Le Infezioni in Medicina, n. 3, 312-322, 2024
doi: 10.53854/liim-3203-5

Frequency and distribution of eschar in patients with scrub typhus in India: systematic review of literature and meta-analysis

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Article received 28 May 2024, accepted 10 July 2024

SUMMARY

Introduction: Scrub typhus is a mite-borne tropical febrile illness with high mortality if untreated. The presence of eschar is pathognomonic, but a wide range of frequencies of eschar positivity has been reported in Indian patients. Therefore, this systematic review and meta-analysis aimed to ascertain the frequency (overall and geographic region-wise) and anatomical distribution of eschar in scrub typhus in India.
Methodology: We searched articles in two databases using: [(scrub OR typhus OR Orientia) AND (eschar) AND (India)]. The articles were independently screened and critically appraised by two authors. The frequency and distribution of eschar in patients with scrub typhus were pooled using a random-effect model.
Results: After the title-abstract and full-text screening, 107 articles (34002 cases of scrub typhus) were finally included. The overall pooled proportion of eschar positivity was 28.5% (95% CI: 24.1 to 32.9%). The pooled eschar positivity varied from ≤12% in Haryana, Rajasthan, Madhya Pradesh, Punjab, and Meghalaya to ≥46% in Tamil Nadu and Tripura. The pooled proportion of eschar positivity in the 'trunk' (39.3%), 'groin' (23.8%), and 'axilla' (16.5%) was higher than in the 'limbs' (9.9%) and 'head' (11.3%).
Conclusion: Eschar is reported in less than a third of the patients with scrub typhus in India. Most eschars were in the groin, axilla, and the trunk. There is a need to create awareness amongst physicians of the need for thorough physical examination.

Keywords: Eschars, scrub typhus, India.

INTRODUCTION

Scrub typhus, caused by the *Orientia tsutsugamushi,* a bacterium of the Rickettsiaceae family, has a high burden in Southeast Asia [1]. This acute febrile illness is transmitted through the bite of larval trombiculid mites, known as chiggers, and is associated with eschar development at the bite site. With increasing awareness, there has been a steady rise in the number of reported cases of scrub typhus from India [1]. Laboratory facilities with capacities to do serological tests [Immunofluorescence assay (IFA), Enzyme-linked immunosorbent assay (ELISA)] or molecular tests are required to confirm scrub typhus diagnoses. A simple physical examination can be fruitful in resource-limited settings where these tests are scarce [2]. Since several other febrile illnesses, such as dengue, malaria, leptospirosis, enteric fever, etc.,

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can have similar presentations, the presence of eschar is useful in making an early confirmatory diagnosis [2].

The classical description of an eschar is a black necrotic lesion with an erythematous base [3]. Three eschar stages are described in the earliest scrub typhus reports [4]. The first stage is a small papule at the site of the mite bite. A shallow ulcer is formed with a red base in the second stage. The ulcer becomes a scab in the third stage, and the red base starts scaling. The scab is shed in two to three weeks. Most patients present in the second stage [4]. It must also be noted that an inexperienced examiner can rarely confuse the morphology of eschar with old scabs or clots. While phenotypic identification is enough for diagnosing scrub typhus in most cases, in cases of atypical appearance, polymerase chain reaction (PCR) assay from eschar material (biopsy or swab) has shown to be useful [5]. In a study of 20 patients in whom both swabs from eschar and whole blood were obtained for PCR, eschar was positive in 85% of the patients, while whole blood was positive in 25% [6]. On ultrastructural visualisation of the eschar biopsy, *Orientia tsutsugamushi* was found in the peripheral erythematous region but not the central necrotic region [7].

Studies worldwide report eschar at frequencies ranging from less than 10% to more than 90% [8]. There is a need to pool data on the frequency of eschar positivity from India systematically to understand the utility of eschar as a stand-alone tool for scrub typhus diagnosis. This will inform us of the need for better clinical decision-making tools and diagnostic tests. There is also a need to identify anatomical sites on the human body where eschar is most localized to educate busy clinicians on "Where to look for an eschar". Therefore, this study aimed to ascertain the overall and geographic region-wise frequency and anatomical distribution of eschar in India.

METHODOLOGY

This systematic review and meta-analysis (SRMA) was registered with PROSPERO (Registration number CD42023483597) and has been reported according to the PRISMA guidelines [9]. We searched PubMed and Embase databases using an appropriate search string: [(scrub OR typhus OR Orientia) AND (eschar) AND (India)]. Articles in all languages from the two databases between 01.01.1900 and 16.11.2023 were included in the study. This SRMA included studies with individuals of any age and sex (including pregnant individuals) who were diagnosed with scrub typhus in India. Those studies that explicitly mentioned the presence or absence of eschar were included. We included randomized controlled trials, non-randomized clinical trials, analytical observational studies, and case series (≥20 cases). Studies on non-human subjects were not included. Case reports, case series (<20 cases), reviews, systematic reviews, conference abstracts and letters to the editor were excluded. After removing the duplicates, two authors (NG and KF) screened the titles and abstracts for eligibility. After the initial screening, the same two authors retrieved full-length articles for full-text screening. The conflicts were resolved by the third author (CB). Articles that met the eligibility criteria were included in the final analysis. Two authors independently appraised the articles using the standardized JBI critical appraisal checklist (CB and NG) [10]. The conflicts were resolved by the third author (TPK). Of the eight critical appraisal criteria, the exposure management criteria were not recorded as they were considered irrelevant to the current SR.

The following data were retrieved from the included articles to meet the study's objective: author details, type of study, geographic region of India in which the study was conducted, details of microbiological diagnostics, age group of the included patients (adult or paediatric or both), number of included patients with confirmed scrub typhus and number of patients with eschar (overall and at each anatomical site).

For the quantitative synthesis, only studies which used diagnostic modalities with considerable specificity were included. Diagnostic modalities considered specific based on published literature were IFA, ELISA, ICT and PCR [11]. Weil-Felix test was not considered diagnostic of scrub typhus as previous studies show its poor diagnostic accuracy [12]. Those studies where serology was used for making a diagnosis, but the type of serology was not specified were also excluded. The anatomical distribution of eschar was also noted in the included studies. The anatomical location of eschar was categorized in the following headings: 'axilla' (includes axilla and infra-axillary location), 'groin' (includes inguinal region, genitals, peri-anal and buttocks),

'trunk' (includes shoulders, chest, breast, abdomen, back, trunk), 'limbs' (includes arm, forearm, hands, thighs, legs and feet), and 'head' (includes face, scalp, ears, peri-oral region and neck).
The data on frequency of eschar positivity in patients with scrub typhus were pooled using a random-effect model (Der Simonian and Laird), and the results were represented by a point estimate with a 95% confidence interval. The frequency of eschar positivity was calculated for different geographic regions (states and union territories) of India. Whenever two or more studies were reported from the same geographic regions, they were pooled using the random-effect model. The frequency of positivity (pooled or otherwise) in different regions was plotted on a map using the function available in Microsoft Excel. The frequencies of eschar in five different anatomical locations (axilla, groin, trunk, limbs and head) were similarly pooled, with the denominator being the total number of eschars in the study. The heterogeneity across studies was tested using the I^2 test. The meta-analysis was performed using the open-source meta-analysis software (developed by Wallace et al.) that uses the R environment as the statistical engine and Python for the graphical user interface [13].

RESULTS

A total of 276 articles from Embase and 169 articles from PubMed were included for screening. After deleting 148 duplicates, 297 articles were included in the title-abstract screening. Out of these, 149 articles were selected for full-text screening. A total of 107 articles (34002 cases of scrub typhus) were finally included for data extraction and critical appraisal after excluding 42 articles [14-120]. The PRISMA flow chart was generated using the package developed by Haddaway et al. (Figure 1) [121]. All the included studies were published between 2010 and 2023. Most of the studies (n=57) were published in or after 2018.
Using the JBI checklist, the criteria for inclusion and study subjects were described in all studies. Most

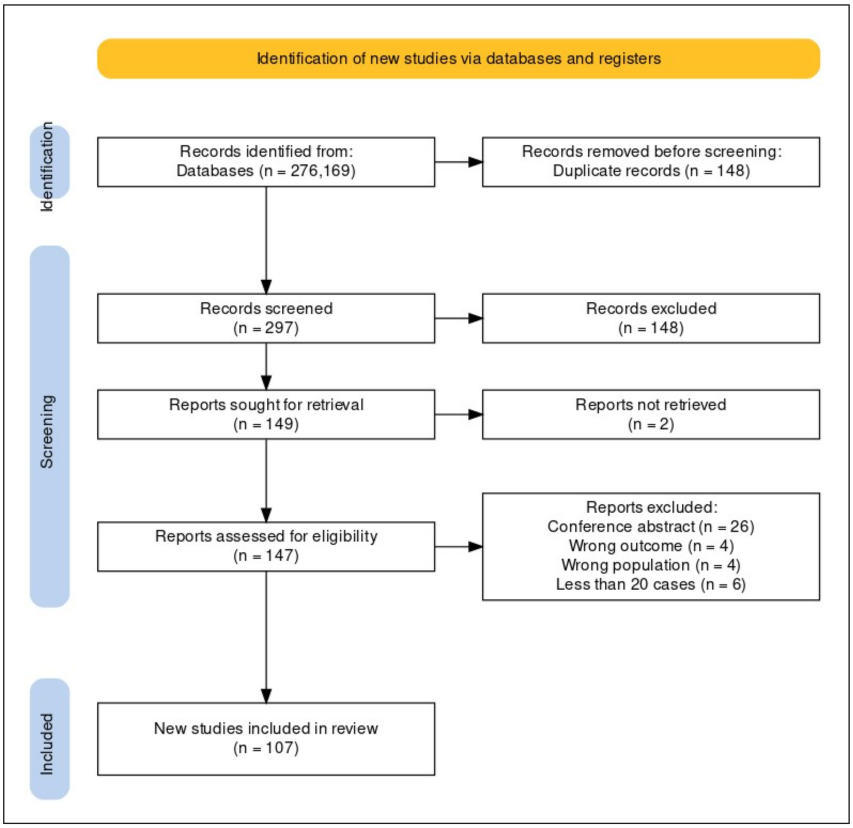


Figure 1
PRISMA flow diagram showing screening and final inclusion of the studies.

