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*Research Article*

# Bleeding phenotypes in primary immune thrombocytopenia patients.

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## Abstract

**Background:** Immune thrombocytopenia (ITP) is an autoimmune disease characterized by low platelet counts with or without mucocutaneous bleeding. Like the majority of autoimmune diseases, ITP is an organ-specific disease and abnormalities in the regulation of immune system have been shown to play an important role in the initiation and/or perpetuation of the disease. **Aim of the study:** The aim of this study was to investigate the demographic characteristics, comorbidities associated with chronic medications, bleeding phenotypes in primary immune thrombocytopenia patients according to the chronicity of the disease. **Patients & Methods:** This current study is a cross-sectional hospital based analytic study. It was carried out at the hematology unit/ internal medicine department of El- Minia University Hospital. It was conducted on a group of patients with ITP who were admitted at the hematology unit / internal medicine department or attended the hematology outpatient clinic of El- Minia University hospital since August 2021 till September 2022. It included 33 subjects, where clinical examination, biochemical tests, ITP bleeding score 2016, and ultrasonography were performed on them whose ages range from 16 to 73 years. **Results:** Life threating bleeding is more common in acute conditions than chronic ones with higher bleeding score (p value = 0.03). **Conclusion:** Chronic patients may have protective effect from life threating bleeding but higher associated comorbidities.

**Keywords:** ITP, Bleeding score, life threating bleeding, chronicity.

## Introduction

Immune thrombocytopenia (ITP) is an auto-immune complaint characterized by low platelet counts with or without mucocutaneous bleeding. Like the most of autoimmune conditions, ITP is an organ-specific complaint and abnormalities in the regulation of vulnerable system have been shown to play an important part in the inauguration and/or perpetuation of the complaint.[1]

Autoantibodies acting against platelet glycol-proteins can cause platelet destruction by the monocyte- macrophage system as well as suppress megakaryocyte proliferation and development. Although autoreactive B lympho-cytes concealing antiplatelet antibodies are considered as the main defect, substantial sub-stantiation suggests that a generalized dysfun-ction of autoreactive "T" cells is the critical immunopathological cause of ITP and the antiplatelet autoantibodies are under the control of T cells and the cytokines they produce. Still

vulnerable thrombocytopenia (ITP) is a significant clinical problem due to chronicity, treatment cost, circumstance substantially in, youthful, and fairly poorer quality of life. And utmost of the current remedial agents for ITP don't break the abecedarian problems that are responsible for the morning and progression of the autoimmune process.

In practice, the presence of bleeding should mandate whether or not treatment and platelet transfusion are demanded because numerous cases, can be safely managed with observation alone. Also Guiding principles for the operation of ITP, grounded on the bleeding threat are (1) Decide when treatment is demanded and when it can safely be withheld; (2) for cases with habitual ITP, use the least poisonous treatment at the smallest cure; (3) exigency treatment of severe thrombocytopenia- associated bleeding requires combination remedy; and (4) early aggressive remedy may affect in durable platelet count responses.[2]

## Aim of the work

Our study question: is the chronicity of the disease can be a guide to the possibility of fair platelet function which may not impose an emergency or combination treatment?

## Patients and methods

**Study design:**

This current study is a cross-sectional hospital-based study. It was carried out at the hematology unit / internal medicine department of El Minia University Hospital in collaboration with clinical pathology department of El Minia University.

It was conducted on a group of patients with ITP who were admitted at the hematology unit / internal medicine department or attended the hematology outpatient clinic of Minia University hospital.

The present study included 2 groups of patients:

- Group 1 (acute patients): included 5 patients of primary ITP, the duration of disease is within 3 months (3 males, 2 females) whose ages range 16-82 years
- Group 2 (persistent patients): included 5 patients of primary ITP the duration of disease is within 3-12 months (2 males, 3 females) whose ages range19-56 years
- Group 3 (chronic patients): included 23 patients of primary ITP the duration of disease is more than 12 months. (1 male, 22 females) whose ages range 19-73

***All patients fulfilled the following criteria:***

**Inclusion Criteria:**

- Primary immune thrombocytopenia**.**
- Both sexes are included.

