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EVALUATION OF D-DIMER, FIBRINOGEN LEVELS AND THEIR CORRELATION WITH PLATELETS COUNT IN B-THALASSEMIA MAJOR PATIENTS

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ABSTRACT

Background: Beta- thalassemia major is a genetic disease characterized by formation of little or no beta-globin chain, leading to premature death of red blood cells and ineffective erythropoiesis. The existence of a high incidence of thrombo-embolic events, led to the identification of a hypercoagulable state in these patients. **Aims**: To evaluate D-dimer, fibrinogen levels in B-thalassemia major patients, and to correlate these parameters with platelets count, splenectomy and complication of disease. **Methods:** A case-control study conducted at "AL-Hadbaa" Blood & Bone Marrow Transplant (BMT) Hospital in Mosul city in Iraq from March to August 2025, including (100) patients diagnosed with β-thalassemia major and 50 age and sex-matched healthy control were compared as regards complete blood count, prothrombin time, activated partial thromboplastin time, fibrinogen, D.dimer and s. ferritin. **Result:** The mean of prothrombin time and activated partial thromboplastin time, D. Dimer were significantly higher in patients with β-thalassemia major in comparison to control with p-value of (0.000),)(0.000), and (0.000) while mean fibrinogen was significantly lower in patients than control group (p-value 0.027). A significant correlation between high platelets count and PT, fibrinogen and D-dimer were noted with p-value (0.044), (0.029), and (0.004) respectively. Mean Fibrinogen and D-dimer were significantly higher in cases with splenectomy than those whom not splenectomized at p-value of (0.001and 0.007) respectively. A significant (p=0.002) and strong positive correlation (r=0.309) was noted between time after starting blood transfusion (years)and fibrinogen level. **Conclusion**: The correlation between high platelets count and some of hemostatic parameters were significant as there is evidence that increased platelets count associated with hypercoagulable state.

KEYWORDS: B-thalassemia major, D-dimer, Fibrinogen, Platelets.

INTRODUCTION

Thalassemia is a group of hereditary blood disorders characterized by defective synthesis of one or more of globin chains of hemoglobin (Hb) consequent in variable phenotypes ranging from asymptomatic individuals to severe transfusion-dependent thalassemia major (TDT). The main subtypes of thalassemia are alpha and beta, which are distinguished by the specific globin chains that are affected. Beta-thalassemia major (TM), commonly called Cooley's anemia, is the most severe manifestation of this condition. It is caused by mutations in both beta-globin genes, resulting in a significant decrease in the production of beta chains and the onset of severe anemia during early infancy. Patients need continuous blood transfusions and iron chelation treatment to sustain their lives.[1,2] While transfusions are lifesaving, chronic transfusion therapy inevitably leads to iron overload affecting about every organ system.[3,4] B-thalassemia can lead to both hypercoagulability (in form of deep vein thrombosis, pulmonary embolism and stroke) and bleeding (in form of easy bruising, epistaxis and subarachnoid hemorrage), with hemostatic changes including thrombocytopenia (low platelet count), prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), and reduced levels of coagulation factors and natural anticoagulants.[1,5,6] A multilateral pathophysiological mechanism is participating in the pathogenesis of thromboembolic

events in thalassemia, including the combination of the distinctive participants of a thrombotic process (endothelium, platelets) along with the disease-specific features (abnormal RBCs, iron overload, splenectomy).[5,6]

The study aims: To evaluate D-dimer, fibrinogen levels in B-thalassemia major patients, and to correlate these parameters with platelets count, splenectomy and complication of disease.

Patients and Methods: This case-control study was performed in Nineveh Province at "AL-Hadbaa" Blood & BMT Hospital from March 2025 to August 2025. It included(100) patients diagnosed as β- thalassemia major, from (7 to 33) years old present at thalassemia center in "AL-Hadbaa" Blood & BMT Hospital. A Total of 50 healthy individuals were included as control group and they are age and sex matched with the patient.

