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Factors Predicting the Outcomes of Second-Line Therapy for Chronic Immune Thrombocytopenia

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Abstract

Background: Immune thrombocytopenia (ITP) is an autoimmune disease, has been defined as isolated thrombocytopenia driven on by platelet destruction via platelet autoantibodies and/or T-cell-mediated damage. Applying guidelines in resource-constrained healthcare systems is usually difficult as a result of the limitations associated with the use of more expensive second-line therapeutics. Determining the predictors of therapeutic response is a much-needed step in the management of ITP.

Aim of Study: This study aimed to identify the outcome of second-line therapy together with the predictive factors for response in patients with persistent and chronic ITP.

Patients and Methods: This retrospective cohort multicentric study was carried out by retrieving data from the records of 103 ITP patients who attended hematology units and outpatient clinics at Kasr Al-Ainy School of Medicine and Maadi Armed Forces Medical Complex between January 2015 and December 2021.

The data included demographic data, clinical findings, diagnostic procedures, including BM examination (if performed) and therapeutic interventions. The collected data were statistically analyzed.

Results: The complete response (CR) rate to splenectomy was 30% at 6 months and 17% at 12 months postsurgery, whereas the CR rate for TPO-RAs treatment was 33.3% at 6 months after the onset of treatment. In patients treated with splenectomy, CR was significantly associated with previous use of mycophenolatemofetil. Previous diagnosis and H. pylori infection eradication were linked to increased CR in patients receiving TPO-RAs treatment.

Conclusion: Treatment of ITP patients with TPO-RAs might lead to a better CR than that after splenectomy at 6 months. Further studies are recommended to explore the possible predictors of response.

Key Words: *Immune thrombocytopenia – TPO-RAs – Splenectomy.*

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Introduction

IMMUNE thrombocytopenia (ITP) is an autoimmune disorder marked by isolated thrombocytopenia. At presentation, patients may remain asymptomatic, alternatively, they may exhibit mild mucocutaneous bleeding or progress to life-threatening hemorrhage. ITP may occur as a primary disorder, or it may be secondary to other diseases. The pathophysiology of ITP is intricate and multifactorial and remains not fully understood. ITP results from platelet destruction via platelet autoantibodies

List of Abbreviations:

BM	: Bone marrow.
CBC	: Complete blood count.
CD	: Cluster of differentiation.
CR	: Complete response.
GP	: Gylycoprotein.
H. pylori	: Helicobacter pylori.
HBV	: Hepatitis B virus.
HCV	: Hepatitis C virus.
HRQoL	: Health-related quality of life.
ITP	: Immune thrombocytopenia.
IVIG	: Intravenous immunoglobulin.
PCT	: Plateletcrit.
PR	: Partial response.
RTX	: Rituximab.
SPSS	: Statistical Packagefor the Social Sciences.
TPO	: Thrombopoietin.
TPO-RAs	: Thrombopoietin receptor agonists.

and/or T-cell-mediated damage. In addition, impaired platelet production by bone marrow-resident megakaryocytes has also been implicated [1].

Every aspect of a patient's life, including everyday activities, emotional well-being, energy level, fatigue, and productivity at work, may be impacted by ITP and its treatment, impairing HRQoLand ultimately making itlower in patients with ITP compared to healthy controls [2].

The most frequently utilized first line therapy in ITP patients is glucocorticoids. After starting the medication, the platelet count usually rises within two days. Corticosteroids initially produce a response in at least 80% of patients with ITP; however, the majority of the initially responding patients relapse when the corticosteroids are tapered [3].

With respect to corticosteroid-dependent or corticosteroid-unresponsive patients, according to the most recent guidelines, Patient preferences should be given priority while selecting a treatment protocol. Determinants of patient's preference usually include treatment effectiveness and potential complications [1].

Intravenous immunoglobulin (IVIG) was initially introduced in the 1980s for ITP treatment. IVIG is believed to prevent the reticuloendothelial system from Fc-mediated destruction of antibody-coated platelets. Following IVIG administration, the platelet count typically rises within 48 hours. To demonstrate the possible predictors of IVIG response, Peng et al., found that patients without anti-GPIb-IX autoantibodies had a significantly higher response rate (80%) compared to those with anti-GPIb-IX autoantibodies (36.4%) [4].

A paradigm shift in the management of ITP was signalled by the 2008 launch of thrombopoietin-receptor agonists (TPO–RAs). With simple daily or weekly medication, patients have a very good chance of maintaining their platelet count.

