



RESPONSE TO STEROID TREATMENT AND FACTORS AFFECTING TREATMENT
RESPONSE AMONG ADULTS WITH IMMUNE THROMBOCYTOPENIA AT SPHMMC,
ADDIS ABABA.

Haymanot Assefa (MD, Internal Medicine Resident)

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Advisors: Simegnew Handebo (MPH, Assistant Professor of public health)

Helen Hilawi (MD, Assistant professor of Internal Medicine, Hematologist)

Tirumebet Mezgebu (MD, Assistant professor of Internal Medicine,
Hematologist)

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Acronyms and Abbreviations

ASH: American Society of Hematology

ITP: Immune Thrombocytopenia

IV: Intra venous

NSAID: Non-steroidal anti-inflammatory drugs

SPHMMC: Saint Paul Hospital Millennium Medical College

TB/HIV: Tuberculosis/Human immunodeficiency virus

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Abstract

Background: Immune Thrombocytopenia is one of the common acquired hematologic conditions which affects an average of two in 100,000 adults per year. Evidence shows that majority of patients who have indications for treatment will be started on steroids as a first line treatment and good response rates have been documented. However, results varied from one setup to another and studies done in our country are very limited. But it is important to have local data in order to implement effective treatment strategies and apply standardized clinical practice based on local factors that significantly and directly affect our patients. It can also be used as the basis for future planning, development of institutional protocols, and guidelines to manage immune thrombocytopenia.

Objectives: The objective of the study was to assess the response to treatment and factors associated among adult Immune thrombocytopenia patients on follow-up at St. Paul Hospital Millennium Medical College

Methods: A facility-based analytical cross-sectional study was conducted on 118 adult patients with Immune thrombocytopenia, who visited the outpatient department of St. Paul hospital Hematology clinics from September 2021 up to October 2022 G.C. Data was collected through an interview-administered structured questionnaire from all patients who visited the hospital during the data collection time. The collected data was entered into Epi Info and analyzed using SPSS version 21 for Windows. The Chi-square test was used to determine the association between dependent and independent variables. Multinomial logistic regression was done to identify factors associated with response to steroid treatment. Adjusted Odds Ratio (AOR), 95% CI for AOR and p-value of less than 0.05 were used to declare statistical significance.

Result: A total of 118 patients' data were participated in this study. For having platelet count above 30,000 at 6 months relative to non-response, the relative risk for response at 12 months would be expected to increase by 10.4 given the other variables are held constant (AOR = 10.4 (1.12,96.62) , 95% CI ,p- Value = .039). Similarly, patients with platelet counts above 100,000 at six months were more likely than no response at six months to have remission over no response at 12 months (AOR=7.33(1.28,42.07, 95% CI, p-Value=.025). In addition, patients with treatment duration between 6 months and 1 year were less likely than those with duration above 2 years to have Remission relative to No response (AOR= .04 95% CI= 0.004-0.409 , p- Value= .007).

Conclusion and recommendations: Significant factor associated with response and remission of ITP at 12 months was found to be achieving sustained response at six months of therapy. This is consistent with findings in other countries. The findings can implicate the general pattern of response in our country but conclusions cannot be drawn about long term remission since the study duration was short and other studies suggest a high relapse rate. Thus, further studies need to be done to assess long term outcomes.

1. Introduction

1.1 Background of the study

Immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenic purpura, is an immune-mediated acquired disease of adults and children characterized by a transient or persistent decrease of the platelet count and depending upon the degree of thrombocytopenia, increased risk of bleeding(1).

The definition was recommended by the international working group on ITP in 2009 stating that the term “idiopathic,” preferring “immune,” to emphasize the immune-mediated mechanism of the disease and to choose “primary” (as opposed to idiopathic) to indicate the absence of any obvious initiating and/or underlying cause. The term “purpura” was felt inappropriate because bleeding symptoms were absent or minimal in a large proportion of cases. The acronym ITP (now proposed to stand for immune thrombocytopenia) was preserved because of its widespread and time-honored use and taking into account its utility for literature use (2, 3).

