

Prognostic Value of Lipid Profile in Pediatric Secondary Hemophagocytic Lymphohistiocytosis Patients

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Abstract

Background: Secondary hemophagocytic lymphohistiocytosis (sHLH) is a severe hyperinflammatory syndrome, with unchecked immune activation and cytokine storm, leading to progressive multiorgan dysfunction. Although therapeutic approaches have improved, morbidity is still very high, especially in children with severe clinical features. The objective is to evaluate the prognostic significance of lipid profile abnormalities in pediatric secondary HLH patients and determine their association with survival outcomes. **Material and Methods:** This prospective observational study was conducted over a period of 2.5 years in the Department of Pediatrics, Government Medical College, Srinagar. Forty-eight pediatric patients aged 4–18 years diagnosed with secondary HLH according to modified HLH-2004 criteria were enrolled. Clinical features, laboratory investigations, lipid profile parameters including triglycerides, HDL-C, LDL cholesterol, and total cholesterol, along with survival outcomes, were analyzed. Statistical analysis included receiver operating characteristic (ROC) analysis, survival comparison, and logistic regression modeling using SPSS version 20.0. **Results:** The mean age of the study population was 12.21 ± 4.28 years. Infectious etiologies accounted for all cases, with enteric fever being the most common trigger (58.3%), followed by sepsis (25.0%) and hepatitis A (16.7%). Significant lipid abnormalities were observed, particularly elevated triglyceride and reduced HDL-C levels. Mean triglyceride levels were significantly higher among non-survivors (544.78 ± 82.72 mg/dL) compared to survivors (376.99 ± 82.34 mg/dL). ROC analysis demonstrated excellent prognostic performance of triglycerides with an AUC of 0.99, while LDL cholesterol showed good predictive performance with an AUC of 0.89. Logistic regression analysis identified triglycerides, LDL cholesterol, and C-reactive protein (CRP) as significant predictors of mortality. Overall mortality in the study population was 29.2%. **Conclusion:** Lipid profile abnormalities are strongly associated with disease severity and mortality in pediatric secondary HLH. Triglycerides demonstrated excellent predictive performance and may serve as reliable, inexpensive prognostic biomarkers for early risk stratification in pediatric sHLH patients. Early identification of severe lipid abnormalities may facilitate timely intervention and improved clinical outcomes.

Keywords: Secondary hemophagocytic lymphohistiocytosis; pediatric HLH; lipid profile; triglycerides; HDL-C; LDL cholesterol; prognosis; mortality predictors.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening hyperinflammatory syndrome that is characterized by unchecked immune activation, too much cytokines and progressive multi-organ dysfunction. The disorder is caused by failure of the hosts cytotoxic cells (natural killer (NK) cells and cytotoxic T lymphocytes (CTLs)) to eliminate macrophages and histiocytes from the body. This hyperactive immune response is ultimately characterized by the cytokine storm that drives extensive tissue damage and marked systemic inflammation. Cytokines like tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6) and interferon-gamma (IFN- γ) have an important role in disease pathogenesis and relevant to organ dysfunction and disease severity.^[1-3]

There are two types of HLH — primary (familial) and secondary (acquired). Primary HLH occurs when there is an underlying inherited defect in the ability of the cytotoxic lymphocytes, while secondary HLH occurs secondary to

infections, malignancies, autoimmune disorders, and/or immunosuppressive disorders. Infection associated HLH is more prevalent in children and is a significant diagnostic and therapeutic challenge, as it is a rapidly progressing and aggressive disease that is associated with a high mortality. Clinical features like prolonged fever and hepatosplenomegaly, cytopenias, liver dysfunction, coagulopathy and neurological involvement overlap frequently with severe sepsis and multiorgan dysfunction syndrome, leading to a delayed

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diagnosis.^[4-6]

Diagnostic criteria (HLH-2004) have enhanced recognition of the disease, but disease prognosis is still problematic. Systemic markers such as ferritin, fibrinogen and triglycerides in the conventional laboratory tests may not be able to predict clinical outcome and disease severity solely. Thus, establishing the presence of easy-to-detect, reliable and affordable prognostic markers is a critical clinical need in the therapy of paediatric HLH.^[7-10]

During severe systemic disease, inflammation plays a significant role in the changes in lipid metabolism. Cytokine induced inhibition of lipoprotein lipase activity leads to hypertriglyceridemia by slowing down the clearance of triglycerides and increasing hepatic production of lipid. At the same time, inflammatory cytokines also suppress the production of high-density lipoprotein cholesterol (HDL-C) and other lipoproteins, resulting in hypocholesterolemia and decreased HDL-C. These lipid abnormalities are emerging as known and significant markers of the severity of inflammation and immune dysfunction in HLH.^[11-13]

