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Original Research Article

THE ROLE OF SERUM FERRITIN IN EVALUATING THE OUTCOMES OF PATIENTS WITH SCRUB TYPHUS

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ABSTRACT

Introduction: Scrub typhus is a common cause of acute undifferentiated fever and poses a significant public health concern in Asian countries. Due to overlapping symptoms, diagnosing the disease is often difficult. So many of the patients were found to end up with complications, which further increases the morbidity and the mortality of the patient. Serum ferritin is one of the common markers used to determine the body's iron stores. Recent studies have shown its use in diagnosing pathologies, such as inflammation, infection, and malignancy. The aim is to assess the efficacy of the serum ferritin level in evaluating the outcome of the patient with scrub typhus.

Materials and Methods: This prospective observational study was conducted at the Department of Paediatrics, Sri Laksmi Narayana Institute of Medical Sciences, Puducherry, India. All patients aged 2 months to 12 years with a laboratory-confirmed diagnosis of scrub typhus were included in the study. After the initial assessment, all patients underwent a complete biochemical evaluation, including serum ferritin levels. The patient's outcomes had been assessed and compared with the serum ferritin level.

Results: A total of 144 patients participated in the study; the majority (40.3%) were aged 6-10 years. And the fever had been noted in all the patients. 10.5% of patients had severe elevation of serum ferritin, and 21.5% had normal levels. The non-survivors were found to be significantly higher in patients with an age between 2 months and one year ($p < 0.001$), low socio-economic status patients ($p < 0.001$), TLC ($p < 0.001$), platelet count ($p = 0.023$) and the serum ferritin level ($p < 0.001$).

Conclusion: The study recommends that clinicians measure serum ferritin levels in addition to other biochemical investigations at the time of admission to predict disease severity earlier and prevent the development of complications.

Keywords: ferritin; survivors; scrub typhus; fever.

INTRODUCTION

Scrub typhus is a severe infectious disease caused by the rickettsial bacterium Orientia tsutsugamushi. Scrub typhus is a common cause of acute undifferentiated fever and poses a significant public health concern in Asian countries.[1] The infection gets transmitted to humans via the bite of a larval trombiculid mite. Scrub typhus is more commonly reported in Asian countries, and the disease prevalence ranged from 9.3% to 27.9% across regions. The studies also noted that scrub typhus affects people of all ages.[2] The pathogenesis of O tsutsugamushi involves infection of endothelial cells, leading to vasculitis and perivascular infiltration by T cells, monocytes, and macrophages. Consequently, an extensive range of inflammatory responses transpires, with both endothelium and non-endothelial cells synthesising numerous cytokines.[3]

The manifestation of the disease is found to vary from the acute undifferentiated fever to the development of the acute respiratory distress syndrome, myocarditis, acute kidney injury,

encephalitis, acute liver failure, and the development of the multiorgan dysfunction syndrome.[4] And in most cases, there is overlap in the symptoms observed between the infection and other viral and certain bacterial infections. And so early identification of the disease and its management were found to help reduce morbidity and mortality.[5] But in most cases, due to symptom overlap with other viral and bacterial infections, diagnosing the condition is difficult. So a syndromic approach is usually recommended. The studies showed that many clinical and laboratory parameters were inconsistent in diagnosing the condition.[6]

In recent years, studies have found that ferritin is among the most promising markers for diagnosing haematological dysfunction, particularly in cases of multi-organ dysfunction syndrome. The significance of ferritin in disease aetiology and immunomodulation is being thoroughly investigated in sepsis.[7] Recent studies have shown that increased serum ferritin levels are observed in patients with hypercytokinemia and are secondary to macrophage activation. And so, the study was designed to assess serum ferritin levels as an outcome measure in scrub typhus cases.

MATERIALS AND METHODS

Study design: This prospective observational study was conducted among children aged less than 5 years at a tertiary care centre (Sri Lakshmi Naraya Institute of Medical Sciences) in Puducherry. The study was conducted for 18 months, from January 2025 to June 2026.

Sampling: The patients were selected using convenience sampling, as described in the study by Dasgupta S et al.[8] The prevalence of scrub typhus was 10.4%, and with a 95% confidence interval and a 5% margin of error, the sample size was calculated to be 144.