ITP is caused by a complex process involving antibodies that react with glycoproteins expressed on platelets and megakaryocytes leading to impaired production and shortened survival of circulating platelets. It affects all age groups with bleeding being the commonest presentation. Bleeding manifestations range from minor mucocutaneous bleeding to severe and life-threatening GI and intracranial hemorrhage. Studies also suggest fatigue and paradoxical thrombosis occur in a significant number of patients (4).

ITP can be Primary where no apparent cause is found, which is further classified into newly diagnosed, Persistent ITP, and Chronic depending on the duration of illness. Secondary ITP occurs due to systemic infection, exposure to drugs, or other autoimmune diseases. So baseline investigations include but are not limited to Peripheral morphology, blood type, and direct antiglobulin test (DAT) viral markers for Hepatitis and HIV and bone marrow examination, when indicated has to be done on all patients to exclude other underlying causes (5).

For patients with a confirmed diagnosis of primary ITP and who indicate treatment, first-line treatment options include corticosteroids (methylprednisone, dexamethasone, and prednisone), intravenous immune globulin (IVIG), and anti-D immunoglobulin. For patients who are refractory to these therapies, those who become corticosteroid-dependent, or relapse following treatment with a corticosteroid, options include splenectomy, rituximab, and thrombopoietin-receptor agonists, alongside a variety of additional immunosuppressive and experimental therapies. Even though corticosteroids are traditional first-line therapy, treatment should be limited to a short period due to adverse outcomes that can significantly affect patients' quality of life. In addition, most adults need treatment for overt hemorrhage (6).

1.2. Statement of the problem

Immune thrombocytopenia (ITP) is an autoimmune process resulting in increased destruction and inadequate production of platelets that can result in bleeding, fatigue, and reduced health-related quality of life. Though most patients respond well to first-line treatment, a significant number of adults develop the persistent disease (7). ITP has a substantial adverse impact on the quality of many patients' daily lives. This is related to persistent and severe symptoms associated with ITP, restrictions on activities, anxiety due to the risk of bleeding, and the burden of treatment and monitoring. Steroids are used as first-line therapy for newly diagnosed ITP and most first relapses to prevent spontaneous bleeding, improve quality of life, and achieve healthy platelet counts. The majority of patients at initial treatment attain symptomatic improvement and achieve treatment goals. But neither long-term nor repeated use of steroids is recommended and reported reasons for changing treatment were lack of efficiency, worsening symptoms, changes in platelet count, treatment-related side effects, and cost (8, 9). Adults with ITP have a 1.3- to 2.2-fold higher mortality rate than the general population due to cardiovascular disease, infection, and bleeding (10).

Steroids are the standard initial treatment for ITP. Though the majority of patients achieve initial response with oral prednisone or dexamethasone, long-term remission is seen only in a few fractions of patients and long-term use is associated with significant adverse outcomes. A large study done in China showed that high-dose dexamethasone compared to prednisone was associated with better outcomes and better side effect profiles (11).

Initial response to steroid treatment shows a consistent pattern in different parts of the world. In developed countries, the majority of patients attain partial or complete responses, with most responses occurring during the first week (12). Similar results were found in the developing world like India and some African countries, but with relapse occurring in half of the patients. The major reason for steroid dependence was attributed to the underlying pathophysiologic mechanism of ITP and platelet indices at baseline (13, 14).

Medical management for immune thrombocytopenia (ITP) is a rapidly evolving science. However, there is still no curative treatment and decisions have to be guided by an understanding of the patients' general condition (15). Though there are advancements in medicine and increasing newer treatment options for ITP, availability, and affordability is major issue in some countries (16).

