Original Article

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Quick Response Code:

Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_51_22

Incidence of portal vein thrombosis in patients with β-thalassemia

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Abstract:

BACKGROUND: Portal vein thrombosis (PVT) is one of the important complication postsplenectomies which is considered part of treatment if hypersplenism developed. It can be diagnosed clearly with advance in the quality of X-ray. It is usually associated with prolonged prothrombin time and increased level of D-dimer and alkaline phosphatase. The treatment includes regular blood transfusion and antithrombotic agents.

OBJECTIVES: The aim was to evaluate incidence of PVT in β-thalassemia patients and its association with splenectomy and nonsplenectomy patients.

PATIENTS AND METHODS: A cross-sectional study was conducted at Babylon hereditary blood disease center, for 12 months beginning from the first of June 2020, and ending in June 2021. It includes 150 patients with β-thalassemia, they classified 70 patients with splenectomy as the first group and 80 patients without splenectomy as the second group, their age ranged between 3 and 18 years. Doppler ultrasound was done for all patients by a single radiologist to confirm the presence or absence of thrombosis in the portal vein.

RESULTS: The results showed that 4.6% of patients had PVT and its incidence increased with age older than 10 years, history of splenectomy, high platelets count, high serum ferritin, low Hb, high white blood count. Abdominal pain was the most common symptoms.

CONCLUSION: PVT occurred in 4.6% and the major risk are splenectomy and older 10 years of age. The Doppler ultrasound is considered as simple, noninvasive technique for the detection of thrombus.

Keywords:

Beta-thalassemia, incidence, portal vein thrombosis

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Submission: 01-11-2022
Revised: 27-12-2022
Accepted: 28-12-2022
Published: 02-06-2023

Introduction

Portal vein thrombosis (PVT) is a rare serious complication in thalassemia patients, especially postsplenectomy and it requires a very high index of suspicion to confirm the early diagnosis and urgent therapy to prevent fatal complications such as portal vein hypertension or bowel infarction.[1]

The risk factors include excessive adhesion to endothelial cells, low levels of Protein C and S, increased prothrombin fragment 1.2 which is a marker of thrombin generation, especially in thalassemia intermediate patients, exposure of external membrane of abnormal red blood cells (RBCs) to phosphatidylserine (PTS), increased circulating and aggregated of platelets,[2] Low nitric oxide (NO), due to hemolysis secondary to reduce the arginine level (it causes pulmonary vasoconstriction and subsequently leads to chronic pulmonary thromboembolism).[3] and the presence of cardiac, hepatic, or endocrine dysfunction.[4]

The incidence of PVT in all thalassemia patients is between 1.7% and 9.2%, and it is approximately 10 times higher than the normal population. The incidence was

How to cite this article: Alwataify AS, Aljanabi ZA, Mahdi AH, Jawaad AM. Incidence of portal vein thrombosis in patients with β-thalassemia. Iraqi J Hematol 2023;12:57-63.

Table 1: Distribution of patients of portal vein thrombosis according to variable factors

Study variables	PVT results		Total (*n*=150), *n* (%)	*P*
	Positive (*n*=7), *n* (%)	Negative (*n*=143), *n* (%)		
Incidence	7 (4.6)	143	150	
Gender				
Males	6 (85.7)	86 (60.1)	92 (61.3)	0.249
Females	1 (14.3)	57 (39.9)	58 (38.7)	
Total	7	143	150	
Residence				
Urban	2 (28.6)	56 (39.2)	58 (38.7)	0.707
Rural	5 (71.4)	87 (60.8)	92 (61.3)	
Total	7	143	150	
Splenectomy				
Yes	7 (100.0)	63 (44.1)	70 (46.7)	0.004*
No	0	80 (55.9)	80 (53.3)	
Total	7 (100.0)	143 (100.0)	150 (100.0)	
β-thalassemia type				
β-thalassemia major	5 (71.4)	77 (53.8)	82 (54.7)	0.457
β-thalassemia intermediate	2 (28.6)	66 (46.2)	68 (45.3)	
Total	7	143	150	
Platelets count				
<300	0	57 (39.9)	57 (38.0)	0.045*
≥300	7 (100.0)	86 (60.1)	93 (62.0)	
Total	7	143	150	
SGPT				
Normal	4 (57.1)	131 (91.6)	135 (90.0)	0.022*
Abnormal	3 (42.9)	12 (8.4)	15 (10.0)	
Total	7	143	150	
Drug therapy (Plavix)				
Yes	1 (14.3)	91 (63.6)	92 (61.7)	1.08
No	6 (85.7)	52 (36.4)	58 (38.3)	
Total	7	143	150	
Adherence with chelation therapy				
Regular	3 (42.9)	137 (95.8)	140 (93.3)	<0.001*
Irregular	4 (57.1)	6 (4.2)	10 (6.7)	
Total	7	143	150	
Hb (g/dL)				
<9	6 (85.7)	98 (68.5)	104 (69.3)	<0.01
≥9	1 (14.3)	45 (31.5)	46 (30.7)	