Inclusion and Exclusion criteria

All children aged 2 months to 12 years admitted to the paediatric ward with an established diagnosis of scrub typhus, confirmed by either Polymerase chain reaction or IgM ELISA, were included in the study. Children with recent blood transfusions, haematological malignancies, autoimmune disorders, and immunosuppressed individuals were also excluded from the study.

Data collection: After obtaining approval from the Institute Ethics Committee and informed written consent, patients with a confirmed diagnosis of Scrub typhus were included in the study. After the initial assessment, all patients underwent a detailed history and physical examination. Followed by the routine baseline investigation, including complete blood count, serum electrolytes, liver function tests, and renal function tests, had been performed. Serum ferritin levels were then measured at admission in all patients.

Patients with ferritin levels <500 µg/L were considered to have normal ferritin levels. Patients with ferritin levels between 500 and 2000 µg/L were considered to have mild hyperferritinemia, and those with levels between 2000 and 10,000 µg/L were considered to have moderate hyperferritinemia. More than 10,000 µg/L had been taken as severe hyperferritinemia. The association between serum ferritin levels and the study outcomes had been assessed.

Data analysis: Data entry was conducted using Epi-Data software, and analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). And a p-value less than 0.05 is considered significant.

Ethical Approval: The study procedure was approved by the Internal Human Ethics Committee of Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, under reference number 9/SLIMS/IEC/0840.

RESULTS

A total of 144 patients participated in the study. and 40.3% of the patients were between 6 and 10 years of age, followed by 25% between 2 and 5 years, and 54.2% were male. And 28.5% of the patients had a socioeconomic status of class V, as shown in [Table 1].

Table 1: Sociodemographic details of the patient

Variable	Frequency (n)	Percentage (%)
Age		
2 months – 1 year	20	13.9
2-5 years	36	25
6-10 years	58	40.3
11-12 years	30	20.8
Gender		
Male	78	54.2
Female	66	45.8
Socio-economic status		
Class I	14	9.7
Class II	23	15.9
Class III	30	20.9
Class IV	36	25
Class V	41	28.5

On reviewing the patient's clinical profile, the study noted that about 49.3% of patients had an illness duration of 5-10 days. And fever was found to be most common clinical presentation of the patients

and all the patients were found to had fever followed by fast breathing noted in 42.4% and the abdominal pain in 39.6% of the patients. and on exploring the various blood investigation, anaemia had been noted in 51.4% of the patients and 58.3% of the patients had been diagnosed with thrombocytopenia, as in [Table 2].

Table 2: Clinical profile of the patient with scrub typhus

Variable	Frequency (n)	Percentage (%)
Duration of illness		
< 5 days	46	31.9
5-10 days	71	49.3
>11 days	27	18.8
Clinical presentation		
Fever	144	100
Fast breathing	61	42.4
Abdominal pain	57	39.6
Disorientation	51	35.4
Seizure	23	15.9
Headache	27	18.8
Rash	22	15.3
Investigations		
Haemoglobin level		
<10 gms%	74	51.4
>10 gms%	70	48.6
Total leucocyte count		
<4000	30	20.8
4000-8000	75	52.1
>8000	39	27.1
Platelet Count		
<1.5 lakhs	84	58.3
>1.5 lakhs	60	41.7

Upon exploring the distribution of patients by outcomes and serum ferritin levels, the study found that about 16.7% of the children were non-survivors. Regarding serum ferritin levels, 10.5% of patients had severe elevation, and 21.5% had normal levels, as shown in [Table 3].

Table 3: Distribution of the patients based on outcomes and the serum ferritin levels

Variable	Frequency (n)	Percentage (%)
Outcome		
Survivor	120	83.3
Non-survivor	24	16.7
Serum Ferritin Levels		
Normal	31	21.5
Normal (< 500)	65	45.1
Moderate (> 2000–10,000)	33	22.9
Severe (> 10,000)	15	10.5

In finding the association between the various factors and the outcome of the study, the study had noted that the non-survivor rate was found to be higher in patients with younger age group (p-<0.001), low socio economic status (p-<0.001), patients with low leucocyte count (p-<0.001), patients with thrombocytopenia (p-<0.001), and the patients with higher serum ferritin levels (p-<0.001), as in [Table 4].