Steroids, particularly prednisone and dexamethasone, are the only widely available and affordable treatment options for most of our patients. And it is important to understand the response rates for these currently available medications in our country. It is also mandatory to acquire enough knowledge and information about the determinants of remission to implement an effective treatment strategy. In this research, a facility-based cross-sectional study was conducted to assess the treatment response of ITP patients on steroids and the factors that affect their response.

1.3 Significance of the study

In Ethiopia, and also in Africa, little is known about the prevalence, the clinical course, the impact of the disease on individuals, their families, or the overall health system, and the treatment response rate in adult ITP patients. There are not enough studies done, and even in those already done generalizability and consistency lacks to recommend them to the general population. There are limited studies done in Ethiopia on Primary ITP or steroid treatment and patient outcomes. However, ITP is one of the chronic hematological conditions we face in our day-to-day clinical practice. So, to implement the most effective treatment strategies, knowing the prevalence and understanding determinant factors of treatment response are crucial for clinicians and institutions to address all barriers against ITP treatment outcomes. This study will be one of the few pieces of research on steroid treatment response and associated factors that determine outcomes among adult ITP patients at SPHMMC. The outcome of this research will be used as the basis for future planning, development of institutional protocols and guidelines.

2 Literature Review

ITP is an autoimmune hematological disease where an isolated low platelet count is the basis for a diagnosis. A platelet count less than $100 \times 10^9/L$ was established as the threshold for diagnosis. This threshold was preferred to the more commonly used level of less than $150 \times 10^9/L$, based upon a prospective cohort of otherwise healthy subjects with a platelet count between 100 and $150 \times 10^9/L$, showing that the 10-year probability of developing more severe thrombocytopenia (persistent platelet count below $100 \times 10^9/L$) is only 6.9% (17). In addition, in some non-Western populations, platelet count values between 100 and $150 \times 10^9/L$ are frequently found in apparently healthy people (18, 19). And it also excludes most women with pregnancy-related thrombocytopenia, which is a well-known physiologic phenomenon. Despite major advances in the understanding of the molecular basis of many blood disorders, the diagnosis of ITP remains one of exclusion (20).

Recent studies have confirmed that the incidence in adults is roughly two in 100 000 per year and maybe more common in older adults than previously recognized. A female predominance occurs only among middle-aged patients, and there is no racial variation in incidence (21).

Severe bleeding is distinctly uncommon when the platelet count is $>30 \times 10^9/L$ and usually only occurs when the platelet count falls $<10 \times 10^9/L$ (22). Female sex, NSAID use, and exposure to anticoagulant drugs are proposed additional factors that increase the risk of bleeding (23). Age, presence of comorbidities like cardiovascular disease, renal disease, cancer, diabetes, and use of

Antiplatelet drugs, antihypertensive and lipid-lowering agents are associated with an increased risk of both bleeding and thrombosis (24).

The likelihood of spontaneous remission is age-related and the clinical course of the disease and treatment response depends on whether it is primary ITP or secondary to other causes and optimization of individual-based diagnostic and treatment approaches (25). Response with first-line treatment (steroids / IVIg) occurs in the majority of patients, but it is only temporary requiring repeated administration or addition of other drugs. A cure is limited only to Splenectomy. Studies have found that initial complete remission, female gender, and shorter duration of disease are associated with a maintained long-term response. There was no difference in response between young and postmenopausal women (26). Another study showed that the majority of adult patients develop chronic disease despite treatment and a positive association with higher platelet count at the baseline for chronicity, while gender, age, presence of bleeding symptoms, and autoimmunity had no effect (27).

