Multi variant analysis of patients with immune thrombocytopenia with paradox of thrombosis

Essam Abd El Wahed Hassan, Hanaa Fathey Abd El Samee, Alia Mohammed Saeed, Mohamed Ali Soliman Saad.
Internal medicine , Hematology and Oncology , Ain Shams university
Corresponding author: Mohamed Ali Soliman Saad, e-mail: m.solimanovic@yahoo.com, 00201008674696

Abstract:

Background and aims: In most patients with ITP, the increased risk of thrombosis is small (relative risk < 2) and not sufficient to influence management. However, more recent studies suggest that certain subpopulations of patients with ITP may be at a significantly higher risk of thrombotic complications. These include patients who have undergone splenectomy, Patients older than 60 years are also at increased risk of thromboembolism, The presence of antiphospholipid antibodies (aPL) has been observed in a substantial proportion of ITP patients and there is increased thrombotic risk associated with thrombopoietin receptor agonists. The aim of this study is to assess the incidence of thrombotic complications in immune thrombocytopenic purpura and to identify the possible risk factors. **Methods:** we performed a retrospective study including 52 patients with primary immune thrombocytopenia ≥18 years old , The patients were selected from Ain Shams University Department of Internal Medicine Clinical Hematology and Oncology Division outpatient clinic, Cairo, Egypt in the period from January 2018 to July 2018. **results:** 10 patients out of 52 developed thrombosis representing one fifth of total cases (19.23 %) 6 of them developed venous thromboembolism and 4 developed arterial thrombosis. All of them were chronic ITP patients (**P-value** 0.038*), 4 patients out of 10 who developed thrombosis were using revolade (TPO RA) (**P-value** 0.016*), the 2 patients who underwent splenectomy developed arterial thrombosis (**P-value** 0.003*), 2 out of the 10 patients who developed thrombosis had hereditary causes of thrombophilia (**P-value** 0.003*). **Conclusion:** there is an increased risk of thromboembolism in patients with primary immune thrombocytopenia especially in those who underwent splenectomy and those using TPO RA.

Key words: ITP, TPO RA, thrombosis, VTE.

introduction: the American Society of Hematology (ASH) defined the abbreviation in common use (ITP) to be Immune Thrombocytopenia (neither Idiopathic nor Purpura) because the pathophysiology is better understood and the majority of both adult and pediatric patients do not present with purpura, even if they have petechiae and bruising [(1)] , It is defined as isolated thrombocytopenia in the absence of other causes of thrombocytopenia ,diagnosed by exclusion, It is characterized by decreased platelets count $< 100 \times 10^9$/L of blood resulting from auto antibody mediated peripheral platelet destruction and suboptimal platelet production [(2)] .

Despite thrombocytopenia, venous and arterial thrombosis cases have been reported in ITP patients. A slightly higher risk of venous thrombosis (maximum of twice the control population) was consistently found in ITP patients who were not treated with TPO-RA. No significant increase of arterial thrombosis risk was apparent [(3)]. However, age, splenectomy, and personal risk factors may put some ITP patients at a particularly higher risk of venous and arterial thrombosis (up to 3-4 times higher than the average control subject). For patients exposed to TPO-RA, there is indirect evidence of a much higher risk of both arterial and venous thrombosis (up to 3-4 times than that reported in nonexposed patients). In these patients, thrombocytopenia itself may not be predictive, as other factors beyond platelet count may be involved. Thromboembolic events in ITP may be due to the disease itself, ITP treatments, or other associated diseases and co morbidities [(4)].

Elevated pro-inflammatory cytokines such as interleukin 6 and interleukin 21, increased level of anti-inflammatory cytokines, such as interleukin 10, and Th17 cells/regulatory T cell imbalance in ITP patients suggest that ITP may be an inflammatory disease. If this is true, inflammatory activity in ITP patients may interfere with various stages of hemostasis through coagulation, inducing thrombosis [(5)]. Platelets Microparticles (MPs) are small vesicles that result from blebbing of the cellular membrane during activation or apoptosis processes. The most prominent property of cell-derived MPs is their procoagulant potential, mainly based on phosphatidylserine exposure and tissue factor expression. An increase in MPs was found in 21% of ITP patients. The higher levels of MPs in ITP patients may point toward a prothrombotic tendency [(6)].

