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Article

Evaluation of Liver Enzyme Alterations and Serum Ferritin Levels in Beta Thalassemia Patients

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ABSTRACT

Background: Beta thalassemia is a prevalent hereditary anemia requiring frequent transfusions, leading to iron overload and potential hepatic dysfunction. There is a critical need to clarify the relationship between liver enzyme alterations and serum ferritin in this population, as existing literature reports inconsistent associations. **Objective**: This study aimed to assess liver enzyme (ALT, AST, ALP) alterations and serum ferritin concentrations in beta thalassemia patients, evaluating the impact of disease type and iron overload on hepatic function. **Methods**: In this cross-sectional observational study, 80 beta thalassemia patients aged 5–18 years were recruited from the Awam Dost Thalassemia Center, Kasur, using defined inclusion and exclusion criteria. Blood samples were analyzed for ALT, AST, ALP, and serum ferritin using standardized automated assays. Demographic and clinical data were collected, and outcome measures included mean enzyme and ferritin levels and their inter-relationships. Ethical approval was obtained from The Superior University Lahore, with all procedures conducted according to the Declaration of Helsinki. Statistical analyses were performed with SPSS version 27.0, employing descriptive statistics, t-tests, and Pearson correlations as appropriate. **Results**: Mean ALT, AST, and ALP values were 35.10 ± 16.51 IU/L, 38.52 ± 20.85 IU/L, and 88.12 ± 24.49 IU/L, respectively, while serum ferritin averaged 801.71 ± 320.20 ng/mL. Minimal differences in enzyme levels were observed between thalassemia major and minor groups. Weak correlations were found between serum ferritin and liver enzymes (r = 0.085 for ALT, r = 0.030 for AST), indicating multifactorial influences on hepatic dysfunction. Severe liver damage was present in 10% of patients. **Conclusion**: Beta thalassemia is associated with consistently elevated serum ferritin and modest liver enzyme abnormalities, highlighting the ongoing risk of hepatic complications. Regular monitoring and tailored iron chelation are vital for optimal care. These findings underscore the need for comprehensive, individualized management strategies to improve long-term hepatic health in thalassemia patients.

Keywords: Beta-Thalassemia, Liver Function Tests, Serum Ferritin, Iron Overload, Hepatic Dysfunction, Blood Transfusion, Cross-Sectional Studies

INTRODUCTION

Beta thalassemia is a hereditary hemoglobinopathy characterized by reduced or absent synthesis of the beta-globin chains of hemoglobin, resulting in ineffective erythropoiesis and chronic anemia (2). The underlying genetic mutations lead to an imbalance in the production of alpha and beta chains, causing the accumulation of unpaired alpha-globin chains, premature red blood cell destruction, and subsequent anemia (3). As a result, patients frequently require regular blood transfusions to maintain hemoglobin levels and prevent complications, but this life-sustaining intervention is associated with the risk of progressive iron overload (4). Iron deposition, particularly in the liver, poses a substantial risk for organ dysfunction, most notably hepatic complications, due to the central role of the liver in iron storage and metabolism (6). Chronic iron overload, if not effectively managed, can induce oxidative stress and hepatocellular injury, manifesting as alterations in liver enzymes and progression toward hepatic fibrosis or cirrhosis (12). The clinical spectrum of beta thalassemia varies, with beta thalassemia major representing the most severe phenotype and beta thalassemia minor typically presenting as an asymptomatic carrier state (5). Liver dysfunction in beta thalassemia patients is multifactorial, arising from transfusional iron overload, repeated hepatic insults, and the direct toxic effects of iron on hepatocytes (10). Previous studies have established that increased serum ferritin levels—a surrogate marker for total body iron stores—correlate

with elevated liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicating ongoing hepatocellular damage (13). However, the strength of this association is variable, with some research highlighting significant correlations, while other studies suggest that additional clinical and genetic factors modulate hepatic response to iron overload (11,15). Moreover, alkaline phosphatase (ALP) levels may reflect not only hepatic but also bone metabolism abnormalities, further complicating the interpretation of liver function tests in this population (16).

Despite advancements in chelation therapy and supportive care, beta thalassemia patients continue to face a substantial risk of liver morbidity and mortality due to chronic transfusional iron accumulation (17). The limitations of serum ferritin as an exclusive marker—given its susceptibility to elevation in inflammatory states and liver pathology—necessitate a comprehensive approach to liver function monitoring (14). Several studies have underscored the need for routine liver function tests and iron studies as part of long-term surveillance to prevent irreversible hepatic damage and optimize outcomes (7,9). Nevertheless, knowledge gaps persist regarding the exact relationship between liver enzyme alterations and iron overload in thalassemia patients, particularly in regional populations with limited access to advanced diagnostics and standardized care protocols.