Patients with newly-diagnosed primary ITP and a platelet count $< 30 \times 10^9/L$ regardless of symptomatic bleeding Corticosteroids, intravenous immunoglobulin (IVIg), and anti-D immunoglobulin are standard first-line treatment options rather than management with observation. Steroids remain the standard initial treatment of newly diagnosed patients and should be used for a limited time, although some patients require long-term, low-dose treatment

with steroids to have maintain platelet response. Studies showed comparable platelet response at six months between prednisone and dexamethasone; however, dexamethasone led to a faster responses without additional toxicity (28, 29). Long-term Steroid use for ITP is associated with significant side effects including mood swings, difficulty sleeping, weight gain, high blood pressure, diabetes, gastric irritation, skin thinning, and osteoporosis. In addition to comorbidities that correlate to the duration of treatment, the unpredictability of response, frequent relapses during tapering or stopping, and increased risk of bleeding, hospital admissions and frequent hospital visits associated with refractory diseases are major concerns (30).

The goal of medical management is aimed at attaining a hemostatic platelet count while preventing toxicities and major side effects associated with treatment (31). As ITP is a chronic illness, it is associated with increased cost, longer hospital stay, and higher age and gender-adjusted mortality, with septicemia and intracranial hemorrhages being the commonest causes (32).

Adult patients with chronic disease may have a better prognosis than previously recognized, but spontaneous remission rates vary by report and range from 5 to 11% (33). Although most adults with primary ITP respond to first-line therapy, the majority relapse after treatment is tapered and require a second-line approach to maintain a hemostatic platelet count (34).

In summary, Primary ITP is a disease diagnosed by the exclusion of other causes of thrombocytopenia. It affects all age groups and both gender groups, but with variable clinical course and prognosis. Guidelines suggest the use of steroids as a first-line treatment modality. But literature showed frequent remitting and relapsing nature of the disease and negative impact on quality of life-related to the chronicity of the illness, associated symptoms, and side effects with long term use of steroids.

