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Original Article

Correlation of Liver Enzymes and Serum Ferritin in Patients With β-Thalassaemia Major

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Abstract

Background: β-Thalassemia major is a hereditary hematological disorder that necessitates regular blood transfusions, leading to iron overload and subsequent liver injury. Elevated serum liver enzymes and ferritin are commonly used to monitor liver function in these patients; however, their reliability in predicting true hepatic dysfunction remains unclear.

Objective: To determine the sensitivity, specificity, and diagnostic accuracy of serum liver enzymes and ferritin in predicting liver dysfunction, with hypoalbuminemia as the gold standard, in pediatric patients with β-thalassemia major.

Methods: This cross-sectional validation study was conducted at the Department of Paediatrics, Combined Military Hospital, Rawalpindi, from July 2022 to February 2024. A total of 75 pediatric patients with β-thalassemia major were included using consecutive non-probability sampling. Patients with concurrent liver diseases, metabolic disorders, or conditions that could alter liver enzyme levels were excluded. Blood samples were collected to measure serum Alanine Transaminase (ALT), Aspartate Transaminase (AST), γ-Glutamyltransferase (γ-GT), ferritin, and albumin levels. Hypoalbuminemia was defined as a serum albumin level <3.5 g/L. The diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ALT, AST, γ-GT, and ferritin in predicting hypoalbuminemia were calculated using 2×2 contingency tables. Data were analyzed using SPSS version 25.

Results: Among the 75 patients, 18 (24.0%) exhibited hypoalbuminemia. The sensitivity, specificity, and diagnostic accuracy of ALT in detecting hypoalbuminemia were 83.33%, 31.58%, and 44.00%, respectively. For AST, these values were 50.00%, 29.82%, and 34.67%, respectively. γ-GT showed a sensitivity of 83.33%, specificity of 14.04%, and diagnostic accuracy of 30.67%. Ferritin had a sensitivity of 83.33%, specificity of 19.30%, and diagnostic accuracy of 34.67%. None of the markers showed satisfactory predictive value for hypoalbuminemia. There was a partial correlation between hyperferritinemia and elevated liver enzymes, with γ-GT showing the highest sensitivity (91.80%) and diagnostic accuracy (82.67%).

Conclusion: Serum liver enzymes and ferritin are not reliable markers for predicting liver dysfunction as indicated by hypoalbuminemia in pediatric patients with β-thalassemia major. These findings suggest that additional clinical assessments and more specific biomarkers are necessary for accurate evaluation of liver health in this population.

1 Introduction

β-Thalassemia major is a hereditary hematological disorder characterized by the reduced or absent synthesis of β-globin chains, leading to severe anemia and a dependence on regular blood transfusions for survival. This condition has a significant prevalence in Pakistan, with an estimated 5.0% to 7.0% of the population carrying the trait, amounting to over 10 million carriers and an annual incidence of approximately 5000 new cases (1). The chronic transfusion therapy required for managing β-thalassemia major results in iron overload, a major contributor to the development of liver injury. The liver is particularly vulnerable to iron deposition, which triggers the production of reactive oxygen species (ROS) and inflammatory cytokines, leading to oxidative stress and hepatic inflammation (2). Over time, this iron-induced hepatocellular damage manifests as elevated levels of liver enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are commonly used as markers of liver injury in clinical practice (3).

Despite the routine use of liver enzyme measurements to monitor liver function in patients with β-thalassemia major, the true extent of liver dysfunction in these individuals remains challenging to assess. Elevated serum ferritin levels, a surrogate marker for iron overload, are also frequently observed in these patients, further complicating the evaluation of liver health (4). However, it is crucial to recognize that neither elevated liver enzymes nor increased ferritin levels are definitive indicators of hepatic dysfunction. Instead, markers such as

serum albumin and prothrombin time are considered more reliable indicators of liver function, yet they are not routinely performed due to cost and practicality considerations (5, 6).

Previous studies have explored the individual roles of liver enzymes and serum ferritin in β-thalassemia major, but there is a paucity of research examining the correlation between these parameters and actual liver dysfunction as evidenced by hypoalbuminemia. Hypoalbuminemia, indicative of impaired liver synthetic function, could provide valuable prognostic information and guide clinical decision-making if correlated with more routinely available tests such as liver enzymes and serum ferritin (7). This study seeks to address this gap in the literature by investigating the relationship between liver enzymes, serum ferritin, and hypoalbuminemia in a cohort of patients with β-thalassemia major. By elucidating this relationship, we aim to determine whether these routinely measured biochemical markers can reliably predict the presence of liver dysfunction, potentially allowing for more cost-effective and accessible monitoring strategies in this high-risk patient population.