Oral corticosteroid use is associated with greater risk of VTE. Low-dose glucocorticoids (prednisolone daily dose equivalent <5 mg)

carried a twofold increased risk of PE, whereas a high dose of glucocorticoids (prednisolone >30 mg) was associated with a 10-fold increased risk [7]. Venous and arterial thrombosis following administration of IVIG has been reported in patients with various disorders including ITP. Incidence rates of post IVIG thrombosis ranged from 0.6 to 3% per patient, and from 0.15 to 1.2% per treatment course [8]. splenectomy could be associated with increased risk of venous thromboembolism (VTE) and cardiovascular (CV) events such as myocardial infarction and stroke as the spleen plays an important role as a filter for platelets and senescent red blood cells [9]. TPO-R agonists are a recent addition to the treatment of chronic ITP. They promote megakaryocyte differentiation, proliferation, and platelet production. In these patients with ITP treated with TPO-R agonists, a significant number of thromboembolic events have been reported due to the release of platelet materials into the circulation [10].

Other risk factors for thrombosis in ITP patients may include patients with positive aPL which includes anticardiolipin antibodies (aCL), anti-ß2- glycoprotein 1 antibodies, and lupus anticoagulant (LA) [3], Strong genetic risk factors for venous thrombosis that lead to a hypercoagulable state include deficiencies in antithrombin, protein C, and protein S [11]. Acquired risk factors for venous thrombosis include age, surgery, obesity, cancer, pregnancy, hormone-based contraceptives, hormone replacement, antiphospholipid syndrome, acute infection, immobilization, paralysis, long-haul travel, smoking, hospitalization, reduced fibrinolysis, and acquired thrombophilia [12], Risk factors for arterial thrombosis include lifestyle diseases such as diabetes mellitus, hypertension, and hyperlipidemia [13].

The Intercontinental Cooperative ITP Study Group (ICIS) expert group recommended that prophylactic dose LMWH should be administered as usual in ITP patients with high-risk surgery such as orthopedic or cancer surgery, if platelet counts are above 30,000/μL [3] . On the other hand, there have been conflicting reports regarding thromboprophylaxis of aspirin in aPL positive patients. For the treatment of thrombosis in patients with ITP, ICIS expert group recommend that treatment of thrombosis should be started with unfractionated heparin (UFH) at half-therapeutic dose while increasing the platelet count in patients with low platelet counts. If the patient tolerates half-therapeutic UFH for a few days, the dose should be increased to the therapeutic level, and later UFH should be replaced by LMWH or warfarin. With a platelet count of >30,000/μL, LMWH should be started with half-therapeutic

dose. If platelet count is >50,000/μL, full dose of LMWH should be given [14].

Aim of the work: To assess the incidence of thrombotic complications in immune thrombocytopenic purpura and to identify the possible risk factors.

Patients and methods: this study is a retrospective study including 52 patients with primary immune thrombocytopenia ≥ 18 years old, the patients were selected from Ain Shams University Department of Internal Medicine Clinical Hematology and Oncology Division outpatient clinic, Cairo, Egypt in the period from January 2018 to July 2018.

Inclusion criteria: All patients with primary thrombocytopenia ≥18 years old.

All patients will be subjected to the following:

1-Full medical history and physical examination with laying special stress on alarming manifestations supportive for alternative diagnosis.

2-laboratory investigations including: complete blood count(CBC) with differential and manual platelet count , ESR, CRP, auto immune markers for example ANA and anti-phospholipid anti bodies , ± bone marrow aspirate or trephine to exclude all other causes of thrombocytopenia, viral markers, H. Pylori antigen in stool and thrombophilia gene screening by PCR if needed (only on those who developed thrombosis) .

3-Face to face interview questionnaire to assess for history of thrombosis.

Ethical considerations: A written informed consent will be taken from all patients who agree to participate in the study. The study is approved by ethical committee board of Ain Shams university and in accordance with declaration of Helsinki.

Statistical analysis: All statistical analyses were performed using SPSS, version 17.0 (SPSS, Chicago, IL, USA), except for the cumulative incidence analyses, which were carried out with NCSS 2004 (Number Cruncher Statistical System, Kaysville, UT, USA).