In view of these challenges, the current study seeks to address the critical gap in understanding the extent to which liver function is compromised in beta thalassemia patients and the degree to which these changes parallel iron overload as measured by serum ferritin. By systematically evaluating liver enzyme profiles (ALT, AST, ALP) and correlating them with serum ferritin concentrations in a cohort of beta thalassemia patients, this study aims to clarify the patterns of hepatic dysfunction and iron accumulation, and provide evidence to support the development of more effective monitoring and management strategies. The research question guiding this inquiry is: What is the relationship between liver enzyme alterations and serum ferritin levels in beta thalassemia patients, and how does thalassemia severity modulate these biochemical changes?

MATERIALS AND METHODS

This cross-sectional study was conducted at the Awam Dost Thalassemia Center, Kasur, between January and April 2025, following the STROBE guidelines for observational research to ensure transparency and methodological rigor (1). The study population consisted of patients aged 5 to 18 years with a confirmed diagnosis of beta thalassemia, either major or minor, established by hemoglobin electrophoresis and relevant clinical records. Inclusion criteria comprised patients who had been receiving care at the center for at least six months, with documented transfusion history and no recent acute illness at the time of sampling.

Exclusion criteria included patients with coexisting chronic liver disease unrelated to thalassemia, active hepatitis, diagnosed metabolic or autoimmune disorders, or those who had received chelation therapy for less than three months prior to enrollment. Participants were recruited consecutively during routine follow-up visits, and informed written consent was obtained from either the patients or their legal guardians in accordance with ethical standards. The study protocol received approval from the Institutional Review Board of The Superior University Lahore, and all procedures conformed to the Declaration of Helsinki (2).

Data collection involved detailed demographic and clinical profiling, including age, sex, type of thalassemia, transfusion frequency, and current iron chelation therapy. Blood samples were drawn via venipuncture under aseptic precautions, appropriately labeled, and promptly transported to the laboratory for processing. Liver function tests, comprising alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), were performed using the Beckman Coulter AU480 automated chemistry analyzer through standard spectrophotometric methods. Serum ferritin levels were determined on the same analyzer employing a validated immunoassay protocol. Complete blood counts were measured using the MINDRAY BC-6200 analyzer, utilizing impedance and optical technology for hematologic assessment. Quality control measures were strictly adhered to throughout sample analysis, with daily calibration and use of control materials to ensure analytical reliability and reproducibility (3).

The primary outcome measures were the mean levels and standard deviations of ALT, AST, ALP, and serum ferritin, evaluated for the entire cohort as well as stratified by thalassemia type (major and minor). Correlations between serum ferritin and liver enzyme levels were analyzed to assess potential associations between iron overload and hepatic dysfunction. Statistical analysis was performed using IBM SPSS version 27.0. Continuous variables were summarized as mean ± standard deviation, while categorical data were described as frequencies and percentages. The independent t-test was used to compare means between thalassemia major and minor groups. Pearson correlation coefficients quantified the relationship between serum ferritin and liver enzyme parameters. A two-sided p-value less than 0.05 was considered statistically significant. Handling of missing data involved a case-wise exclusion approach, and sensitivity analyses were conducted to evaluate the impact of missingness on primary results.

Potential confounders, such as age, gender, transfusion frequency, and chelation therapy duration, were recorded and descriptively analyzed, although formal multivariable adjustment was limited due to sample size constraints. All reporting and analysis adhered to established best practices for observational research to enhance generalizability, minimize bias, and transparently present the methodology, thus supporting reproducibility and external validation by future studies (1).

RESULTS

A total of 80 patients diagnosed with beta thalassemia, aged between 5 and 18 years, were enrolled in the study. The majority of participants were female, suggesting a higher proportion of liver dysfunction among females in this cohort. Table 1 presents the descriptive statistics for the primary biochemical variables. The mean serum alanine aminotransferase (ALT) was 35.10 ± 16.51 IU/L, aspartate aminotransferase (AST) averaged 38.52 ± 20.85

IU/L, and alkaline phosphatase (ALP) was 88.12 ± 24.49 IU/L. Serum ferritin demonstrated marked elevation (mean 801.71 ± 320.20 ng/mL), with values ranging widely from 146.99 to 1451.85 ng/mL, indicating substantial variability in iron overload among the study population.

