Original Article

Association of serum ferritin trends with liver enzyme patterns in β-thalassemia major: A longitudinal correlational study

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Abstract

Background: β-Thalassemia major patients require lifelong blood transfusions, leading to iron overload and liver injury. This study examines the longitudinal association between serum ferritin and liver function over 5 years in pediatric patients. **Methods:** This retrospective study included 582 transfusion-dependent thalassemia patients aged 1–18 years. Serum ferritin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin were measured annually. Correlation and linear regression analyses assessed associations between ferritin trajectories and liver enzymes. **Results:** Mean ferritin rose from 1820 ± 960 ng/mL at baseline to 4500 ± 1900 ng/mL at year 5, indicating worsening iron overload. AST and ALT levels also steadily climbed over follow-up, whereas albumin declined slightly. Ferritin correlated positively with AST ($r = 0.675$, $P < 0.01$) and ALT ($r = 0.607$, $P < 0.01$), but not with albumin ($r = -0.143$, $P = 0.153$) annually. The regression interaction term showed within-patient ferritin increases over time were independently associated with escalating AST and ALT ($P < 0.05$), after adjusting for confounders. **Conclusion:** Rising ferritin levels predict progressive liver injury in regularly transfused pediatric thalassemia patients. Tighter control of iron overload may help preserve hepatic function.

Keywords: Ferritin, liver function tests, Indian population, iron overload, thalassemia

Introduction

β-Thalassemia major is an inherited blood disorder characterized by reduced or absent β-globin chain synthesis, resulting in severe anemia and a requirement for lifelong blood transfusions.[1] Frequent transfusions lead to iron overload, which can cause significant morbidity and early mortality if left untreated.[2] Iron deposition occurs in the liver, heart, and endocrine glands, with the liver being the primary site of iron storage.[3] Excess iron catalyzes the production of reactive oxygen species, leading to oxidative damage, fibrosis, and eventual cirrhosis.[4]

Serum ferritin provides a convenient indirect measure of total body iron stores. Studies have consistently shown that higher ferritin levels correlate with hepatic iron concentration and are predictive of hepatic complications in thalassemia major.[5,6] Elevated serum aminotransferases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), indicate hepatocellular injury, while declining albumin may reflect synthetic dysfunction in advanced liver disease.[7] Several researchers have reported derangements in liver enzymes and synthetic function in transfused thalassemia patients.[8,9] However,

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data on pediatric thalassemic populations is limited, especially from developing countries bearing the major disease burden, like India.[10]

As frontline health-care providers, primary care doctors play a key role in monitoring iron overload and its complications in patients with transfusion-dependent thalassemia. However, data guiding evidence-based screening and management of hepatic dysfunction in this population are lacking, especially for pediatric patients. This study aimed to determine the longitudinal relationship between serum ferritin trends and liver injury patterns to inform guidelines for primary care providers overseeing thalassemia care.

Therefore, this study aimed to determine the longitudinal association between serum ferritin trends and liver enzyme levels over a 5-year follow-up. We hypothesized that higher ferritin would correlate with elevated AST and ALT as markers of hepatic injury, but not with albumin.

Methodology

This was a retrospective study of 582 transfusion-dependent β-thalassemia patients aged 1–18 years enrolled in a tertiary care pediatric hospital in Gujarat managing a major thalassemia center. Patients with liver function test (LFT) and serum ferritin reports in the file report were only included. The sample was identified by reviewing medical records to identify all pediatric thalassemia patients treated at the facility within a defined past timeframe (2008–2022).

The inclusion criteria were as follows:

- Patients (aged 1–18 years) diagnosed with a transfusion-dependent β-thalassemia major, who received care at the thalassemia treatment center between Jan 2008 and Dec 2022;
- Availability of at least 5 years of longitudinal medical records documenting ferritin levels, liver function tests, and other relevant clinical data; and
- Patients who received regular blood transfusions and iron chelation therapy as per the clinical protocols.