Results:

A total number of 52 ITP patients were recruited from Ain Shams University hospital, hematology and oncology out patient clinic, with age

ranging from 18-63 years old (median age 37.5 years). 10 of them were males representing 19.2% of the total number and 42 were females representing 80.7% of the total number (table 1). Patients were classified according to the duration of the disease into newly diagnosed, persistent and chronic. The majority of cases were chronic cases making up 65% whereas the newly diagnosed cases had the least contribution to the cohort with only 5 cases representing 9.62% of the total, persistent cases represent 25% of the total number (figure 1). All were using corticosteroids as first line of treatment, only 8 were using revolade (figure 2) and 2 underwent splenectomy.

Table (1): gender distribution of cases

Sex		
	N	**%**
Male	10	19.23
Female	42	80.77
Total	52	100.00

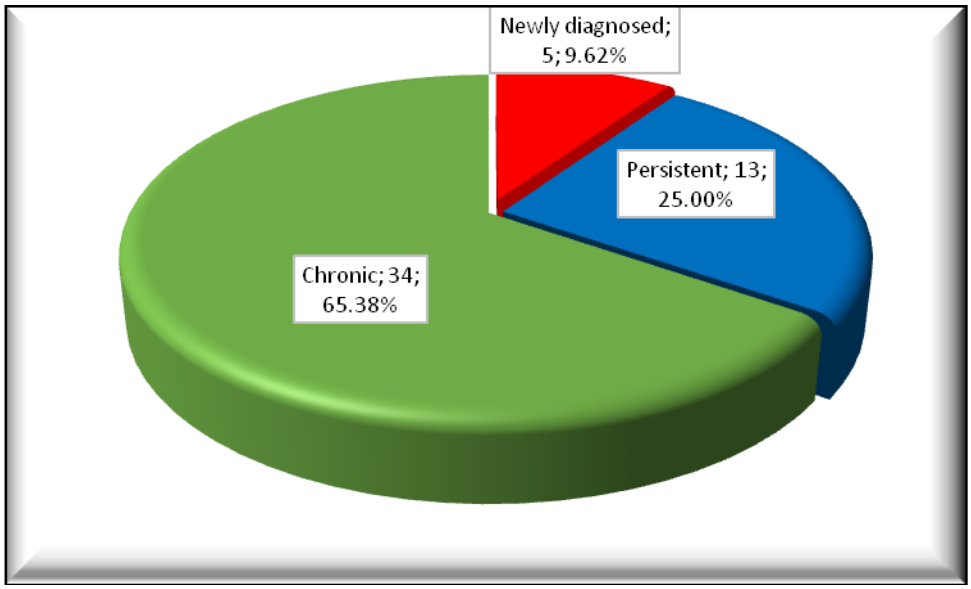

Figure (1): duration of the disease (65.3% were chronic, 25% were persistent and 9.62% were newly diagnosed).

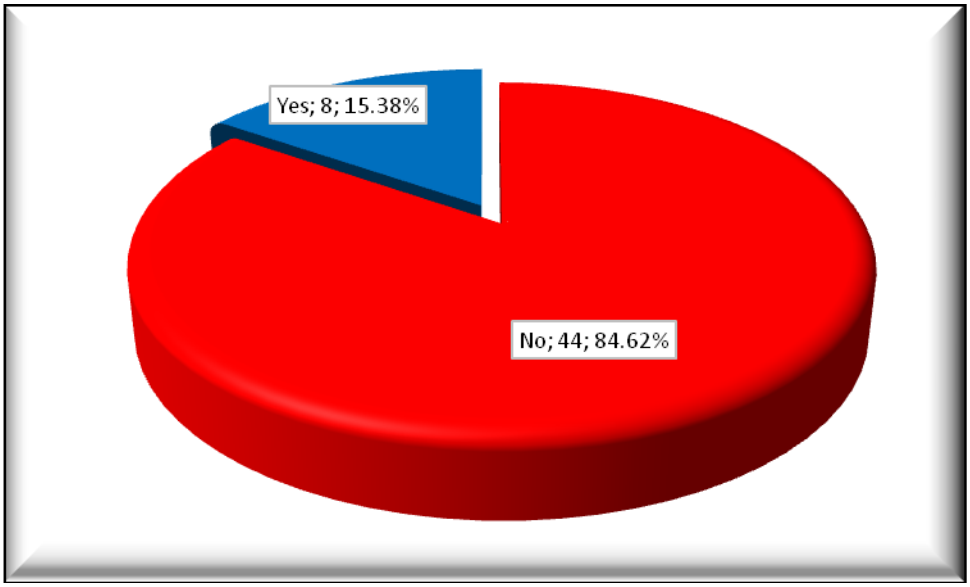

Figure (2): 8 patients out of 52 were using revolade (eltrombopag)(15.38%)

