Original Article

Coagulation Profile in Patients with β Thalassemia

Nidhi Yadav[1,*], Vandana Porwal[1], Vandana Yadav[1], Kamlesh Tanwani[2]

[1]Department of Pathology, J.L.N Medical College, Ajmer, Rajasthan, India
[2]Department of Biochemistry, J.L.N Medical College, Ajmer, Rajasthan, India

***Correspondence:** nidhiyadav94@gmail.com

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Abstract

Background: Thalassemia is a genetic blood disorder characterized by defective hemoglobin synthesis, leading to anemia and requiring regular blood transfusions. The present study investigates coagulation profile changes in thalassemia patients and their correlation with hematological and biochemical parameters.
Methods: This is hospital-based cross-sectional type of prospective study and was conducted at JLN Hospital, Ajmer, from April 2022 to April 2024. Fifty thalassemia patients and fifty healthy controls were selected. Hematological parameters, liver function tests, coagulation markers (PT, APTT, D-Dimer, Fibrinogen), and ferritin levels were assessed. Statistical analysis was performed using SPSS software.
Result: The study revealed significant differences in Hb levels, liver enzymes (AST, ALT, ALP), coagulation parameters (PT, APTT), D-dimer and serum ferritin between thalassemia patients and controls. Thalassemia major patients exhibited more severe abnormalities than intermedia patients. No significant difference was observed in WBC count, Platelet count, Total Bilirubin, Albumin levels and Serum Fibrinogen.
Conclusion: Thalassemia patients exhibit distinct hematological and coagulation abnormalities, with implications for clinical management and transfusion strategies. Further research is needed to explore targeted interventions to mitigate these complications.

Keywords: Thalassemia; Coagulation Profile; Hematological Parameters; Blood Transfusion; Hypercoagulability

Introduction

Thalassemia: An Overview

Thalassemia is a hereditary blood disorder caused by mutations affecting the synthesis of hemoglobin, leading to chronic anemia, ineffective erythropoiesis, and systemic complications. It is classified into alpha-thalassemia and β-thalassemia, depending on the affected globin chain. β-thalassemia, which results from mutations in the HBB gene, is the most clinically significant form and manifests in three major phenotypes: β-thalassemia major (TM), β-thalassemia intermedia (TI), and β-thalassemia minor (trait) [1].

β-thalassemia major is the most severe form, requiring lifelong blood transfusions and iron chelation therapy [2]. β-thalassemia intermedia presents with moderate anemia, while β-thalassemia minor is usually asymptomatic [3]. Chronic blood transfusions in thalassemia major lead to iron overload, affecting multiple organs, including the heart, liver, and endocrine glands, increasing the risk of complications such as cardiomyopathy, diabetes, and cirrhosis [4].Although thalassemia is highly prevalent in India, particularly in high-risk communities, there is limited data on the coagulation profile and thrombotic risk in Indian patients with TM and TI. This study aims to address this gap by systematically evaluating coagulation parameters in Indian thalassemia patients, providing insights that may guide risk stratification and clinical management in this population.

Pathophysiology and Hematological Abnormalities

In β-thalassemia, ineffective erythropoiesis occurs due to the excess accumulation of unpaired alpha-globin chains, leading to intramedullary apoptosis of erythroid precursors [5]. This results in severe anemia, compensatory bone marrow expansion, and extramedullary hematopoiesis. Chronic anemia triggers an increase in iron absorption from the gastrointestinal tract, exacerbating iron overload [6].

One of the most significant complications of β-thalassemia is coagulation abnormalities, which can predispose patients to both thrombotic and hemorrhagic complications [7]. Studies have demonstrated that β-thalassemia major and intermedia patients exhibit elevated D-dimer levels, prolonged Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT), Serum Fibrinogen, and hypercoagulable states [8, 9].

Iron Overload and its Effect on Hemostasis

Iron overload in thalassemia patients is primarily due to frequent blood transfusions and increased intestinal iron absorption. Excess iron gets deposited in various organs, leading to complications such as cardiomyopathy, liver fibrosis, and endocrine dysfunction [10]. Liver dysfunction in thalassemia affects the synthesis of coagulation factors, leading to prolonged PT, APTT, and increased bleeding risk [11].

