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# Significance of De Ritis Ratio (AST/ALT) in the Prognosis of Pediatric Hemophagocytic Lymphohistiocytosis (Postprint)

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**Date:** 2023-01-09T00:00:00+00:00

## Abstract

Background The De Ritis ratio has emerged as a novel indicator for evaluating the prognosis of acute and critical illnesses in recent years. Currently, the De Ritis ratio has only been reported for assessing prognosis in adult hemophagocytic lymphohistiocytosis, with no relevant studies conducted in pediatric hemophagocytic lymphohistiocytosis.

Objective To investigate the relationship between the De Ritis ratio and clinical characteristics and its prognostic significance in pediatric patients with hemophagocytic lymphohistiocytosis, thereby providing a theoretical basis for early clinical identification and diagnosis.

Methods Clinical data of 128 pediatric patients diagnosed with hemophagocytic lymphohistiocytosis in our hospital from January 2013 to May 2022 were collected. Based on tertile levels of the De Ritis ratio (serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT)), patients were divided into: Group T1 (De Ritis ratio $ $1.57), Group T2 (1.57 < De Ritis ratio < 3.22), and Group T3 (De Ritis ratio $ $3.22). Differences in clinical characteristics and prognosis among the three groups, correlations between the De Ritis ratio and clinical characteristics were analyzed, and Cox regression analysis was employed to identify risk factors for poor prognosis.

Results The proportions of PICU admission, respiratory failure, central nervous system damage, shock occurrence, mortality, creatine kinase isoenzyme, lactate dehydrogenase, activated partial thromboplastin time, and serum ferritin levels in Group T3 were significantly higher than those in Groups T1 and T2, whereas albumin and fibrinogen levels were significantly lower. Regarding treatment, the proportion of patients receiving blood purification therapy in Groups

T2 and T3 was significantly higher than in Group T1. Correlation analysis revealed that the De Ritis ratio was positively correlated with absolute neutrophil count, C-reactive protein, total bilirubin, creatine kinase, creatine kinase isoenzyme, lactate dehydrogenase, activated partial thromboplastin time, and serum ferritin; and negatively correlated with albumin, fibrinogen, Ca2+, and Na+ levels. Univariate Cox regression analysis demonstrated that PICU admission, respiratory failure, shock, central nervous system damage, platelet count $< 100 \times 10\hat{}9$/L, Na+ $\leq 130$ mmol/L, albumin $\leq 30$ g/L, creatine kinase isoenzyme $\geq 40.5$ U/L, lactate dehydrogenase $\geq 927.5$ U/L, activated partial thromboplastin time $\geq 53.95$ s, fibrinogen $\leq 1.45$ g/L, and serum ferritin $\geq 1897$ g/L were risk factors affecting patient prognosis ($P < 0.05$). Multivariate Cox regression analysis indicated that respiratory failure (HR = 6.41, 95% CI = 2.24, 18.30), albumin $\leq 30$ g/L (OR = 3.13, 95% CI = 1.17, 8.41), and fibrinogen $\leq 1.45$ g/L (OR = 5.18, 95% CI = 1.68, 15.9) were independent risk factors affecting the prognosis of pediatric patients with hemophagocytic lymphohistiocytosis ($P < 0.05$). Survival analysis showed that the overall survival of Group T3 and Group T2 was lower than that of Group T1 ($P = 0.001$; $P = 0.038$), while no statistically significant difference in overall survival was observed between Group T3 and Group T2 ($P > 0.05$).

Conclusion In pediatric patients with hemophagocytic lymphohistiocytosis, a higher De Ritis ratio is associated with a higher incidence of poor prognosis and shorter overall survival, indicating worse outcomes. Therefore, early monitoring of changes in the De Ritis ratio is of significant clinical importance for prognostic assessment in pediatric patients with hemophagocytic lymphohistiocytosis.