Both Romiplostim and eltrombopag bind to the thrombopoietin receptor, changing its conformation, and triggering the JAK2/STAT5 pathway. This leads to an increase in megakaryocyte progenitor proliferation and platelet production. In a study conducted by Forsthye and colleagues, they analyzed and compared bleeding-related adverse events in patients treated with romiplostim and eltrombopag. The study found that patients receiving eltrombopag experienced significantly fewer bleeding episodes compared to those treated with romiplostim (7% versus 14%) [5].

Rituximab (RTX), an anti-CD20 monoclonal antibody, reduces antiplatelet antibody production by depleting CD20+ B cells. Compared with glucocorticoids or placebo, RTX achieves a considerably greater incidence of complete response at six months (46.8% vs. 32.5%) in nonsplenectomized patients with ITP. The one-year response rate was 38%, with over half of the patients having response that lasted for at least a year. Hammond et al., reported that in ITP patients who were treated with rituximab after an unsuccessful splenectomy, the response rate was 70% after two years [6].

The spleen is the main site for the production of autoantibodies and the destruction of platelets. For ITP patients who fail to respond to corticosteroids, splenectomy is considered the gold standard treatment. The absence of dependable predictors for splenectomy outcomes hinders the ability to identify patients who are most likely to benefit from the procedure. Determining the primary platelet sequestration site can assist in predicting the effectiveness of splenectomy. Although autologous platelet scanning can pinpoint the sequestration site, it is technically challenging and not easily available [7].

The intricate and diverse nature of ITP pathophysiology, coupled with the varying phases of the disease, makes its treatment particularly challenging. Resistance to therapy, relapses, and refractoriness are common obstacles, highlighting the critical need for reliable predictors of therapeutic response to improve the management of ITP patients [8].

The main objectives of this study were to evaluate the outcomes of second-line therapy in patients with persistent and chronic ITP and to identify the predictive factors of response to second-line treatment on the basis of published consensus recommendations. The ultimate goals are to individualize treatment according to patient and disease characteristics and to develop a model that aids in therapeutic decision-making on the basis of identified predictors of response, which is hoped to be realized in future research.

Patients and Methods

Study design: This retrospective cohort study included 103 patients who had persistent and chronic ITP who were recruited from both the Kasr Al-Ainy School of Medicine and the Maadi Military Complex Clinical Hematology Clinic.

The inclusion criteria were Egyptian patients aged 18 years and older diagnosed with persistent or chronic immune thrombocytopenia (ITP). Diagnosis was made based on isolated thrombocytopenia after ruling out other causes such as drug-induced thrombocytopenia and primary bone marrow failure syndromes.

The exclusion criteriaincluded patients under 18 years of age and those with thrombocytopenia secondary to bone marrow failure syndromes (e.g., aplastic anemia) or myelodysplastic syndromes.

Data collection: We retrieved data from the records of ITP patients attending Hematology Units and Outpatient Clinics at Kasr Al-Ainy School of Medicine and Maadi Armed Forces Medical Complex between January 2015 and December 2021. Patients with incomplete medical records, including those lacking follow-up laboratory results, were not included in the study.

A provisional diagnosis of immune thrombocytopenic purpura (ITP) is established when the patient's history, physical examination, complete blood count, and peripheral blood smear evaluation do not indicate alternative causes of thrombocytopenia. Bone marrow examination is conducted when necessary.

Using the standard terminology, the disease stages were categorised as follows: Newly diagnosed ITP if the interval between the onset of clinical symptoms and diagnosis was less than three months, persistent ITP if it had been diagnosed for three to twelve months, and chronic ITP if it had persisted for more than twelve months.

The data retrieved from records included demographic data (age, sex, occupation, and special habits such as smoking), clinical findings (comorbid factors, bleeding history, and complications), diagnosis-related data (date of diagnosis, complete blood count (CBC), and other diagnostic procedures, including BM examination if performed), and therapeutic interventions (transfusion of blood components and the details of medical and/or surgical treatment offered).

Confidentiality of the data: There are no conflicts of interest associated with this research. Each patient was assigned a code number, and identifying information such as their name and address was stored in a secure file. The results were solely used for scientific publications.

Ethical consideration: The study proposal received approval from the Ethical Review Committee of the Armed Forces College of Medicine (IRB: 37; meeting date: 25 September 2021; serial number: 75). The research was conducted in alignment with the Revised Helsinki Declaration on Biomedical Ethics. The data confidentiality policy was properly followed.