A few recent studies have emphasized the importance of lipid profile abnormalities as a prognostic factor in HLH. Yu et al. showed that high levels of triglycerides were correlated with mortality among children with HLH. Zhou et al. also found the HDL-C significantly decreased in HLH infants and that metabolic impairment was a significant predictor of outcome. Likewise, Xiao Li et al. showed that having severe hypocholesterolemia was an independent predictor of early mortality of pediatric HLH cases. These results indicate that lipid profile parameters can be used as a useful prognostic biomarker that can reflect the severity of the disease and the extent of cytokine storm.^[14-17]

The key to successful treatment in children with HLH is early diagnosis, as there is a strong correlation between delayed

diagnosis and treatment, and a higher mortality rate. Many of these more sophisticated inflammatory markers are expensive, technically challenging and unavailable in resource-poor health care environments, though. Lipid profile tests, on the other hand, are simple, easily obtainable, and quickly prognosticatory laboratory tests. They might thus be useful in early risk stratification, tracking disease course and informing treatment choices in critically ill children with HLH.^[18-21]

While there is growing evidence demonstrating a link between lipid abnormalities and prognosis in HLH, prospective pediatric studies in this field are limited, especially in populations with secondary HLH due to an infection. Hence, in the present study, lipid profile abnormalities in secondary HLH patients in children were studied and the relationship of these abnormalities with disease severity and survival were analyzed.^[22-24]

MATERIALS AND METHODS

The purpose of this study is to determine the prognostic value of the lipid profile (LP) abnormalities in secondary hemophagocytic lymphohistiocytosis (sHLH) in children. This study aimed at evaluating the relationship of changes in lipid parameters to disease activity, inflammation, and survival in the children treated for HLH. A systematic analysis of clinical and laboratory data, lipid profile parameters and outcome measures was carried out to assess the potential of lipid abnormalities as predictive biomarkers in pediatric sHLH.

Students design and setting: After securing the ethical clearance from the hospital, this was a prospective observational study carried out in the Department of Pediatrics, Government Medical College, Srinagar for a period of 2.5 years.

Study Population: We consecutively recruited 48 children aged 4–18 years with secondary HLH according to the modified HLH-2004 criteria from the pediatric wards and pediatric intensive care units.

Table 1: Age Distribution of Patients

Age Group	Frequency	Percentage
4–6 years	4	8.3%
7–9 years	6	12.5%
10–12 years	14	29.2%
13–15 years	15	31.3%
16–18 years	9	18.7%

Table 1 shows the age distribution of patients included in the study. The highest number of patients belonged to the 13–15 years age group (31.3%), followed by the 10–12 years group (29.2%). The lowest percentage of patients was observed in the 4–6 years age group (8.3%). This indicates that most patients in the study were between 10 and 15 years of age.

Inclusion Criteria

Pediatric patients aged from 4–18 years, fulfilling the HLH-2004 diagnostic criteria, for secondary hemophagocytic lymphohistiocytosis (sHLH) were included in the study. Eligible patients with clinical, laboratory and biochemical characteristics supportive of the diagnosis of HLH were included in the study. Criteria for diagnosis were based on the presence of characteristic features of HLH, as outlined in the guidelines from the HLH Consortium of the last decade: prolonged fever, splenomegaly, cytopenias,

hyperferritinemia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis and reduction in natural killer (NK) cell activity, and elevated soluble CD25 (sCD25). The study population included only patients with acquired or secondary HLH who had infectious or inflammatory triggers.

Exclusion Criteria

Patients with lipid associated disorders that could affect the result of the lipid profile and lipid metabolism were excluded. Unlike children with metabolic syndrome, who may have underlying dyslipidaemia due to obesity or insulin resistance or endocrinopathy, which could affect the specific assessment of lipid changes due to HLH. Patients with prior liver disease (both hepatic impairment or cholestasis) were also excluded because liver dysfunction has a profound impact on lipid synthesis, metabolism and clearance, and therefore can impact serum levels of cholesterol and triglycerides not related to inflammation.

Patients with known storage disorders, inherited metabolic diseases, were also excluded as there was a fear that this could cause a baseline abnormality in lipid metabolism and systemic inflammatory responses that could affect the interpretation of the prognostic role of lipid abnormalities in the secondary HLH patient population.