studies did not identify confounding factors (n=91) and/or did not have strategies to deal with confounding (n=101), but these are unlikely to affect the primary objectives of this SRMA. Although outcomes were measured in the included studies, very few studies mentioned active strategies to search for eschars. The criteria for defining the disease (scrub typhus) were not mentioned in the five studies [18, 41, 42, 74, 116]. Studies that used only the Weil-Felix test (n=17) for diagnosis were excluded from the quantitative synthesis [17, 20, 24, 31, 40, 45, 53, 56, 63, 66, 73, 76, 79, 90, 92, 100, 118]. Additionally, two studies that included only patients with eschar were excluded from the prevalence of eschar estimation [65, 67]. IgM ELISA (n=81), ICT (n=10), IFA (n=6), and PCR (n=9) were the diagnostic modalities used in the included studies.

Of the 83 studies (n=11,471) included for the estimation of the prevalence of eschar, most studies were published in Tamil Nadu and Puducherry region (n=23) (Supplementary Table 1). Thirty-two studies focused entirely on the paediatric population. In contrast, 51 studies included adults or both adult and paediatric patients. The prevalence of eschar in patients ranged from 0 to 74% (Figure 2). Fifteen studies found the prevalence of eschar to be less than or equal to 10%, while only 14 found a prevalence of 50% or more.

The pooled prevalence of the eschar was 28.5% (95% CI: 24.1 to 32.9) with high heterogeneity (I^2-97.5%) (Supplementary Figure 1). The pooled frequency of eschar positivity in different geographic regions is summarized in Figure 3 and Supplementary Table 1. The forest plots for the pooled

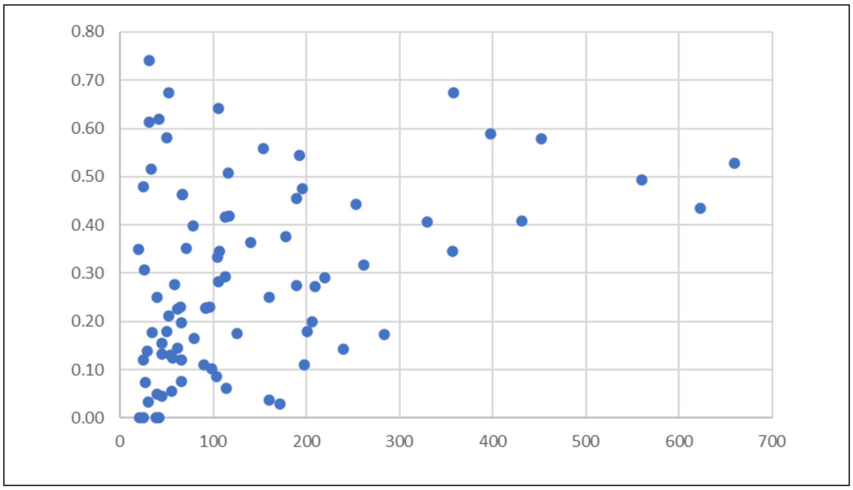


Figure 2
Frequency of eschar positivity in patients with scrub typhus (X-axis: number of scrub typhus patients, Y-axis: proportion of eschar positivity).

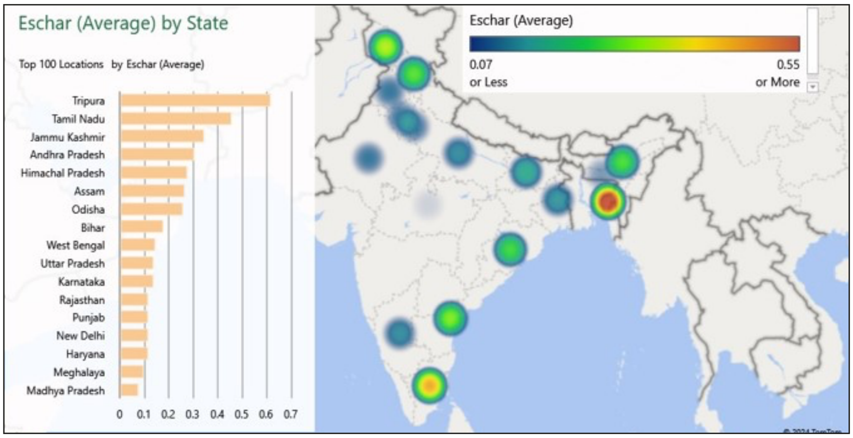


Figure 3
Frequency of eschar positivity in different geographic regions (states and union territories) of India. (As the colour gradient moves from violet to red, the frequency of eschar positivity increases).

prevalence of geographic regions with two or more studies on eschar frequency are in the Supplementary Appendix (Supplementary Figures 2-11).

There was no significant difference when the pooled proportion of eschar positivity was calculated for retrospective [29.2% (95%CI: 21.2%-37.3%)] and prospective studies [28.2% (95%CI: 22.8%-33.5%)] separately (Supplementary Figure 12,13). When the frequency of eschar positivity was calculated separately for the paediatric population, it was not significantly different from the overall population [30.1% (95%CI: 22.5%-37.9%)] (Supplementary Figure 14).

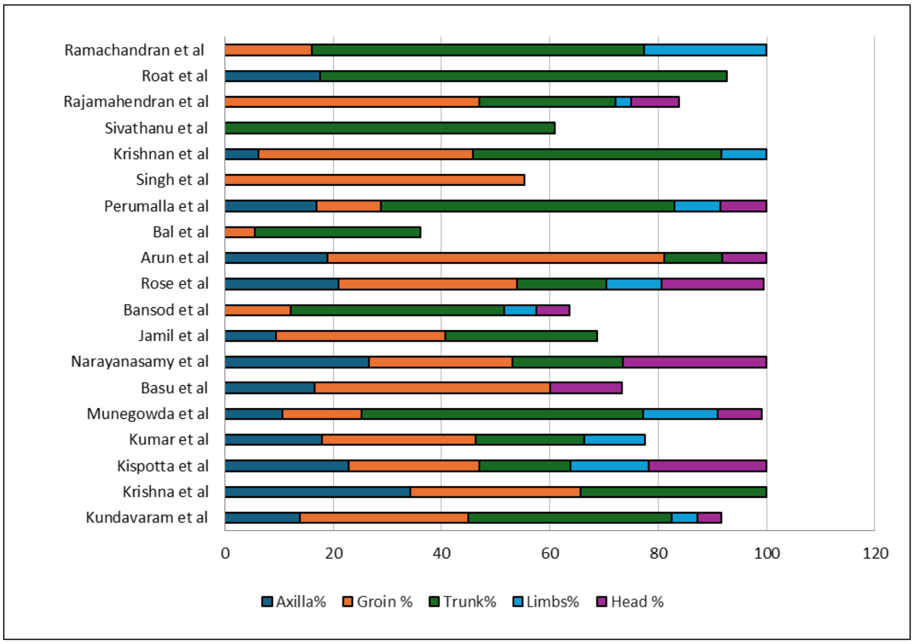
The pooled proportion of eschar in various anatomical sites was as follows: 'trunk' [39.3% (95% CI: 29.4%-49.3%)], 'groin' [23.8% (95%CI: 17.6%-30%)], 'axilla' [16.5% (95% CI: 13.4%-19.6%)], 'head' [11.3% (95%CI: 7.4%-15.3%)] and 'limbs' [9.9% (95% CI: 7-12.9%] (Supplementary Figures 15-19). The most common location of eschar in those studies that did not report the exact frequency is summarized in Supplementary Table 2. For studies that reported eschars in more than 20 participants, the relative frequency of eschar at various locations is summarized in Figure 4 [16, 19-21, 24, 25, 31, 33, 40, 41, 46, 49, 57, 62, 64-67, 76, 82, 85, 90-92, 105, 108, 111-113].

Most studies showed a high frequency of localization of eschar in the 'groin' and 'trunk'. Of the 427 cases in the 'groin', where individual details of the location were available, most eschars were localized in the inguinal region (n=242, 57%), followed by perineal/anogenital region (n=167, 39%) and buttocks (n=18, 4%) [16, 19, 20, 21, 24, 25, 33, 40, 41, 49, 57, 64-67, 6, 82, 85, 92, 108, 113]. Of 403 patients with eschar on the 'trunk' with details of localization available, 222 (55%) were on the abdomen, 97 (24%) on the chest/breast and 84 (21%) on the back [16, 19, 21, 24, 25, 31, 33, 41, 46, 49, 57, 62-67, 76, 82, 85, 90, 105, 108, 111-113]. Many patients with eschar on the abdomen were localized around the umbilicus and the inframammary region (in women) [16, 19]. Of the 107 patients with details of localization of eschar on the 'head', 66 (61.6%) were on the neck, while 41 were on the scalp/face (38.3%) [16, 21, 24, 25, 40, 41, 49, 57, 64, 66, 67, 111, 113. In some studies, eschar on the ears and eyelids were also reported. [21, 41]. Four studies reported some patients with multiple eschars as well [40, 65-67].

