International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

D-Dimer Assessment as a Marker of Hypercoagulabilty in Egyptian Thalassemia Patients

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Abstract

Beta thalassemia is a prevalent form of hereditary haemolytic anaemia that is frequently observed in the Mediterranean region. The prevalence of thromboembolism among patients diagnosed with beta thalassemia ranges from 1.7% to 9.2%. The prevalence is roughly tenfold greater than that observed in the general population. to assess D-dimer level as a marker for hypercoagulability among Egyptian Beta thalassemia patients. we conducted a prospective cross section analytical; we enrolled 30 patients diagnosed with beta thalassemia who are regularly following up in the haematology outpatient clinic, and internal medicine and inpatient wards of Kasr AlAiny hospital. comparison of demographics, clinical characteristics, transfusion therapy, and laboratory findings showed that transfusion dependent patients had significantly higher rate of activated coagulation with p value 0.007, transfusion rate was significantly higher among patients with activated coagulation with p value 0.045, and TLC was significantly higher among patients with activated coagulation compared to those with normal coagulation profile with p value 0.034. hypercoagulability status is significantly associated with splenectomy and transfusion dependence among Egyptian beta-thalassemia patients.

Keywords: D-dimer, hypercoagulability, Beta thalassemia.

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1. Introduction

Patients with β-thalassemia, particularly those with non-transfusion-dependent thalassemia (NTDT), have been found to have a hypercoagulable condition. The main cause of this hypercoagulable condition is mostly due to anomalies in pathological erythrocytes and thrombocytes, which ultimately result in thrombosis or other forms of vascular illness [1]. Individuals diagnosed with β-thalassemia experience heightened platelet aggregation and sustained activation of platelets, as seen by the elevated presence of CD62P (P-selectin) and CD63, which serve as indicators of platelet activation inside the body [2]. β-thalassemia patients have significantly elevated levels of thromboxane A2 and prostacyclin (PG I2) metabolites, which serve as indicators of hemostatic activity, ranging from 4 to 10 times greater than those found in healthy persons [3]. Hypercoagulability in elderly adults with substantial iron excess may be influenced by the coexistence of endocrine or hepatic disorders [4]. There is a lack of comprehensive data on the occurrence of blood clotting episodes in individuals with β-thalassemia. Through a meta-analysis, eight case-control studies were combined to determine that individuals with β-Thalassemia trait have a decreased likelihood of developing arterial cardiovascular disease. Furthermore, the beneficial impact of β-thalassemia trait was limited to male patients and was not detected in female individuals [5]. A comprehensive analysis of 8860 individuals with thalassemia in the Mediterranean region and Iran revealed that thrombotic events, primarily venous in nature, were 4.38 times more prevalent in individuals with non-transfusion-dependent thalassemia (NTDT), namely β-thalassemia intermedia, compared to those with routinely transfused β-thalassemia major [6]. A study revealed that thrombotic events accounted for 14% of deaths in the entire cohort. The primary risk factors for thrombosis in patients with β-thalassemia intermedia have been determined to include individuals above the age of 20, prior splenectomy, and a personal or family history of thrombosis [6]. The Overview on Practices in Thalassemia Intermedia Management Aiming for Lowering Complication Rates Across a Region of Endemicity (OPTIMAL CARE) study evaluated on 584 individuals with β-thalassemia intermedia

in 6 comprehensive care facilities (located in Lebanon, Italy, Iran, Egypt, United Arab Emirates, and Oman) revealed that thrombotic illness, primarily venous, was the sixth most prevalent complication, affecting around 14% of the participants [7]. Thus, we conducted a prospective cross section analytical, to assess D-dimer level as a marker for hypercoagulability among Egyptian Beta thalassemia patients.

