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DIAGNOSTIC CHALLENGES AND CLINICAL IMPLICATIONS OF PSEUDOTHROMBOCYTOPENIA IN PATIENTS WITH SCRUB TYPHUS

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Abstract

Introduction

Scrub typhus, caused by the bacterium *Orientia tsutsugamushi*, is an acute, febrile illness that poses significant health challenges, particularly in endemic regions of Asia-Pacific. The study aims to elucidate the diagnostic challenges and clinical implications of pseudothrombocytopenia in patients with scrub typhus.

Material and methods

This retrospective observational study was conducted at Saveetha Medical College and Hospital, a tertiary care center in Chennai, India, over a one-year period from June 2023 to June 2024. A total of 200 patient records were reviewed, including those diagnosed with scrub typhus confirmed by serology (IgM ELISA) or polymerase chain reaction (PCR) for *Orientia tsutsugamushi* and had available complete blood count (CBC) and platelet count data. Inclusion criteria consisted of patients aged 18 years and above with a confirmed diagnosis and available laboratory data. Exclusion criteria included patients with pre-existing hematological disorders, those on medications affecting platelet count or function, and records with incomplete or missing laboratory data.

Results

The study analyzed demographic and clinical characteristics of patients with scrub typhus and other acute febrile illnesses (AFI). Fever was universally present, with high prevalence of myalgia and headache. Pseudothrombocytopenia was more common in scrub typhus (49 cases) than in AFI (29 cases), while true thrombocytopenia was more frequent in AFI (55 cases) compared to scrub typhus (5 cases). Statistical analysis revealed significant differences in platelet count distributions between the groups. The findings highlight the importance of accurately diagnosing pseudothrombocytopenia to avoid unnecessary treatments.

Conclusion

The findings highlight the prevalence of pseudothrombocytopenia in scrub typhus, the need for accurate differentiation from true thrombocytopenia, and the significant differences in platelet count distributions between scrub typhus and other AFIs.

Keywords: Scrub typhus, Pseudothrombocytopenia, Orientia, Eschar

INTRODUCTION

Scrub typhus, caused by the bacterium *Orientia tsutsugamushi*, is an acute, febrile illness that poses significant health challenges, particularly in endemic regions of Asia-Pacific.[11]Transmitted through the bite of infected chiggers (larval mites), scrub typhus manifests with nonspecific symptoms such as fever, headache, myalgia, and rash, often leading to diagnostic difficulties.[2] In severe cases, complications can include pneumonitis, myocarditis, encephalitis, and multi-organ failure, making early and accurate diagnosis critical for effective management.[3]One of the hematological abnormalities frequently associated with scrub typhus is thrombocytopenia, a condition characterized by an abnormally low platelet count.[4] Thrombocytopenia in scrub typhus can result from various mechanisms, including direct bone marrow suppression by the pathogen, immune-mediated destruction of platelets, or increased peripheral consumption due to disseminated

intravascular coagulation.[5] However, an often-overlooked diagnostic challenge in this context is pseudothrombocytopenia (PTCP), a laboratory artifact where platelet clumping leads to falsely low platelet counts on automated analyzers.[2,7]

Pseudothrombocytopenia is a well-documented but frequently misdiagnosed condition that arises from in vitro platelet agglutination, primarily due to the presence of ethylenediaminetetraacetic acid (EDTA)-dependent antibodies.[8-10] This phenomenon can occur in otherwise healthy individuals but is particularly problematic in patients with underlying conditions such as infections, where accurate platelet counts are crucial for diagnosis and treatment.[11-13] In the case of scrub typhus, misdiagnosing PTCP as true thrombocytopenia can lead to unnecessary investigations, inappropriate treatment modifications, and increased patient anxiety.[14,15]The primary rationale for this study stems from the need to differentiate between true thrombocytopenia and PTCP in patients with scrub typhus. Given the significant overlap in clinical presentations and the potential for severe complications, understanding the prevalence and implications of PTCP in this patient population is critical. By addressing this diagnostic challenge, the study aims to improve the accuracy of platelet count assessments, leading to better clinical decision-making and patient outcomes. The study aims to elucidate the diagnostic challenges and clinical implications of pseudothrombocytopenia in patients with scrub typhus.