DISCUSSION

In this SRMA, the frequency of eschar in confirmed scrub typhus cases ranged from 0 to 74%,

Figure 4
Relative frequency of eschar at various locations in percentage in those studies that reported eschars in more than 20 participants. (Note- Some studies do not add up to 100% because of incomplete details or difficult categorization).



with a pooled proportion of 29%. Some geographical disparities were observed within India, but not between age groups or study design. Most eschars were located on the trunk, groins and axilla. A previous SRMA by Yoo et al. that included studies till 2019 on the global prevalence of eschars reported that the prevalence of eschar in India was 33.3%. as opposed to a prevalence of 79% in East Asia and 52% in Oceania [122]. That SRMA concluded that the variation in eschar presence might be associated with differences in strains or mite species [122]. In India, the Kato-like and Karp-like genotype is common [123]. Additionally, previous studies have noted that eschar is challenging to spot in dark-skinned individuals, which might partially explain the low positivity in India [4]. One of the aims of the current SRMA is to explore the low eschar positivity in India further. More than 20 additional studies from India have been published since 2019 (the last date of inclusion for the previous SRMA) that explored the frequency and distribution of eschars in various regions of India. Additionally, the previous SRMA did not explore the geographic regional differences in eschar distribution in India.

The regional pooled eschar positivity varied from 12% or below in Haryana, Rajasthan, Madhya Pradesh, Punjab (including Chandigarh), and Meghalaya to 46% or above in Tamil Nadu (including Puducherry) and Tripura (Figure 3). In general, we noted that the frequency of eschar positivity in South Indian centres (Tamil Nadu, Andhra Pradesh) was higher than in other geographic regions. This could be because of their longer experience in diagnosing and managing scrub typhus, as evidenced by the number of reported studies [26, 35-37, 39, 43, 46, 56-58, 64, 86, 95, 98, 101, 107-109, 113]. Also, as evident from Figure 2, studies with a larger sample size (≥300 scrub typhus patients) generally had a higher frequency of eschar positivity than the average. It is also possible that cultural and regional differences in practices might have played a role in physicians' reluctance to examine private areas of the body, such as genitals, where eschars are commonly located. Since all hospitals in India do not have temperature regulators, it can be assumed that a full body examination would be particularly difficult in colder regions. Since the hospital catchment area and population density vary from region to region, the consultation time per patient also varies. It is possible that eschar might be more frequently missed in a busy hospital. There is some variation in the prevalent genotypes in the different regions, which might have had an impact on the eschar positivity. In a multi-centric study, the Kato-like genotype was common in all regions, but North India and Northeast India also had Karp-like genotypes [123].

Since the larval stage of mites is not visible easily by the naked eye and the bite is painless, patients frequently miss these lesions. In the case of children, vigilant parents can often localize and report these lesions [40]. We postulated that eschar positivity in paediatric patients would be higher because of the vigilant parents and the ease of examination. However, we found no significant difference between adult and paediatric patients. Typical eschars are easy to identify, but they might get missed if the patient presents early with a non-specific lesion or presents late when the eschar has already healed [124]. It is also possible that previous exposure to the organism or use of antibiotics before presentation can impact the morphology of eschar [65]. Similarly, early eschar lesions may be easily missed by an inexperienced eye. An in-vitro study showed that intradermal inoculation produces eschar, but subcutaneous bite does not [124]. Therefore, the variation in the size of the proboscis of the mite may explain the absence of eschar [124].

Studies that included IgM ELISA often did not mention the cut-off they used for the diagnosis. Previous studies have shown that the cut-off optical density value in various regions is higher than the cut-off of 0.5 recommended by some guidelines [125]. Using a lower cut-off may have led to the inclusion of false positives, thereby decreasing the prevalence of eschar. We postulated that the proportion of eschars would be higher in prospective studies because we expected the search would be more thorough in a well-planned prospective study. However, the eschar positivity in India did not change significantly with the type of study (prospective or retrospective). Observational studies (both prospective and retrospective) often rely on documentation of eschar by the treating physicians. Poor documentation may have underestimated the frequency in both types of studies.

It is postulated that the chigger of the trombiculid bite latches on to the human and migrates up on a foreign object (at a speed of 2.2 inches per minute)

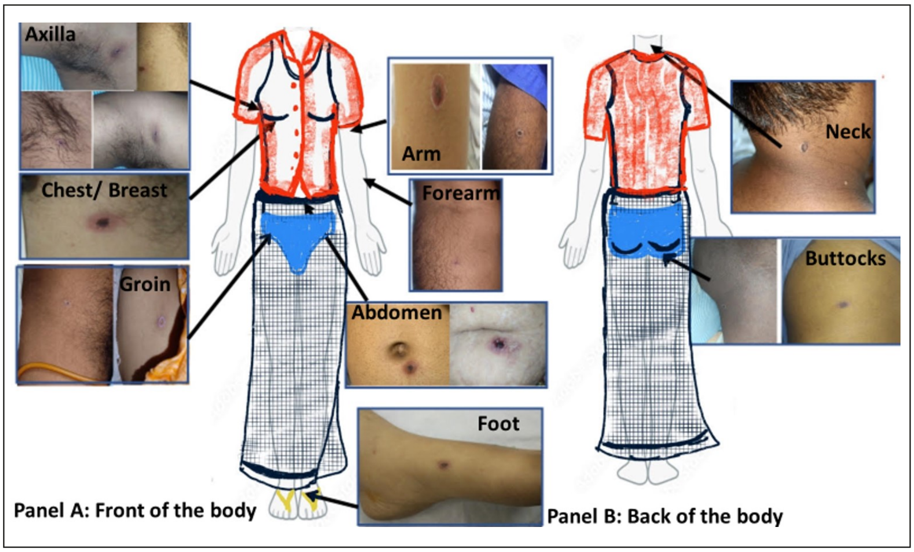


Figure 5 Representative image of a human body clothed in a representative Indian attire with eschar images (obtained from patients after consent) in different locations. Panel A shows the front of the body with eschars in the axilla, chest/breast, abdomen, groin and limbs. Panel B shows the back of the body with eschars on the neck and buttocks.

till it finds resistance [3]. The site of the bite is usually at warm and moist locations where there is resistance, either due to the shape of the body (e.g. axilla, groin, inframammary region) or in regions where there is an artificial pressure point due to tight clothing (e.g. edges of the underwear) (Figure 5). The most common location of eschar in the SR was the 'trunk', with a pooled proportion of 39%. It is worth noting that many studies localized the eschar site around the inframammary region in women. It is also commonplace to see the eschar near the umbilicus, where traditional Indian clothing (Dhoti/lungi in men and saree in women) is tied [112]. Some studies reported eschar in unusual locations such as ears or eyelids. These regions should also be examined in patients with suspected scrub typhus.

Limitations of the systematic review: We excluded case reports and case series with less than 20 cases to get the maximum number of studies with good-quality data. Of the included studies, very few studies had a primary objective of locating eschars, and the researchers often relied on the documentation of treating physicians. Although we tried to include studies that utilized a serological test of reasonable specificity, it was often not possible, as discussed earlier. Several studies combined the distribution of eschar in different regions (e.g. eschars in arm and axilla), which made it difficult to include all the available data for quantitative synthesis [113].

The study concluded that eschar is reported in less than a third of the patients with scrub typhus in India. Most eschars were located in the groin, axilla, around the umbilicus and inframammary region. There was a regional variation in the eschar positivity. In scrub typhus endemic areas, physicians need to be aware of the importance of a focused dermatologic examination of the trunk, groin and axilla of patients presenting with acute febrile illness. Other reasons for low eschar positivity among scrub typhus cases in certain regions deserve further study.

Authors contribution

NG and TPK contributed equally to the manuscript and should be considered as joint first authors.

Conflict of interest

None.

Funding

None to declare.