The inclusion criteria

- Age : above 6 years of age
- Phenotype: diagnosed as β- thalassemia major by clinical, hematological (CBP, HPLC) and some of them molecular tests.

The exclusion criteria: Patients with hepatitis B and hepatitis C.
Comorbidity conditions known to alter hemostasis, on anticoagulants drugs, known case of hemoglobinopathies other than beta thalassemia.

Blood sampling and sample handling: seven milliliters (ml) of venous blood were collected from every patients by appropriate venipuncture method. The EDTA anticoagulated sample (3 ml) kept at room temperature to be used within less than one hour to perform full blood count, Two and half milliliters of drawn blood were placed in trisodium citrate tube, (9 volume of blood are added to 1 volume of trisodium citrate), and centrifuged at 2500 gm for 10 minutes to obtain platelets poor plasma (PPP) that used for determination of Prothrombin time (PT), Activated partial thromboplastin time (APTT), D-dimer, and fibrinogen. The rest of drawn blood were placed in serum separating tubes allowed to clot at room temperature for 30 minutes then centrifuged at 2000 rpm for 10 minutes to obtain serum for biochemical analysis.

Investigations
Complete blood count, CBC from EDTA container by using electronic haematology analyzer (5 Differential Counter) from SYSMEX which was calibrated everyday by quality assurance reagents provided by the manufactures.

Biochemical test: Serum Ferritin was done by an immunoassay for the in vitro quantitative determination of ferritin using cobas e 411 analyzer from Roche according to instruction of Elecsys Ferritin kit.

Coagulation tests: Prothrombin Time (PT), Activated partial thromboplastin time(APTT)and Fibrinogen were performed manually according to standard procedure recommended by the manufactures of BIO-FIBRI kit from BIOLABO. D.Dimer was done by Vidus instrument using VIDAS® D-dimer Exclusion™ kit from bioMerieux.

Statistical analysis: Data were analyzed using IBM-SPSS 26 and summarized in Excel 2010. Normality was tested with the Shapiro-Wilk test. Categorical data were reported as frequencies, numerical data as means, and standard deviations. One-way ANOVA and Tukey's post hoc test evaluated multiple groups, and paired t-tests assessed group differences. Pearson correlation coefficients were calculated, with $p \leq 0.05$ considered significant.

RESULT
A total of 100 B-thalassemia major patients with mean age 17.70 ± 6.03 years, ranged from 7 to 33 years and 50 healthy controls with mean age 17.4 ± 5.90 years, ranged from 8-34 years were included in the study. According to sex, female predominance was noticed representing 56(56%) females with M:F ratio 0.78:1. All diagnosed cases were divided into three age groups as in figure 1 with most of the patients were in the second and third decade of life. Mean RBC, Hb and Hct were significantly lower in patients than in control subjects (p=0.000). However the mean level of WBC and PLT was significantly higher in patients than that among control (p=0.000). Serum ferritin levels was significantly higher in patients with B-thalassemia major than those with control group (p=0.000). (Table 1).

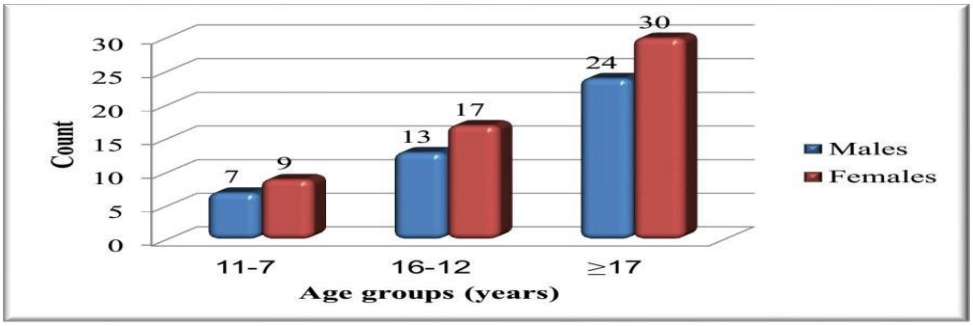

Figure 1: Distribution of studied cases according to age groups.