Statistical analysis:

The data were entered and coded into a Microsoft Excel spreadsheet and analyzed using SPSS version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Categorical variables were presented as frequencies (n) and percentages (%) and analyzed using Fisher's exact test. For normally distributed variables, the mean and standard deviation were used, while the median and interquartile range were applied to non-normally distributed quantitative variables, and the number and percentage were reported for qualitative variables. Nonparametric data were analyzed using the Mann-Whitney test for non-normally distributed quantitative variables and the chi-square test for qualitative variables. Correlation analysis was conducted to assess linear relationships between variables. Statistical comparisons were two-tailed, with a p-value ≤ 0.05 indicating a significant difference, a p-value <0.001 indicating a highly significant difference, and a p-value >0.05 indicating no significant difference **[9,10]**.

Results

Demographics and clinical characteristics of the study population:

This study included 103 patients who were diagnosed with chronic and persistent ITP.

The mean age was 36.75±12.63 years. A total of 54.4% of the patients were female, whereas 45.6% were male. The mean body mass index of the patients was 27.54±3.69 kg/m^2.

Among the presenting features of ITP in our patients, cutaneous bleeding was present in all the patients (100%), whereas gastrointestinal tract bleeding was the least common type of bleeding, accounting for only (6) 5.8% of all cases. The distribution of other types of bleeding in the studied patients was as follows: (50) 48.5% with oral bleeding, (35) 34% with epistaxis, (26) 25.2% with hematuria, and (31) 55% of the females included in the study had uterine bleeding.

The laboratory parameters of the studied population are shown in Table (1). Among our patients, HCV, HBV, and H. pylori were positive in 10 (9.7%), 4 (3.9%), and 4 (3.9%) patients, respectively.

Abdominal ultrasound (US) and bone marrow findings: Abdominal US revealed splenomegaly in 64 patients (62.1%), hepatomegaly in 8 patients (8.3%) and hepatosplenomegalyin 6 patients (5.8%).

Treatment modalities: The treating physician selected the initial treatment based on the patients' clinical history, comorbidities, and the severity of bleeding. The treatment protocol options included corticosteroids in the form of prednisone (1mg/kg) prescribed to nearly all patients (102) (99%), whereas high-dose dexamethasone (40mg/day for four consecutive doses) was given to 71 patients (68.9%). Other treatment modalities used included mycophenolatemofetil, cyclosporin and intravenous immunoglobulins (Table 2).

Following relapse, steroid failure, or steroid dependence, second-line treatment modalities were used. Splenectomy was performed in 20 patients (19.4%), and TPO agonists were used in 54 patients

(52.4%). Thirty-five patients (64.8%) received eltrombopag, 8 patients (14.8%) received romiplostim, and 11 (20.4%) received both drugs. Rituximab was prescribed to 10 patients (9.7%).

Treatment response:

A complete response (CR) was specified as having a platelet count of at least 100×10^9/L.

A partial response (PR) was defined as a minimumtwofold increase in the PLT and PLT between 30×10^9/L and 100×10^9/L with no bleeding symptoms.

No response was defined as a platelet count less than 30×10^9/L, a less than two fold increase in the PLT or bleeding symptoms.

Splenectomy:

At 6 months postoperatively, the mean platelet count (PLT) was $116.95 \pm 52.82 \times 10^3$/µL. Six patients (30%) achieved complete remission (CR), and 14 patients (70%) achieved partial remission (PR). At 12 months postsurgery, 3 patients (15%) achieved complete response, 14 patients (70%) achieved partial response, and 3 patients (15%) achieved no response. (Table 3).

TPO agonists:

At 6 months after treatment with TPO agonists, the mean platelet count was $110.95 \pm 59.23 \times 10^3$/µL. Complete remission (CR) was documented in 33.3% of patients, while 66.7% of patients attained partial response. (Table 3).

Correlations of patient characteristics with second-line treatment response:

Tables (4,5) present the characteristics related to demographics and clinical factors of patients who responded at 6 and 12 months following splenectomy. In patients treated with splenectomy, CR was significantly associated with previous use of mycophenolatemofetil. The use of mycophenolate was more prevalent in the CR group at both 6 and 12 months postoperatively (*p*-values = .000 and .003, respectively).

Table (6) shows the characteristics related to demographics and clinical factors of patients who responded to TPO agonist treatment at 6 months. At 6 months post-TPO treatment, there was no significant difference between patients who achieved CR and those who achieved PR regarding the demographic characteristics of the patients except for age. The laboratory parameters did not significantly differ between the 2 groups except for ALT levels, which were higher in the CR group (*p*-value .015). Previous diagnosis and H. pylori infection eradication were associated with increased CR (*p*-value .042).

Table (1): Laboratory parameters in the studied cohort of patients (N = 103).