MATERIAL AND METHODS

This retrospective observational study was conducted at Saveetha Medical College and Hospital, a tertiary care center in Chennai, India, over a one-year period from June 2023 to June 2024. The study aimed to evaluate the diagnostic challenges and clinical implications of pseudothrombocytopenia (PTCP) in patients diagnosed with scrub typhus. A total of 200 patient records were reviewed, including those diagnosed with scrub typhus confirmed by serology (IgM ELISA) or polymerase chain reaction (PCR) for *Orientia tsutsugamushi* and had available complete blood count (CBC) and platelet count data. Inclusion criteria consisted of patients aged 18 years and above with a confirmed diagnosis and available laboratory data. Exclusion criteria included patients with pre-existing hematological disorders, those on medications affecting platelet count or function, and records with incomplete or missing laboratory data. The sample size of 200 was determined based on the prevalence of scrub typhus and the expected incidence of PTCP, aiming for a precision of ±5% with a 95% confidence level.[16]

Data were collected retrospectively from the hospital's electronic medical records and laboratory information system. The process involved identifying patients who met the inclusion criteria, reviewing medical records to extract demographic and clinical data such as age, gender, presenting symptoms, duration of illness, and comorbid conditions, and reviewing laboratory investigations primarily focusing on CBC and platelet count results. PTCP was diagnosed based on unusually low platelet counts in CBC results with indications of potential platelet clumping noted in the medical records, whereas true thrombocytopenia was defined as a platelet count less than 150,000/µL without any notation of clumping or artifacts.

Data were analysed using SPSS version 25.0. Descriptive statistics summarized demographic and clinical characteristics, and the prevalence of PTCP was calculated. Comparisons between patients with true thrombocytopenia and PTCP were made using chi-square tests for categorical variables and t-tests for continuous variables, with a p-value of less than 0.05 considered statistically significant. The study protocol was reviewed and approved by the Institutional Ethics Committee of Saveetha Medical College and Hospital. As the study used anonymized patient data from medical records, the requirement for informed consent was waived, and patient confidentiality was maintained throughout, with data anonymized for analysis.

RESULTS

The age of participants ranged from 1 to 90 years, divided into nine categories. The frequency and corresponding percentages for each age group are as follows: 1-10 years: 36 participants (18%), 11-20 years: 12 participants (6%), 21-30 years: 32 participants (16%), 31-40 years: 34 participants (17%), 41-50 years: 32 participants (16%), 51-60 years: 34 participants (17%), 61-70 years: 8 participants (4%), 71-80 years: 6 participants (3%), and 81-90 years: 6 participants (3%). This distribution indicates a relatively balanced representation across most age groups, with a slightly higher concentration of participants in the 31-40 and 51-60 age ranges. The study included 200 participants, with a gender distribution of 94 males (47%) and 106 females (53%), showing a relatively balanced gender representation with a slightly higher proportion of female participants. The frequency and percentage of participants exhibiting various clinical manifestations are as follows: fever affected 200 participants (100%), myalgia affected 176 participants (88%), headache affected 166 participants (83%), and eschar affected 98 participants (49%). Fever was a universal symptom among the

participants, followed by a high prevalence of myalgia and headache, and nearly half of the participants exhibited eschar, a notable clinical sign often associated with scrub typhus. In summary, the study population is well-distributed across various age groups and gender, with fever being the most common clinical manifestation, affecting all participants, while myalgia, headache, and eschar are also prevalent to varying degrees. These findings provide valuable insights into the demographic and clinical characteristics of the study population (Table 1).

Table 1: Distribution of study variables among the study participants (N=200)

Slno	Variable	Frequency	Percentage
1	**Age**		
	1-10	36	18
	11-20	12	6
	21-30	32	16
	31-40	34	17
	41-50	32	16
	51-60	34	17
	61-70	8	4
	71-80	6	3
	81-90	6	3
2	**Gender**		
	Male	94	47
	Female	106	53
3	**Clinical manifestations**		
	Fever	200	100
	Myalgia	176	88
	Headache	166	83
	Eschar	98	49

Figure 1: Distribution of Thrombocytopenia Distribution by gender (n=60)