**Exclusion criteria:**

1- Secondary causes of ITP as systemic lupus erythematous (SLE), viral infections (HIV, hepatitis B or C infections)
2- Other underlying medical diseases that may cause thrombocytopenia as:
- malignancy
- megaloblastic anemia
- aplastic anemia
- lymphoproliferative disorders
- liver disease
- renal impairment
- pregnancy

3- Organomegally and/or lymphadenopathy.
4- Recent history of vaccination or any offending drug preceding the onset of disease.
5- Recent evidence of bacterial infection.

***All patients were subjected to the following;***

Detailed history taking, clinical examination, routine and specific laboratory investigations in addition to radiological assessment.

## Results

This current study is a cross-sectional hospital based analytic study. It was carried out at the hematology unit / internal medicine department of El- Minia University Hospital in collaboration with clinical pathology department of El- Minia University.

It was conducted on a group of patients with ITP who were admitted at the hematology unit / internal medicine department or attended the hematology outpatient clinic of El-Minia

University hospital since August 2021 till September 2022.

**The patients are classified into 3 groups according to disease duration:**

- Group 1 (acute patients): included 5 patients of primary ITP, the duration of disease is within 3 months (3 males, 2 females) whose ages range 16-82 years
- Group 2 (persistent patients): included 5 patients of primary ITP the duration of disease is within 3-12 months (2 males, 3 females) whose ages range19-56 years
- Group 3 (chronic patients): included 5 patients of primary ITP the duration of disease is more than 12 months. (1 male, 22 females) whose ages range 19-73

**Table (1): comparison between the studied groups regarding demographic and clinical characteristics:**

| Data | | Acute (G1) No=5 | Persistent (G2) No=5 | Chronic (G3) No=23 | p |
|---|---|---|---|---|---|
| [1]Age (year) | Range | 16-82 | 19-56 | 16-73 | 0.8 |
| | Mean ±SD | 38.2±26.6 | 32.6±16.8 | 36.3±15.4 | |
| [2]Sex | Male | 3(60%) | 2(40%) | 1(4.3%) | **0.005*** |
| | Female | 2(40%) | 3(60%) | 22(95.7%) | |
| [2]Smoking | No | 4(80%) | 4(80%) | 23(100%) | 0.08 |
| | Yes | 1(20%) | 1(20%) | | |
| [2]Comorbidities | No | 5(100%) | 4(80%) | 18(78.3%) | 0.9 |
| | HTN | 0 | 0 | 1(4.3%) | |
| | DM | 0 | 0 | 1(4.3%) | |
| | HTN&DM | 0 | 1(20%) | 3(13%) | |
| [1]Disease duration (month) | Range | 1-24 | 4-60 | 18-240 | **0.01*** |
| | Mean ±SD | 1.6±0.5 | 19±23.1 | 80.6±66.3 | |

G refers to group number, SD standard deviation. HTN hypertension…DM diabetes mellitus. Bold values mean significant results.. 1- Quantitative data by Kruskal Wallis testn 2- Qualititative data by Chi square.

Table (1) shows that females are more in G3 rather than G1 with statistical significance (no. (%) of 22(95.7%) vs 2(40%); p value 0.005). Also, HTN and DM are increased in G2 more than G1 but without statistical significance. (no. (%) of 1(20%) vs 0; p value 0.9). Also, disease duration is significantly increased in G3 more than the other 2 groups (Mean ± SD of 80.6±66.3 vs 19±23.1 vs 1.6±0.5; p value 0.01)