Parameter	Mean ± SD	Range
Hb (g/dl)	10.13±1.6	7 – 13
TLC ($x10^3$/µL)	7.1±1.85	4.5 – 13
PLT ($x10^3$/µL)	18.35±6.94	4 – 39
Creatinine (mg/dl)	0.981±0.200	0.4 – 1.4
Urea (mg/dl)	34.3±8.69	19 – 63
ALT (U/L)	60.3±16.1	22 – 96
PT (sec)	12.45±2.59	0 – 16
Test	**Number**	**Percent**
ANA:		
Negative	103	100%
Positive	0	–
Anti-DNA:		
Negative	103	100%
Positive	0	–
LA:		
Negative	103	100%
Positive	0	–
ACL IgM :		
Negative	103	100%
Positive	0	–
ACL IgG:		
Negative	103	100%
Positive	0	–
B2 glycoprotein:		
Negative	103	100%
Positive	0	–
HCV:		
Negative	93	90.3%
Positive	10	9.7%
HBV:		
Negative	99	96.1%
Positive	4	3.9%
HIV:		
Negative	103	100%
Positive	0	–
H. pylori:		
Negative	99	96.1%
Positive	4	3.9%

Hb : Hemoglobin.
TLC : Total leukocyte counts.
PLT : Platelet.
ALT : Alanine transaminase.
PT : Prothrombin time.
ANA : Antinuclear antibody.
ACL : Anticardiolipin.
H. Pylori : Helicobacter Pylori.
HCV : Hepatitis C virus.
HBV : Hepatitis B virus.
HIV : Human immunodeficiency virus.

Table (2): Treatment modalities used in the treatment of ITP in the studied patients (n = 103).

Treatment	Number	Percent
Prednisone	102	99%
Dexamethasone	71	68.9%
Danazol	0	–
Mycophenolate	47	45.6%
Cyclosporin	33	32%
Cyclophosphamide	0	–
Azathioprine	0	–
Anti D	0	–
IVIG	7	6.8%
Rituximab	10	9.7%
Splenectomy	20	19.4%
TPO – agonist	54	52.4%
Tranexamic Acid	2	1.9%
Platelets transfusion	100	97.1%

IVIG: Intravenous immunoglobulin.
TPO : Thrombopoietin.

Table (3): Characteristics of response in patients treated with Splenectomy and TPO – Ras.

Treatment type	Response after 6 months	Count (Percent)
	PLT ($x10^9$/L) Mean ± SD	116.95±52.82
	Complete response	6 (30%)
	Partial or no response	14 (70%)
Splenectomy	Response after 12 months	Count (Percent)
	PLT ($x10^9$/L) Mean ± SD	94.18±21.46
	Complete response	3 (15%)
	Partial response	14 (70%)
	No response	3 (15%)
	Eltrombopag	35 (64.8%)
	Eltrombopag and Romiplostim	11 (20.4%)
	Romiplostim	8 (14.8%)
	PLT after 6 months (Mean ± SD)	110.95±59.23
	Response after 6 months	Count (Percent)
TPO - RAs	Complete response	18 (33.3%)
	Partial response	36 (66.7%)

Plt : Platelet.
TPO-Ras: Thrombopoietin receptor agonist.
SD: Standard deviation.

Table (4): Demographic and clinical characteristics of patients with the response 6 months following splenectomy.

Parameter	CR (n=6)	PR (n=14)	Test	*p*
Age (years):				
Mean ± SD	22.5±4.5	24±5	0.704@	0.49
BMI (kg/m^2):				
Mean ± SD	26.8±2.8	27±3.7	0.241@	0.812
Gender:				
Female	2 (33.3%)	3 (21.4%)	0.318#	0.573
Male	4 (66.7%)	11 (78.6%)		
Smokers	1 (16.7%)	4 (28.6%)	0.317#	0.573
Hb (g/dl)	9.9±0.9	10±1.8	0.33@	0.745
TLC ($x10^3$/µL)	6.7±1.5	6.7±1.5	0.055@	0.957
PLT ($x10^3$/µL)	18.7±8.7	17±6.7	0.386@	0.704
Creatinine(mg/dl)	0.9±0.2	0.9±0.24	0.102@	0.92
Urea (mg/dl)	40±7	33.8±7.8	1.7@	0.107
ALT (U/L)	46±14	59.6±15.6	1.73@	0.101
PT (sec)	13±1.4	12.1±3.7	0.738@	0.47
HCV:				
Negative	6 (100%)	13 (92.9%)	0.502#	0.502
Positive	0	1 (7.1%)		
HBV:				
Negative	6 (100%)	13 (92.9%)	0.541#	0.502
Positive	0	1 (7.1%)		
H. pylori:				
Negative	6 (100%)	14 (100%)	–	–
Positive	0	0		
US:				
Normal	1 (16.7%)	4 (28.6%)	1.26#	0.869
Hepatomegaly	1 (16.7%)	1 (7.1%)		
Splenomegaly	4 (66.7%)	9 (64.3%)		
BM:				
No Megakary-ocytosis	0	0	–	–
Megakaryocytosis	6 (100%)	14 (100%)		
Treatment:				
Prednisone	6 (100%)	14 (100%)	–	–
Dexamethasone	5 (83.3%)	12 (85.7%)	0.019#	0.891
Mycophenolate	6 (100%)	2 (14.3%)	12.9#	.000**
Cyclosporin	2 (33.3%)	5 (35.7%)	0.01#	0.919
IVIG	1 (16.7%)	0	2.46#	0.117
Rituximab	0	4 (28.6%)	2.14#	0.143
Tranexamic Acid	2 (33.3%)	5 (35.7%)	0.01#	0.919
Platelet transfusion	6 (100%)	13 (92.9%)	0.451#	0.502