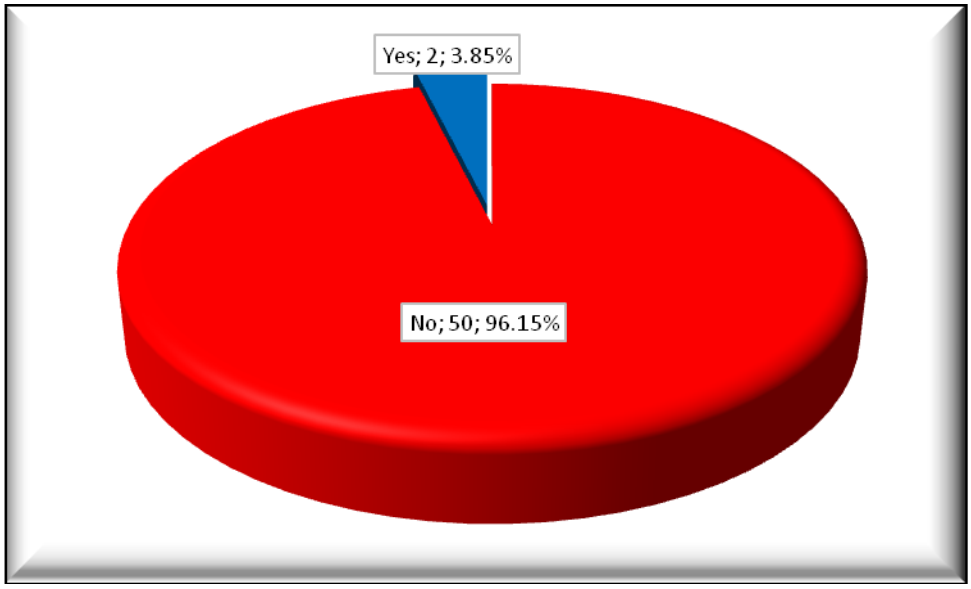

Figure (3): 2 patients out of 52 underwent splenectomy (3.85%)

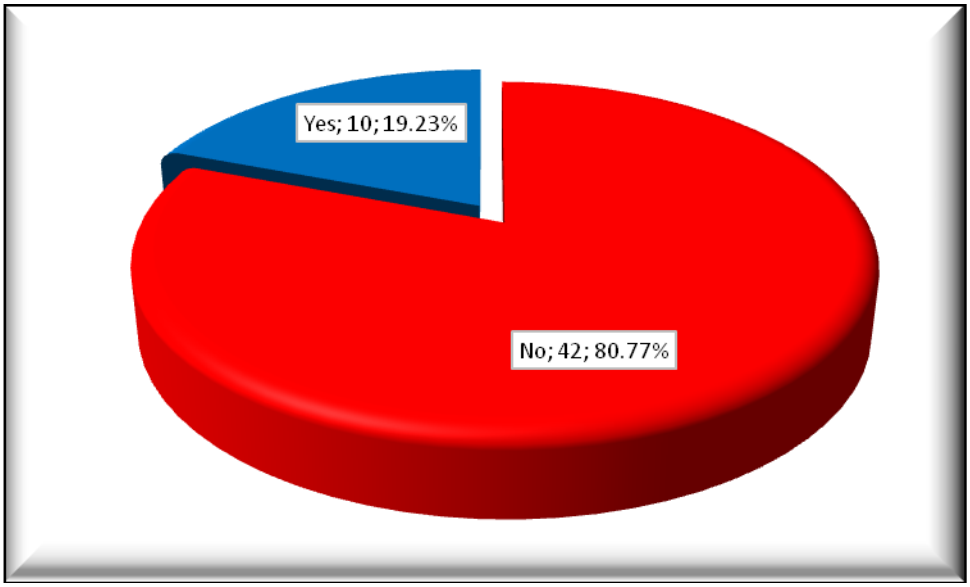

Figure (4): incidence of thrombosis.