**Table (2): comparison between the studied groups regarding Laboratory data**

| Data | | Acute (G1) No=5 | Persistent (G2) No=5 | Chronic (G3) No=23 | P |
|---|---|---|---|---|---|
| **[1]HB** | **Range** | 6-15 | 12-15 | 10-15 | 0.1 |
| | **Mean ±SD** | 10.8±3.2 | 13.4±1.1 | 12.6±1.3 | |
| **[1]TLC** | **Range** | 5-21 | 6-16 | 5-20 | 0.3 |
| | **Mean ±SD** | 11.2±6.05 | 11.4±3.7 | 9.1±4.1 | |
| **[1]PLT** | **Range** | 6000-580000 | 37000-260000 | 6000-484000 | 0.9 |
| | **Mean ±SD** | 193000±242276.7 | 122200±78070.1 | 131739.1±117516.8 | |
| **[1]PC** | **Range** | 76-100% | 78-100% | 72-100% | 0.9 |
| | **Mean ±SD** | 89.04±12.03% | 91.4±9.3% | 91.6±8.9% | |
| **[1]PTT** | **Range** | 1-24 | 4-60 | 18-240 | 0.7 |
| | **Mean ±SD** | 1.6±0.5 | 19±23.1 | 80.6±66.3 | |
| **[1]ESR 1st** | **Range** | 12-70 | 7-40 | 10-70 | 0.7 |
| | **Mean ±SD** | 32.4±23.6 | 22.4±12.8 | 26.3±18.1 | |
| **[1]ESR 2nd** | **Range** | 22-140 | 14-80 | 20-140 | 0.7 |
| | **Mean ±SD** | 65.4±47.4 | 44.8±25.7 | 51.8±34.6 | |

G refers to group number, SD standard deviation. HB hemoglobin, TLC total leucocytic count, PLT platelet, PC prothrombin concentration, PTT partial thromboplastin time, ESR erythrocyte sedimentation rate. Bold values mean significant results.

1- Quantitative data by Kruskal Wallis test

Table (2) shows that TLC is increased in G1 compared to G2 and G3 but without statistical importance (5-21 Mean ± SD of (11.2±6.05) vs 6-16 (11.4±3.7) vs 5-20 (9.1±4.1); p value 0.3). PLT count in G1 is lower than G2 but without statistical significance. (Mean ± SD of 193000± 242276.7 vs 122200±78070.1; p value 0.9). PC shows no statistical difference between the 3 groups. However, PTT is prolonged in G3 more than G2 and G1 but without statistical difference (Mean ± SD of 80.6±66.3 vs 19±23.1 vs 1.6±0.5; p value 0.7). ESR 1st and 2nd hours are elevated in G1 more than G2 and G3 (Mean ± SD of 32.4±23.6 vs 22.4±12.8 vs 26.3±18.1; p value 0.7) but also without statistical significance.

**Table (3): comparison between the studied groups regarding Bleeding phenotype:**

| | | Acute (G1) No=5 | Persistent (G2) No=5 | Chronic (G3) No=23 | p |
|---|---|---|---|---|---|
| [2]Type of bleeding | Epistaxis and vaginal bleeding | 0 | 0 | 1(4.3%) | 0.06 |
| | Bleeding per gum | 0 | 0 | 2(8.7%) | |
| | Bleeding piles | 0 | 1(20%) | 0 | |
| | Ecchymosis | 0 | 3(60%) | 2(8.7%) | |
| | Ecchymosis and vaginal | 0 | 0 | 1(4.3%) | |
| | Ecchymosis. Epistaxis | 1(20%) | 0 | 0 | |
| | Epistaxis | 2(40%) | 1(20%) | 5(21.7%) | |
| | Epistaxis, subdural hematoma | 1(20%) | 0 | 0 | |
| | Hematuria | 1(20%) | 0 | 0 | |
| | Petechiae | 0 | 0 | 4(17.4%) | |
| | petechiae, vaginal | 0 | 0 | 1(4.3%) | |
| | vagina bleeding. ecchymosis | 0 | 0 | 1(4.3%) | |
| | Vaginal bleeding | 0 | 0 | 5(21.7%) | |
| | Vaginal ecchymosis | 0 | 0 | 1(4.3%) | |
| [1]ITP bleeding score | Range<br>Mean ±SD | 2-17<br>7±5.8 | 1-5<br>2±1.7 | 1-6<br>2.9±1.5 | **0.03*** |

G: refers to group number, SD standard deviation,
1 - Quantitative data by Kruskal Wallis test
2- Qualititative data by Chi square.