Exclusion criteria were as follows:

- Incomplete medical records were found to be missing more than 20% of the expected ferritin or LFT measurements during the 5-years retrospective follow-up period.
- Diagnosis of other concomitant liver diseases that could affect LFTs (e.g., viral hepatitis, autoimmune hepatitis, metabolic liver disease);
- Received liver transplantation during the 5-year retrospective follow-up period;
- Initiation of experimental treatment protocols that could substantially impact ferritin or LFT trends; and
- Presence of serious medical complications unrelated to thalassemia, which could potentially affect the liver function (e.g., heart failure, sepsis).

Serum ferritin, liver enzymes AST/ALT, albumin, and platelet counts were measured annually. Other data like demographics, nutritional intake, hepatitis serology, chelation details, and volume/frequency of blood transfusions were documented. Clinically significant liver injury was defined as elevated ALT >2 times the upper limit of normal (ULN). Ethical committee approval was taken from the institutional ethical committee (M. P. Shah Govt. Medical College) before the start of the study (Approval No.: 90/02/2023).

Data analysis

Statistical analysis was conducted using Statistical Package for the Social Sciences version 26.0. Descriptive statistics were presented for all variables. Gender and age group comparisons were made using independent sample *t*-tests. Correlations between ferritin and liver function tests were assessed using Spearman's rank correlation. Multilevel mixed-effects linear regression models were employed to assess temporal associations between longitudinal ferritin trajectories and AST/ALT levels. In addition, repeated measures analysis of variance (RM-ANOVA) was utilized to examine within-subject changes in ferritin levels over time in association with liver function tests. Furthermore, logistic regression analysis was carried out to evaluate the predictive utility of peak ferritin values for clinically significant liver injury. All statistical models were appropriately adjusted for relevant clinical and demographic confounders, including age, body mass index (BMI), hepatitis status, and chelation dose. A *P*- value of less than 0.05 was considered statistically significant in determining the associations between variables and outcomes.

Results

Table 1 shows the baseline characteristics for the 582 participants. Their mean age was 9.2 ± 3.1 years, and 69% (402/582) of them were male. The mean BMI was 16.4 ± 2.1 kg/m^2. Also, 19.2% (112/582) had hepatitis C coinfection and 13.6% (79/582) had hepatitis B coinfection. The mean pretransfusion hemoglobin level was 8.4 ± 1.3 g/dL. The mean baseline serum ferritin level was 1820 ± 960 ng/mL. Mean AST was 45.2 ± 13.6 U/L, mean ALT was 38.4 ± 10.5 U/L, and mean albumin was 44 ± 3.8 g/L.

Table 2 shows that the mean ferritin level increased from 1820 ± 960 ng/mL at baseline to 4500 ± 1900 ng/mL at year 5, indicating worsening iron overload over time. The mean AST level rose from 45.2 ± 13.6 U/L at baseline to 71.3 ± 31.2 U/L at year 5. The mean ALT also increased from 38.4 ± 10.5 U/L to 58.6 ± 26.7 U/L over 5 years. In contrast, the mean albumin level decreased slightly from 44 ± 3.8 g/L at baseline to 43.0 ± 3.2 g/L at year 5. There was a statistically significant effect of time on ferritin, AST, ALT, and albumin levels over the 5 years in this cohort based on RM-ANOVA (all $P < 0.05$). However, the small difference detected in albumin levels may not be clinically significant to indicate deterioration in liver synthetic function.