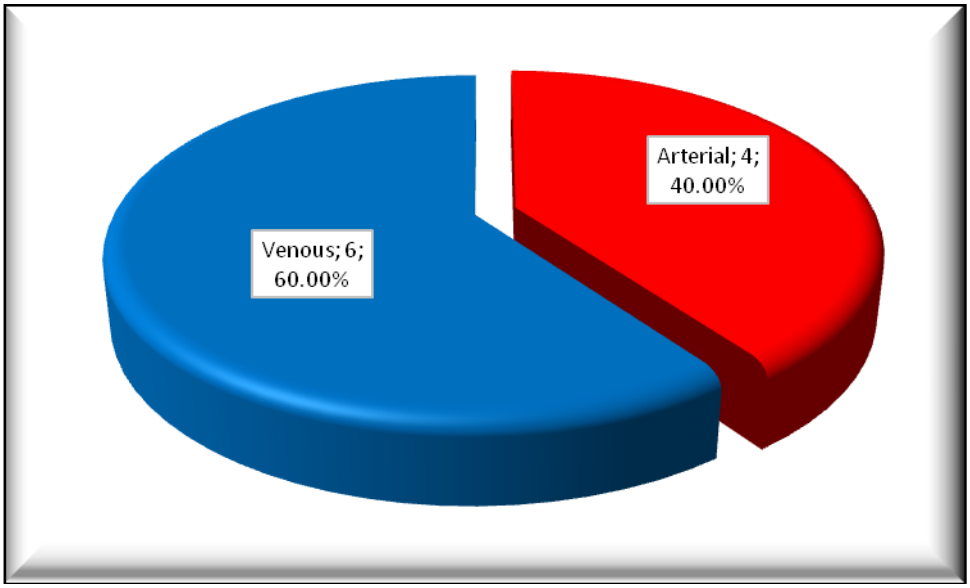

Figure (5) nature of thrombosis.

All the patients who developed both arterial and venous thrombosis were chronic ITP patients as seen in table (2) (statistically significant)

Table (2) relation between the duration of the disease and thrombosis

Diagnosis	History of thrombosis						Chi-Square	
	No		Yes		Total			
	N	%	N	%	N	%	X^2	P-value
Newly diagnosed	5	11.90	0	0.00	5	9.62	6.555	0.038*
Persistent	13	30.95	0	0.00	13	25.00		
Chronic	24	57.14	10	100.00	34	65.38		
Total	42	100.00	10	100.00	52	100.00		

2 patients out of the 10 who developed thrombosis had hereditary causes for thrombophilia as seen in table (3). (Statistically significant).

Table (3): thrombosis and hereditary causes of thrombophilia

Thrombophilia gene screening inf needed	History of thrombosis						Chi-Square	
	No		Yes		Total			
	N	%	N	%	N	%	X^2	P-value
Negative	42	100.00	8	80.00	50	96.15	8.736	0.003*
Positive	0	0.00	2	20.00	2	3.85		
Total	42	100.00	10	100.00	52	100.00		

2 patients who underwent splenectomy developed arterial thrombosis one of them was stroke in young age (36 years old) and it was 8 months after splenectomy and the other developed MI was diabetic for 10 years on oral hypoglycemics and hypertensive for 2 years on calcium channel blockers and it was 3 years after splenectomy as seen in table (4) (statistically significant)

Table(4): splenectomy and thrombosis

Splenectomy	History of thrombosis						Chi-Square	
	No		Yes		Total			
	N	%	N	%	N	%	X^2	P-value
No	42	100.00	8	80.00	50	96.15	8.736	0.003*
Yes	0	0.00	2	20.00	2	3.85		
Total	42	100.00	10	100.00	52	100.00		

4 out of 6 patients who developed venous thromboembolism were on revolade; 2 of them developed pulmonary embolism and the other 2 developed lower limb DVT as seen in Table (5) (statistically significant)

