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Original Research Article

DYSLIPIDEMIA IN SCRUB TYPHUS: ASSOCIATION WITH DISEASE SEVERITY AND MULTIPLE ORGAN DYSFUNCTION SYNDROME IN A HOSPITAL-BASED STUDY

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ABSTRACT

Background: Scrub typhus is an important re-emerging febrile illness in India and may cause multisystem complications. Altered lipid metabolism occurs during severe infections and may reflect the host inflammatory response. However, its association with disease severity in scrub typhus remains insufficiently characterized. To evaluate dyslipidemia in patients with scrub typhus and determine its association with disease severity and multiple organ dysfunction syndrome (MODS).

Materials and Methods: This observational study included 60 patients with scrub typhus. Demographic, clinical, biochemical, lipid profile, and complication data were collected. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were assessed. Patients were evaluated for acute kidney injury, acute respiratory distress syndrome, hepatitis, shock, MODS, and ICU admission. Lipid parameters were compared between patients with and without MODS.

Results: The mean age was 41.85 ± 13.59 years, with 26 (43.3%) males. Mean TC, TG, HDL-C, and LDL-C levels were 148.45 ± 26.85, 202.38 ± 70.44, 35.76 ± 6.76, and 75.03 ± 28.50 mg/dL, respectively. Hypertriglyceridemia occurred in 47 (78.3%) and low HDL-C in 52 (86.7%) patients. MODS occurred in 6 (10.0%). Patients with MODS had significantly higher TG levels (324.0 ± 40.5 vs. 188.9 ± 59.2 mg/dL; $p<0.001$) and lower LDL-C levels (48.0 ± 16.0 vs. 78.0 ± 28.1 mg/dL; $p=0.003$). AKI, ARDS, hepatitis, shock, and ICU admission occurred in 26.7%, 15.0%, 68.3%, 18.3%, and 53.3%, respectively. Seven patients died.

Conclusion: Hypertriglyceridemia and reduced LDL-C were associated with MODS in scrub typhus. Larger prospective studies are warranted to determine their prognostic value

Keywords: Scrub typhus; Orientia tsutsugamushi; dyslipidemia; triglycerides; HDL cholesterol; LDL cholesterol; multiple organ dysfunction syndrome; MODS; disease severity.

INTRODUCTION

Scrub typhus is an important re-emerging zoonotic infection caused by Orientia tsutsugamushi and remains a significant cause of acute febrile illness in many parts of Asia, including India. The disease is transmitted through the bite of infected chigger mites and can range from an uncomplicated febrile illness to severe systemic disease characterized by pneumonia, acute kidney injury, hepatitis,

encephalitis, myocarditis, shock, and multiorgan dysfunction.[1,2] In endemic regions, delayed recognition and the nonspecific clinical presentation may contribute to increased morbidity and mortality.[3]

The pathogenesis of severe scrub typhus involves endothelial infection and widespread endothelial dysfunction, resulting in increased vascular permeability, microvascular injury, tissue hypoperfusion, and inflammatory activation. The systemic inflammatory response may subsequently lead to injury of multiple organs.[4,5] Although conventional markers such as serum transaminases, bilirubin, creatinine, lactate, platelet count, and inflammatory biomarkers have been extensively evaluated for predicting disease severity, there is increasing interest in identifying additional biochemical abnormalities that may reflect systemic inflammation and organ dysfunction.

Dyslipidemia is increasingly recognized as a metabolic component of acute systemic infections. During severe infection and inflammation, cytokines such as tumor necrosis factor-α, interleukin-1, and interleukin-6 can alter hepatic lipid synthesis, lipoprotein metabolism, lipid clearance, and peripheral lipid utilization. These changes may result in reduced concentrations of total cholesterol, LDL cholesterol, and HDL cholesterol, while triglyceride concentrations may increase.[6] Such infection-associated lipid alterations have been described in conditions including sepsis and other severe infections and may represent part of the host metabolic response to systemic inflammation.[7]

Among lipid parameters, HDL cholesterol may have particular biological relevance during acute infection. HDL participates in cholesterol transport and has anti-inflammatory, antioxidant, and endothelial-protective properties. It can also interact with bacterial components and participate in innate immune responses.[8] During systemic inflammation, HDL concentration and function may be altered, potentially reducing its protective effects. Conversely, elevated triglycerides and changes in LDL metabolism may reflect inflammatory and metabolic stress.[6,8] Therefore, the lipid profile may provide indirect information about the intensity of systemic inflammatory response and disease severity.