*$P \leq 0.05$ was significant. Fisher-exact test. There was significant association between PVT results and splenectomy, platelets count, SGPT, adherence with chelating therapy and Hb level. PVT=Portal vein thrombosis, SGPT=Serum glutamate pyruvate transaminase, Hb=Hemoglobin

4.4 times more prevalent in nontransfusion-dependent thalassemia patients than ones with transfusion-dependent thalassemia. However, PVT can occur in both patients with alpha- and beta-thalassemia diseases.[3]

Around 4% of the β-thalassemia major (TM) patients and 9.6% of the thalassemia intermediate patients had developed thromboembolic event (TEE). The same group showed 6 years later that 1.1% of β-TM patients in seven Italian centers had thrombosis.[2]

It presents clinically as acute or chronic. While the presence of collateral circulation and partial re canalization with cavernous transformation indicate chronic form. Acute form usually appears within 60 days from hospital investigations and assessment. It may present initially as upper gastrointestinal tract bleeding or bowel ischemia which suggests by increased portal vein progresses as bleeding, abdominal pain, abdominal distention, vomiting, and melena.[5]

Although these complications initially may be without symptoms and they are developed gradually when thrombosis progresses. The easiest way to differentiate it through using imaging study like Doppler ultrasound (to look for the presence or the absence in significant portal collateral) or it can use a computed tomography (CT) of abdomen, angiography, and magnetic resonance imaging (MRI) technique.[6]

The aims of the study were to evaluate the incidence of PVT in β-thalassemia patients and its correlation

Table 2: Distribution of cases of portal vein thrombosis according to mean level of variable factors

Study variables	PVT	*n*	Mean±SD	*t*-test	*P*
Age (years)	Positive	7	13.71±1.11	3.589	0.001*
	Negative	143	11.49±1.61		
Hb (g/dL)	Positive	7	8.35±1.40	2.575	0.011*
	Negative	143	10.79±2.47		
WBC count (10^3 cell/L)	Positive	7	15.64±3.38	3.438	0.0001*
	Negative	143	12.06±2.65		
SGPT (IU/L)	Positive	7	48.11±4.46	8.223	0.0001*
	Negative	143	33.48±4.60		
Blood urea (mg/dL)	Positive	7	16.20±1.65	7.344	0.0001*
	Negative	143	11.15±3.36		
Serum ferritin (μg/L)	Positive	7	1614.29±279.45	3.075	0.003*
	Negative	143	1133.57±408.31		
Platelets count	Positive	7	550±415	1.908	0.01
	Negative	143	250±130		
Time interval from splenectomy (years)					
<3	Positive	7	13.7±11.11	3.589	0.001
	Negative	73	11.29±1.43		
≥3	Positive	0	0	1.809	
	Negative	70	12.42±1.22		

There were significant differences between mean level of (age, Hb level, WBC count, SGPT, blood urea, serum ferritin, platelets count and time interval from splenectomy according to study group) with study patients. Hb=Hemoglobin, WBC=White blood cell, SGPT=Serum glutamate pyruvate transaminase, SD=Standard deviation, PVT=Portal vein thrombosis

with variable factors such as age of patient, type of thalassemia, splenectomy, liver function test (LFT), hemoglobin, platelets, serum ferritin with PVT.

Patients and Methods

A prospective cross-sectional study was conducted at Babylon hereditary blood disease center, Babylon Governorate/Iraq for 12 months beginning from first of June 2020, ending at June 2021. The study was included 150 patients with β-thalassemia (82 as β-TM and 68 patients as β-thalassemia intermediate, 92 males, and 58 females, 70 patients with splenectomy as first group and 80 patients without splenectomy as second group, their age ranged between 3 and 18 years with mean age 12 ± 3 years.