Table 1: Comparison of complete count parameters and s.ferritin among B-thalassemia major and control groups.

	Cases	Controls	p-value*
	Mean ±SD	**Mean ±SD**	
WBC (*10^9/L)	12.25±5.427	7.12±1.208	**0.000**
RBC (*10^12/L)	3.09±0.700	5.11±0.482	**0.000**
HGB (g/L)	80.54±14.610	122.16±5.063	**0.000**
HCT (%)	23.46±4.311	36.65±1.519	**0.000**
Platelets (*10^9/L)	391.38±193.630	248.04±45.839	**0.000**
S.ferritin (ng/ml)	3979.47±2472.811	27.36±11.485	**0.000**
*Independent t-test for two means			

Coagulation parameters differences between patients and control is shown in Table (2). Both PT and APTT means of patients were statically significant higher than that of control group (p=0.000). The mean level of fibrinogen in patients groups was statistically significant (p=0.027) lower when compared with that of control groups .The result of D-dimer marker showed significant (p=0.000) increase in the mean level of D-dimer in patients group as compared with control groups.

Table 2: Coagulation parameters differences between patients and control.

	Cases	Controls	p-value*
	Mean ±SD	Mean ±SD	
PT (s)	14.36±1.123	12.89±1.194	**0.000**
APTT (s)	41.85±6.341	30.85±2.783	**0.000**
Fibrinogen (g/L)	2.53±0.647	2.76±0.428	**0.027**
D.dimer (ng/ml)	585.77±271.857	570.28±81.361	**0.000**
*Independent t-test for two means			

There was statistically significant increase in mean PT (p=0.044), mean fibrinogen level (p=0.029) and mean level of D-dimer (p=0.004) in correlation with high platelet count. No significant difference was found regarding the APTT. (Table 3).

Table 3: Correlation of coagulation parameters with platelets count in patients with B-thalassemia major.

	Platelet		p-value*
	Normal (150-450*10^9/L)	**High (>450 *10^9/L)**	
	Mean ±SD	Mean ±SD	
PT (s)	14.09±1.157	14.55±1.031	**0.044**
APTT (s)	42.53±6.133	40.90±6.573	0.206
Fibrinogen (g/L)	2.41±0.542	2.70±0.745	**0.029**
D.dimer (ng/ml)	449.10±473.058	774.50±641.314	**0.004**
*Independent t-test for two means			

The mean of fibrinogen and D- dimer among cases with splenectomy were statistically significant (p=0.001) and (p=0.007) higher when compared among cases without splenectomy, while PT and APTT showed no statistically significant differences between splenectomized and non splenectomized thalassemic patients. (Table 4).

Table 4: Coagulation parameters in relation to splenectomy among cases.

	Splenectomized	Non-splenectomized	p-value*
	Mean ±SD	**Mean ±SD**	
PT (s)	14.12±1.180	14.51±1.065	0.088
APTT (s)	40.50±6.524	42.75±6.105	0.082
Fibrinogen (g/L)	2.79±0.651	2.36±0.590	**0.001**
D.dimer (ng/ml)	771.75±548.568	461.78±554.726	**0.007**
*Independent t-test for two means			

The patients were divided into three groups according to the time after starting blood transfusion, correlation was done with PT, APT, fibrinogen and D-Dimer. There was no statistically significant differences in mean PT, APTT as compared between three groups. (Figure 2,3).