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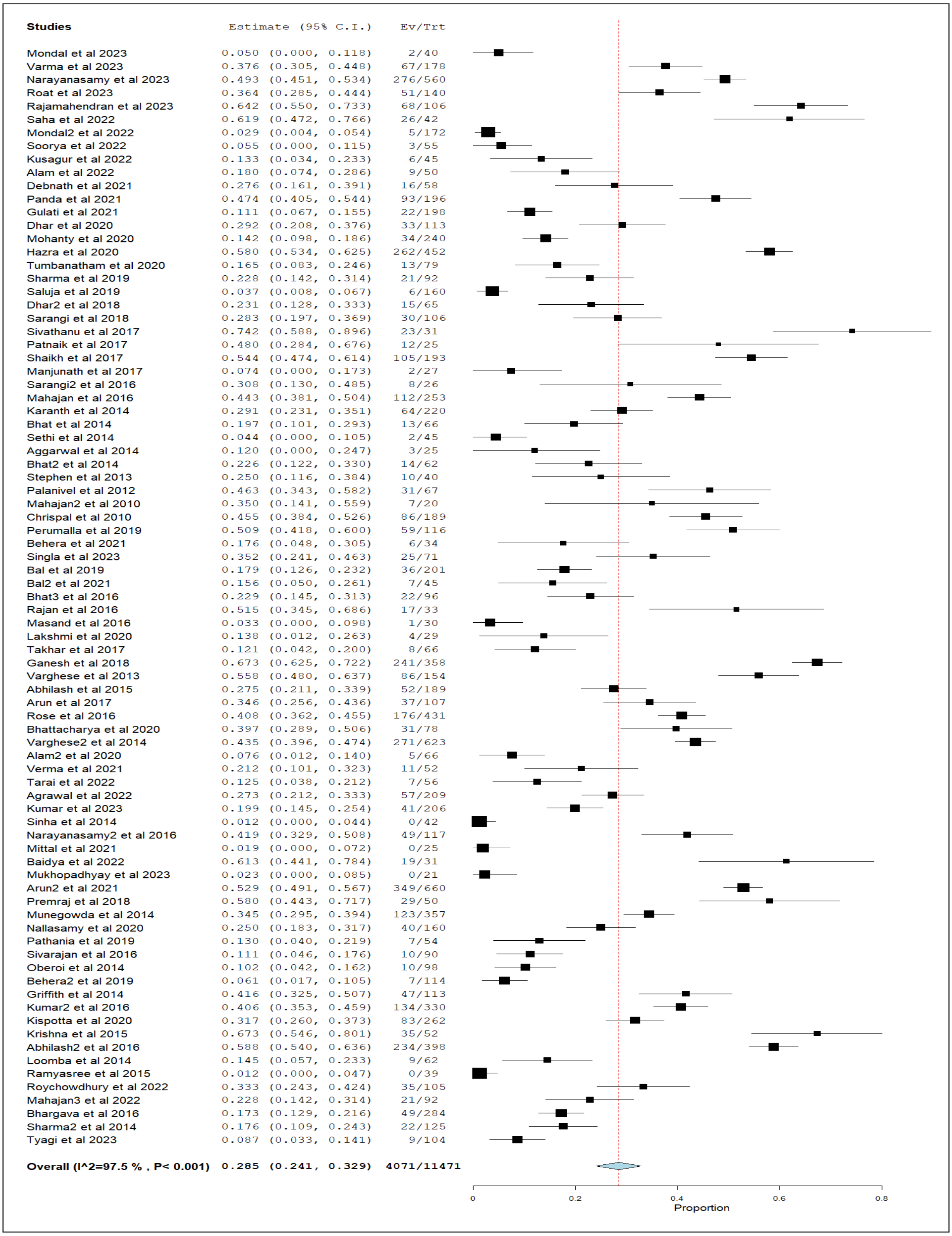
Supplementary Table 1 - Geographic region-wise frequency of eschar patients with scrub typhus.

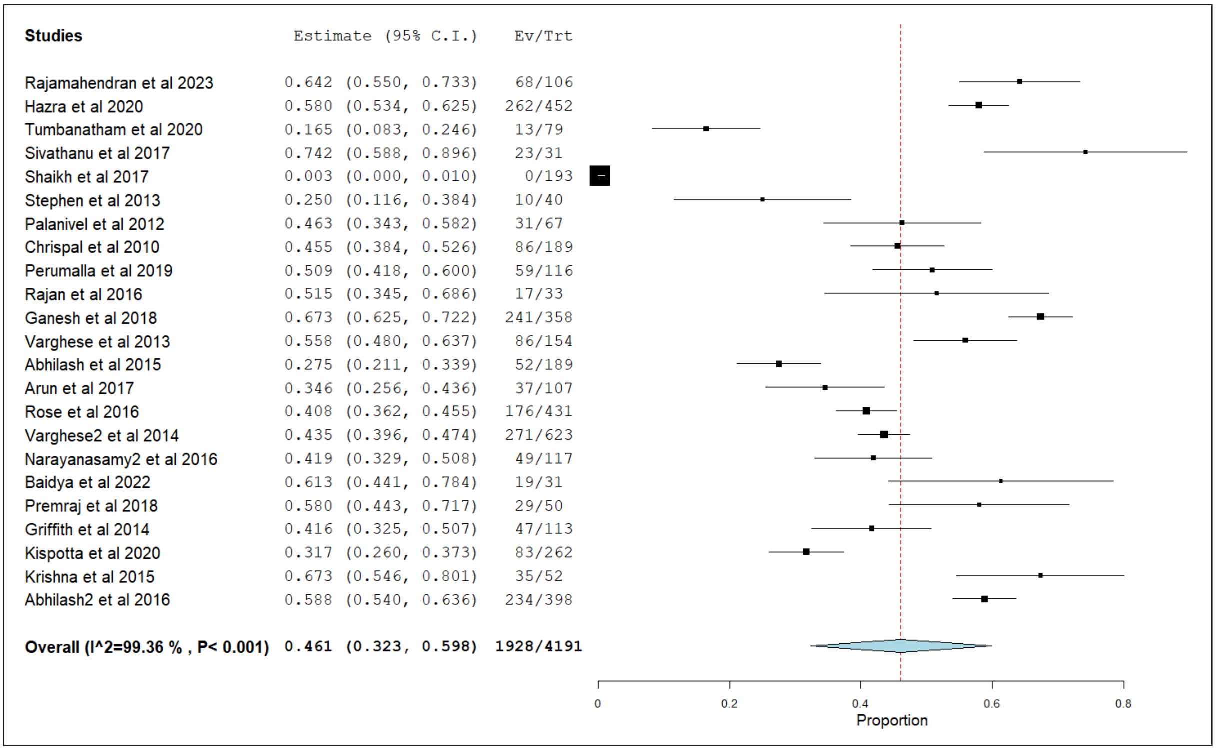
State	*Total Scrub*	*Number of studies*	*Prevalence*
Tamil Nadu and Puducherry	4191	23	46.10%
Andhra Pradesh and Telangana	1466	5	31.10%
Odisha	1260	11	26.40%
Himachal Pradesh	893	6	28.50%
Karnataka	847	5	14.20%
Uttar Pradesh and Uttarakhand	726	9	13.60%
Rajasthan	563	6	11.90%
West Bengal	523	4	14.90%
Punjab and Chandigarh	479	5	11.80%
Meghalaya	168	2	10%
Madhya Pradesh	104	1	8.60%
Assam	58	1	27.50%
New Delhi	56	1	12.50%
Bihar	50	1	18%
Tripura	42	1	61.90%
Haryana	25	1	12%
Jammu Kashmir	20	1	35%

Supplementary Table 2 - Distribution and localization of eschar in studies where the exact frequency of positivity in each location was not mentioned.

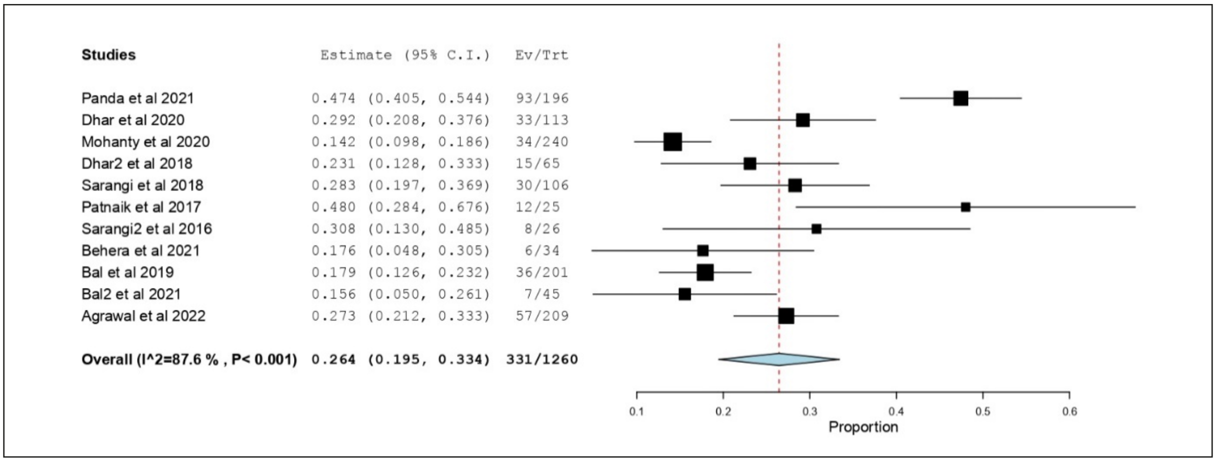
Sn	*Authors*	*State*	*Eschar (n)*	*Distribution of eschar*
1	Saha 2022 et al.	Tripura	26	Inguinal/peri-inguinal, axilla, below breast
2	Debnath 2021 et al.	Assam	16	Medial aspect of thigh, perineum, abdomen, armpit, upper back
3	Saluja 2019 et al.	Rajasthan	6	Groin, back and lower extremities
4	Dhar 2018 et al.	Odisha	15	Extremities, abdomen and thorax, groin and axilla, male genitalia
5	Patnaik 2017 et al.	Odisha	12	Axilla, abdomen, ear, groin, genitals
6	Shaikh 2017 et al.	Tamil Nadu	105	Groin, genitalia, axilla, chest
7	Chellamma 2016 et al.	Tamil Nadu	7	Abdomen, axilla, groin
8	Agarwal 2014 et al.	Andhra Pradesh	20	Abdomen, chest and neck
9	Aggarwal 2014 et al.	Haryana	3	Lower limbs
10	Bhat 2014 et al.	Uttarakhand	14	Groin and axilla
11	Stephen 2013 et al.	Pondicherry	10	Axilla, nipple, scrotum, forehead, shoulder, back, abdomen, leg, knee and foot
12	Palanivel 2012 et al.	TN	31	Axilla, genitalia, inguinal area
13	Vivekanandan 2010 et al.	Pondicherry	23	axilla, breast, groin
14	Varghese 2013 et al.	Tamil Nadu	86	groin, axilla, neck, breast folds
15	Abhilash 2015 et al.	Tamil Nadu	52	groin, genitalia, axilla, neck, inframammary folds
16	Verma 2021 et al.	Uttar Pradesh	11	abdomen, thighs and arms
17	Abhilash 2016 et al.	Tamil Nadu	234	groin, axilla, genitalia, neck, breast folds
18	Palanivel 2012 et al.	Tamil Nadu	31	axilla, genitalia, inguinal area
19	Bhargava 2016 et al.	Uttarakhand	49	neck, axilla, abdomen, inguinal and pubic regions
20	Sharma 2014 et al.	Rajasthan	22	axilla, breast, groin