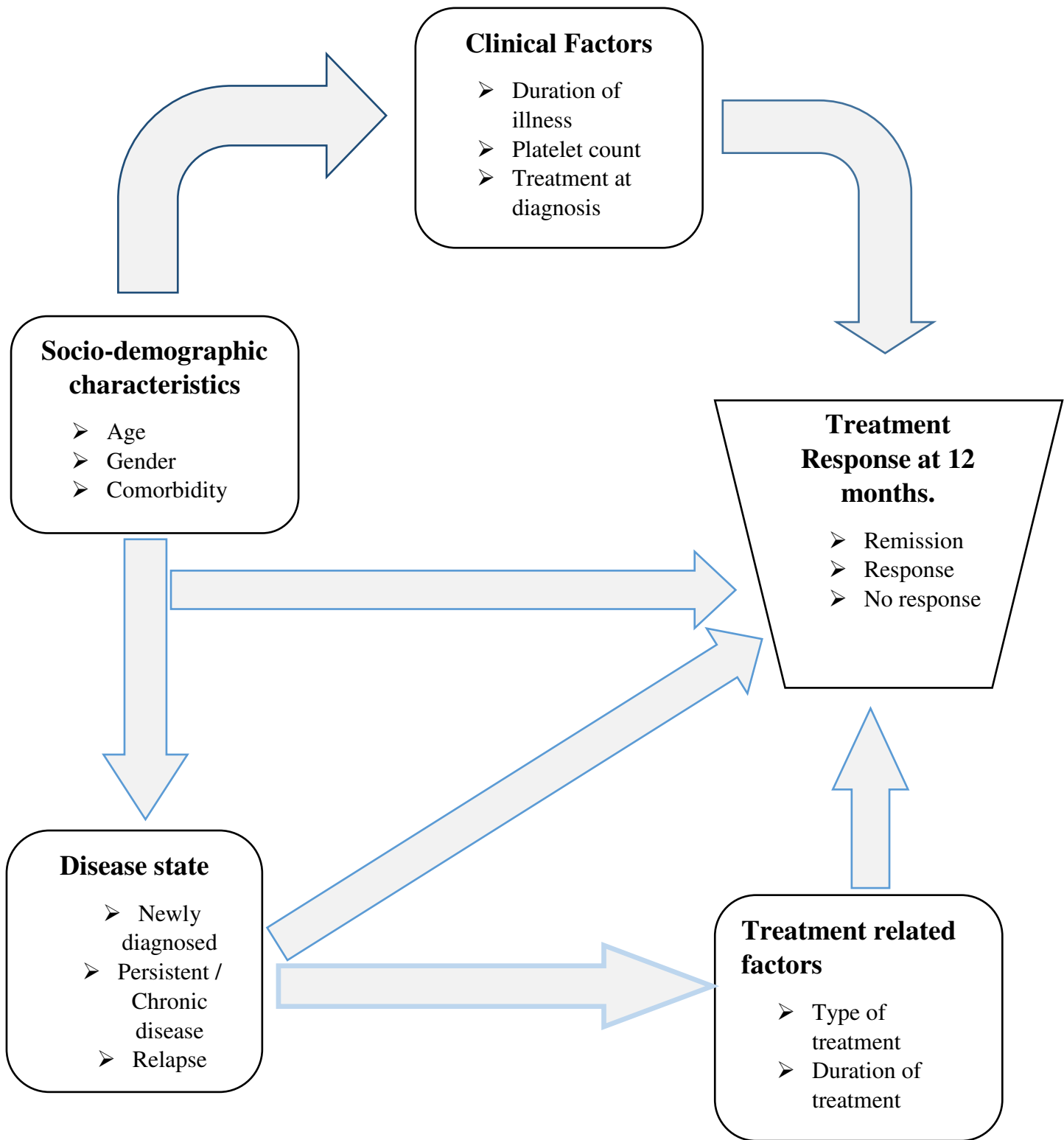


*Figure 1*conceptual framework of response to steroid treatment and associated factors among adults with Immune thrombocytopenia at St. Paul Hospital Millennium Medical College

3. Objective of the study

3.1 General Objective

- To assess response to steroid treatment and associated factors among adult ITP patients at SPHMMC, Hematology clinics, Addis Ababa, Ethiopia

3.2 Specific objectives

- To determine response to steroid treatment among adult ITP patients at SPHMMC, Hematology Clinics, Addis Ababa, Ethiopia
- To identify associated factors that affect response to steroid treatment among adult ITP patients at SPHMMC, Hematology clinics, Addis Ababa, Ethiopia

4. Methods

4.1 Study design, setting and study population

An institution based analytic cross-sectional study was conducted at SPHMMC, a tertiary hospital located in Gulele sub city of Addis Ababa, which is the capital city of Ethiopia. The hospital is one of the rapidly growing tertiary care centers in Ethiopia, with more than 200,000 patients being served annually on average and a catchment population of more than 5 million. SPHMMC provides almost all specialty programs including Hematology, sub-specialty. It has a well-established Hematology subspecialty outpatient follow-up clinics in which patients are seen by Hematologist's and residents with hematologist's consultation.

The source population of the study was all patients with hematologic conditions who visited Hematology clinics at SPHMMC. Whereas the study population was all patients above 16 years of age with the diagnosis of Immune thrombocytopenia who visited the outpatient department of the SPHMMC, Hematology Clinics during data collection time.

4.2 Sample Size determination and sampling technique

All immune thrombocytopenia patients who visited the center from September, 2021 up to September 2022 G.C were included in the study. From a total of 120 patients, two were excluded because one was pregnant and one patient had hematologic malignancy. 118 patients were included in the study. Data from patients who visited the clinics over the last six months was collected by face- to-face interviews and charts were reviewed for relevant diagnostic and follow-up investigations. For the rest of the patients through chart review was done to collect all the important information.

4.3 Inclusion and exclusion criteria

All patients above 16 years of age who were on treatment and/or follow-up and with the diagnosis of newly diagnosed or relapsed / Persistent/ & Chronic ITP during the observation period were included in the study. Thrombocytopenic patients who were pregnant / post-partum for whom cause of thrombocytopenia was not settled and patients with underlying hematologic malignancy were excluded.