Data Collection

All patients were evaluated clinically in detail and systematically on enrolment. Data on demographic characteristics, such as age and gender, and detailed clinical data regarding the duration of the fever, presenting complaints, previous infections and associated comorbidities were carefully documented. Complete physical examination was done, and findings showed hepatomegaly, splenomegaly, lymphadenopathy, neurological symptoms, respiratory symptoms, and shock symptoms. Other details about the course of the disease, treatment received, need for intensive care provision and any subsequent clinical outcomes, such as survival, were also obtained during the patient's stay in hospital. Detailed laboratory investigations were performed as part of routine diagnostic and prognostic work-up of all patients including complete blood count, serum ferritin and C-reactive protein (CRP), absolute neutrophil count (ANC) and lipid profile analysis (serum triglycerides, high density lipoproteins Chl (HDL-C), low density lipoproteins Chl (LDL) and total cholesterol). These

were analyzed in the lab to assess the relationship between these parameters and the severity and survival in pediatric patients with secondary Hemophagocytic lymphohistiocytosis.

Statistical Analysis

Data analysis was performed using SPSS version 20.0. Continuous variables were expressed as mean with ± standard deviation, while categorical variables were expressed as frequencies and percentages. Comparative analysis between survivors and non-survivors was performed using appropriate statistical tests. Hence ROC analysis was conducted to evaluate predictive performance of lipid parameters. Additionally Logistic regression analysis was performed to identify independent mortality predictors. Finally A p-value <0.05 was considered statistically significant.

RESULTS

Demographic and Baseline Characteristics

A total of 48 pediatric patients diagnosed with secondary hemophagocytic lymphohistiocytosis (sHLH) were enrolled during the study period. The mean age of the study population was 12.21 ± 4.28 years, with the majority of patients belonging to the 13–15 years age group. Infectious etiologies accounted for all cases included in the study, with enteric fever representing the most common underlying trigger, followed by sepsis and hepatitis A infection.

Table 2: Demographic and Etiological Characteristics of Study Population (n = 48)

Characteristic	n (%) / Mean ± SD
Mean age (years)	12.21 ± 4.28
Enteric fever	28 (58.3%)
Sepsis	12 (25.0%)
Hepatitis A	8 (16.7%)

The predominance of infectious triggers highlights the important role of infection-associated immune dysregulation in pediatric secondary HLH.

Clinical Profile and Disease Severity

Clinical evaluation demonstrated significant hematological and systemic involvement among the study population. Pancytopenia was the most common hematological abnormality, observed in 56.3% of patients, followed by splenomegaly (47.9%) and bicytopenia (43.8%). Hepatosplenomegaly was present in 29.2% of patients, whereas isolated hepatomegaly was observed less frequently.

A substantial proportion of patients demonstrated severe clinical manifestations requiring intensive care management. Shock was the most common severity indicator, affecting 66.7% of patients. Central nervous system (CNS) involvement and invasive mechanical ventilation (IMV) requirement were each observed in 29.2% of patients, while non-invasive ventilation (NIV) support was required in 8.3% of cases.

Table 3: Clinical Profile and Severity Indicators

Variable	Frequency (%)
Splenomegaly	23 (47.9%)
Hepatomegaly	5 (10.4%)
Hepatosplenomegaly	14 (29.2%)
Pancytopenia	27 (56.3%)
Bicytopenia	21 (43.8%)
CNS involvement	14 (29.2%)
Shock	32 (66.7%)
IMV requirement	14 (29.2%)
NIV requirement	4 (8.3%)

These findings indicate that pediatric secondary HLH was associated with significant hematological abnormalities and severe systemic manifestations.

Lipid Profile Parameters: Marked alterations in lipid metabolism were observed among the studied patients. The mean triglyceride level was significantly elevated (424.95 ±

122.96 mg/dL), whereas HDL-C levels were markedly reduced (18.56 ± 11.55 mg/dL), indicating severe inflammatory and metabolic dysregulation.

Table 4: Mean Lipid Profile Parameters

Parameter	Mean ± SD
Triglycerides (mg/dL)	424.95 ± 122.96
HDL-C (mg/dL)	18.56 ± 11.55

These findings suggest that pediatric secondary HLH is associated with profound disturbances in lipid metabolism.

Comparison of Lipid Parameters Between Survivors and Non-survivors: Comparison between survivors and non-survivors revealed significant differences in lipid profile

parameters. Non-survivors demonstrated markedly elevated triglyceride and LDL levels, whereas survivors had comparatively higher HDL-C and total cholesterol levels.