## Full Text

# Prognostic Significance of De Ritis Ratio (AST/ALT) in Children with Hemophagocytic Lymphohistiocytosis

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**Funding:** National Natural Science Foundation of China (82260036); Guizhou Provincial Science and Technology Program (Qiankehe Platform Talent-CXTD[2021]010); Provincial and Ministerial Co-construction Collaborative Innovation Center Project (Education Science and Technology Department Letter [2020]39); Guizhou Provincial Graduate Research Fund Project (Qianjiahe

YJSKYJJ[2021]178)

**Abstract**

**Background:** The De Ritis ratio has emerged in recent years as a novel indicator for evaluating prognosis in critically ill patients. Currently, the De Ritis ratio has only been reported for assessing prognosis in adult hemophagocytic lymphohistiocytosis (HLH), with no relevant studies in pediatric HLH.

**Objective:** To investigate the relationship between the De Ritis ratio and clinical characteristics in children with HLH and its prognostic significance, thereby providing a theoretical basis for early clinical identification and diagnosis of HLH.

**Methods:** Clinical data from 128 children diagnosed with HLH at our hospital between January 2013 and May 2022 were collected. Based on tertile levels of the De Ritis ratio (serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT)), the patients were divided into three groups: T1 (De Ritis ratio $ $1.57), T2 (De Ritis ratio 1.57–3.22), and T3 (De Ritis ratio $ $3.22). We analyzed differences in clinical characteristics and prognosis among the three groups, examined correlations between the De Ritis ratio and clinical features, and identified risk factors for poor prognosis using Cox regression analysis.

**Results:** The T3 group showed significantly higher rates of PICU admission, respiratory failure, central nervous system damage, and shock, along with higher mortality, creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), activated partial thromboplastin time (APTT), and serum ferritin levels compared to T1 and T2 groups. Albumin and fibrinogen levels were significantly lower in T3. Regarding treatment, the proportion of children receiving blood purification therapy was significantly higher in T2 and T3 groups than in T1. Correlation analysis revealed that the De Ritis ratio was positively correlated with absolute neutrophil count, C-reactive protein, total bilirubin, creatine kinase, CK-MB, LDH, APTT, and serum ferritin, and negatively correlated with albumin, fibrinogen, $Ca^{2+}$, and $Na^{+}$ levels. Univariate Cox regression analysis showed that PICU admission, respiratory failure, shock, central nervous system damage, platelet count <100$\times 10^{\{9\}/L, Na}\{+\}$ $ $130 mmol/L, albumin $ $30 g/L, CK-MB $ $40.5 U/L, LDH $ $927.5 U/L, APTT $ $53.95 s, fibrinogen $ $1.45 g/L, and serum ferritin $ $1897 g/L were risk factors affecting prognosis (P<0.05). Multivariate Cox regression analysis identified respiratory failure (HR=6.41, 95% CI=2.24–18.30), albumin $ $30 g/L (OR=3.13, 95% CI=1.17–8.41), and fibrinogen $ $1.45 g/L (OR=5.18, 95% CI=1.68–15.9) as independent risk factors for poor prognosis (P<0.05). Survival analysis demonstrated that overall survival was significantly shorter in T3 and T2 groups compared to T1 (P=0.001 and P=0.038, respectively), with no significant difference between T3 and T2 (P>0.05).

**Conclusion:** Higher De Ritis ratios in children with HLH are associated with higher incidence of poor prognosis and shorter overall survival. Early monitoring of De Ritis ratio changes is clinically significant for predicting outcomes in pediatric HLH patients.

**Keywords:** Hemophagocytic lymphohistiocytosis; Children; De Ritis ratio; Survival; Prognosis

## Introduction

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a fatal inflammatory response syndrome caused by excessive activation and massive proliferation of immune cells with secretion of large amounts of inflammatory cytokines. HLH has acute onset and rapid progression, frequently leading to multiple organ dysfunction syndrome (MODS), with mortality rates reaching up to 60% in severe pediatric cases. Therefore, identifying effective early prognostic indicators is clinically crucial for improving outcomes in children with HLH.