Inclusion criteria

1. β-TM and intermediate
2. Age ranged 3–18 years
3. No other diseases associated with the risk of thrombosis such as hypertension, diabetic mellitus, collagen disease, isolated protein C and S deficiency, and drugs were taken like contraceptive pill or FEIBA.

Before study initiation, this protocol was reviewed and approved by scientific committee of Babylon pediatric branch of Iraqi and Arab board in May 15, 2020.

A written informed consent was obtained from their parents or relative responsible for the patients after explaining detailed of the study.

The questioner was done for every patient as demographic information, history taking as (age, sex, and type of thalassemia), splenectomy or not, concomitant with chelation therapy or not, anti-platelets therapy, time, interval between splenectomy and the incidence of thrombosis. Good history was taken for the symptoms and signs including nausea, vomiting, hematemesis, and hematuria. An accurate examination was done, it includes abdominal examination, vital signs and growth measures (body weight and height).

Five milliliters of blood was aspirated and it sent for many investigations:

- 3 ml added with ethylenediaminetetraacetic acid for (packed cell volume, white blood count [WBC], platelets) and
- 2 ml added with plain tube for LFT, blood urea, serum ferritin).

Platelets count in healthy pediatric between 150 and 450 × 10^9/L, thrombocytopenia refers to a reduction to <150 × 10^9/L and thrombocytosis consider 2 standard deviation (SD) above mean.[7]

Serum ferritin was measured by minividus and its normal level is between 7 and 150 ng/ml.[7]

Doppler U/S was done for all patients by single radiologist to confirm the presence or absence of thrombosis in the portal vein and it is the preferred method of investigation to display any solid hypo or hyperechoic or iso echoic lesion in the portal vein either filling lumen completely or partially or presence as

Table 3: Distribution of portal vein thrombosis patients with splenectomy and nonsplenectomy groups

Study variables	Splenectomy		*P*	Nonsplenectomy		*P*
	Positive (*n*=7), *n* (%)	Negative (*n*=63), *n* (%)		Positive (*n*=0), *n* (%)	Negative (*n*=80), *n* (%)	
Age (years)						
<10	0	0	0.01*	0	40 (50.0)	NS
≥10	7 (100.0)	63 (0.0)		0	40 (50.0)	
Total	7 (100.0)	63 (100.0)		0	80 (100.0)	
Thalassemia type						
β thalassemia major	5 (71.4)	27 (42.9)	0.15	0	50 (38.8)	NS
β thalassemia intermediate	2 (28.6)	36 (57.1)		0	30 (61.2)	
Total	7	63		0	80	
Hb (g/dL)						
<9	6 (85.7)	47 (74.6)	1.000	0	51 (63.8)	NS
≥9	1 (14.3)	16 (25.4)		0	29 (36.2)	
Total	7	63		0	80	
Platelets count						
<300	0	36 (57.1)	0.004*	0	21 (26.2)	NS
≥300	7	27 (42.9)		0	59 (73.8)	
Total	7	63		0	80	
Serum ferritin (ng/mL)		9 (14.3)				
<1000	1 (14.3)	31 (49.2)	0.934	0	14 (17.5)	NS
≥1000-<2500	3 (42.85)	23 (36.5)		0	43 (53.8)	
≥2500	3 (42.85)	63		0	23 (28.7)	
Total	7			0	80	
WBC						
<15,000	2 (28.6)	47 (74.6)	0.022*	0	61 (76.3)	NS
≥15,000	5 (71.4)	16 (25.4)		0	19 (23.7)	
Total	7	63		0	80	

*$P \leq 0.05$ is significant. Fisher-exact test. There was significant association of splenectomised patients of positive cases with age, high platelets count and WBC. NS=Mean nonsignificant, Hb=Hemoglobin, WBC=White blood cell

Table 4: Frequency of signs and symptoms in positive cases of portal vein thrombosis