Table 5: Comparison of Lipid Profile Parameters Between Survivors and Non-survivors

Parameter	Survivors	Non-survivors
Triglycerides (mg/dL)	376.99 ± 82.34	544.78 ± 82.72
Total cholesterol (mg/dL)	211.27 ± 133.84	105.28 ± 65.58
HDL-C (mg/dL)	21.00 ± 11.76	12.66 ± 8.84
LDL (mg/dL)	103.57 ± 50.46	158.47 ± 14.57

These findings suggest a strong association between altered lipid metabolism and adverse clinical outcomes in pediatric secondary HLH patients.

Clinical Outcomes: Overall survival was observed in 70.8% of patients, whereas mortality occurred in 29.2% of cases. The relatively high mortality rate reflects the aggressive clinical course of pediatric secondary HLH and emphasizes the importance of early diagnosis and prognostic assessment.

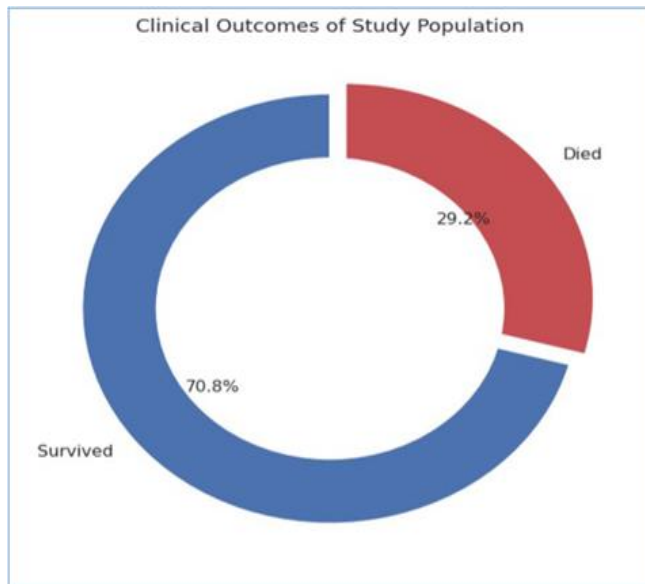


Figure 1: Clinical Outcomes of Study Population

The clinical outcome analysis demonstrated that severe lipid abnormalities, particularly elevated triglycerides and LDL levels, were associated with poorer survival outcomes, suggesting that metabolic dysfunction may reflect the severity of systemic inflammation and immune dysregulation in HLH.

Pairwise Distribution of Laboratory Parameters According to Survival Outcomes

Distinct clustering patterns were seen in Pairplot analysis, between survivors and non-survivors. Non-survivors had significantly higher levels of triglycerides, ferritin and lower platelet count reflecting intense inflammatory activation and disturbed haematological function.

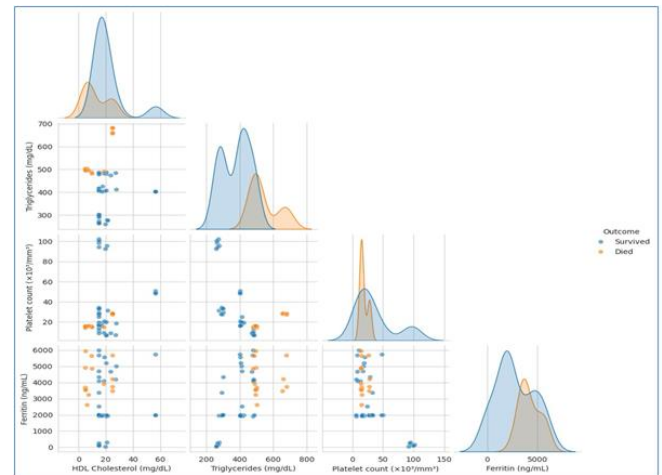


Figure 2: Pairwise Distribution and Relationships of Key Laboratory Parameters According to Survival Outcomes