Additionally, iron overload promotes oxidative stress, endothelial dysfunction, and platelet activation, which contribute to a prothrombotic state in thalassemia patients [12]. Splenectomy, often performed in patients with hypersplenism and severe anemia, further increases the risk of deep vein thrombosis (DVT), pulmonary embolism, and cerebrovascular events [13].

Clinical Implications and Rationale for This Study

β-thalassemia patients are at high risk of both thrombotic and hemorrhagic complications, necessitating regular monitoring of coagulation parameters, iron levels, and liver function. While numerous studies have focused on transfusion protocols and iron chelation therapy, limited research has investigated the precise relationship between iron overload, liver dysfunction, and coagulation abnormalities in thalassemia patients in India [14, 15].

This study aims to evaluate the coagulation profile of β-thalassemia patients, correlate these findings with serum ferritin, liver function tests, and coagulation parameters, and propose recommendations for optimizing treatment strategies. Understanding these interactions will help develop personalized anticoagulation and transfusion strategies, ultimately improving patient outcomes and quality of life [16].

Materials and Methods

This study was conducted at the Thalassemia Ward of Jawahar Lal Nehru (JLN) Hospitals, Ajmer, Rajasthan, over a period of two years (April 2022 to April 2024). The sample size of the study was $= 45$. The study aimed to evaluate the coagulation profile and hematological abnormalities in β-thalassemia patients, with a focus on correlating these findings with serum ferritin levels, liver function, coagulation parameters and transfusion dependency.

Sample Size:

Based on Naithani R et al., mean prothrombin time in thalassemia was 13.7 $\pm$ 2.7 vs 12.1 $\pm$ 0.6 in controls. At 95% confidence and 90% power, sample size was calculated as 45 per group using standard formula: m_1 = 13.7, m_2 = 12.1 σ_1 = 2.7, σ_2 = 0.6 $Z_{1-\alpha/2}$ = 1.96, $Z_{1-\beta}$ = 1.28

Statistical Analysis:

Data was entered in MS Excel and analyzed using SPSS v25. Normality was checked with Kolmogorov-Smirnov and Shapiro-Wilk tests. Quantitative data was presented as mean $\pm$ SD or median (IQR). Group differences was tested using Student's t-test or Mann–Whitney U test as appropriate. Qualitative variables was expressed in percentages and compared with Chi-square or Fisher's exact test. $P < 0.05$ will be considered statistically significant.

Written informed consent was obtained from all participants with relevant clinical evaluation ans routine investigations was performed. The study was conducted after approval from the Institutional Ethical Committee.

Study Design and Population

The study was designed as a comparative, cross-sectional analysis, enrolling 45 diagnosed cases of β-thalassemia (major and intermedia) who attended the thalassemia ward for regular blood transfusion. These patients were compared with 45 age and sex-matched healthy controls from the general population. The selection criteria ensured that all participants were pre-transfusion patients, preventing transient fluctuations in coagulation markers due to recent transfusions.

Inclusion and Exclusion Criteria

The study included patients clinically diagnosed with β-thalassemia major and thalassemia intermedia within the age range of 1–18 years. Among the thalassemia intermedia group (n=24), 41.7% were between 1–10 years, 16.7% were between 11–15 years, and 41.7% were older than 15 years. In the thalassemia major group (n=26), 30.8% belonged to the 1–10 years age group, 23.1% to the 11–15 years age group, and 46.2% were older than 15 years. For comparison, the control group (n=50) was age-matched, with 28.0% in the 1–10 years range, 36.0% in the 11–15 years range, and 36.0% above 15 years. Patients with β-thalassemia minor, those who were splenectomized, or had pre-existing coagulation disorders, thromboembolic events, or liver failure were excluded. Additionally, individuals on anticoagulant therapy or those with positive serology for hepatitis were omitted from the study to eliminate confounding variables.