Signs and symptoms	*n* (%)
Abdominal pain	5 (71.4)
Headache	4 (57.1)
Nausea and vomiting	3 (42.8)
Hematemesis	0
Melena	0
Hematuria	0
Splenomegaly	3 (42.8)
Hepatomegaly	2 (28.5)

echogenic foci in the vessel, collateral of portal vein, dilatation behind part of thrombotic region and cavernous formation in color Doppler sonography. Acute thrombus is characterized by iso or hypoechoic thrombus, enlarged portal vein, no flow inside on Doppler, while the presence of collateral circulation, partial re-canalization with cavernous transformation with or without sign of portal hypertension indicate chronic form.[5]

Data analysis

Statistical analysis was carried out by using SPSS version 25 (Statistical Package for Social Science SPSS The Statistical Package for Social Science, Chicago, Illinois, United State). Categorical variables were presented as percentages and frequencies. Continuous variables are presented as (means ± SD). Student's *t*-test was used to compare the means between the two groups. Fisher's exact test was used to find any association between categorical variables. A $P \leq 0.05$ was considered statistically significant.

Results

Table 1 present the study variable as gender, residence, whether splenectomized or not, type of thalassemia, Hb, platelets count, SGPT and drugs therapy .

A total of 150 patients were included, classified as 92 males, 58 females with positive cases in 7 cases only (4.6%) had PVT (6 males and one female), all of them were splenectomized, platelets of more than 300, and Hb of less than 9 gm/dl .

Table 2 presents of positive cases according to mean level.

It showed that positive cases with mean level (mean age 13.7± 1.11, time of splenectomy of less than 3 years 13.7±

1.11, Hb 8.35± 1.40, platelets count 550± 415 and ferritin level 1614.29 ± 279.45).

Table 3 showed evidence of PVT among splenectomy and not according to study variable factors.

It showed all of positive cases (of more than 10 years, platelets count of more than 300, while they were occurred in 85.7% of Hb less than 9 gm/dl, 85.7% in serum ferritin of more than 1000ng/dl and 71 % with WBC of more than 15000) in splenectomized patients, while we had no positive cases among non splenectomy patients.

Table 4 showed frequency symptoms and signs among cases with PVT.

It appeared that abdominal pain in 71.4%, headache in 57.1%, nausea vomiting and splenomegaly in 42.8%, while hepatomegaly in 28.5% of positive cases.

There was a significant association between PVT results and splenectomy, platelets count, serum glutamic pyruvic transaminase (SGPT), adherence with chelating therapy, and Hb level.

There were significant differences between mean level of (age, hemoglobin level, WBC count, SGPT, blood urea, serum ferritin, platelets count, and time interval from splenectomy according to the study group) with study patients.

There was significant association of splenectomised patients of positive cases with age, high platelets count, and WBC.

Discussion

Hypercoagulable state with subsequent TEE has been recognized as a fundamental feature of the β-thalassemia.[8]

However, the accurate incidence and risk factors of PVT is not clearly detected and even the appearance of symptom are vague.[9,10]

Although splenectomy and low transfusion rate suggested by low Hb of less than 9 gm/dl are leading risk factors in the study.

In this study, PVT developed in 7 cases only (4.6%) and its incidence approximately was similar to other studies done in Iraq (Al-Nagaf Ashraf 5.5%),[6] Iran (Ahvas (3.5%).[9] Babol 3.12%),[10,11] and Lebanon (6.6%),[12] while it is lower than in Greece (8.3).[13]

Also, this study showed that 10% (7/70) of splenectomized thalassemia had PVT, in comparison to zero cases in nonsplenectomized group, this is indicated that β- thalassemia is not inherently prone to thrombosis.[10] While those patients are liable to get thrombosis mainly postsplenectomy due to the increasing risk factors like increment in the number of platelets of more than 300 × 10^9/L in 48.5% of patients, thrombophilia, increased endothelium activation due to excess WBC in 30% and monocyte activation, decrease the production of NO due to the hemolysis (which is secondary to reduce the arginine level[3]).

RBCs may provide a source of negative charge phospholipid lead to a production of thrombosis,[14] in addition there are other risk factors contributed to thrombosis as poor compliance to anti-platelets therapy and irregular iron chelating therapy suggested by 10.34% (6/58) of patients had thrombosis not received anti-platelets prophylaxis and 40% (4/10) patients with irregular chelating therapy compared to 1.08% and 2.14% received Plavix and regular chelating therapy respectively (this can lead to iron overload and platelets aggregation lead to thrombosis). Furthermore, all positive cases appeared within 3 years from the onset of splenectomy (Four cases developed in 1st year, two cases in 2nd year, and only one case diagnosed within 3rd year).