4.4 Operational Definitions (Terminologies (international working force on ITP, 2009)

Newly diagnosed ITP: Within 3 months from diagnosis

Persistent ITP: Between 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy.

Chronic ITP: lasting for more than 12 months

Severe ITP: Presence of bleeding symptoms at presentation sufficient to mandate treatment, or

occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose.

Corticosteroid-dependent: Ongoing need for continuous prednisone 5 mg/d (or corticosteroid equivalent) or frequent courses of corticosteroids to maintain a platelet count $>30 \times 10^9/L$ and/or to avoid bleeding

Remission: Platelet count $\geq 100 \times 10^9/L$ at 12 month

Response (R): A platelet count $\geq 30 \times 10^9/L$ and a greater than two fold increase in platelet count from baseline measured on two occasions > 7 days apart and the absence of bleeding.

No response (NR) : A platelet count $< 30 \times 10^9/L$ or a less than two fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on two occasions more than a day apart.

4.5 Study Variables

4.5.1 The independent variables

- Patient related factors
 - Socio-demographic characters which includes age and gender.
 - Comorbidities
 - Concomitant treatment
- Disease related factors
 - Clinical presentation
 - Peak platelet count at baseline and during follow up
 - Duration of illness
- Treatment related factors
 - Duration of treatment

4.5.2 The dependent variable

- Response to Prednisone treatment of ITP.
 - Response
 - No response
 - Remission

4.6 Data collection procedures and quality assurance

An interview-administered structured questioner was used to collect information regarding demographic data, clinical presentation, laboratory investigations, treatment used for ITP and medication adherence. Platelet counts at baseline, one week, one month, six months and twelve months after initiation of treatment were collected for all patients who had records on their chart. Baseline WBC and Hemoglobin levels were also collected. For those patients who presented with bleeding severity was assessed using The Immune thrombocytopenia Bleeding Score (IBLS). Based on site and degree of bleeding patients were scored from 0 (none) to 2 (marked bleeding). Treatment compliance was also assessed using Morisky Medication Adherence Scale (MMAS) where patients were scored out of 8 (≤ 5 = low adherence; 6-7 = moderate adherence and 8 = high adherence).

All of the information was collected by three data collectors after a one-day short training was given about the aim of the study and how to collect the data. The data collection was supervised by the investigator for data consistency and completeness.

4.7 Data Management and Analysis procedures

Data entry was done by an experienced data clerk at the data collection site. Data collected was coded and entered into Epi-Data version 7 and exported to the Statistical Package for Social Science (SPSS) version 25.0 software for cleaning, organizing, and analysis. Data is analyzed and interpreted using descriptive statistical measures. Frequency and percentage are used to describe the categorical variables, whereas mean/median with standard deviation/Interquartile range for continuous variables. A chi-square test was run to compare the baseline characteristics of patients based on treatment response. A statistically significant difference was detected for variables with p-Value of ≤ 0.05 . The presence of multicollinearity was checked for the independent variables fit on the final model and the VIF result range from 1.055 to 1.406.

Univariate analysis at a 25% level of significance was run to determine factors with significant association to fit into the Multinomial logistic regression model that was used. The multivariable analysis was done for the independent variables with significant association with the dependent variables. The adequacy of the final model was assessed using the goodness of fit test and the final model fitted the data well (Pearson; p-value = 0.031 and Deviance; p-value = 0.139). To measure the presence and strength of association between the independent and dependent variables Odds ratio, P-value, and confidence intervals were used. The final results is interpreted and presented in tables and graphs.

4.8 Ethical Considerations

Ethical clearance was obtained from the department of Internal Medicine and from the hospital's ethical review committee. Importance of study explained to the participant and confidentiality assured through code numbers. Once reassured and informed consent obtained, checklist was administered to collect data from patients who were willing to participate.