Table 3 shows that while there was a negative link between ferritin levels and albumin, there was a positive correlation between

Table 1: Baseline characteristics of study participants (*n*=582)

Parameter	Number (%) or Mean±SD
Age (years)	9.2±3.1
Gender – males	402 (69%)
BMI (kg/m^2)	16.4±2.1
Viral hepatitis coinfection	
Hepatitis C	112 (19.2%)
Hepatitis B	79 (13.6%)
Pretransfusion hemoglobin (g/dL)	8.4±1.3
Serum ferritin (ng/mL)	1820±960
AST (U/L)	45.2±13.6
ALT (U/L)	38.4±10.5
Albumin (g/L)	44±3.8

ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, BMI=Body mass index, SD=Standard deviation

Table 2: Annual average ferritin levels and liver function parameters over follow-up

Year	Ferritin (ng/mL)	AST (U/L)	ALT (U/L)	Albumin (g/L)
1	1820±960	45.2±13.6	38.4±10.5	44±3.8
2	2564±1124	52.3±19.4	42.1±12.8	43.8±3.6
3	3159±1352	58.7±21.5	46.5±16.2	43.5±3.3
4	3690±1488	63.2±27.3	51.8±20.1	43.1±3.5
5	4500±1900	71.3±31.2	58.6±26.7	43.0±3.2
P	<0.001	<0.001	<0.001	0.012

P<0.05 - significant, *P*<0.001 - highly significant. ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

Table 3: Relationship between ferritin levels with SGOT, SGPT, and albumin

Variables	Correlation coefficient (*r*)	*P*
Ferritin–SGOT	0.675	<0.01*
Ferritin–SGPT	0.607	<0.01*
Ferritin–albumin	-0.143	0.153
Ferritin- transfusion rate	0.45	<0.001**
Ferritin- chelation duration	-0.34	0.02*

**P*<0.05 - significant, ***P*<0.001 - highly significant. ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

ferritin levels and serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). With a *P*- value of 0.05, the correlation coefficient between ferritin levels and SGOT was 0.675. In addition, there was a substantial positive link between serum ferritin levels and SGPT levels, as shown by the correlation coefficient of 0.607 between ferritin and SGPT levels and the test *P*- value of 0.05. However, there was only a -0.143 correlation between ferritin and albumin levels, with a *P*- value of 0.153. The only substantial relationships between ferritin levels and SGOT and SGPT levels may be inferred. The *P*- value larger than 0.05 indicates that there was no statistically significant correlation between ferritin and albumin levels.

Correlations with transfusion/chelation: Higher ferritin levels were correlated positively with increased transfusion rate ($r = 0.45$, $P < 0.001$) and negatively with chelator treatment duration since transfusions drive iron loading while chelation removes excess iron ($r = -0.34$, $P = 0.02$).

The SGOT and SGPT readings will rise as ferritin levels rise. The SGOT and SGPT readings will likewise drop in response to reduced ferritin levels. Patients with thalassemia major who participated in this study did not show any differences in albumin levels due to changes in serum ferritin levels. The scatterplot illustrating the relationship between ferritin levels and the other three levels is shown in Figure 1.

The multivariable linear regression model presented in Table 4 assesses whether rising ferritin trends over time are associated with worsening liver enzymes while adjusting for confounders. The interaction term coefficient (β6) was statistically significant, indicating that within individual patients, worsening ferritin levels over follow-up were independently associated with increasing AST and ALT, even after controlling for other factors.

The unadjusted model presented in Table 5, comparing ferritin >2500 to <1000 ng/mL, shows an odds ratio (OR) of 5.12 [95% confidence interval: 3.02, 8.56], indicating a significant association between higher peak ferritin levels and increased risk of ALT ≥2 times ULN.

After adjusting for confounders (age, BMI, hepatitis, and chelation dose), the association remained significant with an OR of 3.62 [2.08, 6.49], suggesting an independent predictive relationship between higher peak ferritin values and eventual clinically significant liver damage.

Discussion

This longitudinal study demonstrates a significant relationship between worsening iron overload, reflected by rising ferritin trends, and progressive liver injury in pediatric transfusion-dependent thalassemia patients. Both transaminase enzymes AST and ALT showed steady increases over follow-up, indicating possible hepatocellular damage, while serum albumin decreased slightly. Correlation and regression analyses confirmed that the ferritin levels were independently associated with liver enzyme elevations over time, even after adjusting for demographic factors, BMI, viral hepatitis, and chelation dose.