Elevated serum transaminase levels represent one of the important early clinical changes in HLH. The possibility of HLH should be considered when children present with fever, cytopenia, and abnormal liver function. Most studies have demonstrated the clinical utility of the De Ritis ratio (the ratio of serum aspartate aminotransferase (AST) to alanine aminotransferase (ALT)) in predicting prognosis for diseases such as COVID-19 and acute kidney injury. However, no studies have reported on the De Ritis ratio in pediatric HLH. This study investigates the relationship between the De Ritis ratio and clinical characteristics in children with HLH and its prognostic significance to provide a reliable theoretical basis for early diagnosis.

## Methods

### 1.1 Case Selection

We conducted a retrospective analysis of clinical data from 128 hospitalized children diagnosed with HLH at the Affiliated Hospital of Zunyi Medical University between January 2013 and May 2022. Inclusion criteria were: (1) fulfillment of the 2004 HLH diagnostic criteria published by the Histiocyte Society; (2) age at onset $ $14 years; and (3) complete clinical data. Exclusion criteria were: (1) failure to meet HLH-2004 diagnostic criteria; (2) age at onset >14 years; and (3) incomplete clinical data. This study was approved by the hospital ethics committee (KLL-2022-617).

### 1.2 Data Collection

Clinical data collected included general information (age, sex, etiology, residence, PICU admission, treatment modalities), clinical symptoms and signs, and laboratory tests (white blood cell count, absolute neutrophil count, hemoglobin, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, serum ferritin, fibrinogen, albumin, etc.).

The median De Ritis ratio among the 128 HLH children was 2.11 (range 0.25-9.61). Patients were divided into three groups based on tertile levels: T1 (De Ritis ratio $ $1.57), T2 (De Ritis ratio 1.57-3.22), and T3 (De Ritis ratio $ 3.22).$Additionalcategorizationsincludedsex(male/female), age($ 1yearvs > 1year), residence(ruralvsurban), diseaseduration($ $7 days vs >7 days), etiology (primary, EBV infection, non-EBV infection, or unknown), and treatment (blood purification group: chemotherapy + single membrane plasma exchange (PE)/continuous renal replacement therapy (CRRT) vs non-blood purification group).

### 1.4 Treatment Modalities

Among the 128 children, 75 (58.59%) received chemotherapy alone with the HLH-94/HLH-2004 protocol, 37 (28.90%) received chemotherapy combined with PE/CRRT, and 16 (12.5%) received supportive treatment such as anti-infection therapy.

### 1.5 Follow-up

Follow-up was conducted through outpatient visits and telephone calls, starting from hospital discharge and ending on June 1, 2022, or at the time of loss to follow-up.

### 1.6 Statistical Analysis

Data were analyzed using SPSS 18.0 and GraphPad Prism 8.0. Normally distributed continuous variables were expressed as mean ± standard deviation (X±S) and compared using one-way ANOVA. Non-normally distributed variables were expressed as median and interquartile range [M(Q1,Q3)] and compared using the Kruskal-Wallis test. Categorical variables were expressed as n(%) and compared using $^2$ tests. Spearman correlation analysis was used to examine correlations between the De Ritis ratio and clinical parameters. Receiver operating characteristic (ROC) curves were constructed to determine optimal cutoff values. Kaplan-Meier curves were used to analyze cumulative survival rates over time. Cox regression models were used to identify independent risk factors for prognosis, with comparisons between groups performed using Log-rank tests. P<0.05 was considered statistically significant.

## Results

### 2.1 Comparison of General Characteristics

This study included 128 children: 43 (33.59%) in T1 group, 42 (32.81%) in T2 group, and 43 (33.59%) in T3 group, with no significant difference in distribution (P>0.05). The median age was 72 (3-168) months in T1, 25 (3-144) months in T2, and 27 (3-156) months in T3. Children older than 1 year comprised 39 (90.7%) in T1, 30 (71.43%) in T2, and 31 (72.1%) in T3, with no significant difference (P>0.05). The T2 group had a significantly higher proportion of males (71.43%) compared to T1 (46.51%) and T3 (48.84%). PICU admission rates were significantly higher in T2 (71.43%) and T3 (83.72%) than in T1 (37.21%). Mortality rates were significantly higher in T2 (33.33%) and T3 (44.19%) compared to T1 (13.95%). Regarding treatment, the proportion of children receiving blood purification therapy was significantly higher in T2 (38.10%) and T3 (34.88%) than in T1 (13.95%). All these differences were statistically significant (P<0.05). No significant differences were observed in disease etiology, onset time, or residence (P>0.05) .