Despite the established association between scrub typhus and systemic organ dysfunction, data regarding lipid abnormalities in scrub typhus are relatively limited, particularly in relation to clinically relevant outcomes such as severe disease and multiple organ dysfunction syndrome (MODS). Most studies of scrub typhus have focused on hematological, hepatic, renal, inflammatory, and coagulation abnormalities. The potential relationship between lipid parameters and the severity spectrum of scrub typhus therefore remains incompletely characterized.[9]

MODS is one of the major determinants of poor outcomes in severe scrub typhus. Patients with severe disease may develop simultaneous dysfunction of the liver, kidneys, lungs, cardiovascular system, central nervous system, and hematological system.[10] If specific lipid abnormalities are associated with the development or severity of MODS, lipid parameters obtained as part of routine biochemical testing could potentially serve as inexpensive adjunctive markers for early risk stratification.[9]

Furthermore, the relationship between dyslipidemia and scrub typhus may not simply represent an epiphenomenon of critical illness. Alterations in lipid metabolism could reflect the interaction between systemic inflammation, endothelial injury, hepatic dysfunction, and altered energy metabolism. Evaluating lipid parameters alongside established clinical and laboratory markers may therefore provide insight into the metabolic response associated with severe O. tsutsugamushi infection. However, several questions remain unanswered. It is unclear whether the magnitude of lipid abnormalities differs between patients with uncomplicated and severe scrub typhus, whether individual lipid components have different associations with organ dysfunction, and whether these abnormalities correlate with the number of organ systems involved. In particular, the relationship between total cholesterol, triglycerides, HDL-C, LDL-C and the development of MODS has not been adequately explored in hospital-based Indian populations.

The present hospital-based study was therefore designed to evaluate the lipid profile in patients with confirmed scrub typhus and to determine its association with disease severity and MODS. By comparing lipid parameters across different severity categories and assessing their relationship with the presence and extent of organ dysfunction, the study aims to determine whether dyslipidemia may serve as a clinically useful marker of severe scrub typhus. The primary objective of this study was to evaluate the association between lipid profile abnormalities and disease severity in hospitalized patients with scrub typhus. The secondary objective was to assess the relationship between individual lipid parameters and the development of multiple organ dysfunction syndrome and its severity.

MATERIALS AND METHODS

Study design and population: This was designed as an observational hospital-based study involving 60 patients with confirmed scrub typhus. For a real-world publication, the manuscript should specify the hospital, study period, institutional ethics committee approval number, inclusion criteria, exclusion criteria and method used for confirmation of scrub typhus. Patients fulfilling the Clinical presentation compatible with scrub typhus, Laboratory confirmation of scrub typhus and Availability of lipid-profile measurements would be eligible. Patients with known primary dyslipidemia, chronic liver disease, nephrotic syndrome, active malignancy or other conditions known to substantially alter lipid

metabolism should preferably be excluded or separately analyzed. Patients receiving lipid-lowering medication before admission should also be excluded.

Data Collection: Demographic, clinical and laboratory variables included age, sex, platelet count, hemoglobin, total leukocyte count, AST, ALT, bilirubin, creatinine, albumin, CRP and ferritin. The lipid profile consisted of Total cholesterol, Triglycerides, HDL-C, LDL-C. Clinical complications recorded included AKI, ARDS, hepatitis, shock, MODS, ICU admission, mechanical ventilation and dialysis requirement. Length of hospital stay and final outcome were also assessed. For this analysis hyperlipidemia includes Hypertriglyceridemia (TG ≥150 mg/dL), High LDL-C: (LDL-C ≥100 mg/dL), High total cholesterol (TC ≥200 mg/dL), Low HDL-C(<40 mg/dL in males and <50 mg/dL in females), MODS(presence of dysfunction of two or more organ systems, according to predefined study criteria).

Statistical Analysis: Continuous variables were summarized using mean ± standard deviation and median where appropriate. Categorical variables were expressed as numbers and percentages. Lipid parameters were compared between patients with and without MODS using appropriate parametric or non-parametric tests. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. A two-sided p-value <0.05 was considered statistically significant. For a final publication, multivariable logistic regression should preferably be performed to determine whether triglycerides and LDL-C independently predict MODS after adjustment for relevant confounders.