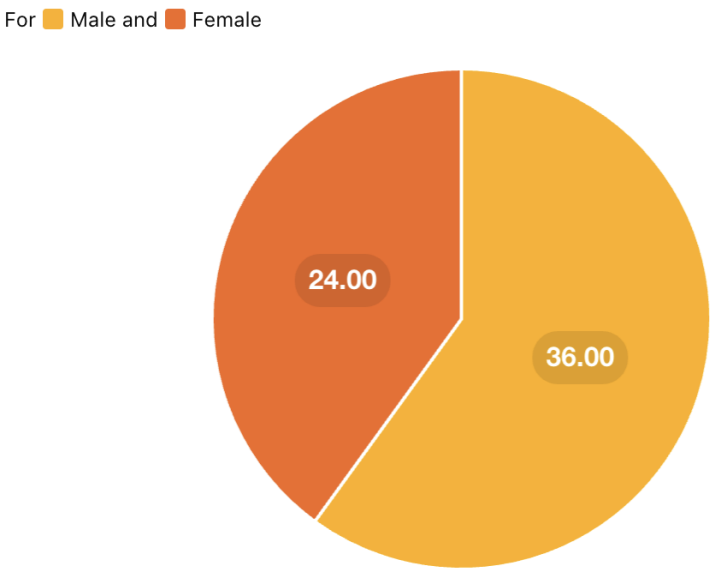
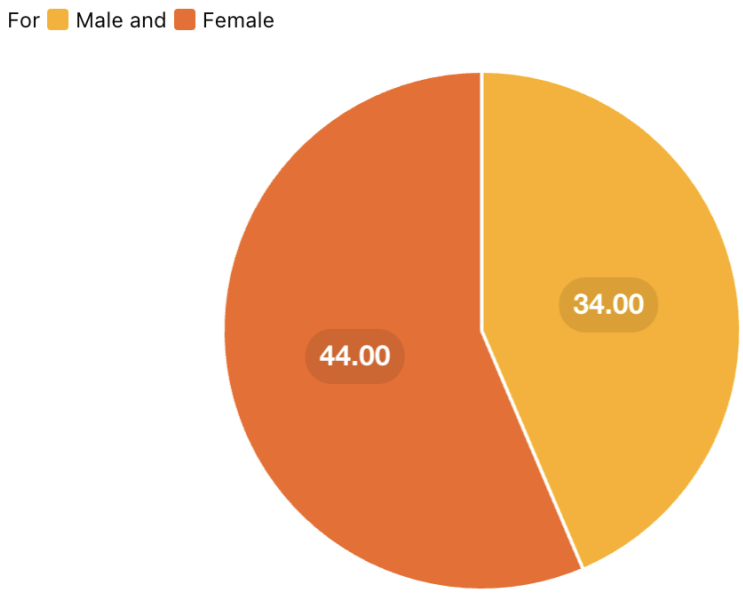


Figure 1 indicates that 60% of the cases are male and 40% are female.

Figure 2: Distribution of Pseudothrombocytopenia Distribution by gender (n=78)



The Figure 2 indicates that 56.4% of the cases are female and 43.6% are male.

Table 2: Comparison of Pseudo Thrombocytopenia, Thrombocytopenia, and Normal Platelet Count in Scrub Typhus and Other Acute Febrile Illnesses (N=200)

Causes	Pseudo Thrombocytopenia	Thrombocytopenia	Normal Platelet Count	Total
SCRUB TYPHUS	49	5	2	56
AFI -OTHERS	29	55	60	144

The table 2 presents a comparison of pseudo thrombocytopenia, thrombocytopenia, and normal platelet counts in patients diagnosed with scrub typhus and other acute febrile illnesses (AFI). In the group with scrub typhus, 49 patients were identified with pseudo thrombocytopenia, 5 with thrombocytopenia, and 2 with normal platelet counts, totaling 56 patients. In the AFI-others group, 29 patients had pseudo thrombocytopenia, 55 had thrombocytopenia, and 60 had normal platelet counts, totaling 144 patients.An independent samples t-test was conducted to compare the mean differences between the groups. For pseudo thrombocytopenia, the t-value was -11.122 with 198 degrees of freedom (df) and a p-value of less than .001, indicating a highly significant difference between the groups. For thrombocytopenia, the t-value was 4.212 with 198 df and a p-value of less than .001, also indicating a significant difference. For normal platelet count, the t-value was 5.512 with 198 df and a p-value of less than .001, showing a significant difference between the groups.The note indicates that the Brown-Forsythe test was significant ($p < .05$) for thrombocytopenia and normal platelet count, suggesting a violation of the equal variance assumption. This means that the variances between the groups were not equal, and the interpretation of the t-test results should consider this violation.