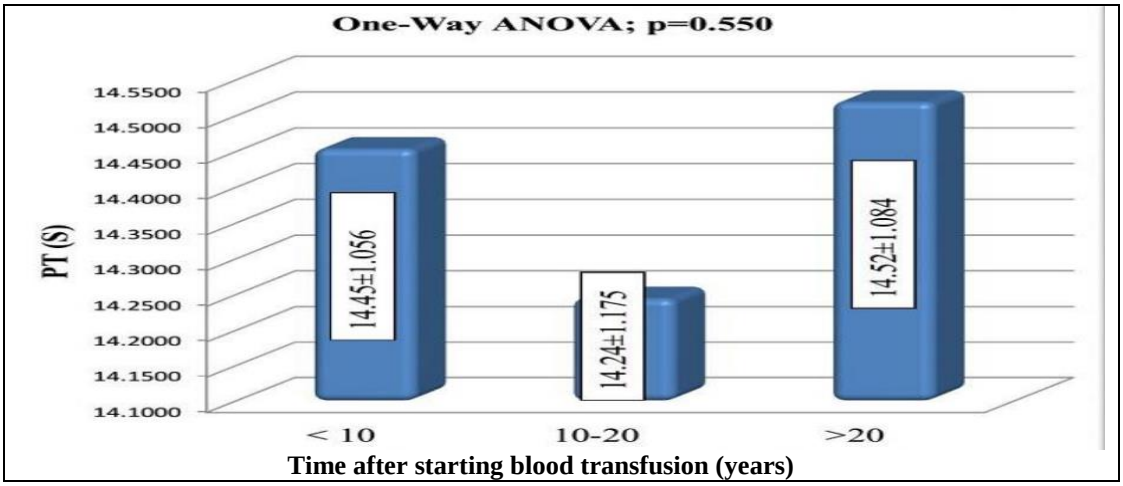

Figure 2: Correlation of PT with time after starting blood transfusion.

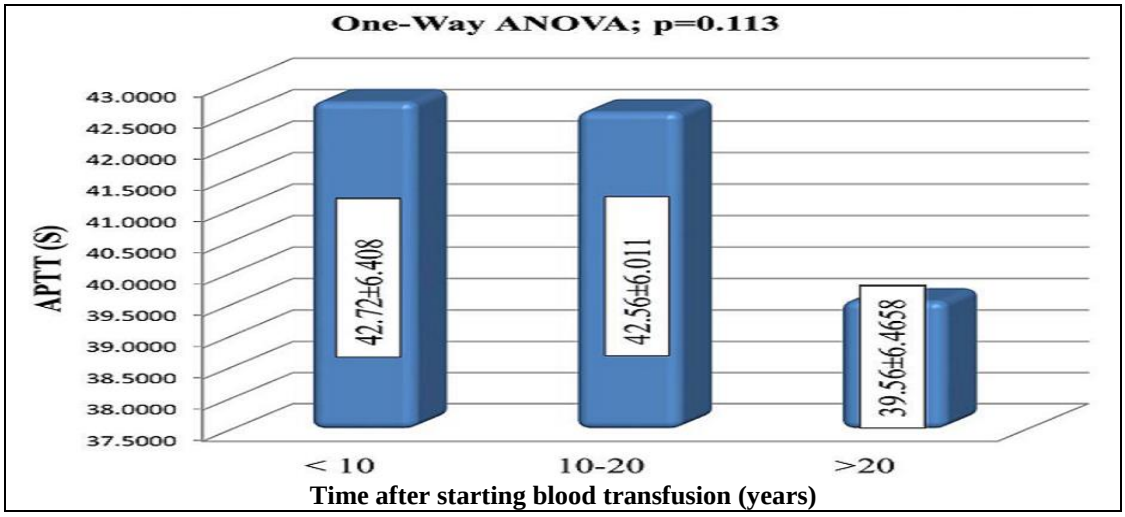

Figure 3: Correlation of APTT with time after starting blood transfusion.

The results revealed increase in the mean level of D-dimer in group (≥20 years) after starting blood transfusion when compared with other groups but no statistically significant differences (p=0.316). (Figure 4).