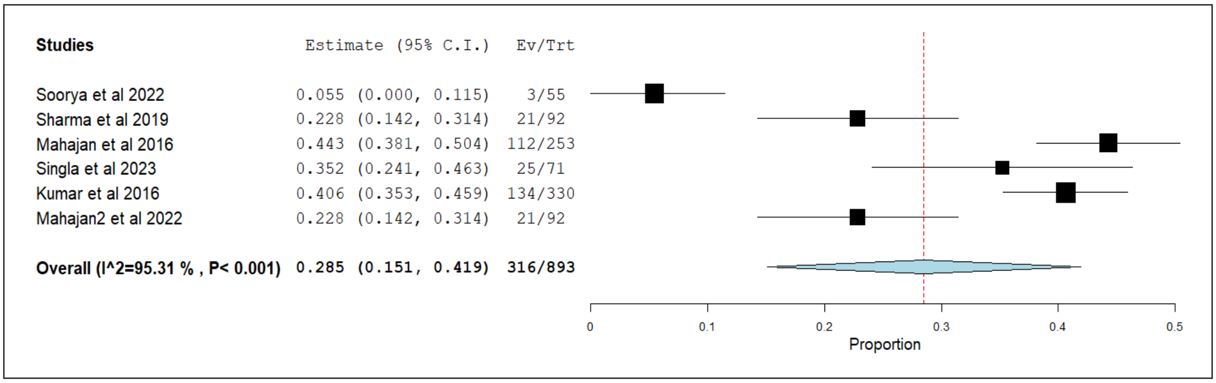
Supplementary Figure 1 - Forest plot showing the pooled prevalence of eschar in India.



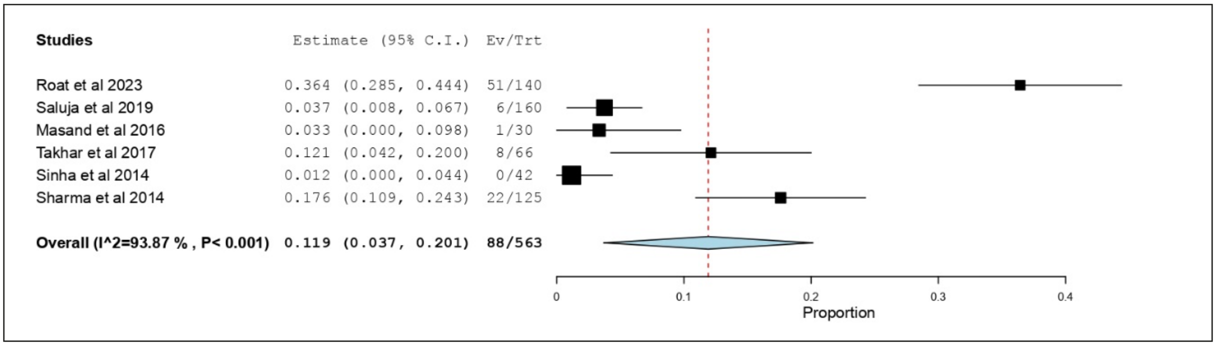
Supplementary Figure 2 - Forest plot showing the pooled prevalence of eschar in Tamil Nadu and Puducherry.



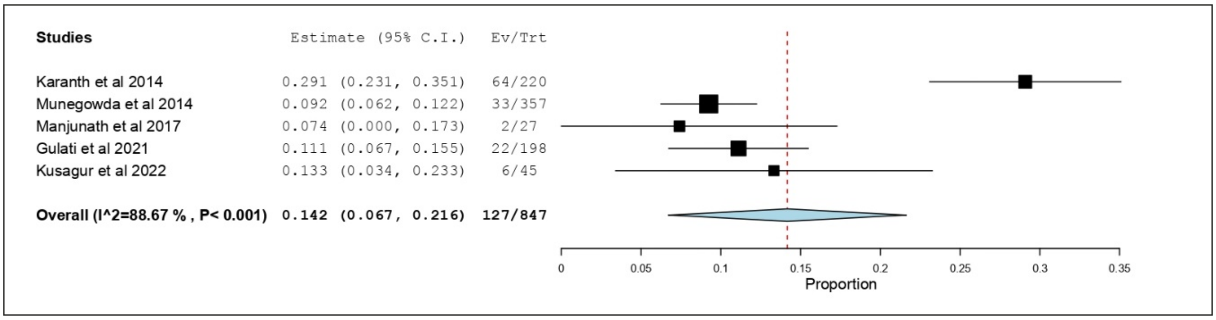
Supplementary Figure 3 - Forest plot showing the pooled prevalence of eschar in Odisha.



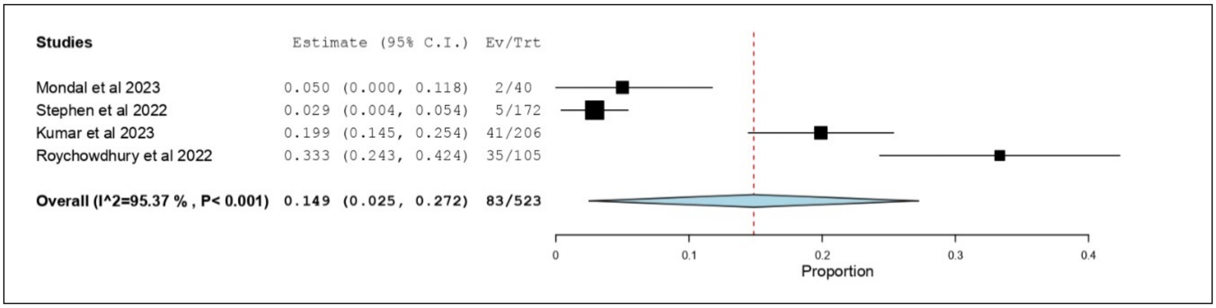
Supplementary Figure 4 - Forest plot showing the pooled prevalence of eschar in Himachal Pradesh.



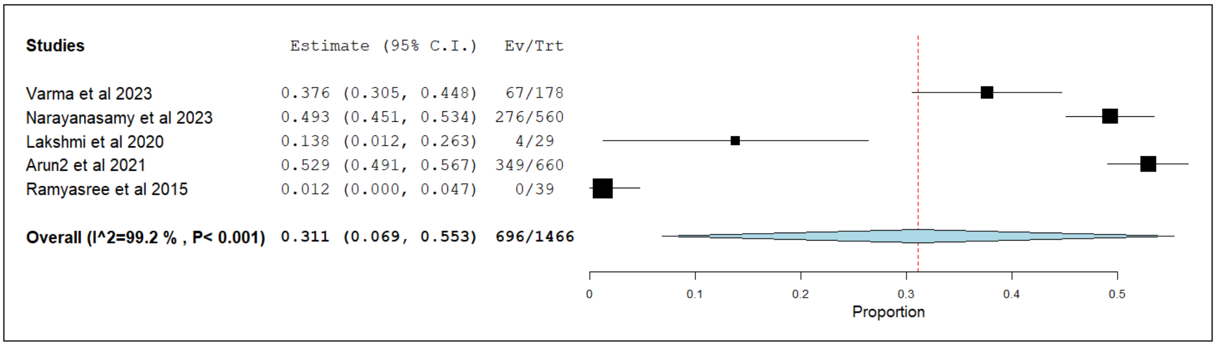
Supplementary Figure 5 - Forest plot showing the pooled prevalence of eschar in Rajasthan.



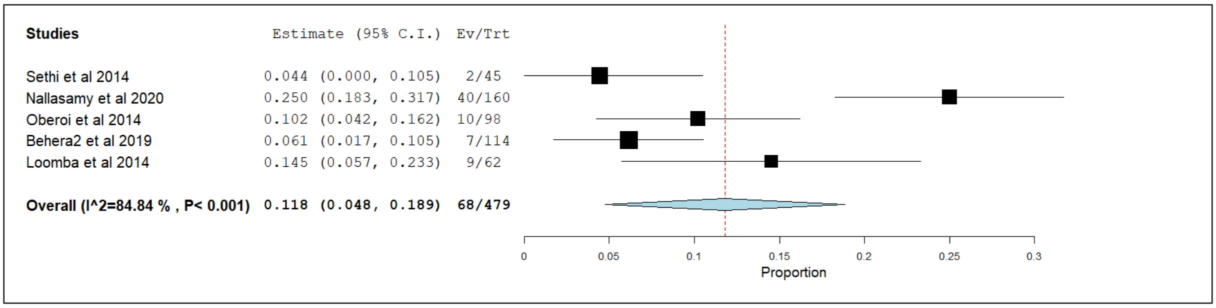
Supplementary Figure 6 - Forest plot showing the pooled prevalence of eschar in Karnataka.