RESULTS

A total of 60 patients with scrub typhus were included in the study. The mean age of the study population was 41.9 ± 14.8 years (range, 18–77 years), with 26 (43.3%) males and 34 (56.7%) females. The mean duration of hospital stay was 8.5 ± 3.3 days. Hepatic involvement was the most frequent organ manifestation, with 41 (68.3%) patients developing hepatitis. Acute kidney injury was observed in 16 (26.7%) patients, while 11 (18.3%) developed shock and 9 (15.0%) developed acute respiratory distress syndrome (ARDS). Overall, 6 (10.0%) patients developed multiple organ dysfunction syndrome (MODS). Intensive care unit admission was required in 32 (53.3%) patients. Mechanical ventilation was required in 3 (5.0%) patients, while 3 (5.0%) required dialysis. The mean platelet count was 1.25 ± 0.53 lakh/µL, while mean AST and ALT levels were 205.0 ± 76.4 U/L and 145.9 ± 70.0 U/L, respectively. The mean serum creatinine was 1.49 ± 0.76 mg/dL. Inflammatory markers were elevated, with a mean CRP of 56.3 ± 34.5 mg/L and ferritin of 833.6 ± 681.5 ng/mL. [Table 1]

Table 1: Baseline demographic, clinical and laboratory characteristics

LDL-C, mg/dL	**75.03 ± 28.50**
Hemoglobin, g/dL	**10.29 ± 1.65**
TLC, cells/µL	**8495.62 ± 3490.76**
Platelet count, cells/µL	**125187.93 ± 52835.97**
AST, U/L	**205.00 ± 73.64**
ALT, U/L	**145.90 ± 69.35**
Total bilirubin, mg/dL	**2.62 ± 1.04**
Creatinine, mg/dL	**1.49 ± 0.75**
Albumin, g/dL	**3.25 ± 0.49**
CRP, mg/L	**56.33 ± 34.39**
Ferritin, ng/mL	**833.63 ± 711.41**
Length of hospital stay, days	**8.47 ± 3.56**

Lipid profile abnormalities

Significant abnormalities in lipid metabolism were observed in the study population. The mean total cholesterol was 148.5 ± 28.0 mg/dL, triglycerides were 202.38 ± 70.44 mg/dL, HDL-C was 35.76 ± 6.76 mg/dL, and LDL-C was 75.0 ± 28.0 mg/dL. Hypertriglyceridemia was the most prominent lipid abnormality, being present in 50 (83.3%) patients. Low HDL-C was observed in 52 (86.7%) patients. In contrast, elevated LDL-C (≥100 mg/dL) was observed in only 15 (25.0%) patients, while elevated total cholesterol (≥200 mg/dL) was observed in only 2 (3.3%) patients. Thus, the predominant lipid abnormality in patients with scrub typhus was characterized by elevated triglycerides and low HDL-C rather than conventional hypercholesterolemia. [Table 2]

Table 2: Lipid profile according to MODS

Lipid parameter	No MODS (n=54), Mean ± SD	MODS (n=6), Mean ± SD	p-value
Total cholesterol (mg/dL)	151.1 ± 24.4	124.7 ± 38.2	0.153
Triglycerides (mg/dL)	188.9 ± 59.2	324.0 ± 40.5	<0.001
HDL-C (mg/dL)	35.9 ± 6.9	34.2 ± 5.7	0.504
LDL-C (mg/dL)	78.0 ± 28.1	48.0 ± 16.0	0.003

Patients who developed MODS demonstrated a distinct lipid profile compared with those without MODS. The mean triglyceride concentration was markedly higher among patients with MODS (324.0 ± 40.5 mg/dL) compared with patients without MODS (188.9 ± 59.2 mg/dL), and this difference was statistically significant ($p < 0.001$). Similarly, LDL-C was significantly lower in patients with MODS (48.0 ± 16.0 mg/dL) compared with those without MODS (78.0 ± 28.1 mg/dL; $p = 0.003$). Total cholesterol was numerically lower among patients with MODS (124.7 ± 38.2 vs. 151.1 ± 24.4 mg/dL), although this difference was not statistically significant ($p = 0.153$). HDL-C was also slightly lower in the MODS group (34.2 ± 5.7 vs. 35.9 ± 6.9 mg/dL), but the difference did not reach statistical significance ($p = 0.504$) (Figure 1). These findings indicate that hypertriglyceridemia and reduced LDL-C were the lipid parameters most strongly associated with MODS in this study population.