Data Collection and Ethical Considerations

All patients were counseled, and informed consent was obtained prior to participation. Ethical clearance was granted by the Research and Ethical Committee of JLN Medical College, Ajmer. Data collection included a detailed clinical history, family history of thalassemia, and demographic information, recorded using structured patient proformas.

Blood Sample Collection and Laboratory Investigations

Venous blood samples were collected before transfusion using standard phlebotomy techniques. The samples were transported to the Central and Biochemistry Laboratories of JLN Hospital and processed within two hours of collection.

Complete Blood Count (CBC):

2 mL of venous blood was collected in K_3EDTA (lavender top) vials. Samples were analyzed using the Sysmex Automated Hematology Analyzer, which provided hemoglobin levels, RBC indices, WBC count, and platelet count.

Liver Function Tests (LFTs):

2 mL of venous blood was collected in a plain vial, followed by centrifugation at 3600 RPM for 1 minute. The plasma was analyzed using Beckman Coulter DXC 700 and AU680 analyzers, measuring AST, ALT, total bilirubin, and albumin levels.

Coagulation Profile (PT, APTT, INR):

2 mL of blood was collected in 3.2% sodium citrate vials, ensuring a 9:1 blood-to-citrate ratio. The samples were centrifuged at 2000 RPM for 1 minute, and the plasma was analyzed using the Stago Start Max coagulation analyzer. PT was measured by adding 50 µL of plasma, 20 µL of PT reagent (Thromboplastin), and silicone balls, with clotting time recorded. APTT estimation involved 50 µL of plasma, 50 µL of APTT reagent (C.K. PREST), and 50 µL of 0.025M $CaCl_2$, with clotting time recorded.

Serum Ferritin Estimation:

2 mL of venous blood was drawn into a plain vial, centrifuged at 3600 RPM for 1 minute, and 40 µL of plasma was extracted. Ferritin levels were measured using the Maglumi 800 (CLIA Technique).

D-Dimer Estimation:

2 mL of venous blood was collected in a plain vial, centrifuged at 3600 RPM for 1 minute, and 20 µL of plasma was extracted. Analysis was performed using the Maglumi 800 machine, with a normal reference range of <0.50 μg/mL.

Serum Fibrinogen Estimation:

2 mL of blood was collected in 3.2% sodium citrate vials, maintaining a proper blood-to-citrate ratio. Samples were centrifuged at 2500 RPM for 1 minute, and fibrinogen levels were quantified using the Clauss Method.

Statistical Analysis

All data were entered into Microsoft Excel and analyzed using SPSS v25. The normality of variables was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Quantitative variables were expressed as mean $\pm$ standard deviation or median (interquartile range).

Results

This section presents the detailed findings of the study, including demographic distribution, hematological parameters, coagulation profile, liver function tests, iron overload markers, and correlation analyses between serum ferritin levels and coagulation parameters.

Hematological Parameters

Table 1: Comparative Analysis of Hemoglobin (Hb) Levels

Group	Mean Hb (g/dL) $\pm$ SD	p-value
Controls (n=50)	11.95 $\pm$ 1.63	< 0.001
Thalassemia Intermedia (n=24)	8.93 $\pm$ 0.89	< 0.001
Thalassemia Major (n=26)	6.85 $\pm$ 1.42	< 0.001

Table 2: Comparison of Ferritin Levels Among Controls, Thalassemia Intermedia, and Thalassemia Major Groups

	Controls (n=50)	Thalassemia Intermedia (n=24)	Thalassemia Major (n=26)	p value
Ferritin (30-300ng/ml)	170.89$\pm$38.06	2494.78$\pm$1028.07	3145.04$\pm$778.22	< 0.001

Table 3: Statistical Significance (p-values) of Ferritin Level Differences Among Controls, Thalassemia Intermedia, and Thalassemia Major Groups

	P value
Between Controls and Thalassemia Intermedia	< 0.001
Between Controls and Thalassemia Major	< 0.001
Between Thalassemia Intermediate and Thalassemia Major	