All three groups had 100% fever rates. The incidence of respiratory failure was higher in T3 (52.38%) than in T1 (20.93%) and T2 (45.24%). Central nervous system damage rates were higher in T2 (30.95%) and T3 (33.33%) than in T1 (13.95%). Shock incidence was higher in T3 (41.86%) than in T1 (18.60%) and T2 (21.43%). All these differences were statistically significant (P<0.05). No significant differences were found in hepatosplenomegaly, fungal infection, disseminated intravascular coagulation, acute respiratory distress syndrome, pneumonia, gastrointestinal bleeding, pulmonary hemorrhage, or number of organs with dysfunction (P>0.05) .

### 2.3 Comparison of Laboratory Indicators

Children in T3 group had significantly higher CK-MB, LDH, APTT, and serum ferritin levels, and significantly lower albumin and fibrinogen levels compared to T1 and T2 groups (P<0.05). No significant differences were observed in white blood cell count, absolute neutrophil count, hemoglobin, platelet count, $K^+$, $Ca^{2+}$, total bilirubin, triglycerides, creatinine, blood urea nitrogen, prothrombin time, immunoglobulin G, immunoglobulin A, immunoglobulin M, immunoglobulin E, interleukin-2, interleukin-4, interleukin-6, interleukin-10, tumor necrosis factor-$\alpha$, or interferon-$\gamma$ levels (P>0.05) .

### 2.4 Correlation Analysis Between De Ritis Ratio and Laboratory Indicators

Correlation analysis showed that the De Ritis ratio was positively correlated with absolute neutrophil count, C-reactive protein, total bilirubin, creatine kinase, CK-MB, LDH, APTT, and serum ferritin, and negatively correlated with albumin, fibrinogen, $Ca^{2+}$, and $Na^+$ levels. These correlations were statistically significant (P<0.05) .

### 2.5 Prognostic Survival Analysis Based on De Ritis Ratio

For non-normally distributed variables (fibrinogen, C-reactive protein, CK-MB, LDH, APTT, serum ferritin), ROC curve analysis was used to determine optimal cutoff values of 1.45, 82.08, 40.5, 927.5, 53.95, and 1897, respectively, with area under the curve values of 0.715, 0.56, 0.666, 0.605, 0.724, and 0.648 [Figure 1: see original paper].

Univariate Cox regression analysis revealed that PICU admission, respiratory failure, shock, central nervous system damage, platelet count $<100\$\times10^{\{9\}/L, Na}\{+\}\$$ $ $130 mmol/L, albumin $ $30 g/L, CK-MB $ $40.5 U/L, LDH $ $927.5 U/L, APTT $ $53.95 s, fibrinogen $ $1.45 g/L, and serum ferritin $ $1897 g/L were risk factors affecting prognosis ($P<0.05$). Multivariate Cox regression analysis identified respiratory failure (HR=6.41, 95% CI=2.24-18.30), albumin $ $30 g/L (OR=3.13, 95% CI=1.17-8.41), and fibrinogen $ $1.45 g/L (OR=5.18, 95% CI=1.68-15.9) as independent risk factors for poor prognosis in children with HLH . Further survival analysis showed that overall survival was significantly shorter in T3 and T2 groups compared to T1 (P=0.001 and P=0.038, respectively), with no significant difference between T2 and T3 (P=0.176) [Figure 2: see original paper].

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## Discussion

HLH is a critical illness characterized by uncontrolled immune activation and cytokine storms, more common in children than adults. Most pediatric HLH cases progress rapidly with poor prognosis. Early identification of factors associated with poor outcomes is essential for improving prognosis. The De Ritis ratio, initially proposed by De Ritis as the ratio of serum AST to ALT, was originally thought to be associated with prognosis in liver damage-related diseases. In recent years, it has become an important prognostic indicator for critical illnesses and malignant tumors, including acute myocardial infarction, COVID-19, and hematologic malignancies. Currently, only one study has reported the prognostic significance of the De Ritis ratio in malignancy-associated HLH in adults, with no reports in pediatric HLH. Therefore, analyzing the significance of the De Ritis ratio in pediatric HLH may have important clinical value for improving patient outcomes.