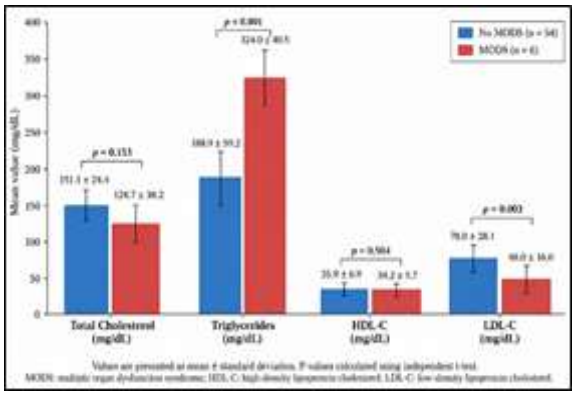

Figure 1: Lipid Profile as per MODS status

Table 3: Lipid profile according to Mortality

Lipid parameter	Survivors (n=56), Mean ± SD	Non-survivors (n=4), Mean ± SD	p-value
Total cholesterol (mg/dL)	151.2 ± 24.5	127.9 ± 36.3	0.145
Triglycerides (mg/dL)	192.3 ± 64.9	278.7 ± 68.0	0.014
HDL-C (mg/dL)	35.6 ± 7.0	37.3 ± 5.0	0.424
LDL-C (mg/dL)	77.8 ± 28.2	53.9 ± 22.4	0.031

A total of 4 (6.7%) patients died, while 56 (93.3%) patients were discharged. Mortality was substantially higher among patients who developed MODS. Among the 6 patients with MODS, 3 (66.7%) died, compared with only 1 (5.6%) deaths among the 54 patients without MODS ($p = 0.001$). Non-survivors also demonstrated significantly higher triglyceride levels compared with survivors (278.7 vs. 192.3 mg/dL; $p = 0.003$). LDL-C was significantly lower among non-survivors (53.9 vs. 77.8 mg/dL; $p = 0.035$). Total cholesterol was lower among non-survivors, although the difference was not statistically significant (127.9 vs. 151.2 mg/dL; $p = 0.163$). HDL-C did not differ significantly between survivors and non-survivors (37.3 vs. 35.6 mg/dL; $p = 0.447$). [Table 3, Figure 2]

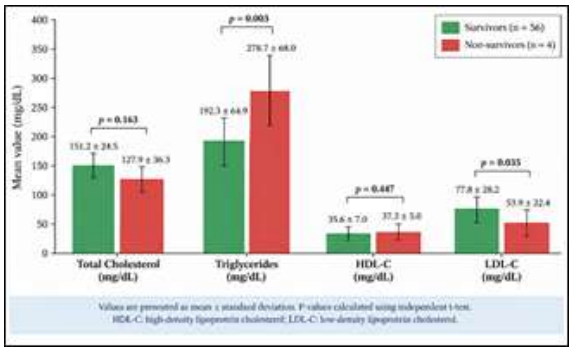

Figure 2: Lipid profile according to mortality in Scrub Typhus

Overall, the study demonstrated that lipid abnormalities were common in hospitalized patients with scrub typhus, with hypertriglyceridemia and low HDL-C being the predominant abnormalities. More importantly, patients who developed MODS had markedly higher triglyceride and lower LDL-C concentrations than patients without MODS. Higher triglyceride and lower LDL-C concentrations were also associated with mortality (Figure 3). These findings suggest that infection-associated alterations in lipid metabolism may reflect the severity of systemic illness in scrub typhus, and that triglycerides and LDL-C may have potential utility as additional biochemical markers for identifying patients at risk of severe disease and MODS.

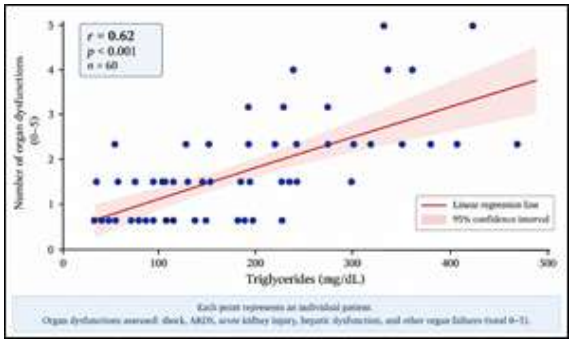

Figure 3: Correlation between Triglycerides and Organ dysfunction in patients with Scrub Typhus

DISCUSSION

Scrub typhus is an important cause of acute febrile illness in India and can progress from an apparently uncomplicated febrile illness to severe systemic disease involving the lungs, liver, kidneys, cardiovascular system, and central nervous system.[9] The present study evaluated the lipid profile of hospitalized patients with scrub typhus and explored

its relationship with disease severity, MODS, and mortality. The principal finding was a characteristic pattern of infection-associated dyslipidemia, particularly hypertriglyceridemia and low HDL-C, with markedly higher triglyceride concentrations and lower LDL-C concentrations among patients who developed MODS. These findings are biologically plausible and are supported by emerging literature specifically addressing lipid abnormalities in scrub typhus.[11]