The lower results of the current study could be explained by the younger patients enrolled and Doppler ultrasound was used only for diagnosis of PVT, in contrast to other studies in Italy, they used more advanced investigations such as MRI, CT scan, and angiography, in addition of Doppler ultrasound and older patients were included.

There was no significant difference statistically among both groups of β-TM and intermediate, although the percentage was more in major form 6.09%, compared to intermediate form 2.9% which disagree with other studies showing more among β-thalassemia intermediate as Italy (9.6%)(4%)[2] and Iran (Ahvas(15.3) (2.19%))[9], respectively.[2]

Higher percentage among intermediate form with other studies cannot explain well but it may be associated with different factors including older patients, more platelets activation, more deficiency of protein C and S,[15] in addition that β-thalassemia intermediate has their own RBC in their circulation and persistence abnormality of erythropoiesis associated with increase the number of enucleated RBC.[9] Which reverse to major form they are using more transfusion to maintain Hb above 9 gm/dl associated with min abnormal RBC.

Increased rate of thrombosis in this study was due to low mean level of Hb (8.35 ± 1.40 gm/dl) in positive case, contrast to the mean level of Hb in negative case, it was 10.7 ± 2.47 gm/dl. A low rate of transfusion may

explain by poor compliance mainly in adolescent patients because of the psychological upset, irregular attending at the center because of poor income, or faraway areas and fearing from COVID-19 infection.

PVT risk was increased with increased serum ferritin, leukocytosis, monocytosis and the age of more than 10 years, elevated blood urea, and LFT.

The mean level of serum ferritin was 1614 ± 279.4 ng/ml in positive case compared to 1133.57 ± 408.3 ng/ml in negative case and statistically was significant.

Free iron or unbound iron results from higher ferritin which induced RBC damage through lipid per oxidant or catalyze the formation of reactive O2 species', formation of red cell senescence antigen like PTS making RBC more rigid, deformed, more aggregation adhesion of abnormal RBC to the endothelium.[6]

Also iron overload may enhance ineffective erythropoiesis with secondary release of RBC damage into circulation.[16]

Iron toxicity was linked to hemolysis leading to decline in the production of NO and endothelium damage and vasculopathy, therefore adequate treated of iron toxicity with adequate iron chelating therapy can improve erythropoiesis and more survival of reticulocyte and RBC.[16]

Excess WBC of more than 15,000 with mainly monocyte play important role in highest endothelium activity or injury, increase in macrophage colony-stimulating factor and phagocyte activity toward RBC leading to more damage of RBC and more risk of thrombosis.[14]

There were statistically significant patients with PVT to abnormal LFT SGPT and renal function test (blood urea).

This study shows that 20% of PVT cases with abnormal SGPT (3/15) with mean level was 48.11 ± 4.46, compared to negative case 33.48 ± 4.65.

This indicates that liver impairment associated with high sensitivity to reduce the production of protein C and S resulting in thrombosis risk.[15]

Hypercoagulable state may associate with renal vein thrombosis which results in acute renal injury or sometimes chronic injury. It is characterized by nausea and vomiting, cross hematuria, decrease in urine output confirmed by ultrasound, showing enlarge kidney and decrease echogenicity, decrease or no flow renal vein[15] in spite, we have no case with renal vein thrombosis in the current study.

Abdominal pain appeared in 71.4% (5/7) of positive cases and its severity depend on the state of thrombosis whether it was acute or chronic or on regular or irregular anticoagulant therapy. It follows by headache in 57.1% (4/7 patients), nausea and vomiting in three cases (3/7) 42.85%, while we had no case got hematemesis or hematuria; this is suggested that PVT was usually asymptomatic.

Thrombosis developed in 6.5% of males patients, compared to 1.7% of females and statistically was not significant, this finding agrees with study done in Iran[11] and disagree with other studies done in Iran and Italy.[17,18] Hence, we need more studies with more samples to answer this.[11]

Conclusion

PVT in β-thalassemia patients was 4.6%, this complication required a high degree of suspension for early detection and diagnosis of thrombosis and the major risk factors were splenectomy, low Hb, iron overload, but not related to gender, residence, and thalassemia types. The Doppler ultrasound provides simple, noninvasive technique and slightly accurate for the detection of thrombus in both acute and chronic.

