, who were lost to follow-up or left against advice were not included in this analysis, unless complications were already present at the first visit. Complications were more common in adults than children, as 53.1% and 38.1%, respectively, showed signs of organ-specific or systemic dysfunction (p = 0.001). Abnormal liver and kidney function test as well as jaundice and shock were the most common complications in the adult group, while children were more prone to developing pneumonia/pneumonitis. Preterm labor/contraction and fetal loss as an obstetric complication was also reported frequently. Other common complications are listed in Table 3.

The most frequently used antibiotic was doxycycline, for adults and children alike. The FCT for that particular drug was 28.0 hours (IQR: 12–55.5). Among other commonly used antibiotics were chloramphenicol and azithromycin; however, the number of patients with an available FCT was too small for analysis.

Six cases in the adult group and three in the children group did not survive the infection, resulting in a mortality rate of 2.3% for adults and 1.5% for children. No pregnant woman was reported to have a fatal outcome; however, fetal loss was observed in six instances.

Discussion

Scrub typhus is a common cause of acute illness in Southeast Asia, especially in rural areas such as the district of Umphang on the Thai-Myanmar border. The numbers presented in this study indicate a high incidence of *O. tsutsugamushi* infections in this area. Demographic data confirmed that it can be contracted by all age groups, from toddlers to elderly, and, with farmers being the most affected profession, that socioeconomic status has an influence on the risk.

The only laboratory-based test routinely available at Umphang Hospital is a qualitative rapid test that does not distinguish between an acute infection and underlying seropositivity. Even though antibodies against *O. tsutsugamushi* wane quickly after a primary infection [12], a high rate of seropositivity has to be expected in an endemic area, which can lead to a false-positive rapid test in an acute febrile illness [13]. In a recent assessment of the diagnostic accuracy of the test used at Umphang Hospital, sensitivity and specificity were 20.9% and 74.4%, respectively, for acute specimens and 76.7% and 76.7%, respectively, for convalescent specimens [14]. This highlights the limitations of this test, especially in an acute stage of the disease. There is an urgent need for objective diagnostic tools for rural and resource-limited healthcare facilities. This is especially true for endemic regions where a high underlying seropositivity undermines the power of rapid detection tests [6].

Most co-infections were diagnosed by a higher level of objectivity, as causative pathogens are discernible (*e.g.*, malaria parasites), while others are based on a solid laboratory diagnosis (*e.g.*, positive blood cultures) or lead to distinctive clinical symptoms (*e.g.*, abscesses). To reduce the probability of a false-

positive rapid test in patients with another plausible cause for symptoms on presentation, analysis was focused on cases without co-infection. A table with a complete list of recorded co-infections is available in Supplementary Table 1.

Scrub typhus is commonly referred to as an acute febrile illness. With an overall prevalence of 93.8%, fever was the most common symptom in the present study. However, atypical presentations are possible, especially if fever is absent. The most common symptoms in patients who did not complain about fever were general symptoms such as myalgia, fatigue, loss of appetite, and gastro-intestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. As shown in Table 1, there were significant differences in clinical presentations between adults and children. Even though children might present with different symptoms, it cannot be assumed that a different pathophysiological mechanism is the reason behind this. The discrepancy could be partially explained by the fact that children, especially if they are very young, are not able to express complaints as can their adult counterparts. The lack of ability to verbalize or distinguish similar symptoms (*e.g.*, nausea and abdominal pain) might contribute to the observed difference in prevalence of headache, chills, myalgia, dyspnea, abdominal pain, dizziness, and dysuria. Symptoms such as skin rash, cough, or coryza, which were more common in children, can be seen by somebody who observes the child, and do not need to be expressed. In the event of eschars, an explanation for the higher prevalence in children is based on the assumption that children are more thoroughly examined than adults.