Table 4: Association between the outcomes and the various parameters of the study

Parameter	Total n (%)	Survivor n (%)	Non-survivor n (%)	p-value chi-square value
Age				
2 months – 1 year	20 (100)	6 (30)	14 (70)	<0.001
2-5 years	36 (100)	31 (86.1)	5 (13.9)	48.837
6-10 years	58 (100)	55 (94.8)	3 (5.2)	
11-12 years	30 (100)	28 (93.3)	2 (6.7)	
Gender				
Male	78 (100)	61 (78.2)	17 (21.8)	0.07
Female	66 (100)	59 (89.4)	7 (10.6)	3.224
Socio-economic status				
Class I	14 (100)	3 (21.4)	11 (78.6)	<0.001
Class II	23 (100)	17 (73.9)	6 (26.1)	49.514
Class III	30 (100)	26 (86.7)	4 (13.3)	
Class IV	36 (100)	34 (94.4)	2 (5.6)	
Class V	41 (100)	40 (97.6)	1 (2.4)	
Haemoglobin level				

<10 gms%	74 (100)	58 (78.4)	16 (21.6)	0.101 2.691
>10 gms%	70 (100)	62 (88.6)	8 (11.4)	
Total leucocyte count				
<4000	30 (100)	27 (90)	3 (10)	<0.001 23.022
4000-8000	75 (100)	70 (93.3)	5 (6.7)	
>8000	39 (100)	23 (58.9)	16 (41.1)	
Platelet Count				
<1.5 lakhs	84 (100)	65 (77.4)	19 (22.6)	0.023 5.143
>1.5 lakhs	60 (100)	55 (91.7)	5 (8.3)	
Serum Ferritin Levels				
Normal	31 (100)	28 (90.3)	3 (9.7)	<0.001 71.858
Mild (500-2000)	65 (100)	62 (95.4)	3 (4.6)	
Moderate (> 2000–10,000)	33 (100)	29 (87.9)	4 (12.1)	
Severe (> 10,000)	15 (100)	1 (6.7)	14 (93.3)	

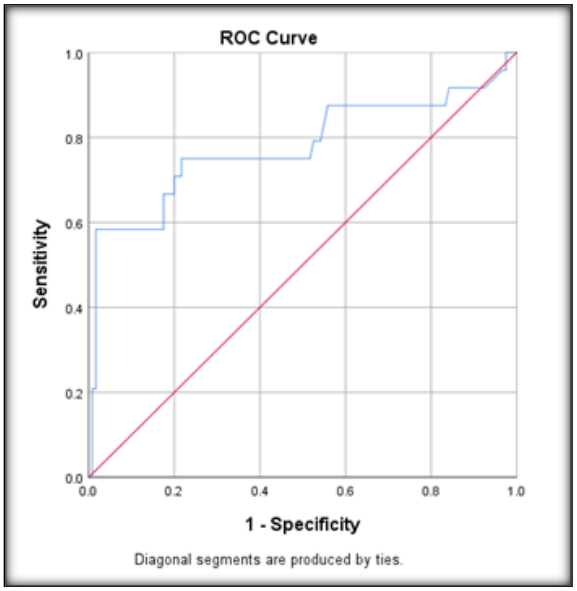

Figure 1: Receiver operating characteristic curve for serum ferritin in predicting mortality

The study showed that an increase in serum ferritin level was associated with increased specificity in predicting patient mortality (AUC: 0.778). Serum ferritin levels above 666 µg/L had a sensitivity of 83.3% and a specificity of 55.8% for predicting mortality in patients with scrub typhus.