Acknowledgments

The authors would like to thank all the patients, their families, all investigators and medical staff in Babylon hereditary blood disease center participated in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Al-Charrakh HH, Al-Agabi AS. Extensive thrombosis of the portal venous system postsplenectomy for a patient with thalassemia intermedia. Iraq J Hematol 2014;3:132-9.
2. Succar J, Musallam KM, Taher AT. Thalassemia and venous thromboembolism. Mediterr J Hematol Infect Dis 2011;3:e2011025.
3. Natestrinilkul R. Rungrote natestrinilkul :Thromboembolism in Beta – thalassemia disease: DOI: htt://dx.doi.org/10.5772/intechopen.89313 ;2019; p 1-12.
4. Sadeghi S, Ahmad MA, Khalili M. Portal Vein Thrombosis Following splenectomy in B thalassemia major. Iran J Blood Cancer 2016;8:90-1.
5. Ponziani FR, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, *et al.* Portal vein thrombosis: Insight into physiopathology, diagnosis, and treatment. World J Gastroenterol 2010;16:143-55.
6. Abbas Zwain KM, Mohamed SM, Al-Wadness AA, Portal vein thrombosis post splenectomy in thalassemia major patients: International Journal of research in Pharmaceutical Sciences: 2019;10, 3356-68.

7. Scott JP, Montgomery RR. Platelets and Blood Vessel Disease; disease of blood. In: Kliegman RM, Behrman RE, St. Geme JW, Stanton BF, editors. Nelson Text Book 20th edition. ???: Elsevier Saunders; 2019. p. 1666-714.
8. Mavra Vasilopoulou , Christos stafylidis , Marianna Poitou :The thrombotic spectrum of β-Thalassemia ; ElSEVIER ; thrombosis update 2022:100102.
9. Sabbagh A, Keikhaei B, Joorabian M, Behzad MM, Momeni M. Retrospective study of the incidence of portal vein thrombosis after splenectomy in hematological disorders: Risk factors and clinical presentation. Blood Cells Mol Dis 2019;74:1-4.
10. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, *et al.* Splenectomy and thrombosis: The case of thalassemia intermedia. J Thromb Haemost 2010;8:2152-8.
11. Hassan MN, Tahereb GM, Ahmad T, Asghar DA, Reza ED, Ali B, *et al.* Correlation of splenectomy with portal vein thrombosis in beta-thalassemia major. J Pak Med Assoc 2011;61:760-2.
12. Krauth MT, Lechner K, Neugebauer EA, Pabinger I. The postoperative splenic/portal vein thrombosis after splenectomy and its prevention--an unresolved issue. Haematologica 2008;93:1227-32.
13. Alexakis N, Dardamanis D, Albanopoulos K, Ptohis N, Skalistira M, Karagiorga M, *et al.* Incidence, risk factors, and outcome of portal vein thrombosis after laparoscopic-assisted splenectomy in β-thalassemia patients: A prospective exploratory study. J Laparoendosc Adv Surg Tech A 2013;23:123-8.
14. Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. Blood 2002;99:36-43.
15. Abd El Mabood S, Fahmy DM, Akef A, El Sallab S. Protein C and Anti-Thrombin-III deficiency in children with beta-thalassemia. J Hematol 2018;7:62-8.
16. Porter J, Viprakasit V. Iron over load and chelation. In: Cappellini M, Taher A, Porter J, Viprakasit V, editors. In: Guide Line for the Management of Transfusion Dependent Thalassemia. ElSEVIER ; thrombosis update 2022;100102.
17. Soyer T, Ciftci AO, Tanyel FC, Senocak ME, Büyükpamukçu N. Portal vein thrombosis after splenectomy in pediatric hematologic disease: risk factors, clinical features, and outcome; J. of Pediatr. Surg. 2006;41:1899-902.
18. Taher A, Bignamini D, Kattamis A, Cappellini M. Prevalence of thromboembolic events among 8,860 patients with thalassaemia major and intermedia in the Mediterranean area and Iran ; blood 2004;104:3623.