Table 4: Liver Function Test (LFT) Results

Group	AST (IU/L) $\pm$ SD	ALT (IU/L) $\pm$ SD	ALP (IU/L) $\pm$ SD	p-value
Controls (n=50)	33.22 $\pm$ 9.68	35.86 $\pm$ 20.23	61.98 $\pm$ 13.40	< 0.001
Thalassemia Intermedia (n=24)	53.24 $\pm$ 10.55	73.67 $\pm$ 35.60	63.54 $\pm$ 12.64	< 0.001
Thalassemia Major (n=26)	63.51 $\pm$ 26.01	76.75 $\pm$ 41.01	87.94 $\pm$ 58.49	< 0.001

Coagulation Profile

From above Table 6 and Figure 1, positive correlation was evident between Serum Ferritin Levels (ng/ml) and PT (seconds)

Table 5: Comparison of Prothrombin Time (PT), INR, and APTT

Group	PT (sec) ± SD	INR ± SD	APTT (sec) ± SD	p-value
Controls (n=50)	13.33 ± 2.56	0.97 ± 0.22	29.33 ± 5.35	< 0.001
Thalassemia Intermedia (n=24)	15.85 ± 1.72	1.13 ± 0.12	35.70 ± 2.84	< 0.001
Thalassemia Major (n=26)	18.55 ± 1.88	1.33 ± 0.13	41.27 ± 3.38	< 0.001

Table 6: Correlation Between Serum Ferritin Levels and Coagulation Profile Parameters

	Serum Ferritin Level	
	r value	P value
PT	0.58	< 0.001
APTT	0.75	< 0.001
Platelet count	0.24	0.06

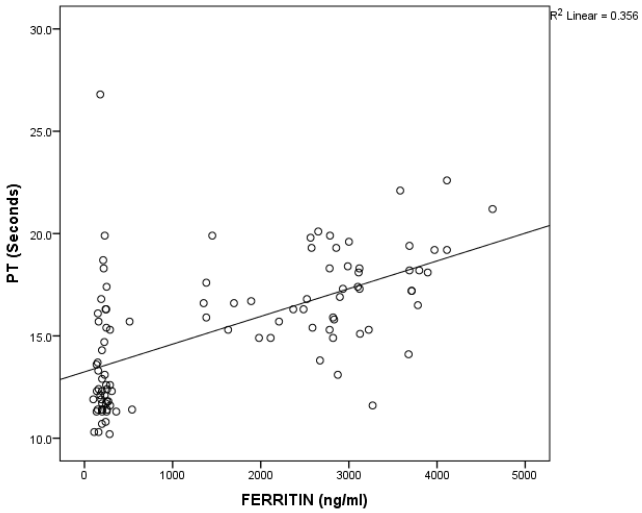

Figure 1: Scatterplot Demonstrating the Correlation Between Serum Ferritin Levels and Prothrombin Time (PT) in Study Groups ($R^2 = 0.356$)

From above Table 6 and Figure 2, positive correlation was evident between Serum Ferritin Levels (ng/ml) and APTT (seconds)