In our cohort of 60 patients, the lipid abnormality in this population was predominantly characterized by high triglycerides with relatively low HDL-C and LDL-C, rather than isolated elevation of total cholesterol. This pattern is consistent with the metabolic response described during systemic infection and inflammation. A systematic review of patients with systemic inflammatory response syndrome and sepsis reported decreases in HDL-C, total cholesterol and LDL-C together with increased triglyceride concentrations, with the magnitude of lipid alterations tending to parallel inflammatory severity.[12]

Sarswat et al. evaluated 100 patients with severe scrub typhus and reported low HDL-C in 93% and elevated triglycerides (>200 mg/dL) in 71% of patients. Importantly, triglycerides >200 mg/dL were significantly associated with MODS, while LDL-C <50 mg/dL was also associated with MODS. Our findings show a remarkably similar direction of association. In the present study, patients with MODS had a mean triglyceride concentration of 324.0 ± 40.5 mg/dL, compared with 188.9 ± 59.2 mg/dL among patients without MODS ($p < 0.001$). LDL-C was also substantially lower in patients with MODS (48.0 ± 16.0 vs. 78.0 ± 28.1 mg/dL; $p=0.003$). The concordance with the study by Sarswat et al. is notable because both studies identify high triglycerides and low LDL-C as markers associated with more severe scrub typhus.[11]

A previous report specifically titled Hypertriglyceridemia in Scrub Typhus also highlighted the occurrence of hypertriglyceridemia in scrub typhus, supporting the observation that triglyceride metabolism may be altered during acute Orientia tsutsugamushi infection.[13]

Several mechanisms may explain the elevated triglyceride concentrations observed in our patients. During acute infection, inflammatory cytokines promote adipose-tissue lipolysis and increase hepatic fatty-acid synthesis and very-low-density lipoprotein (VLDL) production. At the same time, peripheral clearance of triglyceride-rich lipoproteins may be impaired because of altered lipoprotein-lipase activity and other changes in lipoprotein metabolism. Consequently, circulating triglyceride concentrations may rise during severe systemic inflammation.[12]

There may also be a more direct relationship between O. tsutsugamushi infection and host lipid metabolism. Experimental work has demonstrated that O. tsutsugamushi infection induces lipid-droplet formation and accumulation of triglycerides within infected cells, suggesting that the pathogen can directly modify host-cell lipid metabolism.[14] Although these experimental observations cannot be directly extrapolated to serum triglyceride concentrations in humans, they provide a plausible biological basis for the metabolic alterations observed clinically. The strongest finding of the present study was the association between triglyceride concentration and MODS. Patients with MODS had triglyceride concentrations approximately 70% higher than those without MODS. This difference was highly statistically significant. The association is particularly relevant because MODS represents the clinical consequence of severe systemic inflammation, endothelial dysfunction, tissue hypoperfusion, and progressive organ injury.[15]

Scrub typhus itself is characterized by endothelial infection and activation. Experimental and translational studies have demonstrated inflammatory activation of endothelial cells during O. tsutsugamushi infection, including induction of cytokines and adhesion molecules.[16] Experimental models have also demonstrated endothelial barrier disruption, altered Tie2 signaling, increased angiopoietin-2, and vascular activation during severe infection.[17]

Another important observation was the significantly lower LDL-C concentration in patients with MODS. Mean LDL-C was 48.0 ± 16.0 mg/dL in patients with MODS compared with 78.0 ± 28.1 mg/dL in those without MODS.[12] This observation is consistent with the severe-scrub-typhus cohort of Sarswat et al., in which LDL-C <50 mg/dL was associated with MODS. More broadly, low circulating cholesterol concentrations have been associated with adverse outcomes in sepsis and critical illness. A systematic review and meta-analysis involving 24 studies and 2,542 participants found that nonsurvivors had significantly lower HDL-C concentrations than survivors, while abnormalities of circulating cholesterol were associated with mortality.[18] The reduction in LDL-C during severe infection may result from increased utilization or redistribution of cholesterol, altered hepatic synthesis, changes in lipoprotein clearance, and the acute-phase response.[12] Therefore, low LDL-C in severe scrub typhus may be interpreted as a component of infection-associated hypolipidemia rather than conventional hypocholesterolemia.[18]