DISCUSSION

Scrub typhus is a common cause of acute febrile illness among children and is among the most neglected tropical diseases. And it is more commonly noted in Asian countries. And the majority of the symptoms of scrub typhus were found to be more commonly similar to those of other viral and bacterial infections.[9] And so many times, the disease's diagnosis is found to be difficult. So many of the patients were found to end up with complications, which further increases the morbidity and the mortality of the patient. Studies have shown that organ dysfunction is more commonly noted among patients with scrub typhus.[10] The patient's mortality rate was found to be directly associated with the severity and number of organs involved. And the ferritin has been used as an important marker in the determination of the body's iron stores. Recent studies have shown its use in various pathologies, such as inflammation, infection, and malignancy.[11]

In our study, the most common presenting complaint of patients with scrub typhus was fever, noted in all patients, followed by fast breathing and abdominal pain, noted in 42.4% and 39.6% of patients, respectively. The study by Peter JV et al [12] also shows that fever was the most common symptom among patients with scrub typhus. The study by Williams V et al,[13] also shows that most patients with scrub typhus had fever, with 37.5% experiencing rapid breathing and 34.7% experiencing abdominal pain. In our study, about 51.4% of patients with scrub typhus had anaemia, with haemoglobin levels below 10 g/dL. The study by Sivaprakasam E et al,[4] also shows that the majority of patients with scrub typhus were anaemic. In our study, about 27.1% of patients had a leukocyte count greater than 8000 cells/mm³, and about 58.3% had thrombocytopenia. In the study by Kim DM et al,[5] it was found that scrub typhus was associated with elevated leucocyte counts. A WBC count greater than 10,000 cells per cu.mm was an independent predictor of disease severity, and elevated WBC levels were also associated with higher mortality. The study by Venkategowda PM et al,[14] showed that scrub typhus was associated with thrombocytopenia.

On examining the distribution of patients by outcomes and serum ferritin levels, the study found that about 16.7% of the children were non-survivors (Williams V et al.),[13] also shows that the patient survival rate for scrub typhus was 83.3%, and the non-survival rate was 16.7% of the total study population. In our study, only 21.5% of patients with scrub typhus had normal serum ferritin levels; 45.1% had mildly elevated levels, and 10.5% had severely elevated levels. And in finding the association between the outcomes and the various parameters of the study, the study had noted that about 70% of the patients in 2 months to one year and about 21.6% of the patients with haemoglobin level of less than 10 grams percentage, 41.4% of the patients with total leucocyte count of more than 8000 and 22.6% of the patients with thrombocytopenia were found to be associated with poor outcome of the patient—the study by Lim HK et al,[14] showed that patients with lower haemoglobin levels had a higher mortality rate. The

study by Prakash JAJ et al,[15] also reported that non-survival among patients with scrub typhus was more common among those with leucocytosis. The study by Song X et al,[17] reported that thrombocytopenia was associated with non-survival in patients. And the studies also mentioned that the presence of thrombocytopenia was found to be associated with the development of multiple organ dysfunction syndrome, which further increases the mortality of the patient. However, the study by Williams V et al,[13] showed that platelet counts were higher in the non-survivors than in the survivors.

Our study showed that an increase in serum ferritin level was associated with a higher non-survival rate in patients. About 93.3% of the patients with severe serum ferritin elevation were found to be non-survivors. And the study by Williams V et al,[13] also showed results similar to ours. And the study by Garcia, PCR et al,[16] reported that patients with serum ferritin levels between 200 and 500 had a 9% mortality rate. In the study by Bennet et al,[17] it was noted that mortality risk increased among scrub typhus patients when serum ferritin levels were raised from 1000 to 3000 µg/L. And the major reason for this elevated serum ferritin level was that, in individuals with relatively normal iron storage, rickettsial infection elicited an M1 macrophage phenotypic response, leading to temporary early hyperferritinemia due to macrophage sequestration of iron and enhanced transcription of the ferritin gene as an acute-phase reactant. This response enhances interferon and pro-inflammatory cytokine release by macrophages, leading to improved infection control and favourable outcomes.[18,19]

Limitations of the study

The study had been done in a single centre, so if the study had been done in different regions, the association of scrub typhus with serum ferritin could have been assessed in different populations.

CONCLUSION

Scrub typhus is a common disease in tropical countries. And due to its overlapping symptoms, the majority of the patients affected with scrub typhus were found to end up in complications, which further increases the mortality risk of the patient. Our study showed that serum ferritin was associated with patient outcome. And so, the study recommends that clinicians measure serum ferritin levels, in addition to other biochemical investigations, at the time of admission to predict disease severity earlier and prevent complications.

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