Hb : Hemoglobin.
TLC : Total leukocyte counts.
PLT : Platelet.
ALT : Alanine transaminase.
PT : Prothrombin time.
ANA: Antinuclear antibody.
H. Pylori: Helicobacter Pylori.
HC V: Hepatitis C virus.
HBV: Hepatitis B virus.
BM : Bone marrow.
US : Ultrasound.
IVIG: Intravenous immunoglobulin.
: Fisher exact test.
@: Mann Whitney U test.
**: High statistical significance .

Table (5): Demographic and clinical characteristics of patients with the response 12 months after splenectomy.

Parameter	CR (n=3)	PR (n=14)	Test	*p*
Age (years):				
Mean ± SD	24.33±5.51	24.21±5.16	.036@	.972
BMI (kg/m^2):				
Mean ± SD	27.15±3.12	27.26±3.71	.145@	.887
Gender:				
Female	2 (66.7%)	3 (21.4%)	2.44#	.119
Male	1 (33.3%)	11 (78.6%)		
Smokers	0	4 (28.6%)	1.12#	.290
Hb (g/dl)	10±1.3	10±1.8	.026@	.980
TLC (x10^3/µL)	8±0.9	6.7±1.5	1.28@	.219
PLT (x10^3/µL)	18±4.5	17±6.7	.243@	.811
Creatinine (mg/dl)	1±0.3	0.9±0.24	.563@	.582
Urea (mg/dl)	43.7±5.7	33.8±7.8	2.03@	.061
ALT (U/L)	48±17.9	59.6±15.6	1.11@	.283
PT (sec)	13±1.1	12.1±3.7	.557@	.586
HCV:				
Negative	3 (100%)	13 (92.9%)	.486#	.784
Positive	0	1 (7.1%)		
HBV:				
Negative	3 (100%)	13 (92.9%)	.228#	.824
Positive	0	1 (7.1%)		
H. pylori:				
Negative	3 (100%)	14 (100%)	–	–
Positive	0	0		
US:				
Normal	1 (33.3%)	4 (28.6%)	2.09#	.719
Hepatomegaly	0	1 (7.1%)		
Splenomegaly	2 (66.7%)	9 (64.3%)		
BM:				
No Megakaryocytosis	0	0	–	–
Megakaryocytosis	3 (100%)	14 (100%)		
Treatment:				
Prednisone	3 (100%)	14 (100%)	–	–
Dexamethasone	2 (66.7%)	12 (85.7%)	1.63#	.202
Mycophenolate	3 (100%)	2 (14.3%)	8.7#	.003**
Cyclosporin	2 (33.3%)	5 (35.7%)	.977#	.323
Rituximab	0	4 (28.6%)	.390#	.533
Tranexamic Acid	2 (66.7%)	5 (35.7%)	.977#	.323
Platelet transfusion	3 (100%)	13 (92.9%)	.228#	.633

Hb : Hemoglobin.
TLC : Total leukocyte counts.
PLT : Platelet.
ALT : Alanine transaminase.
PT : Prothrombin time.
ANA: Antinuclear antibody.
H. Pylori: Helicobacter Pylori.
HC V: Hepatitis C virus.
HBV: Hepatitis B virus.
BM : Bone marrow.
US : Ultrasound.
IVIG: Intravenous immunoglobulin.
: Fisher exact test.
@: Mann Whitney U test.
**: High stataistical significance .