This study demonstrated that mortality rates increased progressively with higher De Ritis ratios, suggesting that higher ratios may indicate greater risk of poor prognosis in pediatric HLH, consistent with reports in adult HLH. Previous studies have noted that children with HLH often require emergency admission or PICU care due to rapidly progressive septic shock-like manifestations, respiratory failure, and central nervous system damage, with extremely high mortality if untreated. Our results showed that higher De Ritis ratios were associated with increased rates of shock, respiratory failure, and central nervous system damage, as well as higher PICU admission rates,

indicating that children with elevated De Ritis ratios may be more prone to multiple organ failure and shock, accelerating disease progression.

We also found that the proportion of children receiving blood purification therapy was significantly higher in T2 and T3 groups than in T1, with mortality rates lower than T1, though the difference was not statistically significant, likely due to insufficient sample size requiring further analysis. Combined with our previous research confirming that early use of CRRT or PE+CRRT can significantly improve survival and organ failure in severe pediatric HLH, these findings suggest that early blood purification therapy may be important for improving prognosis in HLH children with elevated De Ritis ratios. Survival analysis further demonstrated that overall survival was significantly shorter in T2 and T3 groups compared to T1 (P=0.038 and P=0.001, respectively), indicating an inverse relationship between De Ritis ratio and overall survival in HLH children, similar to findings in COVID-19 and cardiovascular diseases.

Pediatric HLH is characterized by cytopenia and elevated serum ferritin, along with increased LDH, CK-MB, and transaminases, and decreased albumin and electrolyte disturbances. Our study showed that CK-MB, LDH, APTT, and serum ferritin levels were significantly higher in T3, while albumin and fibrinogen were lower than in T1 and T2. Correlation analysis revealed positive correlations between De Ritis ratio and absolute neutrophil count, total bilirubin, creatine kinase, CK-MB, LDH, APTT, and serum ferritin, and negative correlations with albumin, fibrinogen, $Ca^{2+}$, and $Na^{+}$ levels, consistent with Yin et al.' s report, suggesting these laboratory abnormalities may be associated with elevated De Ritis ratio in HLH children. Therefore, clinical management should include early monitoring of LDH, serum ferritin, albumin, and fibrinogen in HLH children with elevated De Ritis ratios.

Previous studies have identified age, multiple organ dysfunction, and prothrombin time as risk factors for poor prognosis in HLH children. Our multivariate analysis identified fibrinogen $ $1.45 g/L, albumin $ $30 g/L, and respiratory failure as independent risk factors. Signoff et al. confirmed that hypofibrinogenemia is associated with HLH complications, and fibrinogen levels <2 g/L correlate with high mortality. Gao et al. also found severely reduced albumin levels in HLH patients. Additionally, severe HLH children are more prone to respiratory failure, consistent with our findings. Therefore, in pediatric HLH, children with high De Ritis ratios require early attention to fibrinogen and albumin levels and respiratory failure status, with early intervention potentially slowing or preventing disease progression.

In conclusion, elevated De Ritis ratio in pediatric HLH warrants vigilance for clinical manifestations including respiratory failure, central nervous system damage, and shock, as well as poor prognosis risk. Monitoring transaminase and fibrinogen levels and preventing respiratory failure complications are clinically important for improving outcomes in HLH children.

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**Author Contributions:** SHI Xiaoqi contributed to conceptualization, data curation, statistical analysis, interpretation of results, and manuscript writing. LUO Nandu, HUANG Jiaojiao, and CAO Xiuli contributed to data collection and organization. DU Zuochen and HUANG Pei contributed to study implementation and feasibility analysis. CHEN Yan and HE Zhixu contributed to manuscript revision, quality control, and supervision.

**Conflict of Interest:** The authors declare no conflicts of interest.

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