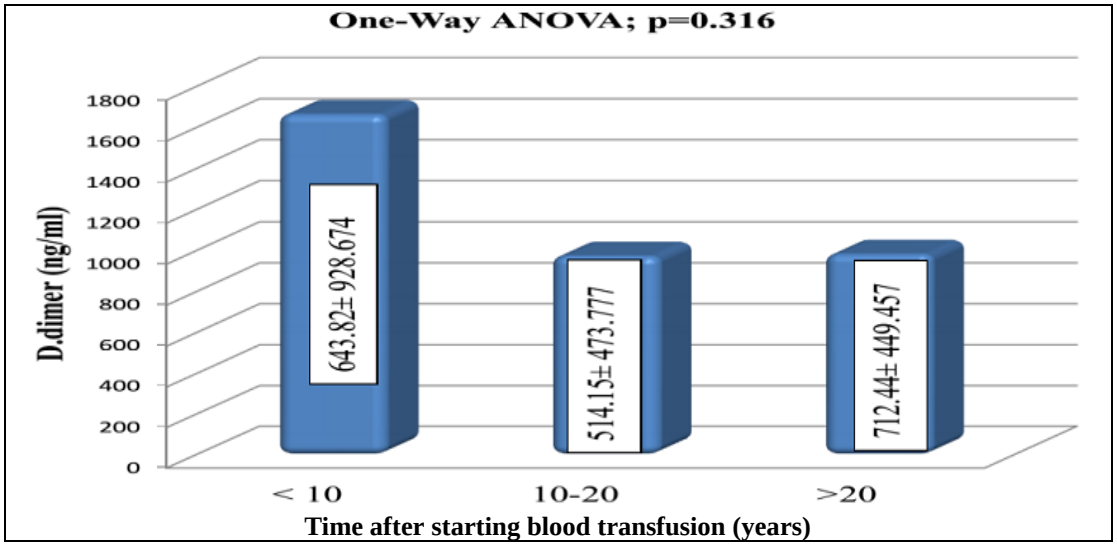

Figure 4: Correlation of D-dimer with duration of blood transfusion.

However there was statistically significant (p=0.012) increase in the mean level of fibrinogen in group (≥20 years) after starting blood transfusion as compared with other groups. (Figure 5).

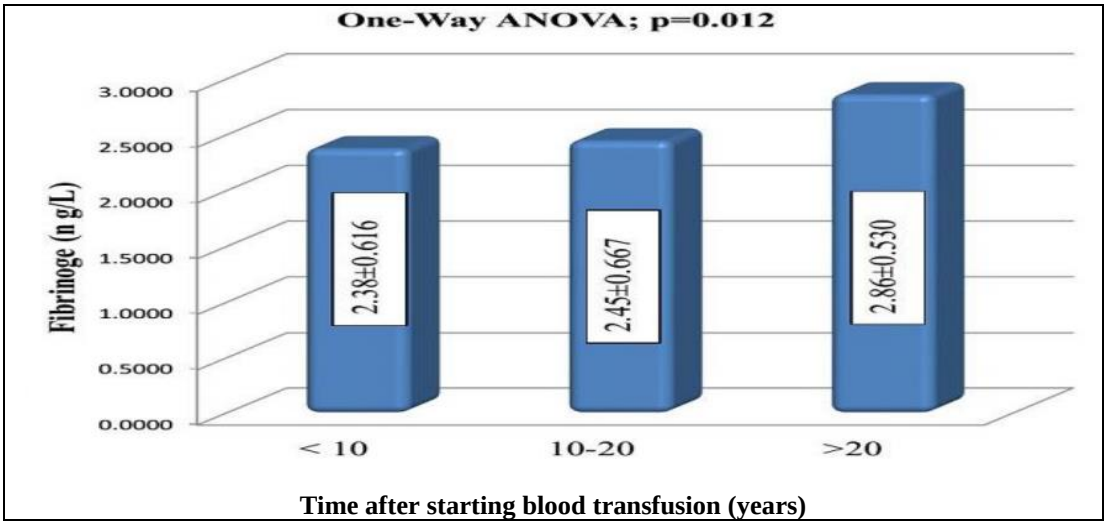

Figure 5: Correlation of fibrinogen with time after starting blood transfusion.