2 Material and Methods

This cross-sectional validation study was conducted at the Department of Paediatrics, Combined Military Hospital, Rawalpindi, from July 2022 to February 2024. The study population comprised pediatric patients diagnosed with β-thalassemia major, aged between two and twelve years. A total of 75 patients were selected for the study using consecutive non-probability sampling. Informed consent was obtained from the guardians or parents of all participants prior to their inclusion in the study. The study adhered to the ethical principles outlined in the Declaration of Helsinki, and approval was obtained from the Institutional Review Board of the Combined Military Hospital, Rawalpindi.

The inclusion criteria for the study were children aged 2-12 years who were confirmed cases of β-thalassemia major. Patients with concurrent liver diseases such as acute viral hepatitis, chronic hepatitis B or C, those with metabolic disorders, or those on medications known to alter liver enzyme levels were excluded. Additionally, patients with iron deficiency, acute or chronic infections, or autoimmune diseases were not considered for inclusion, ensuring the study's focus on the impact of β-thalassemia major itself on liver function(8-10).

Clinical data were collected through structured patient interviews and a thorough review of medical records. Relevant demographic information, including age and gender, as well as medical history and current medications, were documented. Blood samples were drawn from each patient for laboratory analysis. The biochemical parameters assessed included serum Alanine Transaminase (ALT), Aspartate Transaminase (AST), γ-Glutamyltransferase (γ-GT), serum ferritin, and serum albumin levels. The normal reference ranges for these parameters were as follows: ALT (0-38 U/L), AST (0-40 U/L), γ-GT (11-49 IU/L for males and 7-32 IU/L for females), serum ferritin (6-180 ng/L for males and 20-400 ng/L for females), and serum albumin (>3.5 g/L). Any value above these ranges was considered elevated, indicative of potential liver dysfunction (11, 2).

The primary objective of the study was to evaluate the correlation between liver enzymes, serum ferritin, and the presence of hypoalbuminemia in β-thalassemia major patients. Hypoalbuminemia, defined as a serum albumin level of less than 3.5 g/L, was used as a marker of liver dysfunction. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of ALT, AST, γ-GT, and ferritin in detecting hypoalbuminemia were calculated.

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 25.0. Descriptive statistics were used to summarize the data, with mean and standard deviation or median and interquartile range presented for quantitative variables, and frequencies and percentages for qualitative variables. The normality of the data was assessed using the Shapiro-Wilk test. The Pearson correlation coefficient was utilized to assess the correlation between serum ferritin and liver enzyme levels with hypoalbuminemia. Chi-square or Fisher's exact test was applied to compare qualitative variables, while independent samples t-test or Mann-Whitney U test was used for quantitative variables depending on the distribution of the data. A two-by-two table was constructed to calculate the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the biochemical tests in predicting hypoalbuminemia.

The study was designed to contribute to the understanding of the utility of routine biochemical markers in predicting liver dysfunction in β-thalassemia major patients, potentially guiding more effective and economical patient management strategies.

3 Results

The study included 75 pediatric patients diagnosed with β-thalassemia major, aged between 2 and 12 years, with a median age of 6.00 years (IQR: 5.00). The study cohort consisted of 38 females (50.7%) and 37 males (49.3%). The key biochemical parameters evaluated included serum Alanine Transaminase (ALT), Aspartate Transaminase (AST), γ-Glutamyltransferase (γ-GT), serum ferritin, and serum albumin levels.