2. Patients and methods

We conducted cross section analytical study including 30 Egyptian Beta thalassemia patients attending outpatients' hematology clinic and internal medicine inpatient wards, in Kasr Al Ainy hospital. We enrolled Adult Egyptian patients diagnosed with beta thalassemia patients. We excluded pediatrics age group, Obese patients with BMI ≥30 kg/m2, Current infections or inflammations, Malignant tumors, Females on hormonal contraceptives, Pregnancy and lactation, and Recent trauma or surgery.

2.1 Methodology

Through medical history including age, sex, residency, history of splenectomy, blood transfusion, iron chelating therapy and any previous thrombotic events) was obtained from included patients. A Thorough clinical examination was performed for included patients.
Laboratory tests included complete blood count, CRP, Ferritin level, LDH, liver functions and enzymes were assessed for included patients, and D-dimer.

2.2 Ethical considerations

All patients signed a written informed consent prior participation, study protocol and informed consent were submitted for and approved by local ethical committee of Cairo university. No conflict of interest as regards this research. Every patient had a code number, symbols to the name and address were kept in a special file. Results were used only in scientific publications.

2.3 Statistical analysis

Statistical analysis was conducted using SPSS 22nd edition, categorical variables were presented in frequency and percentages, it was compared between study groups using Chi2 test. Continuous variables were presented in mean, standard deviation, and range. It was compared using Mann Whitney U test between studied groups. Any p value <0.05 was considered significant.

3. Results and Discussion

We enrolled 30 patients diagnosed with beta thalassemia during the period between March 2022 and January 2023 in the hematology department of Kasr AlAiny, Cairo university. We divided the study population into two groups, group I: normal D-Dimer levels, group II: elevated D-Dimer (activated coagulations), comparison of demographics, clinical characteristics, transfusion therapy, and laboratory findings showed that transfusion dependent patients had significantly higher rate of activated coagulation with p value 0.007, transfusion rate was significantly higher among patients with activated coagulation with p value 0.045, and TLC was significantly higher among patients with activated coagulation compared to those with normal coagulation profile with p value 0.034. Otherwise, age, gender, BMI, splenectomy, severity of thalassemia, and other laboratory findings showed no statistically significant differences between groups. The prevalence of thromboembolism among patients diagnosed with β-thalassemia ranges from 1.7% to 9.2%. The prevalence is roughly ten folds greater than that observed in the general population. The presence of prior splenectomy and transfusion experience are recognized as significant risk factors for thromboembolism, particularly in individuals with non-transfusion-dependent thalassemia [8]. The prevalence of the condition is 4.4 times higher in individuals with non-transfusion dependent thalassemia compared to those with transfusion dependent thalassemia. Additionally, the incidence is greater in thalassemia intermedia as opposed to thalassemia major [9]. The prognosis of β-thalassemia has shown a notable improvement in recent decades due to therapeutic advancements. Consequently, individuals residing in regions where disease-specific initiatives providing modern therapeutic access are established encounter a novel epoch of extended longevity that approximates that of the general population [10]. In a prospective cohort study with long follow up period, higher level of D-dimer was reported early post splenectomy compared to pre-splenectomy levels. As well, after 5 years of splenectomy D-dimer levels showed no significant fluctuation and showed no correlation with portal vein thrombosis and blood flow, Elalfy et al., concluded that splenectomy was not associated with portal venous thrombosis either clinically or by duplex sonography [11]. In a single institution study, that included Eighty-three patients with thalassemia, twenty-four (29%) patients with thalassemia intermedia developed deep venous thrombosis during a period of follow up 10 years, most of them were splenectomized, all were males and One patient experienced three thrombotic events. Three patients developed deep vein thromboses of the legs, and 10 patients with superficial thrombophlebitis events of the legs, the remaining were diagnosed with thromboembolic events in lungs, and portal veins [12].