DISCUSSION

The presence of significant hemostatic changes (either bleeding or thrombosis) has been documented in patients with BTM. These changes have been attributed to hepatic dysfunction caused by an iron overload due to repeated blood transfusions.[7-9] This study included 100 β-thalassemia patients and 50 control, they were age and sex matched. A mean age of patients was 17.70 ± 6.03 years and a range of 7-33 years; therefore, a substantial proportion of patients with β-thalassemia may reach the third decade of life and the extension of life expectancy of β-thalassemia patients may be related to medical intervention in the form of blood transfusion and chelation therapy which have greatly increased the life of patients with β-thalassemia major. This observation is consistent with that of Wadaha HA et al(2022), Karimi M et al (2011) and Shamshirsaz AA et al (2003) in Iraq and Iran respectively[10-12], while it disagrees with studies mentioned by Haji LO et al (2024), AL-Saleh SM and Jaffat HS in Iraq (2019), Faraj SA(2016) in Iraq[1,13,14], Ghafoor MB et al in Pakistan (2023) and Al-Sanabra OM et al in Jordan (2025) that reported mean age of 23.21 years, 13.56 ± 0.66 years,13.2 ± 6.6years, 11.7±3.39, 20.22±6.87 respectively.[15,16] The current study included 44 males and 56 females with male: female ratio was 0.78:1 that agree with study conducted in Kerbala by Al-Ghanimi HH et al (2019)[17],while inconsistent with previous studies which noted male: female ratio of 1.5:1 by Faraj SA et al in Iraq (2016) and 1.7:1 by Srevatsa K et al in India (2019), this differences may be attributed to random collection of cases.[14,18] The thalassemia group had significantly (p value=0.000) lower Hb, Hct, and RBC count as compared with control group that show similarity with studies mentioned by Haji LO et al (2024), AL-saleh SM and Jaffat HS (2019), Abdalzehra et al (2022), Palit S et al (2012) and Wdaha HA et al (2022).[1,10,13,19,20] This is reflecting the fact that this specific type of blood disease occur mainly due to defective formation of beta globin chain of the hemoglobin part of the RBC excessive destruction of red blood cells at an early stage which in turn leads to anemia.[21-23] The WBC and platelet counts were statistically significant (p value =0.000) higher in thalassemic patients group than control group. This observation was in accordance with those demonstrated by AL Saleh SM and Jaffat HS(2019), Wadah HA(2022), Haji LO(2024), Fawzy A et al (2022) and AL-Sanabra et al (2025).[1,10,13,16,24]

Leucocytosis and thrombocytosis are typical findings, particularly in splenectomized thalassemic patients. These have been associated with comprehensive cytokine-mediated proliferation of myeloid precursors in reaction to chronic anemia and hemolysis.[25] Caocci et al study reported normal platelets count for all patients that disagree with our finding.[26] PT and PTT assessment were done for the patients and control group, and there was statistically significant (p value 0.000) prolonged time in patients when compared to control, this result is in line with those of previous studies.[7,14,24,27] Our finding was inconsistent with the result of Wadaha HA et al (2022) that mentioned mean PT and APTT of patients with β-thalassemia were significantly lower than in the control group. The prolongation of PT and APTT in thalassemic patients can be explained by some mild deficiency in a number of coagulation factors that result from frequent blood transfusion and hemosiderosis as suggested by previous authors.[10,28,29] The results of this study showed mean level of fibrinogen in patients groups was statistically significant (p value=0.027) lower when compared with that of control groups, that is consistent with previous study in Iraq.[1] Several mechanisms have been proposed, including inflammation leading to damaged RBC membranes with a phosphatidyl serine background, extreme plasma heme.[30-32] Other study in Jordan conducted by Al-Sanabra OM (2025) revealed that there is no significant differences in fibrinogen level between patients and control groups.[16] The result of D-dimer marker showed statistically significant (p value =0.000) increase in mean level of D-dimer in patients group as compared with control groups which agree with Al-Saleh SM and Jaffat HS(2019), AL-Sanabra OM et