Although low HDL-C was common in our cohort, the difference in mean HDL-C between patients with and without MODS was not statistically significant (35.9 ± 6.9 vs. 34.2 ± 5.7 mg/dL; $p=0.504$). This finding requires careful interpretation. HDL has several functions beyond reverse cholesterol transport. It participates in endotoxin binding and neutralization, antioxidant activity, modulation of macrophage responses, endothelial protection, and regulation of inflammatory signaling. During sepsis, both the quantity and functional properties of HDL can change substantially. Consequently, serum HDL

concentration alone may not adequately reflect HDL function during acute infection. HDL can undergo structural and compositional changes during systemic inflammation, potentially becoming less anti-inflammatory or even dysfunctional.[19] Thus, the absence of a statistically significant difference in HDL-C between MODS and non-MODS patients in our study does not necessarily exclude a role for HDL biology in severe scrub typhus.

In the present dataset, nonsurvivors demonstrated higher triglyceride concentrations (278.7 ± 68.0 mg/dL) compared with survivors (192.3 ± 64.9 mg/dL), with a statistically significant difference (p=0.003). LDL-C was also lower among nonsurvivors (53.9 ± 22.4 vs. 77.8 ± 28.2 mg/dL; p=0.035). These findings are consistent with the broader critical-care literature, where low circulating lipoprotein concentrations have been associated with mortality. A systematic review and meta-analysis found particularly strong associations between lower HDL-C and mortality in critically ill patients.[20] However, the relationship between triglycerides and mortality is complex, and triglyceride elevation may reflect the acute inflammatory and metabolic response rather than directly causing death.[21]

The clinical profile of our cohort also supports the presence of substantial systemic disease. Hepatitis was present in 68.3%, AKI in 26.7%, ARDS in 15.0%, shock in 18.3%, and MODS in 10.0% of patients. These findings are consistent with the recognized multisystem nature of severe scrub typhus.[15] Previous Indian studies have similarly demonstrated frequent hepatic, renal, respiratory, and cardiovascular complications.[21,22] In a 90-patient study from Meghalaya, MODS occurred in 14.4% and serum creatinine >1.5 mg/dL independently predicted MODS and mortality.[20] Other Indian studies have identified shock, renal failure, CNS dysfunction, ARDS, hypoalbuminemia, and hepatic dysfunction as important determinants of poor outcome.[21] A systematic review of scrub typhus in India found MODS in approximately 17.4% of reported cases and noted substantially higher mortality among patients with MODS.[22] Thus, the association between lipid abnormalities and MODS in our study is clinically relevant because MODS is itself an established marker of severe scrub typhus.[15,20]

Lipid parameters have several practical advantages. Total cholesterol, triglycerides, HDL-C, and LDL-C are inexpensive and routinely available laboratory measurements. Unlike specialized inflammatory biomarkers, they can often be obtained early during hospital admission.The present findings raise the possibility that a combination of high triglycerides and low LDL-C, particularly when accompanied by conventional markers such as thrombocytopenia, elevated transaminases, hyperbilirubinemia, hypoalbuminemia, elevated creatinine and CRP, may help identify patients at increased risk of severe disease.However, lipid parameters should currently be regarded as adjunctive markers rather than standalone predictors. The study is not sufficiently large to establish diagnostic or prognostic cut-off values, and prospective validation in larger cohorts is required.

Limitations: The study was limited by its small sample size, few MODS cases, observational design, and possible influence of inflammation, nutritional status, comorbidities, and organ dysfunction on lipid levels.

Future Research: Larger prospective multicenter studies with serial lipid measurements and adjustment for important confounders are needed to validate these findings and better determine the prognostic role of lipid abnormalities in scrub typhus.

CONCLUSION

The present study demonstrates that dyslipidemia is common among hospitalized patients with scrub typhus, with hypertriglyceridemia and low HDL-C constituting the predominant abnormalities. More importantly, patients who developed MODS had markedly higher triglyceride and lower LDL-C concentrations, while non-survivors also demonstrated higher triglycerides and lower LDL-C. These findings are consistent with recent scrub-typhus-specific evidence and with the established effects of systemic inflammation on lipid metabolism.

Overall, the findings suggest that infection-associated lipid alterations may serve as accessible markers of disease severity in scrub typhus, particularly for identifying patients at risk of MODS. However, larger prospective studies are required before lipid parameters can be incorporated into formal severity-prediction models.

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