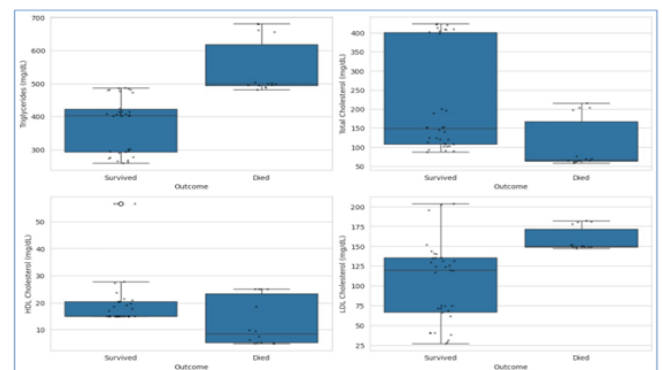


Figure 3: Boxplot Comparison of Lipid Profile Parameters Between Survivors and Non-survivors

The analysis further demonstrated that survivors generally had lower triglyceride levels and comparatively preserved platelet counts, whereas non-survivors exhibited pronounced hypertriglyceridemia and hyperferritinemia.

Boxplot Comparison of Lipid Profile Parameters

Boxplot analysis demonstrated significant differences in lipid profile parameters between survivors and non-

survivors. Non-survivors exhibited markedly elevated triglyceride and LDL levels along with comparatively reduced HDL-C and total cholesterol levels.

These findings further support the prognostic significance of lipid profile abnormalities in pediatric secondary HLH.

ROC Analysis of Lipid Parameters

Receiver operating characteristic (ROC) analysis was

performed to evaluate the predictive performance of lipid profile parameters for mortality in pediatric secondary HLH patients. Triglycerides demonstrated excellent predictive ability with an AUC of 0.99, indicating near-perfect discrimination for mortality prediction. LDL cholesterol also demonstrated good prognostic performance with an AUC of 0.89.

Table 6: ROC Analysis of Lipid Parameters

Parameter	AUC
Triglycerides	0.99
LDL	0.89
HDL-C	0.45
Total cholesterol	0.20

In contrast, HDL-C and total cholesterol demonstrated poor predictive performance with AUC values of 0.45 and 0.20, respectively.

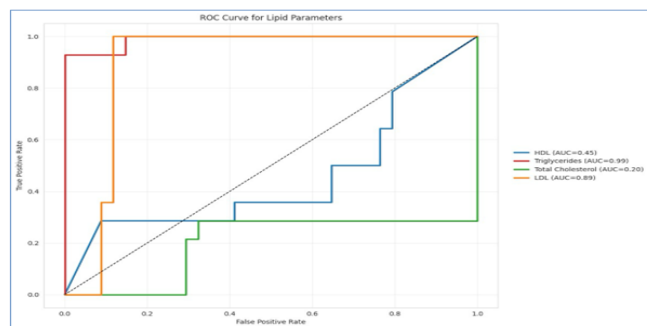


Figure 4: Receiver Operating Characteristic (ROC) Curves of Lipid Parameters for Predicting Mortality

ROC curve analysis further demonstrated the superior prognostic performance of triglycerides and LDL cholesterol compared to HDL-C and total cholesterol.

Association of Lipid Parameters With Survival Outcomes

Association analysis demonstrated statistically significant relationships between survival outcomes and serum triglycerides, LDL cholesterol, and total cholesterol levels. Elevated triglycerides and LDL levels were strongly associated with increased mortality.

Table 7: Association of Lipid Parameters With Survival Outcomes

Parameter	p-value
Triglycerides	<0.001
LDL	<0.001
Total cholesterol	0.001
HDL-C	0.600

HDL-C did not demonstrate statistically significant association with mortality.

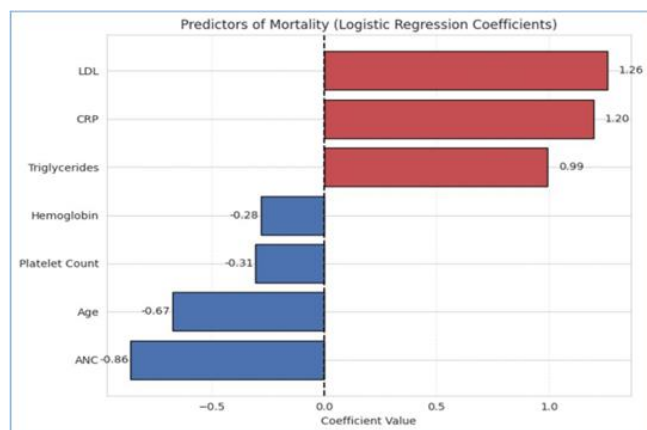


Figure 5: Logistic Regression Analysis Showing Predictors of Mortality in Pediatric Secondary HLH

Logistic Regression Analysis of Mortality Predictors

Logistic regression analysis identified LDL cholesterol, C-reactive protein (CRP), and triglycerides as significant predictors of mortality among pediatric secondary HLH

patients. LDL demonstrated the highest positive regression coefficient ($\beta = 1.26$), followed by CRP ($\beta = 1.20$) and triglycerides ($\beta = 0.99$), indicating strong association with adverse clinical outcomes.