al(2025), Tripatara A et al (2007), Abosedrea MM et al (2017), Ali AN and Kashmoola MA (2024).[13,16,33-35] However Naithani R et al (2006) reported similar D-dimer levels in thalassmic patients and healthy control group that did not match our report.[7] D-dimer is a marker for enhanced fibrinolysis and there are conflicting results about the level of D-dimer in different studies. It seems possible that this finding as a result to incidences of several serious complications related with optimizing transfusion, iron chelation and splenectomy therapy in patients with β-thalassemia which increase thromboembolic events in patients. High D-dimer levels may indicate increased fibrin formation and degradation, suggesting activation of the coagulation and fibrinolytic systems.[13,16,32-34] In the current study we have found that patients with β-thalassemia had statistically significant increase in mean serum ferritin level (p value=0.000) as compared with control group because multiple blood transfusions which believe life-saving therapy for β-thalassemia patients lead to iron overload and deposition of iron in tissue organ like liver caused hepatotoxicity. Similar observation was made by Sengsuk C et al (2014), AL- Saleh SM (2019), Faraj SA (2016), Haji LO et al (2024), Wadaha HA et al (2022) and Fawzy A et al (2022).[1,10,13,14,24,36] This study showed statistically significant increase in mean PT (p value=0.044), mean fibrinogen level (p value =0.029) and mean level of D-dimer (p value =0.004) in correlation with high platelet count. In thalassemia, there is evidence of increased platelets aggregation and increase platelets expression of CD62P,CD63 that associated with hypercoagulable state.[37] Our study reported statistically significant (p value=0.007) higher mean D-dimer in splenectomized patients as compared to non splenectomized patients, which was in accordance with previous studies by Cappellini MD et al (2000), Ali AN and Kashmoola MA (2024), Hassan TH et al (2010), Tripatara A et al (2007).[8,33,35,38] However other studies conducted by Abosdera MM et al (2016), Hadi TK et al (2020) noted no significant difference in mean D- dimer between two groups which disagree with our finding.[34,39] In conducted study, the mean level of fibrinogen was statistically significant higher in splenectomized patients as compared to non splenectomized patients with p value =0.001, this was in agreement with finding reported by Al-Sanabra OM et al (2025).[16] Splenectomy has been established as a leading cause of thrombotic events in beta thalassemia patients due to hypercoagulable state owing to the role of the spleen in scavenging thrombogenic red blood cells and to increased numbers of activated platelets in splenectomized patients.[40] Our result revealed increase in mean level of D-dimer in the group (≥20 years) after starting blood transfusion when compared with other groups that is not statistically significant (p value=0.316) and there was statistically significant (p value =0.012) increase in mean fibrinogen level in group (≥20 years) after starting blood transfusion as compared with other groups. This finding disagreed with that mentioned by previous authors as a result to increase complications of blood transfusion with increased years of blood transfusion.[41]

CONCLUSIONS

A significant alteration in hemostatic system exist in patients with B-thalassemia major in the form of prolonged prothrombin time, activated partial thromboplastin time and high fibrinogen, D-dimer levels which suggest the role of liver impairment resulting from iron overload due to frequent blood transfusion. The correlation between high platelets count and some of hemostatic parameters were significant as there is evidence that increased platelets count associated with hypercoagulable state. The hemostatic changes are more pronounced in splenectomized patients. A significant increase of fibrinogen in group (≥20 years) time after starting blood transfusion as compared with other groups as a result to increase complications with increased years of blood transfusion.

Conflict of Interest: All authors declare no conflict of interest.

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