These findings align with previous studies showing elevated liver enzymes and increased risk of liver fibrosis and cirrhosis among thalassemia patients with iron overload.[11-17] Excess iron is believed to cause oxidative damage and cell death in the liver through several mechanisms involving reactive oxygen species.[18] Effective iron chelation is, therefore, considered essential for preventing the progression of hepatic dysfunction.[19] However, average ferritin levels continued increasing in this cohort despite chelation, reflecting the challenges of maintaining iron balance with chronic transfusion therapy.

Thiobarbituric acid reactant levels and aldehyde protein adduct levels in the liver are higher in patients with iron overload, both of which indicate lipid peroxidation. Portal fibrosis and collagen formation can begin as early as 2 years after the initiation of

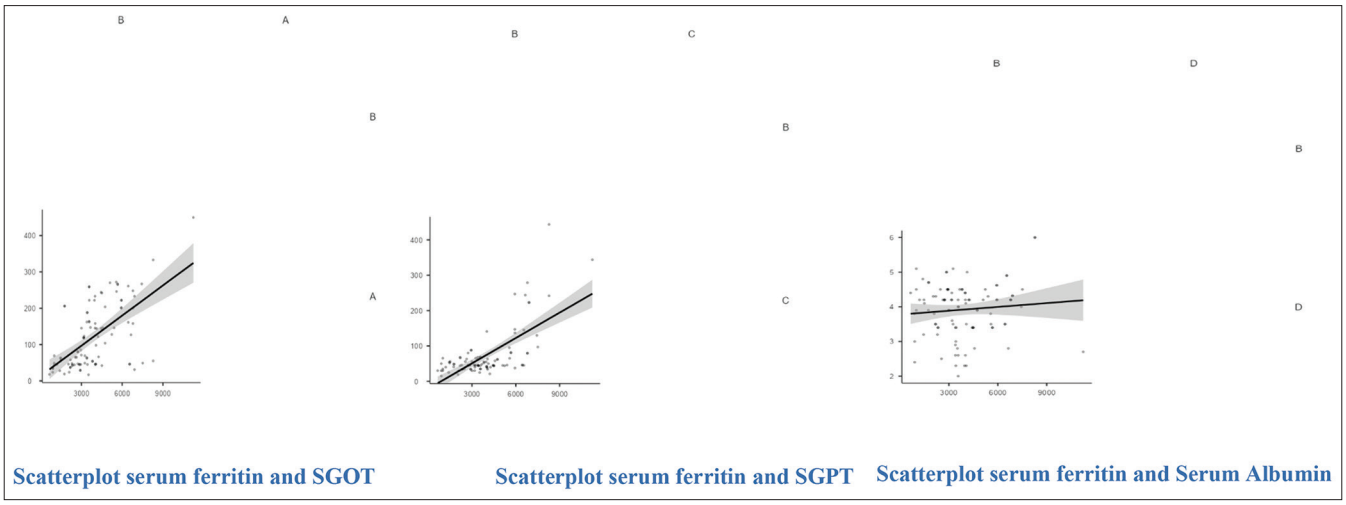

Figure 1: A scatterplot between ferritin levels with SGOT, SGPT, and albumin

Table 4: Multilevel mixed effects linear regression model

Model specification:
AST/ALT = β0 + β1*ferritin + β2*age + β3*BMI + β4*hepatitis + β5*chelation dose + β6*(ferritin*time)
Dependent variables: AST and ALT enzymes
Key independent variable: Ferritin*time (interaction)
Adjusted for age, BMI, viral hepatitis, and chelation dose
Random effect: Patient ID for intrasubject correlations
Results:
β6 (Interaction term coefficient) indicates the average change in liver enzymes per unit change in ferritin per year
Significant positive association between rising ferritin trends and worsening AST/ALT levels within patients over follow-up

ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, BMI=Body mass index

Table 5: Logistic regression model of altered LFT and serum ferritin

Model	Outcome	Key predictors	Results
Unadjusted	ALT ≥2*ULN	Peak ferritin level	OR 5.12 [95% CI: 3.02, 8.56]
Adjusted	ALT ≥2*ULN	Peak ferritin level	OR 3.62 [95% CI: 2.08, 6.49]

CI: Confidence interval, OR: Odds ratio, ULN: Upper limit of normal

transfusion. Cirrhosis may appear in the first 10 years of life without chelation.