Table (6): Demographic and clinical characteristics of patients with the response 6 months following TPO agonist treatment

Parameter	CR (n=18)	PR (n=36)	Test	*p*
Age (years):				
Mean ± SD	24.9±5.1	29.1±7.5	2.17@	.034*
BMI (kg/m^2):				
Mean ± SD	27.1±3.42	27.7±3.6	.539@	.592
Sex:				
Female	11 (61.1%)	12 (33.3%)	6.3#	.178
Male	7 (38.9%)	24 (66.7%)		
Smokers	3 (16.7%)	8 (22.2%)	.228#	.463
Hb (g/dl)	9.9±1.5	10.5±1.7	1.05@	.298
TLC (x10^3/µL)	7.4±1.9	6.6±1.6	1.6@	.116
PLT (x10^3/µL)	17.9±5.9	19.8±8.1	.857@	.395
Creatinine (mg/dl	0.9±0.2	0.9±0.2	.217@	.829
Urea (mg/dl)	33.9±8.3	31.5±6.9	1.13@	.265
ALT (U/L)	61.9±12.2	51.3±15.7	2.52@	.015*
PT (sec)	12±3	12.9±1.5	1.42@	.162
HCV:				
Negative	16 (88.9%)	35 (97.2%)	1.59#	.451
Positive	2 (11.1%)	1 (2.8%)		
HBV:				
Negative	17 (94.4%)	36 (100%)	2.04#	.333
Positive	1 (5.6%)	0		
H. pylori:				
Negative	16 (88.9%)	36 (100%)	4.15#	.042*
Positive	2 (11.1%)	0		
US:				
Normal	4 (16.7%)	10 (27.8%)	33#	<0.001**
Hepatomegaly	0	2 (5.6%)		
Splenomegaly	12 (66.7%)	0		
Hepatosplenomegaly	2 (66.7%)	24 (66.7%)		
BM:				
No Megakaryocytosis	1 (5.6%)	3 (8.3%)	–	–
Megakaryocytosis	17 (94.4%)	33 (91.7%)		
Treatment:				
Prednisone	18 (100%)	35 (97.2%)	.509#	.475
Dexamethasone	13 (72.2%)	26 (72.2%)	–	–
Mycophenolate	10 (55.6%)	16 (44.4%)	.593#	.315
Cyclosporin	6 (33.3%)	13 (36.1%)	.041#	.544
IVIG	2 (11.1%)	3 (8.3%)	.110#	.546
Rituximab	1 (5.6%)	6 (16.7%)	1.31#	.245
TA	9 (50%)	13 (36.1%)	.959#	.386
Platelet transfusion	18 (100%)	35 (97.2%)	.509#	.475

Hb : Hemoglobin.
TLC : Total leukocyte counts.
PLT : Platelet.
ALT : Alanine transaminase.
PT : Prothrombin time.
ANA: Antinuclear antibody.
H. Pylori: Helicobacter Pylori.
HC V: Hepatitis C virus.
HBV: Hepatitis B virus.
BM : Bone marrow.
US : Ultrasound.
IVIG: Intravenous immunoglobulin.
: Fisher exact test.
@: Mann Whitney U test.
* : Statistically significant.
**: High statistical significance .

Discussion

Immune thrombocytopenic purpura is an acquired condition of autoimmune origin, marked by a decrease in platelet counts leading to an elevated risk of bleeding. Treatment is generally recommended for individuals with ITP who have platelet counts below 30×10^9/L, even if they do not exhibit bleeding symptoms. This recommendation is derived from observational research studies and predictive models indicating an increased bleeding risk in older patients with platelet counts under 30×10^9/L. However, in the absence of additional risk factors, most patients do not encounter significant bleeding episodes even when platelet counts are at or above 20×10^9/L *[8]*.

In our study, the initial treatment was selected based on the patient's clinical history, comorbidities, and bleeding severity. Among the treatment modalities used for treatment, the most common was prednisone in 99% of patients, whereas dexamethasone was used in 68%, TPO in 52%, mycophenolate in 45%, and cyclosporin in 32%. Platelet transfusion was given as supportive therapy in 97% of patients. Following relapse, steroid failure, or steroid dependence, second-line therapeutic modalities were used.

Thrombopoietin receptor agonists (TPO-RAs), rituximab, and splenectomy are commonly utilized as second-line treatments for immune thrombocytopenic purpura. TPO-RAs, such as eltrombopag and romiplostim, along with rituximab, have demonstrated that response rates have varied within a wide range 50% to 80%. However, the proportion of patients maintaining a sustained response after discontinuing these medications is relatively low, between 10% and 25% *[11]*.