Of 129 eschars, 128 could be allocated to an anatomical region. The distribution was different when comparing adults and children, as children were more likely to have eschars in the genital, axillar, and inguinal areas, while the predilection site in adults was the front trunk. This could also be because physicians might be reluctant to expose adult patients and check for eschars in anatomical areas where they tend to be more common. Pressure points of clothing and areas where the skin folds have been linked to a more frequent formation of eschars in certain anatomical areas [15]. Hence, a different way of dressing might partially explain a different anatomical eschar distribution in adults and children. Generally, the findings in this study confirm that a very wide range of symptoms must be expected when being confronted with a potential scrub typhus case, with fever being the most sensitive clinical symptom.

A similar picture was seen for complications. *O. tsutsugamushi* primarily affects endothelial cells of small capillaries and was also found in many other cells (*e.g.*, macrophages, monocytes, dendritic cells, or cardiac myocytes); therefore, scrub typhus can lead to variety of complications [16,17]. Generally, complications were more common in adults than in children. Organ-specific complications were most commonly found to affect the liver and kidneys, resulting in abnormal laboratory markers, with actual organ failure being rarely observed in the adult population only.

The overall prevalence of abnormal liver function tests was 20.1%, which is lower than that reported in other publications [18,19]. However, only a little over 17% of all the cases had liver function tests available, leading observers to assume that the doctors in charge did not see a reason to perform the tests. However, an absent clinical suspicion does not rule out an elevation of hepatic enzymes; hence, this number might underrepresent the real picture. A similar conclusion can be drawn for kidney function tests, as not all patients were tested. Additionally, other influencing factors such as age or hydration status could not be taken into consideration. Atypical presentations can be a manifestation of a complication, such as melena or hematochezia, which are known to be a potential complications of scrub typhus [20]. These presentations pushed some patients to seek medical advice, and it was later discovered that they had a scrub typhus infection. Some of the recorded complications cannot be interpreted independently because they are linked to each other (*e.g.*, profound headache, seizures, or alteration of consciousness can be early signs of meningoencephalitis, and impaired liver function can lead to jaundice).

Obstetric complications should be addressed separately, as they can lead to grave complications. Data on pregnancy outcomes in conjunction with a scrub typhus infection are scarce. However, scrub typhus was linked to poor pregnancy outcomes; this was also reported in a fever cohort study in a nearby district [21-23]. The number of pregnant women presenting with obstetric complications (*e.g.*, preterm labor or contraction and fetal loss) related to scrub typhus was very high. Considering these findings, it must be emphasized that pregnant women need special attention. Azithromycin is an alternative that can be safely prescribed during pregnancy [21,24]. If clinical presentation is the only diagnostic tool, empiric treatment should not be delayed if there is suspicion of a scrub typhus infection in a pregnant woman.

In total, 120 patients who received doxycycline met the definitions and an FCT was computable. The median FCT for doxycycline was 28 hours, which is very similar to a report by Watt *et al.*, who found a median FCT of 30 hours in patients from Mae Sot, Thailand [25]. However, the treatment response to doxycycline in Umphang seems to be superior when compared to other parts of the country [26,27]. With an overall mortality rate of 1.9%, the outcome was favorable, indicating effective treatment.

Conclusions

The numbers seen in this study indicate that Umphang district has a high incidence of scrub typhus; it should be in the differential diagnosis of every patient presenting with an acute febrile illness. Clinicians must be vigilant, as patients can present with a variety of clinical symptoms, regardless of the presence of fever. Every patient with a suspected *O. tsutsugamushi* infection should be examined thoroughly for eschar lesions, as it is of diagnostic value. If diagnosed early, treatment is effective and a favorable outcome can be expected.

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Authors' contributions

TB and YW conceived the study. TB, YW, CK, VC, and SL designed the study protocol. TB and CNL collected the data. TB, YW, CK, CV, SL, and CNL analyzed the data. TB drafted the manuscript; TB, YW, CK, CV, SL and CNL critically revised the manuscript. All authors read and approved the final manuscript.