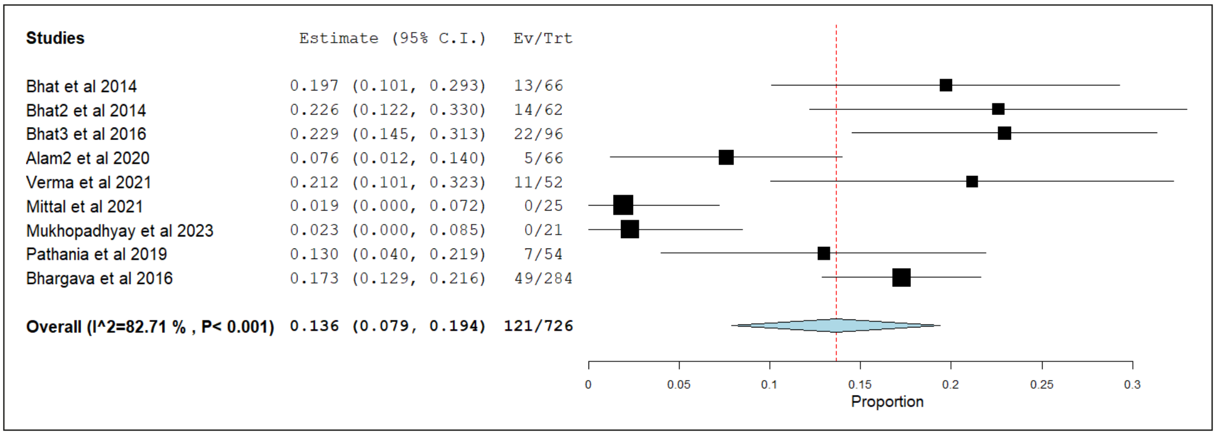
Supplementary Figure 7 - Forest plot showing the pooled prevalence of eschar in West Bengal.



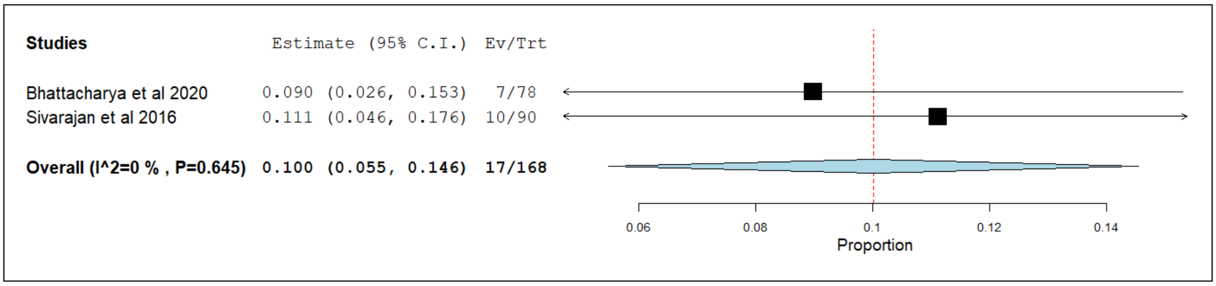
Supplementary Figure 8 - Forest plot showing the pooled prevalence of eschar in Andhra Pradesh and Telangana.



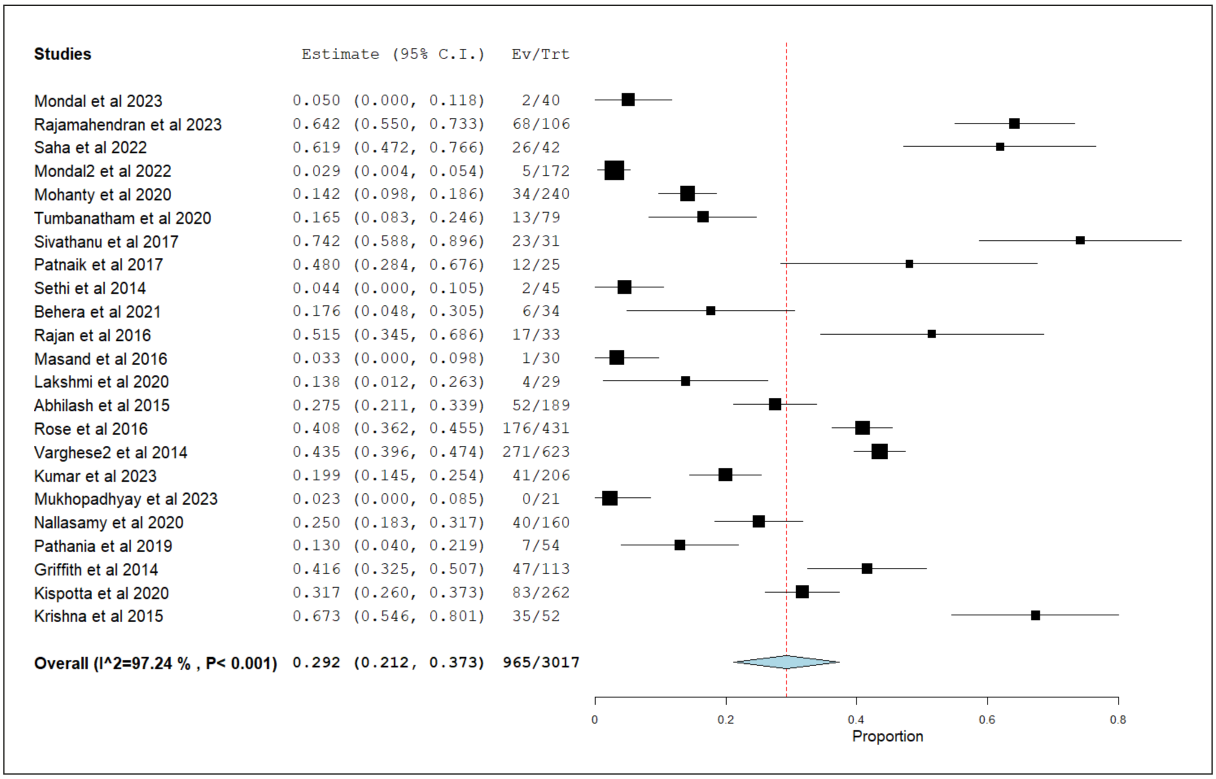
Supplementary Figure 9 - Forest plot showing the pooled prevalence of eschar in Punjab and Chandigarh.



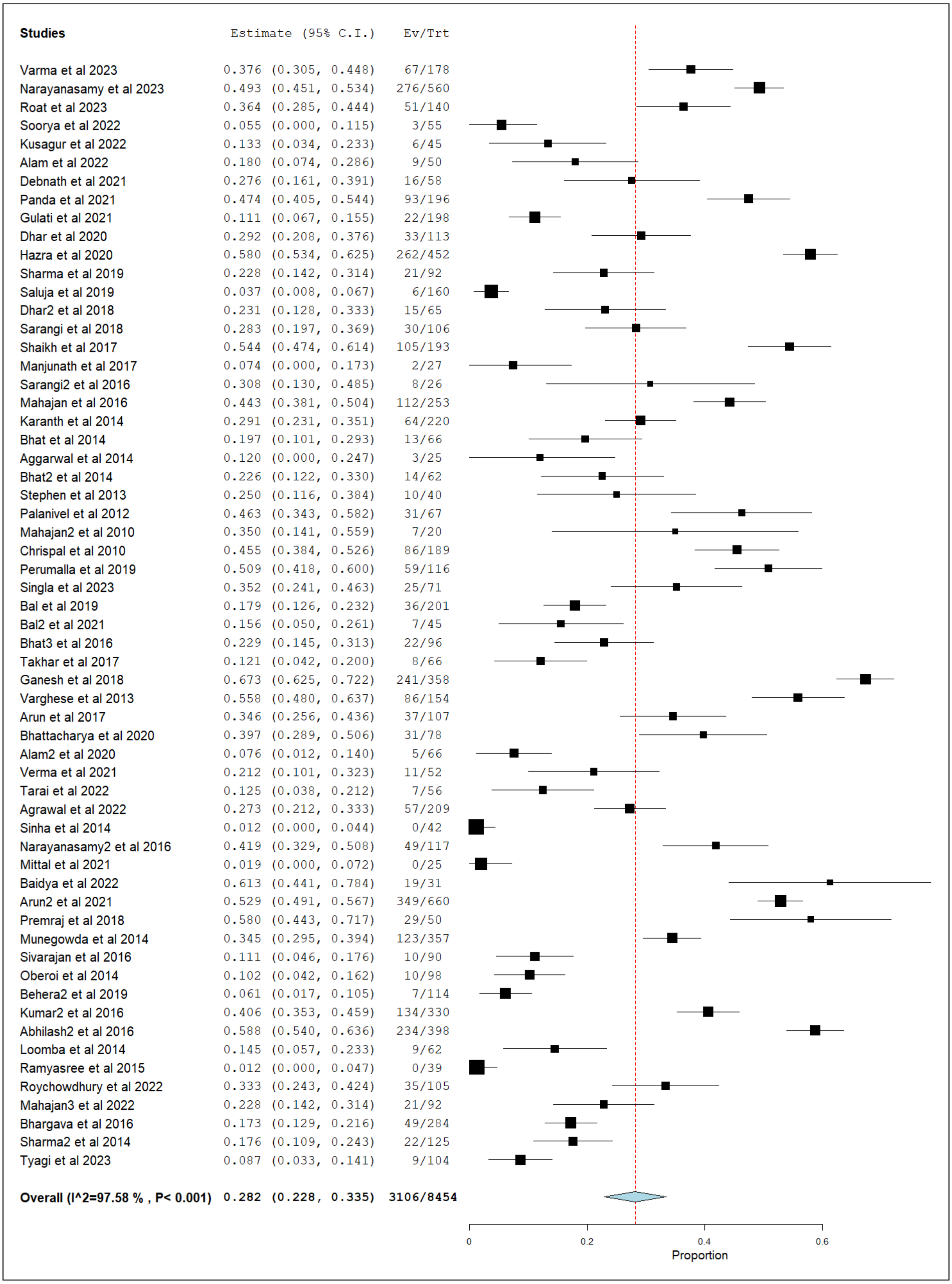
Supplementary Figure 10 - Forest plot showing the pooled prevalence of eschar in Uttar Pradesh and Uttarakhand.