In the present study, twenty patients (19.4%) underwent splenectomy; at the 6-month follow-up, 6 (30%) patients achieved complete response (CR), and 14 (70%) patients achieved partial response (PR). Follow-up at 12 months postsurgery revealed that only 3 (17.6%) patients achieved CR, and 14 (82.4%) patients achieved PR. A comparison between patients with partial response and complete response at 6 and 12 months after splenectomy revealed that there was no notable difference was observed between the groups regarding age or sex.

Supe et al., noted that younger age offers a benefit in achieving treatment success *[12]*, whereas Kwag et al., reported no significant relationship *[13]*.

ITP occurs more frequently in females, with a female-to-male ratio is 2:1. While sex hormones may contribute to greater susceptibility to the disease, their impact on treatment response remains unclear. Andrès and coworkers performed a gender-related analysis of 225 ITP patients and reported no statistically significant difference in outcome or treatment response regarding sex *[14]*. Ozkok et al., investigated the effect of sex on the response rate following splenectomy and reported no difference in the response rate between males and females. Although the time to loss of response tended to be shorter in females than in males, this difference was not statistically significant *[15]*.

The present study demonstrated the absence of association between smoking and the splenectomy response in ITP patients. We could not find studies in the literature that assessed the direct relationship between smoking and the splenectomy response in ITP patients. However, Ghahremanfard et al., concluded that in healthy individuals, cigarette smoking leads to substantial impacts on platelet morphological indices. In comparison to nonsmokers, individuals who smoke exhibited a significantly greater mean platelet count and lower plateletcrit (PCT) values *[16]*.

Our study revealed no notable difference in baseline laboratory data between patients who achieved CR and those who achieved PR following splenectomy. In agreement with our results, Simsek and Dogan revealed that there was no significant difference between patients with CR and those with no response with respect to complete blood count findings *[17]*.

Our study also revealed that there was no statistically significant difference between patients who achieved CR and those who achieved PR with respect to the incidence rates of HCV, HBV, and H. pylori. A study by Huang et al., concluded that HCV was associated with a higher incidence of thrombocytopenia than was HBV. Risk factors for developing thrombocytopenia vary with virus type and severity. Patients with HCV had a greater mean spleen index and a higher prevalence of splenomegaly compared to HBV patients (15.79 vs. 13.91, $p<0.001$; 23.47 vs. 12.88%, $p<0.001$) *[18]*.

No significant difference was observed between patients who achieved CR and those who achieved PR in terms of the bone marrow findings at both 6 and 12 months. However, Guan et al., suggested that megakaryocytosis at diagnosis could predict a better response to splenectomy. The disagreement may be due to differences in sample size and inclusion criteria *[19]*.

This study revealed a statistically significant difference in mycophenolate use between the two groups. The use of mycophenolate was more prevalent in the CR group than in the control group at both 6 and 12 months post-CR (*p*-values of .000 and .003, respectively).

Mycophenolatemofetil is generally used as a second-line treatment for ITP, as it is less costly than many alternative treatments. Despite the lack of published data from randomised, controlled tri-

als, evidence from retrospective research suggests that mycophenolatemofetil is effective with response rates ranging from 50 to 80%. However, the platelet response usually takes 4–6 weeks **[20,21].**

Mycophenolatemofetil is active against autoreactive T and B cells and has demonstrated efficacy in refractory ITP, including in patients resistant to glucocorticoids, indicating additional mechanism of action **[22].**

In our study, TPO-RA was used in 54 patients (52%), eltrombopag was used in 35 patients (64.8%), romiplostim was used in 8 patients (14.8%), and 11 patients (20.4%) were on eltrombopag and romiplostim. We found that the mean PLT after 6 months was 110.95±59.23, with 18 patients (33.3%) showing CR and 36 patients (66.7%) showing partial or no response. At 6 months post-TPO treatment, there was no statistically significant difference among patients who achieved CR and those who achieved PR with respect to age, sex, smoking status, or occupation.