Table 1: Patient Characteristics and Biochemical Parameters

Variable	Overall (n=75)	Hypoalbuminemia Present (n=18)	Hypoalbuminemia Absent (n=57)	p-value
Age (years)	6.00 (IQR: 5.00)	5.00 (IQR: 5.00)	6.00 (IQR: 5.00)	0.925
Gender				0.545
- Male	37 (49.3%)	10 (55.6%)	27 (47.4%)	
- Female	38 (50.7%)	8 (44.4%)	30 (52.6%)	
ALT (U/L)	54.00 (IQR: 56.00)	56.00 (IQR: 56.00)	54.0 (IQR: 55.0)	0.581
- Raised ALT	54 (72.0%)	15 (83.3%)	39 (68.4%)	0.250
AST (U/L)	52.00 (IQR: 54.00)	42.50 (IQR: 34.00)	56.00 (IQR: 55.00)	0.238
- Raised AST	49 (65.3%)	9 (50.0%)	40 (70.2%)	0.117
γ-GT (U/L)	68.00 (IQR: 67.00)	75.50 (IQR: 59.00)	64.00 (IQR: 70.00)	0.911
- Raised γ-GT	64 (85.3%)	15 (83.3%)	49 (85.9%)	0.783
Ferritin (ng/L)	759.00 (IQR: 689.00)	1043.00 (IQR: 1466.00)	689.00 (IQR: 584.00)	0.222
- Raised Ferritin	61 (81.3%)	15 (83.3%)	46 (80.7%)	0.803
Albumin (g/L)	3.67 ± 0.38	3.20 (IQR: 0.40)	3.80 (IQR: 0.30)	<0.001

The majority of the study population exhibited elevated levels of liver enzymes and ferritin, with 54 patients (72.0%) showing raised ALT levels, 49 patients (65.3%) with raised AST levels, and 64 patients (85.3%) with raised γ-GT levels. Notably, hypoalbuminemia was observed in 18 patients (24.0%). The comparison of biochemical parameters between patients with and without hypoalbuminemia revealed that there was no statistically significant difference in ALT, AST, or γ-GT levels between the two groups. However, serum albumin levels were significantly lower in the hypoalbuminemia group ($p<0.001$).

Table II. presents the 2x2 tables for ALT, AST, γ-GT, and Ferritin in predicting the presence of hypoalbuminemia, and Table III. shows the corresponding test characteristics.

Table 2: 2x2 Table for ALT, AST, γ-GT, and Ferritin in Predicting the Presence of Hypoalbuminemia

Test	True Positive	False Positive	False Negative	True Negative	Total
ALT	15	39	3	18	75
AST	9	40	9	17	75
γ-GT	15	49	3	8	75
Ferritin	15	46	3	11	75

Table 3: Test Characteristics in Predicting the Presence of Hypoalbuminemia

Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Diagnostic Accuracy (%)
ALT	83.33	31.58	27.78	85.71	44.0
AST	50.0	29.82	18.37	65.38	34.67
γ-GT	83.33	14.04	23.44	72.73	30.67
Ferritin	83.33	19.3	24.59	78.57	34.67

The results demonstrated that none of the evaluated tests—ALT, AST, γ-GT, or ferritin—exhibited satisfactory sensitivity, specificity, or diagnostic accuracy for predicting hypoalbuminemia. The highest sensitivity was observed for ALT and γ-GT (both 83.33%), but their specificity was notably low (31.58% and 14.04%, respectively). Similarly, while ferritin showed a sensitivity of 83.33%, its specificity was only 19.30%, reflecting the poor predictive value of these biochemical markers for detecting hypoalbuminemia.

Table IV. shows the correlation of hyperferritinemia with elevated liver enzymes, assessing the test characteristics for ALT, AST, and γ-GT.

Table 4: Test Characteristics of Hyperferritinemia in Predicting the Presence of Elevated Liver Enzymes

Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Diagnostic Accuracy (%)
ALT	78.69	57.14	88.89	38.1	74.67
AST	72.13	64.29	89.8	34.62	70.67
γ-GT	91.8	42.86	87.5	54.55	82.67

When analyzing the correlation of hyperferritinemia with liver enzymes, it was found that γ-GT exhibited the highest sensitivity (91.80%) and diagnostic accuracy (82.67%), suggesting a partial correlation between elevated serum ferritin and liver enzymes. However, none of the tests demonstrated ideal characteristics for clinical utility.

Overall, the results indicate that while elevated liver enzymes and serum ferritin are common in patients with β-thalassemia major, they are not reliable markers for the presence of liver dysfunction as defined by hypoalbuminemia. These findings highlight the need for more robust biomarkers to accurately assess liver function in this patient population.

4 Discussion

The study aimed to explore the correlation between serum liver enzymes, serum ferritin, and hypoalbuminemia in pediatric patients with β-thalassemia major, a population at high risk for liver dysfunction due to chronic iron overload from repeated blood transfusions. The findings of this study revealed that elevated liver enzymes, including ALT, AST, and γ-GT, were prevalent in the majority of patients. However, these enzymes, along with serum ferritin, demonstrated poor sensitivity, specificity, and diagnostic accuracy in predicting hypoalbuminemia, a marker of significant liver dysfunction. This outcome suggests that while elevated liver enzymes and serum ferritin are commonly observed in β-thalassemia major, they do not reliably indicate the presence of true hepatic dysfunction as evidenced by hypoalbuminemia(12-15).