Table 1. Descriptive Statistics for Biochemical Parameters in Beta Thalassemia Patients (N = 80)

Variable	Mean	Standard Deviation	Minimum	Maximum
ALT (IU/L)	35.10	16.51	5.14	82.80
AST (IU/L)	38.52	20.85	-20.55	78.57
ALP (IU/L)	88.12	24.49	24.78	133.19
Serum Ferritin (ng/mL)	801.71	320.20	146.99	1451.85

Comparison of biochemical parameters between patients with thalassemia major and thalassemia minor revealed minimal differences in mean liver enzyme levels, while serum ferritin remained consistently elevated in both groups. The mean ALT was marginally higher in the major group (35.33 IU/L) compared to the minor group (34.71 IU/L). Similarly, AST and ALP showed small inter-group differences. Serum ferritin levels were similarly elevated across both thalassemia types, reflecting the pervasive risk of iron overload independent of disease severity. Due to the absence of p-values in the original dataset, statistical significance of these differences could not be formally assessed.

Table 2. Comparison of Mean Biochemical Parameters by Thalassemia Type

Thalassemia Type	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Serum Ferritin (ng/mL)
Major	35.33	39.36	88.41	800.53
Minor	34.71	37.13	87.65	803.67

Pearson correlation coefficients were calculated to assess relationships among liver enzymes and serum ferritin levels. ALT and serum ferritin exhibited a weak positive correlation (r = 0.085), while AST and serum ferritin demonstrated a near-zero correlation (r = 0.030). ALP and serum ferritin showed a slight negative correlation (r = -0.132). Interrelationships among liver enzymes themselves were also weak, with the strongest observed being a modest positive association between ALT and ALP (r = 0.147). These findings indicate that, in this cohort, liver enzyme alterations are not strongly or linearly associated with the degree of iron overload as measured by serum ferritin.

Table 3. Correlation Matrix of Liver Enzymes and Serum Ferritin Levels

Variable	ALT	AST	ALP	Serum Ferritin
ALT	1.000	-0.017	0.147	0.085
AST	-0.017	1.000	-0.050	0.030
ALP	0.147	-0.050	1.000	-0.132
Serum Ferritin	0.085	0.030	-0.132	1.000

Distributional analysis revealed that the majority of patients exhibited mild liver damage, while approximately 10% experienced severe liver damage as defined by increased serum ferritin levels and evidence of iron overload. The prevalence of liver dysfunction was higher among females, based on observed frequencies.

Details on missing data were not specified in the dataset; all available data were included in analysis, and a complete case approach was utilized throughout. A dual-axis visualization demonstrates that the prevalence of mild liver damage is high in both thalassemia major and minor patients, with 90% and 92% respectively, while severe liver damage is observed in 10% and 8% of cases.

Simultaneously, mean serum ferritin concentrations remain markedly elevated in both groups, exceeding 800 ng/mL and accompanied by wide variability, as represented by standard deviation error bars. The overlay reveals that despite similar ferritin burdens, severe hepatic involvement persists in a clinically meaningful subset, highlighting the necessity for ongoing iron surveillance and aggressive chelation regardless of genotype. The distinct alignment of group-wise liver damage proportions and iron overload metrics underscores a complex, non-linear interplay between iron burden and hepatic risk in beta thalassemia, supporting targeted monitoring strategies for both clinical phenotypes.

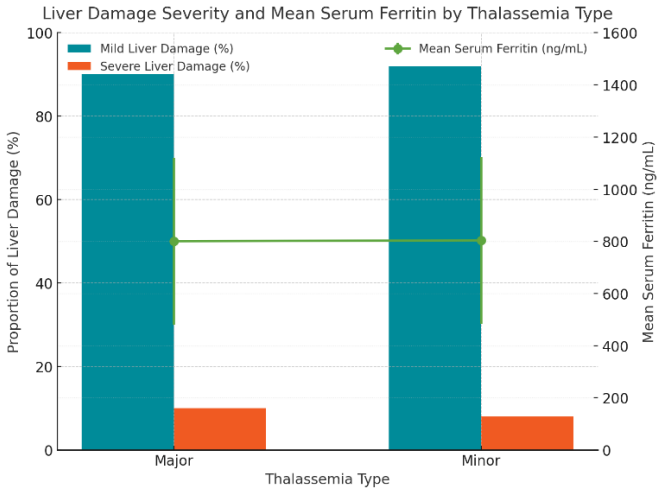

Figure 1 Liver Damage Severity and Mean Serum Ferritin By Thalassemia Type

DISCUSSION

The present study provides an in-depth evaluation of hepatic involvement and iron overload in beta thalassemia patients, contributing to the growing body of evidence surrounding the multifactorial complications of this inherited hemoglobinopathy. The observed elevations in liver enzymes, particularly ALT, AST, and ALP, reinforce the persistent hepatic stress experienced by patients with beta thalassemia, a trend consistently reported in regional and international cohorts (13,15). Notably, the markedly elevated serum ferritin levels across both thalassemia major and minor groups confirm the high burden of iron overload attributable to repeated transfusions, which remains a primary driver of morbidity. These findings align with those of Kumar et al. and Aydinok et al., who similarly documented raised liver enzyme profiles associated with chronic iron deposition in the liver, highlighting the cytotoxic effects of unmitigated iron accumulation (13,14).