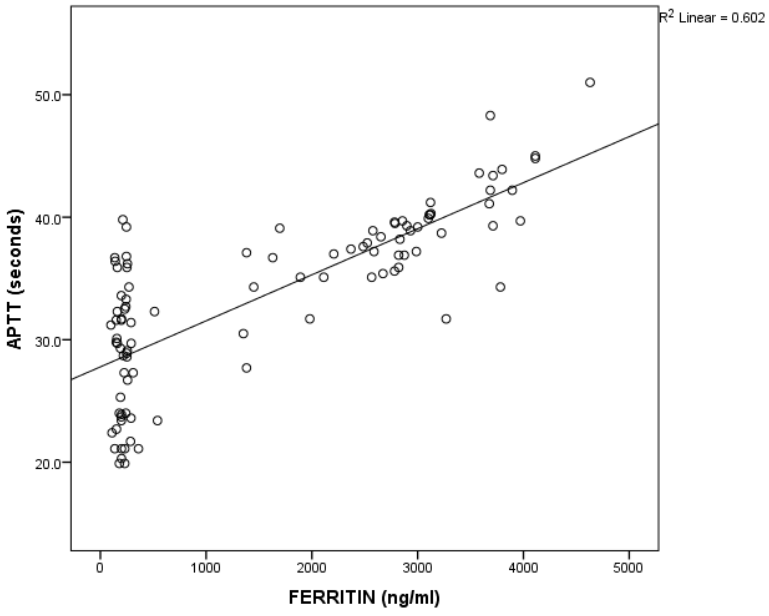

Figure 2: Scatterplot Demonstrating the Correlation Between Serum Ferritin Levels and Activated Partial Thromboplastin Time (APTT) in Study Groups ($R^2 = 0.602$)

Discussion

Our findings show pronounced reductions in Hb levels among thalassemia patients ($p < 0.001$), particularly in TM individuals, reflecting ineffective erythropoiesis and hemolysis [17].

WBC and platelet counts did not differ significantly between groups ($p > 0.05$), possibly due to compensatory mechanisms or variable transfusion practices [19].

Ferritin levels were markedly elevated—especially in TM patients—indicating severe iron overload and supporting the need for chelation therapy [20]. Elevated AST and ALT levels suggest hepatic injury, likely secondary to iron-induced oxidative stress [21].

The significant prolongation of PT, INR, and APTT—particularly in major patients—points to compromised hepatic synthesis of clotting factors, potentially aggravated by chronic DIC and fibrinolysis [22, 23]. Elevated D-dimer levels reinforce the hypercoagulable status in this population.

Strong positive correlations between ferritin levels and coagulation abnormalities highlight iron overload as a driver of disrupted hemostasis.

Hematological Findings

The hemoglobin levels in thalassemia patients were significantly lower compared to controls ($p < 0.001$). Among the cases, thalassemia major patients exhibited the lowest hemoglobin levels (6.85 $\pm$ 1.42 g/dL), whereas thalassemia intermedia patients had slightly higher levels (8.93 $\pm$ 0.89 g/dL). These findings align with previous studies by Situmorang et al., who reported a mean hemoglobin of 7.02 $\pm$ 1.77 g/dL in thalassemia patients, and Wadaha et al., who observed a similar value of 7.26 $\pm$ 1.07 g/dL. The reduced hemoglobin in thalassemia major can be attributed to ineffective erythropoiesis, chronic hemolysis, and increased erythrocyte destruction.

While white blood cell (WBC) count and platelet count showed no significant differences between groups ($p > 0.05$), studies have shown that splenomegaly and chronic inflammation in thalassemia may contribute to fluctuating WBC counts. Platelet counts in our study were non-significant, supporting the findings by Naithani et al., where platelet values in controls and cases were 237 $\pm$ 132 and 226 $\pm$ 123, respectively. The absence of significant differences could be due to compensatory mechanisms or variable transfusion practices affecting platelet dynamics.

Iron Overload and Liver Dysfunction

Serum ferritin, a marker of iron overload, was markedly elevated in thalassemia patients ($p < 0.001$), with thalassemia major patients showing significantly higher values (3145.04 $\pm$ 778.22 ng/mL) than thalassemia intermedia (2494.78 $\pm$ 1028.07 ng/mL). Our findings were consistent with those of Srevetsva et al., who reported mean ferritin levels of 3801 $\pm$ 1585 ng/mL in thalassemia major patients. The increased ferritin levels reflect excessive iron accumulation due to recurrent transfusions and increased gastrointestinal iron absorption, necessitating iron chelation therapy to prevent iron-mediated organ damage.

Liver dysfunction was evident in our cohort, with significantly higher AST and ALT levels in thalassemia patients compared to controls ($p < 0.001$). In our study, AST levels were 63.51 $\pm$ 26.01 IU/L in thalassemia major and 53.24 $\pm$ 10.55 IU/L in thalassemia intermedia, while ALT levels were 76.75 $\pm$ 41.01 IU/L and 73.67 IU/L, respectively. Similar findings were reported by Naithani et al., where AST and ALT values in cases were 55.7 $\pm$ 27.4 IU/L and 75.5 $\pm$ 59.8 IU/L, respectively. These elevations can be attributed to iron-induced hepatic damage and chronic hemolysis, which result in hepatic hemosiderosis and oxidative stress, contributing to liver dysfunction.