Absolute neutrophil count (ANC), age, platelet count and hemoglobin had negative regression coefficients, indicating a protective role for survival. These data suggest that inflammatory derangement (together with lipid abnormalities and hematologic abnormalities) plays a significant role in pediatric secondary HLH mortality.

DISCUSSION

The present study proved that lipid metabolism abnormalities were significant in the secondary HLH pediatric patients and that they were closely related to the severity and mortality of the disease. Most of the infections led to the development of infection associated-HLH, while enteric fever was the most frequent infectious trigger.^[25]

Hypertriglyceridemia was noted in non-survivors, indicating severe state-related cytokine-mediated metabolic derangements in severe diseases. Prolonged hypertriglyceridaemia, due to a

reduction of the activity of lipoprotein lipase caused by high levels of inflammatory cytokines such as tumour necrosis factor (TNF- α) and interleucin 6 (IL-6), which in turn affects the clearance of triglycerides. At the same time, inflammatory pathways inhibit hepatic HDL production and modify the cholesterol metabolism.^[26-28]

The other most interesting results of the present study are the excellent AUCs of triglycerides (0.99) compared with other indicators. This study results suggest near perfect discrimination in predicting mortality and suggest the possible clinical value of triglycerides use as a low-cost, easily available prognostic biomarker in pediatric HLH.^[29,30] Similarly, LDL cholesterol had good predictive performance, AUC of 0.89, whereas HDL-C and total cholesterol had relatively poor predictive performances. The results indicate that triglycerides and LDL may provide a better index of the magnitude of inflammatory and metabolic dysregulation that might reflect severity of disease progression.^[31-33]

The results of the present study are in line with an earlier study by Yu TY et al that showed hypertriglyceridemia as a significant predictor of mortality in pediatric HLH. Likewise, Xiao Li et al. showed strong correlations with hypocholesterolemia and bad outcomes.^[34]

In the present study, it was also noted that lipid abnormalities was strongly associated with clinical severity markers such as shock or need for respiratory support or multiorgan dysfunction. The observations here support the emerging view that metabolic dysfunction is not simply a secondary inflammatory event, but is part of the HLH pathophysiology. As they are readily available, inexpensive and have a good prognostic value, lipid profile parameters could be included in clinical assessment and early risk stratification in children with secondary HLH.^[35]

CONCLUSION

Pediatric secondary, hemophagocytic lymphohistiocytosis is associated with lipid profile abnormalities, and there is a strong correlation between lipid profile abnormalities and disease severity, inflammatory burden, and survival. Among sHLH pediatric patients, significant changes in lipid metabolism would be identified: increased level of triglycerides and decreased level of HDL-C. These defects were more severe in non-survivors and implied that metabolic dysfunction is closely related to the severity of immune dysregulation and cytokine storm in HLH.

On the basis of all lipid parameters analysed, triglycerides showed the best predictive value for mortality with almost 100% discriminatory capacity in ROC analysis. The level of LDL cholesterol also was a significant prognostic factor, and low total cholesterol and HDL-C levels were linked with the development of severe disease and worse clinical outcomes. The results contribute to the emerging data indicating that lipid metabolic disturbance is not only a secondary biochemical phenomenon, but could also be a key determinant for disease progression and prognosis in children with HLH.

Highlights of the study include the clinical value of lipid profile measurement as an inexpensive, readily available, and

readily reproducible predictor of risk. The inclusion of lipid parameters in routine prognostic assessment could aid in early recognition of high-risk pediatric HLH patients, enhance the risk stratification process, and enable prompt therapeutic intervention and intense monitoring of these patients. With the advanced immunological testing not always easily available in resource-poor settings, the use of lipid profile abnormalities in resource-rich countries offers important prognostic information of relevance to clinical practice.

The current study offers valuable information regarding the value of lipid abnormalities as prognostic markers for pediatric sHLH, though larger multicenter prospective studies are needed to confirm the results and develop lipid based prognostic models. Additional studies which investigate interactions between lipid metabolism, cytokine dysregulation and immune activation could help elucidate the mechanisms underlying HLH, and help develop specific therapeutic interventions.

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Conflicts of interest

There are no conflicts of interest.

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