Table (5) : TPO RA and thrombosis

TPO receptor agonists	History of thrombosis						Chi-Square	
	No		Yes		Total			
	N	%	N	%	N	%	X^2	P-value
No	38	90.48	6	60.00	44	84.62	5.763	0.016*
Yes	4	9.52	4	40.00	8	15.38		
Total	42	100.00	10	100.00	52	100.00		

Discussion:

the results obtained from this study showed that there is an increased risk of thrombosis in patients with immune thrombocytopenia; 10 patients out of 52 developed thrombosis representing one fifth of the

total number of cases(19.2%).4 of them developed arterial thrombosis(40% of patients with thrombosis and 7.69% of total number of patients) and 6 developed venous thromboembolism (60% of patients with thrombosis and 11.53% of total number), 2 of them had hereditary causes of thrombophilia , 4 of them were using revolade(TPO RA) and 2 of them underwent splenectomy. It was demonstrated in a study done by ***Francesco R (2017)*** [4] who found that there is A slightly higher risk of venous thrombosis (maximum of twice the control population) in ITP patients, also with ***Norgaard et al. (2012)*** [15] who analyzed Danish National Patient Registry (DNPR) data to evaluate incidence of arterial thrombosis in patients with chronic ITP. A total of 29 arterial thrombosis events were identified in the chronic ITP cohort (379 patients with no prior history of arterial thrombosis) representing (7.65%). ***Aledort et al. (2004)*** [16] found that 10 (5%) of 186 adult patients with ITP reported having 18 thrombotic/ischemic events, 5 events were arterial and 13 were venous.

In our study 34 patients were chronic ITP (≥12 months), 13 patients were persistent ITP (3-12 months) and 5 patients were newly diagnosed (<3 months). In our study the risk of thrombosis was more in patients with chronic ITP (P-value 0.038), this result agrees with the finding reported by ***M. Ruggeri et al. (2014)*** [5] who found that the thrombotic events occurred after a median of 27 months from diagnosis.

In our study 2 patients out of 52 underwent splenectomy as a second line of treatment after failure of the first line, both of them developed arterial thrombosis, one of them was stroke in young age (36 years old) and it was 8 months after splenectomy, the patient was negative for LAC and ACL and hereditary causes of thrombophilia. the other developed MI was diabetic for 10 years on oral hypoglycemics, hypertensive for 2 years on calcium channel blockers and dyslipidemic on Ator 40 with previous attacks of chest pain and it was 3 years after splenectomy (p-value 0.003*) which is significant statistically. ***Vianelli et al. (2013)*** [8] retrospectively analyzed the data of 233 splenectomized ITP patients with a minimum follow-up of 10 years. Eighteen patients (8%) developed 26 thrombotic events, after median of 36 months (range, 0 - 363 months) following splenectomy, which shows that there is increased risk of thrombosis with splenectomy.

In our study 8 patients out of 52 were using TPO RA (eltrombopag) as second line of treatment after failure of the first line, 4

of them develop thrombosis, 2 of them developed pulmonary embolism and the other 2 developed DVT (P-value 0.016) which is significant statistically. ***Catalá-López et al. (2012)*** [17] conducted a meta-analysis of 8 randomized controlled trials of TPO-R agonists (n=1,180 patients) to identify possible risk factors for thromboembolism. The estimated frequency of TEEs was 3.1% (95% CI, 1.8-4.4%) for TPO-R agonists compared with 1.7% (95% CI, 0.3-3.1%) for controls. Patients receiving TPO-R agonists versus controls showed an absolute risk increase of 1.8% (95% CI, -0.1-3.6%) and a 49.3% risk increase of thromboembolism [meta-relative risk (RR)=1.5; 95% CI, 0.7-3.3]. They concluded that TPO-R agonists show a numerically but non- statistically significant trend to increase the occurrence of thromboembolisms compared to controls. ***Catalá-López F et al.(2015)***[18] conducted an updated meta analysis suggested that TPO R agonists are associated with a higher risk of thromboemboembolic events compared with controls.

Conclusion:

there is an increased risk of thromboembolism in patients with primary immune thrombocytopenia especially in those who underwent spelenctomy and those using TPO RA. As thrombopoietin receptor agonists are associated with increased risk of thrombosis, patients using TPO RA as second line of treatment must be monitored for thromboembolism. More studies with more sample size and over longer period of time are needed for better assessment of thrombosis in patients with ITP.

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