Coagulation Profile and Hypercoagulability

Our study demonstrated significant prolongation of PT, APTT, and INR in thalassemia patients compared to controls ($p < 0.001$), with more profound changes observed in thalassemia major patients. PT was 18.55 $\pm$ 1.88 sec in thalassemia major and 15.85 $\pm$ 1.72 sec in thalassemia intermedia, compared to 13.33 $\pm$ 2.56 sec in controls. Similarly, APTT values were 41.27 $\pm$ 3.38 sec (thalassemia major), 35.70 $\pm$ 2.84 sec (thalassemia intermedia), and 29.33 $\pm$ 5.35 sec (controls). These findings align with those of Singh and Yadav et al., who reported PT of 14.6 $\pm$ 1.24 sec and APTT of 36.41 $\pm$ 7.42 sec in thalassemia major patients.

The prolonged PT and APTT suggest impaired coagulation factor synthesis, likely due to iron-induced liver dysfunction, which disrupts the production of vitamin K-dependent clotting factors. In addition, chronic low-grade disseminated intravascular coagulation (DIC) and compensatory fibrinolysis contribute to hypercoagulability in these patients.

D-dimer, a marker of ongoing fibrinolysis, was significantly elevated in thalassemia major patients (0.44 ± 0.26 μg/ml) compared to controls ($p < 0.001$). Abosdera et al. reported similar findings, highlighting the thrombotic risk in transfusion-dependent thalassemia patients.

Correlation Between Serum Ferritin and Coagulation Parameters

A positive correlation was observed between serum ferritin levels and coagulation abnormalities, suggesting that iron overload directly impacts clotting mechanisms. The increase in PT, INR, and APTT values with rising ferritin levels indicates a progressive decline in hepatic synthetic function, leading to impaired hemostasis and increased bleeding tendencies. The hypercoagulable state in β-thalassemia intermedia and splenectomized patients may explain the increased risk of thrombotic events, a finding consistent with previous research by Cappellini et al.

Clinical Implications and Future Directions

The findings of this study underscore the importance of routine coagulation monitoring in thalassemia patients, particularly those on chronic transfusion therapy. Our results emphasize the need for individualized transfusion regimens, iron chelation therapy, and periodic liver function assessments to minimize hematological and thrombotic complications.

Future studies should focus on assessing protein C, protein S, and antithrombin III levels, as deficiencies in these anticoagulant proteins contribute to increased thrombotic risks. Additionally, evaluating the role of endothelial dysfunction, platelet activation, and novel anticoagulant therapies may provide further insights into mitigating coagulation-related complications in thalassemia.

Conclusion

This study highlights the significant alterations in hematological, biochemical, and coagulation profiles of β-thalassemia patients, demonstrating that thalassemia major patients exhibit more severe abnormalities than thalassemia intermedia patients.

Hemoglobin levels were significantly reduced in thalassemia patients ($p < 0.001$).

Ferritin levels were significantly higher in thalassemia intermedia compared to controls ($p < 0.001$), in thalassemia major compared to controls ($p < 0.001$), and also between thalassemia major and thalassemia intermedia ($p = 0.02$).

Liver function tests (AST, ALT, ALP) were significantly elevated, suggesting hepatic dysfunction ($p < 0.001$).

Prolonged PT, APTT, and INR indicated coagulation disturbances due to liver dysfunction ($p < 0.001$).

D-dimer levels were significantly elevated, reinforcing the hypercoagulable state ($p < 0.001$).

A significant correlation between serum ferritin and coagulation markers was established.

Our study suggests that routine hematological, coagulation, and biochemical monitoring in thalassemia patients is essential for early detection and management of complications. Optimizing transfusion protocols, ensuring adequate iron chelation therapy, and monitoring liver function and coagulation status can significantly improve patient outcomes. Future research should explore targeted anticoagulation strategies to mitigate thrombotic risks in this high-risk population.

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