Fifty-six thalassemic children were the subjects of research by Kassab-Chekir *et al.*,[13] which identified several metabolic markers. According to the study, the liver was the first organ to suffer damage in β-thalassemia. Thiobarbituric acid reactive substances in plasma were markedly increased, which resulted in abnormal liver functioning. In a study carried out in Iran in 2006, Ameli *et al.*[14] obtained the same results. Their research discovered that thalassemic children with high serum ferritin and a high transfusion index had mean serum ALT levels that were noticeably elevated.

The findings underscore the importance of regular ferritin and liver enzyme testing by primary care providers for pediatric thalassemia patients on chronic transfusions. Worsening ferritin levels can predict escalations in AST and ALT, prompting earlier chelation adjustments and closer monitoring. However, albumin appears unaffected initially and is a less-useful screening test. Appropriate timing of blood draws and coordination with transfusions is key. Primary care doctors can play a vital role in counseling families about chelation adherence and avoiding hepatotoxic medications or supplements to preserve liver function.

These findings help us comprehend the pathogenesis of -thalassemia major and offer important clinical management insights.

Recommendations

Based on the findings of this study, the following recommendations can be made:

1. Regular monitoring: Clinicians should consider regular monitoring of serum ferritin, SGOT, SGPT, and albumin levels in children with β-thalassemia major to assess the progression of iron overload and liver damage.
2. Early intervention: Early intervention strategies, such as iron chelation therapy, should be implemented to manage iron overload and prevent or minimize liver damage in children with β-thalassemia major.
3. Individualized treatment: Individual variations in iron overload severity, transfusion history, and chelation therapy response should be taken into account when designing treatment plans. Tailoring treatment to each patient's specific needs can help optimize outcomes and reduce the risk of liver complications.
4. Nutritional support: Considering the potential influence of nutritional status on albumin levels, health-care providers should ensure that children with β-thalassemia major receive adequate nutrition and address any deficiencies that may impact the liver function.

The study had several limitations that needed to be noted in interpreting the results. Since it was an observational study, definitive causal conclusions could not be determined. Accounting for potential confounders related to chelation adherence and dose adjustments was challenging in the analysis. In addition, information on histologic liver iron content or fibrosis staging from biopsy was lacking. It was important to note that findings from this single-center study might not be fully generalized to other settings. A more comprehensive understanding of the topic could have been obtained through multicenter studies involving different geographic regions and diverse populations.

In summary, the study provides longitudinal evidence that iron overload portends an increased risk of liver injury in regularly transfused patients with thalassemia. Further research is necessary to address whether tight control of ferritin could slow the progression of liver disease. Providers are recommended to monitor ferritin and liver tests closely and optimize chelation regimens when the iron burden becomes excessive.[20] Future directions could also explore add-on therapies like antioxidants that might mitigate some hepatic effects of iron deposition.[21] Achieving better control of iron balance remains an important therapeutic goal for reducing morbidity in thalassemia.

Conclusion

The present study found a significant positive association between serum ferritin levels and liver enzymes AST and ALT in pediatric β-thalassemia major patients. However, albumin levels were not related to ferritin, suggesting preserved synthetic liver function despite some degree of hepatocellular injury from iron overload. These findings highlight the need for regular hepatic monitoring and the use of iron chelators to prevent the progression of liver complications in this population.

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Conflicts of interest

There are no conflicts of interest.