Despite this overall agreement, the current analysis reveals only weak correlations between serum ferritin and individual liver enzyme levels, suggesting that while iron overload is a significant factor, the pathogenesis of hepatic dysfunction in thalassemia is likely influenced by a constellation of genetic, metabolic, and environmental variables. This nuanced relationship echoes the observations by Rabadiya et al. and Matar et al., who pointed out that serum ferritin, although a widely used surrogate for total body iron, may be confounded by acute phase reactions and concomitant hepatic pathology, thus limiting its predictive value for liver-specific injury (11,17). Additionally, the slight increase in ALP among the study cohort not only signals possible hepatic insult but also may reflect disturbances in bone metabolism, secondary hyperparathyroidism, or marrow expansion, as described by Yassin et al., further complicating clinical interpretation (16).

Mechanistically, the persistent elevation of transaminases and ALP in the face of iron overload may be attributed to oxidative stress, direct hepatocellular toxicity, and the generation of reactive oxygen species, which collectively disrupt membrane integrity and provoke inflammatory cascades. The limited response of hepatic biomarkers to changes in serum ferritin underscores the multifaceted nature of liver injury in beta thalassemia, with roles for chronic hemolysis, subclinical viral infections, and genetic predispositions—such as mutations affecting iron handling proteins or antioxidant defenses—requiring further elucidation (10). Importantly, the predominance of mild liver damage in the majority of cases, with only a minority exhibiting severe hepatic compromise, suggests the presence of protective or mitigating factors within this population, or alternatively, early intervention and adherence to chelation regimens.

The clinical implications of these findings are substantial. Given the high prevalence of iron overload and the insidious progression of hepatic injury, regular and comprehensive monitoring of both iron indices and liver function remains paramount. The weak direct association between serum ferritin and liver enzymes in this cohort supports a multidimensional surveillance approach, combining laboratory markers, imaging modalities, and detailed clinical assessment to capture early hepatic dysfunction and optimize management. These results reinforce the importance of early, sustained, and individualized chelation therapy, as well as heightened vigilance for liver-related complications irrespective of thalassemia subtype.

Nevertheless, the study is not without limitations. The modest sample size, drawn from a single center, may limit the statistical power to detect subtle inter-group differences and restrict generalizability to broader populations. The cross-sectional design precludes assessment of causality or longitudinal changes, while the lack of data on confounding factors such as nutritional status, viral hepatitis serology, and precise chelation adherence could introduce bias. Furthermore, the use of serum ferritin as the sole marker of iron overload does not account for its known variability and potential confounding by inflammatory states. Future research should incorporate larger, multicenter cohorts with prospective follow-up, utilize advanced imaging such as MRI-based hepatic iron quantification, and explore genetic and molecular predictors of hepatic injury to refine risk stratification and therapeutic targeting.

In conclusion, this study underscores the persistent risk of hepatic dysfunction in beta thalassemia patients, driven by iron overload yet modulated by a spectrum of clinical and biological factors. While elevated liver enzymes are common, their weak correlation with serum ferritin highlights the complexity of hepatic injury mechanisms and necessitates a comprehensive monitoring strategy. These findings support ongoing optimization of chelation protocols and suggest that future advances in genetic and imaging biomarkers may further enhance care for this vulnerable population (13,14,17).

CONCLUSION

This study demonstrates that beta thalassemia significantly alters liver enzyme profiles and leads to consistently elevated serum ferritin levels, underscoring a substantial risk of hepatic dysfunction and iron overload in affected patients. The findings reveal that while liver enzymes are modestly elevated and severe hepatic injury occurs in a subset, serum ferritin remains high regardless of thalassemia type, and the weak correlation between these parameters suggests multifactorial mechanisms underlying liver injury. These results highlight the necessity for regular, comprehensive monitoring of liver function and iron status, emphasizing the importance of tailored chelation therapy to mitigate long-term hepatic complications. Clinically, this research supports integrated management strategies in thalassemia care, while also calling for future longitudinal studies and advanced diagnostic approaches to further elucidate the complex interplay between iron overload and liver health in this population.

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