DISCUSSION

The study offers a comprehensive analysis of the demographic and clinical characteristics of patients diagnosed with scrub typhus and other acute febrile illnesses (AFI), with a specific focus on platelet count abnormalities, including pseudothrombocytopenia and thrombocytopenia. The age distribution of participants in this study ranged from 1 to 90 years, categorized into nine distinct age groups. The representation was relatively balanced across most age groups, with slightly higher concentrations in the 31-40 and 51-60 age ranges. This distribution suggests that scrub typhus and other AFIs affect a broad spectrum of the population, from young children to the

elderly. The slight peaks in the 31-40 and 51-60 age groups could be attributed to higher exposure risks due to occupational and environmental factors prevalent in these age ranges. The gender distribution was fairly balanced, with 47% male and 53% female participants. This slight female predominance might reflect the community structure or healthcare-seeking behavior where women might be more likely to seek medical attention or be brought to medical facilities. Understanding the gender distribution is crucial for tailoring public health interventions and awareness programs to target the more affected gender effectively.

The clinical manifestations of the study population were dominated by fever, affecting 100% of participants, highlighting its prominence as a primary symptom of scrub typhus and AFIs. Myalgia and headache were also highly prevalent, affecting 88% and 83% of participants, respectively. Eschar, a more specific sign associated with scrub typhus, was present in 49% of the cases. The presence of eschar is a crucial diagnostic marker for scrub typhus, aiding in differentiating it from other febrile illnesses. The high prevalence of fever, myalgia, and headache underscores the nonspecific nature of early symptoms of scrub typhus and AFIs, complicating the initial clinical diagnosis without laboratory confirmation.

The study's primary focus on platelet count abnormalities revealed significant findings. Pseudothrombocytopenia was observed in 49 patients with scrub typhus and 29 patients with other AFIs. Thrombocytopenia was identified in 5 scrub typhus patients and 55 AFI patients, while normal platelet counts were noted in 2 scrub typhus patients and 60 AFI patients. These findings indicate that pseudothrombocytopenia is more prevalent in scrub typhus patients compared to other AFIs, whereas true thrombocytopenia is more common in AFI patients.

The findings of this studyhas many implications clinically. First, the high prevalence of pseudothrombocytopenia in scrub typhus patients highlights the need for clinicians to confirm low platelet counts with peripheral blood smears or alternative anticoagulants to avoid misdiagnosis and unnecessary treatments. Pseudothrombocytopenia, if not identified correctly, can lead to inappropriate management strategies, including unnecessary platelet transfusions or alterations in treatment plans. Second, the significant differences in thrombocytopenia prevalence between scrub typhus and other AFIs suggest that thrombocytopenia in scrub typhus might not be as common as previously thought. This finding can help refine the differential diagnosis process in febrile patients presenting with low platelet counts, prompting clinicians to consider other AFIs more strongly in the presence of thrombocytopenia. Third, the presence of normal platelet counts in a subset of scrub typhus patients indicates that while thrombocytopenia and pseudothrombocytopenia are common, they are not universal. This variability underscores the need for comprehensive clinical and laboratory evaluation in suspected cases of scrub typhus.[17-19]

In a case series by Rajajee et al[20]. involving 108 children with confirmed scrub typhus serology, 93 children (83%) exhibited pseudothrombocytopenia. The study concluded that pseudothrombocytopenia demonstrated a sensitivity of 83%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 93.5% for diagnosing scrub typhus. Similarly, Lamech et al[6]. reported on 12 patients with scrub typhus who also had pseudothrombocytopenia. The connection between scrub typhus and pseudothrombocytopenia has only recently been recognized. Pseudothrombocytopenia can sometimes accompany acute scrub typhus infections, and distinguishing it from true thrombocytopenia is crucial. Unlike true thrombocytopenia, pseudothrombocytopenia is a laboratory artifact and does not necessitate blood product transfusions, even when platelet counts appear significantly reduced.

CONCLUSION

This study provides valuable insights into the demographic and clinical characteristics of patients with scrub typhus and other AFIs, with a particular focus on platelet count abnormalities. The findings highlight the prevalence of pseudothrombocytopenia in scrub typhus, the need for accurate differentiation from true thrombocytopenia, and the significant differences in platelet count distributions between scrub typhus and other AFIs. These insights can inform clinical practice, enhance diagnostic accuracy, and improve patient outcomes in regions endemic to these conditions.

Future research should focus on elucidating the mechanisms underlying pseudothrombocytopenia in scrub typhus and its differentiation from true thrombocytopenia. Molecular and immunological studies could provide insights into the specific pathways involved in platelet count abnormalities in these conditions. Additionally,

larger multi-center studies could help validate these findings and establish standardized diagnostic criteria for pseudothrombocytopenia in scrub typhus.

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