References

1. Cao A, Galanello R. Beta-thalassemia. Genet Med 2010;12:61-76.
2. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, *et al.* Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 2004;89:1187-93.
3. Origa R, Galanello R, Ganz T, Giagu N, Maccioni L, Faa G, *et al.* Liver iron concentrations and urinary hepcidin in beta-thalassemia. Haematologica. 2007;92:583-8.
4. Walter PB, Fung EB, Killilea DW, Jiang Q, Hudes M, Madden J, *et al.* Oxidative stress and inflammation in iron-overloaded patients with β-thalassemia or sickle cell disease. Br J Haematol 2006;135:254-63.
5. Taher AT, Saliba AN. Iron overload in thalassemia: Different organs at different rates. Hematology Am Soc Hematol Educ Program 2017;2017:265-71.
6. Darvishi-Khezri H, Aliasgharian A, Naderisorki M, Kosaryan M, Ghazaiean M, Fallah H, *et al.* Ferritin thresholds for cardiac and liver hemosiderosis in β-thalassemia patients: A diagnostic accuracy study. Sci Rep 2022;12:17996.
7. Yin LK, Kew ST. Elevated Alt and Ast in an asymptomatic person: What the primary care doctor should do?. Malays Fam Physician 2009;4:98-9.
8. Mourad FH, Hoffbrand AV, Sheikh-Taha M, Koussa S, Khoriaty AI, Taher A. Comparison between desferrioxamine and combined therapy with desferrioxamine and deferiprone in iron overloaded thalassemia patients. Br J Haematol 2003;121:187-9.
9. Zamani F, Shakeri R, Eslami SM, Razavi SM, Basi A. Hydroxyurea therapy in 49 patients with major beta-thalassemia. Arch Iran Med 2009;12:295-7.
10. Colah RB, Italia KY, Gorakshakar AC. Burden of thalassemia in India: The road map for control. Pediatr Hematol Oncol J 2017;2:79-84.
11. Salama KM, Ibrahim OM, Kaddah AM, Boseila S, Ismail LA, Hamid MM. Liver enzymes in children with beta-thalassemia major: Correlation with iron overload and viral hepatitis. Open Access Maced J Med Sci 2015;3:287-92.
12. Livrea MA, Tesoriere L, Pintaudi AM. Oxidative stress and antioxidant status in beta-thalassemia major: Iron overload and depletion of lipid-soluble antioxidants. Blood 1996;88:3608-14.
13. Kassab-Chekir A, Laradi S, Ferchichi S, Haj Khelil A, Feki M, Amri F, *et al.* Oxidant, antioxidant status and metabolic data in patients with beta-thalassemia. Clin Chim Acta 2003;338:79-86.
14. Ameli M, Besharati S, Nemati K, Zamani F. Relationship between elevated liver enzyme with iron overload and viral hepatitis in thalassemia major patients in Northern Iran. Saudi Med J 2008;29:1611-5.
15. Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C, *et al.* Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med 2000;343:327-31.
16. Ardalan FA, Osquei MR, Toori MA, Sadeghi R. Liver abnormalities in transfusion-dependent β-thalassemia major patients. Blood Res 2019;54:41-5.
17. Origa R, Galanello R, Perseu L, Tavazzi D, Domenica Cappellini M, Terenzani L, *et al.* Cholelithiasis in thalassemia major. Eur J Haematol 2009;82:22-5.
18. Britton RS, Leicester KL, Bacon BR. Iron toxicity and chelation therapy. Int J Hematol 2002;76:219-28.
19. Gattermann N. Iron overload in myelodysplastic syndromes (MDS). Int J Hematol 2018;107:55-63.
20. Choudhry VP, Naithani R. Current status of iron overload and chelation with deferasirox. Indian J Pediatr 2007;74:759-64.
21. Elalfy MS, Adly AA, Attia AA, Ibrahim FA, Mohammed AS, Sayed AM. Effect of antioxidant therapy on hepatic fibrosis and liver iron concentrations in β-thalassemia major patients. Hemoglobin 2013;37:257-76.