The prevalence of elevated liver enzymes observed in this study aligns with the pathophysiology of β-thalassemia major, where chronic iron overload leads to oxidative stress and hepatocellular damage. Previous studies, such as those conducted by Arshad et al., have similarly reported high rates of elevated liver enzymes in patients with β-thalassemia major, particularly in settings with suboptimal management of iron overload and high rates of viral hepatitis (16,17). This study's findings corroborate these observations, reinforcing the notion that while liver enzymes are indicative of hepatic stress, they may not accurately reflect the liver's functional capacity, particularly in the context of hypoalbuminemia.

Interestingly, despite the high frequency of elevated liver enzymes and serum ferritin, hypoalbuminemia was present in only a subset of the study population. This suggests that while liver dysfunction is common among these patients, the progression to clinically significant hypoalbuminemia is not universal. This disparity could be attributed to several factors, including the varying degrees of iron overload, differences in the effectiveness and adherence to chelation therapy, and the presence of other comorbid conditions that may influence liver function. Previous research has also highlighted the complexity of liver dysfunction in β-thalassemia major, with studies like that of Ayulinda et al. reporting a lack of correlation between serum ferritin and albumin levels, thereby supporting the findings of this study (2,18,19).

The correlation analysis between hyperferritinemia and elevated liver enzymes further demonstrated that while there was some degree of association, particularly with γ-GT, the overall predictive value of ferritin for liver enzyme elevation was modest. This partial correlation suggests that while serum ferritin reflects iron burden, its relationship with liver enzyme levels is not straightforward and may be influenced by other factors such as ongoing inflammation or underlying liver pathology. These findings echo those of Suman et al., who also reported a positive but not definitive correlation between ferritin and liver enzyme levels (3,20).

One of the strengths of this study was its systematic approach to evaluating the commonly used biochemical markers in the context of β-thalassemia major. By focusing on a well-defined cohort and using standardized laboratory measurements, the study was able to provide valuable insights into the limitations of relying solely on liver enzymes and ferritin to assess liver function in this population. However, the study also had several limitations that warrant consideration. The relatively small sample size, despite being determined by a sample size calculator, may have limited the power of the study to detect subtle correlations or differences. Additionally, the exclusion of patients with concurrent liver diseases or other confounding conditions, while necessary to isolate the effects of β-thalassemia major, may have resulted in a study population that is not fully representative of the broader patient population(11,20).

Moreover, the study did not account for the potential impact of malnutrition, which is a common issue in developing countries and could independently affect serum albumin levels, potentially confounding the results. This limitation highlights the need for future research to include more comprehensive assessments of nutritional status and other factors that may influence liver function.

In conclusion, this study provided important evidence that while serum liver enzymes and ferritin are elevated in a significant proportion of patients with β-thalassemia major, they are not reliable markers for the presence of true liver dysfunction as indicated by hypoalbuminemia. Clinicians should be cautious when interpreting these laboratory parameters and consider the need for additional clinical assessments and more specific biomarkers when evaluating liver function in this patient population. Future research should aim to identify more accurate and accessible biomarkers for early detection and monitoring of liver complications in patients with β-thalassemia major, with an emphasis on larger, more diverse study populations and consideration of additional confounding factors.

5 Conclusion

In conclusion, this study highlights the significant limitations of relying solely on serum liver enzymes and ferritin levels to assess liver dysfunction in pediatric patients with β-thalassemia major. While these biochemical markers are frequently elevated in this population, their poor sensitivity, specificity, and overall diagnostic accuracy in predicting hypoalbuminemia—a key indicator of liver dysfunction—suggest that they are not reliable stand-alone indicators of hepatic health. The findings underscore the complexity of liver injury in β-thalassemia major, where elevated liver enzymes and hyperferritinemia may reflect hepatic stress or iron overload but do not necessarily correspond to true functional impairment. This calls for a more nuanced approach to monitoring liver function in these patients, incorporating additional clinical assessments and potentially more specific biomarkers to accurately detect and manage liver complications. The study also emphasizes the need for future research to explore more reliable and cost-effective diagnostic tools for early identification of liver dysfunction, aiming to improve patient outcomes and guide more effective management strategies in this vulnerable patient population.

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