In our study, activated coagulopathy was not significantly associated with splenectomy but it was significantly associated with transfusion dependance and lower rate of transfusion. These findings are inconsistent with Hassan et al., who found that D- Dimer was elevated among patients who underwent splenectomy But, was elevated more with NTDT patients [13]. A review of the literature reports that thromboembolic complications following splenectomy for hematologic diseases occur in up to 10% of patients and may range from portal vein thrombosis (PVT) to pulmonary embolism (PE) and deep vein thrombosis (DVT) [14-16]. We found that high D-dimer level was significantly associated with higher TLC levels. Leukocytes have a crucial function in the development of disseminated intravascular coagulation [17] and multiple organ failure that is linked to sepsis. Tumor necrosis factor-a (TNF-α) and interleukin-1β (IL-1β) stimulate the activation of monocytes, neutrophils, and endothelial cells [18]. Severely and critically sick patients had a higher likelihood of aberrant D-dimer levels compared to moderate and ordinary cases. D-dimer levels are associated with the clinical categorization and can serve as a prognostic indicator for COVID-19 patients [19].

Table 1: Comparison of demographics, clinical characteristics, transfusion therapy, and laboratory findings between studies groups.

		Groups				
		Group I		Group II		
		Mean ±SD	Min-Max	Mean ±SD	Min-Max	P value
Age in years		33.9±11.5	20-60	37.9±12.7	19-65	0.355
		Count	%	Count	%	
Gender	Female	11	68.8%	8	57.1%	0.510
	Male	5	31.3%	6	42.9%	
BMI (kg/m2)		25.3±4.3	19.1-33.2	26.3±6.4	15.8-37.7	0.637
Smoking	No	15	93.8%	14	100.0%	0.341
	Yes	1	6.3%	0	0.0%	
Type of thalassemia	Intermediate	8	50.0%	4	28.6%	0.338
	Major	4	25.0%	7	50.0%	
	Minor	4	25.0%	3	21.4%	
Splenectomy	No	8	50.0%	5	35.7%	0.431
	Yes	8	50.0%	9	64.3%	
Transfusion dependent	No	13	81.3%	7	50.0%	0.007
	Yes	3	18.8%	7	50.0%	
Rate of transfusion		12±18	0-60	4±7	0-24	0.045
Iron chelator	No	10	62.5%	7	50.0%	0.491
	Yes	6	37.5%	7	50.0%	
Hb (mg/dL)		8.8±1.5	6.2-11.6	8.3±1.8	3.2-11.3	0.448
RBCs (10/cc)		4±0.6	3.2-5	3.7±0.9	1.5-5.2	0.525
MCV (ml)		65.6±5.1	56-73	66.9±7.1	58-84	0.854
MCH (mg)		21±2.4	17-25	19.6±2.3	15-24	0.120
TLC (10/cc)		9.5±5.6	4-21	20.6±15.2	4.6-59	0.034
PLT (10/cc)		497.4±424.7	145-1560	559.7±356.6	62-1273	0.580
Ferritin (mg/dL)		1066.6±733.4	209-2987	2234.9±2451.1	504-8822	0.017
LDH (mg/dL)		273.1±96.2	142-450	289.1±197.8	143-933	0.608
ALT (IU)		23.6±11	12-45	34.8±22.4	5-91	0.110
Albumin (gm/dL)		4.13±0.31	3.8-5	3.99±0.5	2.8-4.8	0.448
Creatinine (mg/dL)		0.69±0.25	0.35-1.3	0.87±0.29	0.3-1.2	0.058

Increase TLC among thalassemia patients is believed to be the yield of immune system activation after repeated blood transfusion from different donors [20]. As well, Splenectomized patients were found to have a greater degree of susceptibility to infections and increased risk of septic complications associated with a high mortality rate than non-splenectomized patients, which could explain the dramatic increases in the WBC count in our splenectomized β-thalassemia major patients [21, 22]. We faced few limitations in the current study in the form of small sample size, we only depend on assessment of D-dimer as a marker of hypercoagulability and not considering the role of protein S, C, and other coagulation factors. We finally concluded that hypercoagulability status is significantly associated with splenectomy and transfusion dependence among egyptian beta-thalassemia patients.

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