**Table (3)** shows that epistaxis is increased in G1 more than G2 and G3 with tendency towards statistical significance (no. (%) of 2(40%) vs 1(20%) vs 5(21.7%); p value 0.06). ecchymosis is increased in G2 as well more than other 2 groups with tendency towards statistical significance (no. (%) of 3(60%) vs 2(8.7%) vs 0; p value 0.06). also, intracerebral hematoma occurred in G1 more than G2 and G3 with tendency towards statistical significance. (no. (%) of 1(20%) vs 0 vs 0; p value 0.06). As regarding ITP bleeding score 2016 it is significantly elevated in G1 more than G2 and G3. (Mean ± SD of 7±5.8 vs 2±1.7 vs 2.9±1.5; p value 0.03)

## Discussion

Primary immune thrombocytopenia (ITP) is defined as an acquired autoimmune disorder characterized by an isolated thrombocytopenia (blood platelet count $<100 \times 10^9$/l) in the absence of other causes that may be accompanied with thrombocytopenia.[3]

Secondary ITP occurs in about 20% of patients where thrombocytopenia is associated with other diseases such as chronic infections, including Hepatitis C virus and human immunodeficiency virus (HIV and patients with other autoimmune disorders [e.g. systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and antiphospholipid antibody syndrome].[4] The phases of ITP are differentiated into three time-based subsets. Newly diagnosed ITP occurs within 3 months of diagnosis, persistent ITP is present between 3 and 12 months post diagnosis and chronic ITP is ITP lasting >12 months.

Classically, ITP is primarily due to immune-globulin G (IgG) autoantibodies opsonizing the individual's platelets, resulting in markedly enhanced Fc receptor (FcR)-mediated phago-cytosis and destruction by macrophages in the

reticuloendothelial system within the spleen. It is now also known that these autoantibodies can mediate megakaryocyte inhibition/destruction both *in vitro* and *in vivo*.[5]

Additionally, T cell-mediated peripheral platelet destruction and megakaryocyte destruction/ inhibition in the bone marrow have been shown to lead to thrombocytopenia. [6]

The pathophysiology of ITP is undoubtedly becoming more complex and, in future, it will be important to try and sort out the predominant initiating and perpetuating factors that are responsible for the disease.

Also, in the current study the patients were assessed according to ITP bleeding score 2016 and our results showed that bleeding score is significantly increased in refractory patients with lower platelet counts more than responders (4.3±3.6 vs 2.5±1.6; p value 0.05) which is consistent with that study of chen.[7] and [8] but our results showed that ecchymosis is increased in refractory patients more than responders but without significant difference (no. (%) of 4(25)% vs 1(5.9%); p value 0.5). Also, epistaxis is more noticed in refractory patients more than responders but also without significant difference (no. (%) of 2(40%) vs 4(23.5%); p value 0.5).

Where, as life threatening bleeding as intracranial bleeding is low in both groups but more in refractory patients than responders (no. (%) of 1(6.2%) vs 0; p value0.5)

So the most prevalent form of bleeding among ITP patients was skin bleeding followed by epistaxis which is consistent with the study of kohli and his colleagues 2019.[9] without dangerous bleeding, this confirms that ITP is rarely associated with life-threatening bleeding events as stated by Michel and his colleagues.[10]

## Conclusion

Chronic patients may have protective effect from life threating bleeding but higher associated comorbidies.

## Recommendations

- Assessment of platelet function in different stages of the disease is important to guide therapy.
- Increasing sample size and multicenter analysis for validation of our results

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