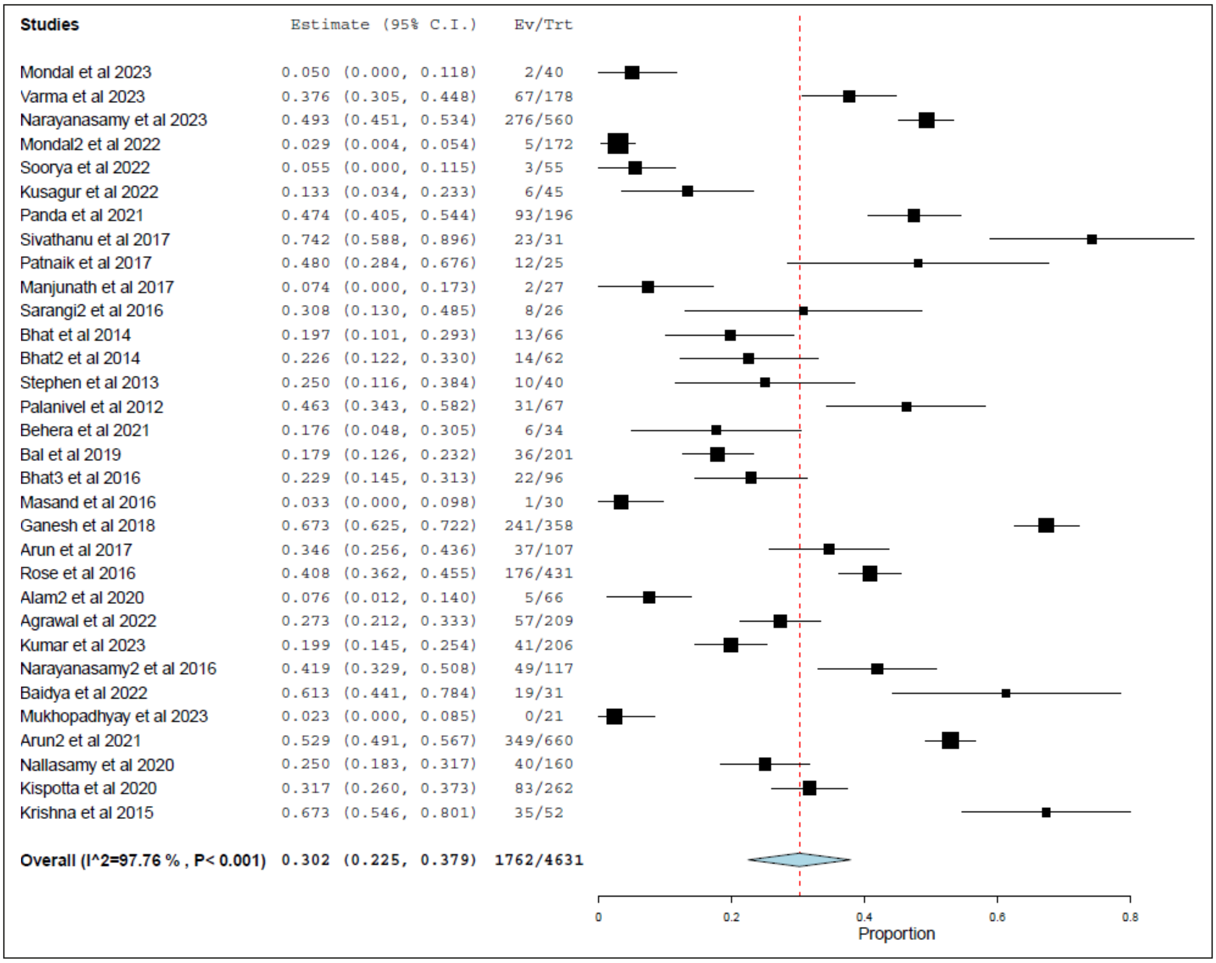
Supplementary Figure 11 - Forest plot showing the pooled prevalence of eschar in Meghalaya.



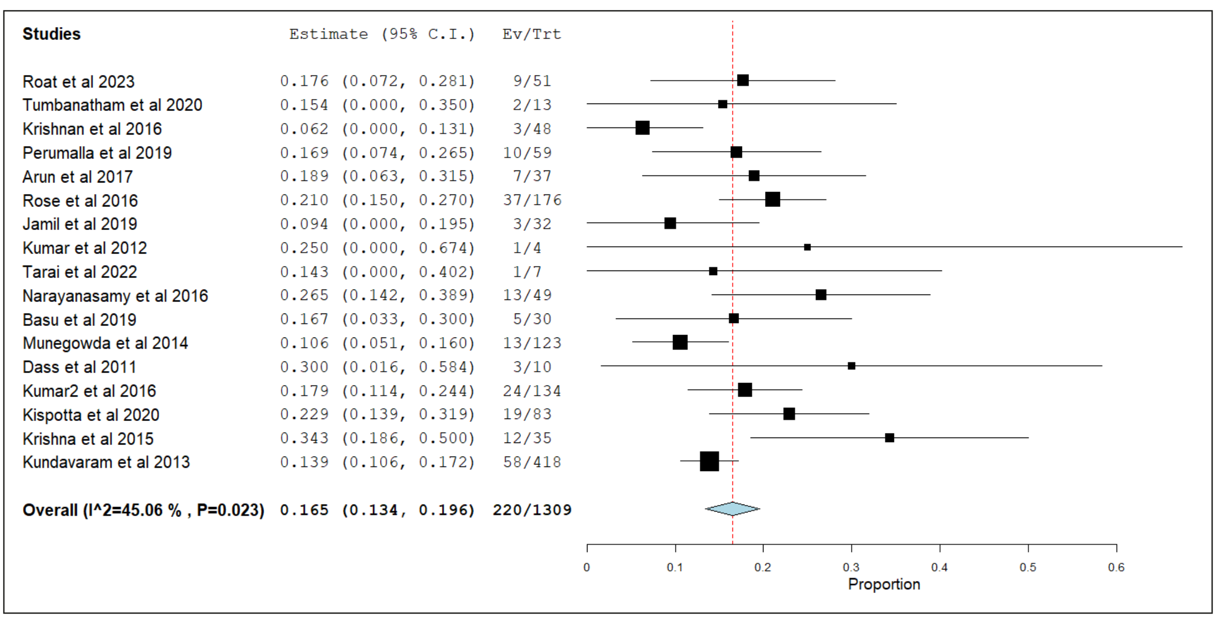
Supplementary Figure 12 - Pooled prevalence of eschar in retrospective studies.



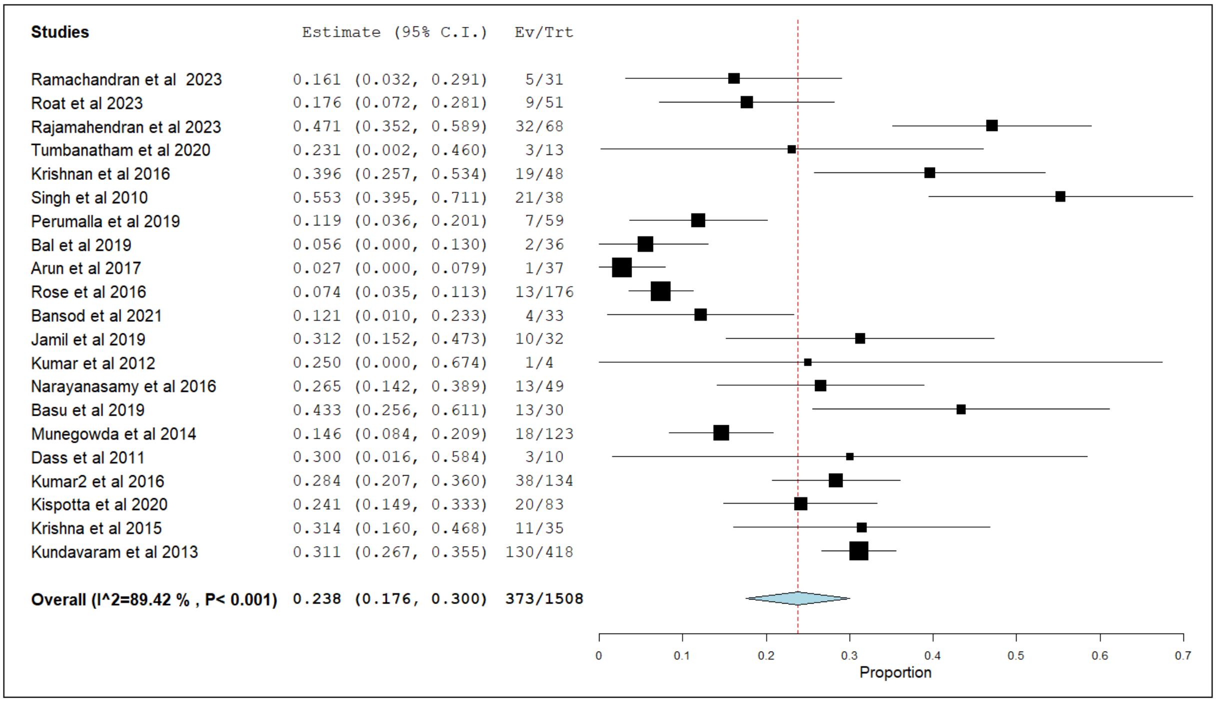
Supplementary Figure 13 - Pooled prevalence of eschar in prospective studies.