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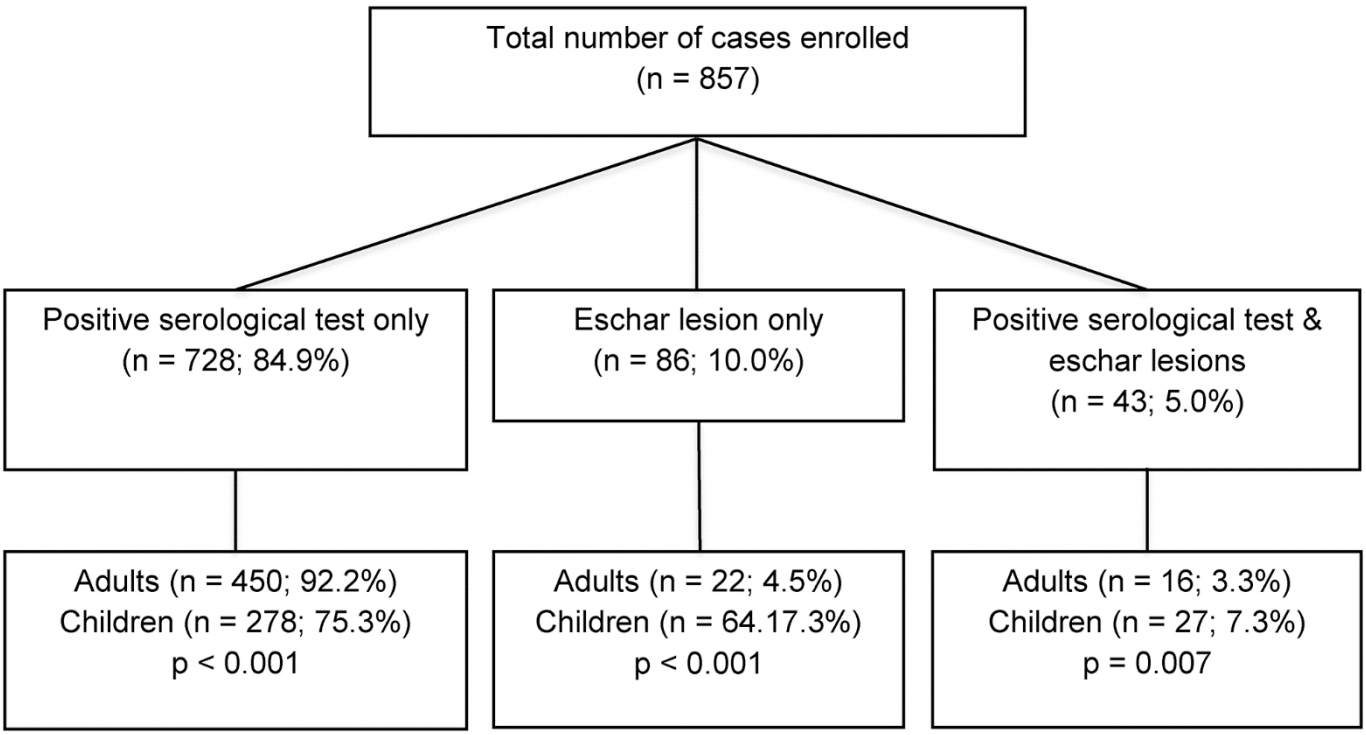
Annex – Supplementary Items

Supplementary Table 1. Recorded co-infections.

	N (%) of cases (n = 857)	
	Adults (n = 488)	**Children (n = 369)**
Plasmodium falciparum	17 (25.8)	34 (54.0)
Plasmodium vivax	9 (13.6)	9 (14.2)
UTI/pyelonephritis	15 (22.7)	4 (6.3)
Dengue virus infection	2 (3.0)	3 (4.8)
Abscess/cellulitis	4 (6.1)	1 (1.6)
Pharyngitis/tonsillitis	1 (1.5)	5 (7.9)
Septicemia	2 (3.0)	3 (4.8)
Other	17 (25.8)	9 (14.3)

UTI: urinary tract infection.

Supplementary Figure 1. Schematic diagram of subjects' enrolment.



Most of the subjects enrolled were included via a positive serologic test. Fifteen percent (n = 129) presented with an eschar lesion, of which 33.3% (n = 43) met both inclusion criteria. A significant difference in the way of inclusion was seen when comparing adults and children, as children were more likely to be diagnosed based on the presence of an eschar lesion.