In agreement with our results, a study by Newland and colleagues showed that the CR rate in adult ITP patients treated with romiplostim was 32%. The study results also demonstrated that age and sex were nonsignificant predictors of the treatment response rate. Our results are supported by those of Lozano and coworkers, who reported that age, sex, and comorbidities were not significantly associated with the treatment-free responses of TPO-RAs in ITP patients **[23].**

In the present study, H. pylori infection was documented in 4 patients. In patients receiving TPO agonists, H. pylori status was significantly correlated with CR. Immune thrombocytopenia and H. pylori infection have been linked in a number of studies. Through molecular mimicry, surface antigens of H. pylori cytotoxin-associated gene A (Cag A) can trigger host immunological response targeting platelet receptors. In a study by Cheng et al., patients infected with CagA+ H. pylori produce a higher number of GPIIb/IIIa antibody-producing B cells compared to those infected with CagA- H. pylori and healthy individuals **[24].**

Eradicating H. pylori in ITP patients is commonly achieved with A regimen consistingamoxicillin, clarithromycin, and a proton-pump inhibitor. This regimen has low toxicity, short treatment duration and high eradication rate of approximately 80%. In addition, it avoids the use of immunosuppressive drugs **[25].** In a systematic review of the literature, Arnold et al., showed that patients with an H. pylori infection had a 14.5-fold increased chance of experiencing a platelet count response after eradication therapy (51.2 vs. 8.8%) **[26]**. Another comprehensive review of the literature by Stasi et al., demonstrated that 696 patients achieved overall response of 50.3% with a mean CR of 42.7% **[27].** This can also be supported by Mahmoud and coworkers, who revealed that effective eradication of H. pylori has been shown to positively influence platelet recovery and sustain platelet counts in individuals with chronic hepatitis C virus-associated thrombocytopenia **[28].**

Study limitations:

In our study, the data were retrieved from medical records, which serve as invaluable sources of data. However, a key limitation of this source of data, as experienced in our study, is incomplete or missing data. This limitation restricted the number of patients who could be included in the analysis.

Conclusion:

The CR rate for those receiving splenectomy as a secondary therapy was 30% at 6 months and 17% at the 12-month follow-up. Among TPO-RA-treated patients, the CR rate was 33.3% at 6 months from the onset of treatment. Among all the studied factors, of the patients who received splenectomy, CR was associated with only the use of mycophenolate, whereas in the TPO-RA treatment group, CR was significantly associated with increased ALT levels and a positive test for H. pylori infection. However, these associations need to be investigated further in larger number of patients.

Recommendations:

Further comparative studies with bigger sample sizes and longer follow-up periods are needed to more completely understand the predictors of response to second-line treatment in ITP patients. Additionally, proper H. pylori testing and eradication remain crucial aspects of ITP management.

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العوامل التى تتنبأ بنتائج علاج الخط الثانى لنقص الصفائح الدموية المناعى المزمن

نقص الصفائح الدموية المناعى هو أحد أمراض المناعة الذاتية، وقد تم تعريفه على أنه نقص الصفائح الدموية الناجم عن تدمير الصفائح الدموية عن طريق الأجسام المضادة للصفائح الدموية و/أو تلف الخلايا T. عادةً ما يكون تطبيق المبادئ التوجيهية فى أنظمة الرعاية الصحية المحدودة الموارد أمرًا صعبًا نتيجة للقيود المرتبطة باستخدام علاجات الخط الثانى الأكثر تكلفة. يعد تحديد تنبؤات الاستجابة العلاجية خطوة مطلوبة بشدة فى علاج مرض نقص الصفائح الدموية المناعى.

نحن نهدف إلى تحديد نتائج علاج الخط الثانى مع العوامل التنبؤية للاستجابة لدى المرضى الذين يعانون من نقص الصفائح الدموية المستمر والمزمن.

تم إجراء هذه الدراسة متعددة المراكز بأثر رجعى من خلال استرجاع البيانات من سجلات ١٠٣ مرضى نقص الصفائح الدموية الذين حضروا وحدات أمراض الدم والعيادات الخارجية فى كلية طب القصر العينى والمجمع الطبى للقوات المسلحة بالمعادى بين يناير ٢٠١٥ وديسمبر ٢٠٢١.

وتضمنت الدراسة البيانات الديموغرافية، والنتائج السريرية، والإجراءات التشخيصية، بما فى ذلك فحص النخاع العظمى (إذا تم إجراؤه) والتدخلات العلاجية. وتم تحليل البيانات التى تم جمعها إحصائياً.

النتائج: كان معدل الاستجابة الكاملة لاستئصال الطحال ٣٠٪ بعد ٦ أشهر و١٧٪ بعد ١٢ شهرًا من الجراحة، فى حين كان معدل الاستجابة الكاملة لعقارات منبهات مستقبلات الثرومبوبيوتين ٣٣,٣٪ بعد ٦ أشهرمن بداية العلاج.

الاستنتاج: علاج مرضى نقص الصفائح الدموية بعقارات منبهات مستقبلات الثرومبوبيوتين قد يؤدى إلى الاستجابة الكاملة أفضل من تلك بعد استئصال الطحال. يوصى بإجراء مزيد من الدراسات لاستكشاف التنبؤات المحتملة للاستجابة.