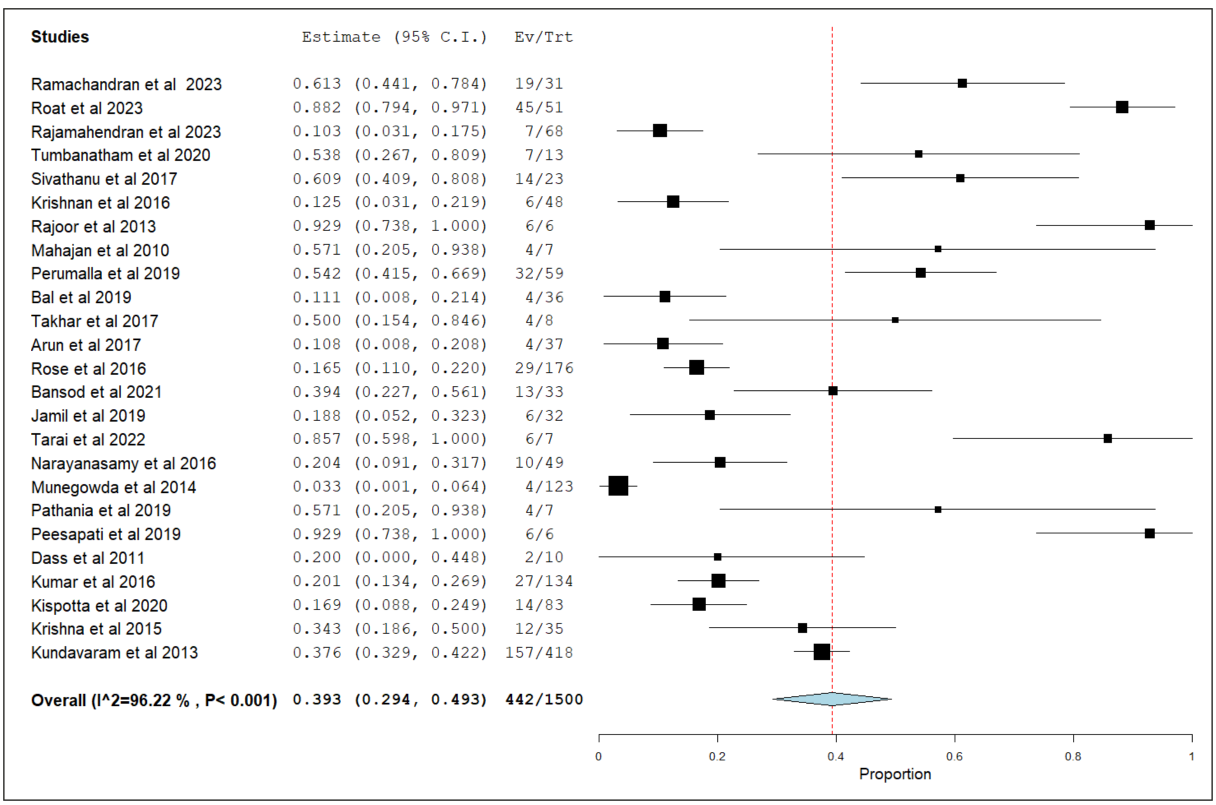
Supplementary Figure 14 - Pooled prevalence in studies done exclusively in the paediatric population.



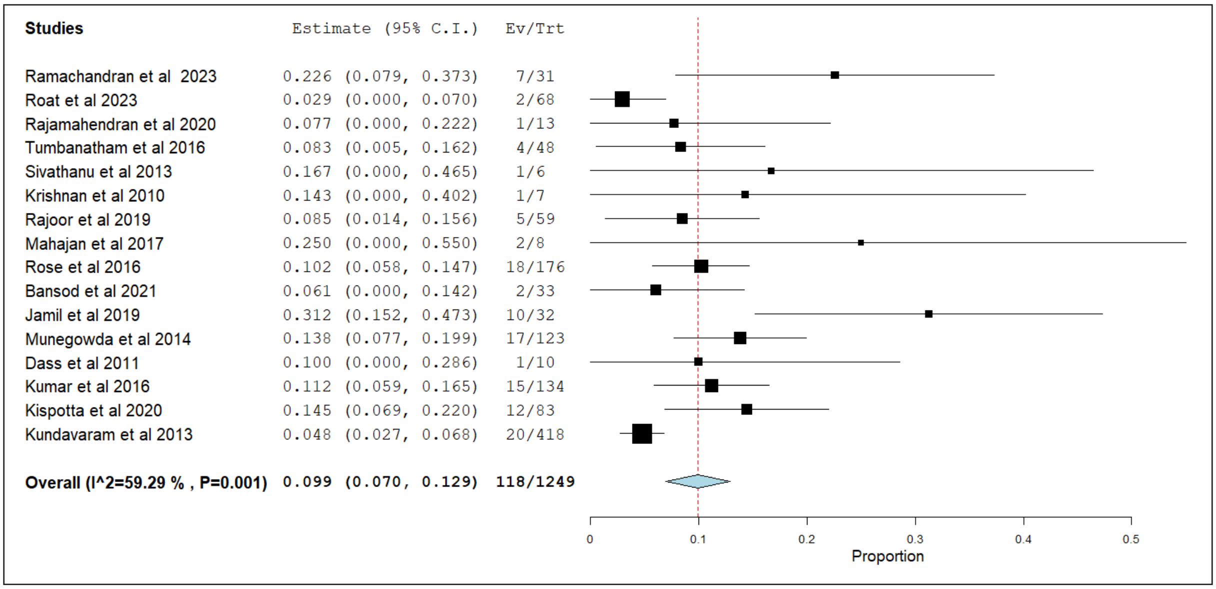
Supplementary Figure 15 - Pooled prevalence of eschar positivity in the axilla in those studies that reported eschar location.



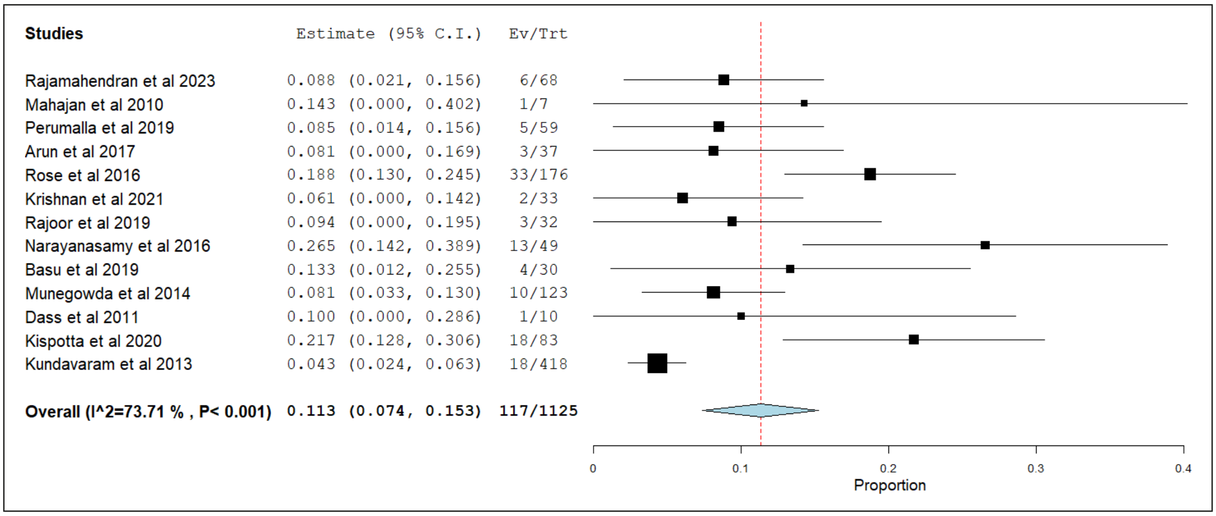
Supplementary Figure 16 - Pooled prevalence of eschar positivity in the groin in those studies that reported eschar location.



Supplementary Figure 17 - Pooled prevalence of eschar positivity in the trunk in those studies that reported eschar location.



Supplementary Figure 18 - Pooled prevalence of eschar positivity in limbs in those studies that reported eschar location.



Supplementary Figure 19 - Pooled prevalence of eschar positivity in head and neck in those studies that reported eschar location