4.9 Dissemination of results

After completion, the result of this study will be disseminated to the SPHMMC Department of Internal Medicine as partial fulfillment of the certificate in the postgraduate course and will be presented to the university community as part of the research thesis defense and disseminated to the SPHMMC, and stakeholders.

5. Result

5.1 Socio-demographic, Co-morbid illness and presenting symptom-related factors

Information was collected from 118 patients who were included in the study. Most of the patients were age 24(14.4%) while only a small proportion of patients were above 55 years old (3.4%). More than two-thirds (74.6 %) of patients were females. Sixty four (54.2%) of the patients were married living with their spouse .Forty-four (37.3%) of the respondents had completed high school education; 22 (18.6 %) completed higher education and 20(16.9%) had no formal education. Around two-thirds (72.9%) were living in urban areas while 26.3 % came from rural areas. Ninety (16.1%) patients had a history of preexisting comorbid illness, where hypertension was the most (n=7) reported one followed by autoimmune disease (n=4). Four patients were hepatitis B positive; three were HIV positive, three were H.Pylori stool antigen positive, and one patient was hepatitis C positive (Table 1).

Table 1 Basic socio-demographic characteristics

(n= 118)

	Frequency	(%)
Age category		
<= 25 years old	41	34.7
26-35 years old	43	36.4
36-45 years old	18	15.3
46-55 years old	12	10.2
above 55 years old	4	3.4
Gender		
Male	30	25.4
Female	88	74.6
Educational status		

No education	20	16.9	
Primary school	32	27.1	
High school	44	37.3	
Higher education	22	18.6	
Residency			
Urban	86	72.9	
Rural	31	26.3	
Semi-urban	22	18.6	
Symptom at diagnosis			
Incidental	31	26.3	
	87	73.7	
Bleeding			
Bleeding severity			
None	29	24.6	
Minor bleeding	30	25.4	
Marked bleeding	59	50.0	
Rescue treatment at diagnosis other than steroid			
No	39	33.1	
Yes	79	66.9	
Comorbid illness			

Autoimmune disease	4	3.4
TB/HIV	2	1.7
Hypertension	7	5.9
Other	105	89.0
Treatment at diagnosis		
No treatment needed	9	7.6
Dexamethasone	1	0.8
High dose prednisone	108	91.5
Current treatment		
Second-line treatment	7	5.9
Prednisone	111	94.1

Among the 118 patients, 56 (47.5%) respondents had chronic ITP; 26 (22%) had persistent ITP; 14 (11.9%) had relapse, and 8 (6.8%) were steroid-dependent (Table 2). One hundred eleven (94.1 %) patients were on Prednisone while seven (5.9%) of patients were on second line treatment. No patient had history of splenectomy. More than two-thirds (73.7%) of them presented with bleeding and 26.3% were found incidentally. Based on the Immune Thrombocytopenia bleeding assessment score (IBLS) half of the respondents had marked bleeding. 25.4% had minor bleeding and, 24.6 % had no bleeding at presentation. Female patients had higher proportions (75%) of bleeding symptoms as compared to male (70%) respondents. Seventy nine (66.9%) patients required rescue treatment other than steroid. Epistaxis was the commonest (45.8%) bleeding symptom reported, followed by, skin/cutaneous (16.1) bleeding, oral/mucosal (10%) bleeding and, gastrointestinal (4.8%) bleeding.

Around ½ of patients had remission; 40(34%) had response and 22(18.6%) had no response (Figure 2). Differences in the proportion of treatment response were found among the different disease-related characteristics of patients. Majority of patients on remission required high dose prednisone treatment (98.2%) at diagnosis. Similarly, higher proportion of patients on prednisone (92.5 %) had a response as compared to those not started on treatment (7.5%) at diagnosis. And 54. % of patients on treatment more than 2 years had remission while 17.5 % had a response and 4.5 % were are non-responders. More female patients had remission than male patients (75% vs. 25%) (Table 4).

Figure 2 Summary of treatment response

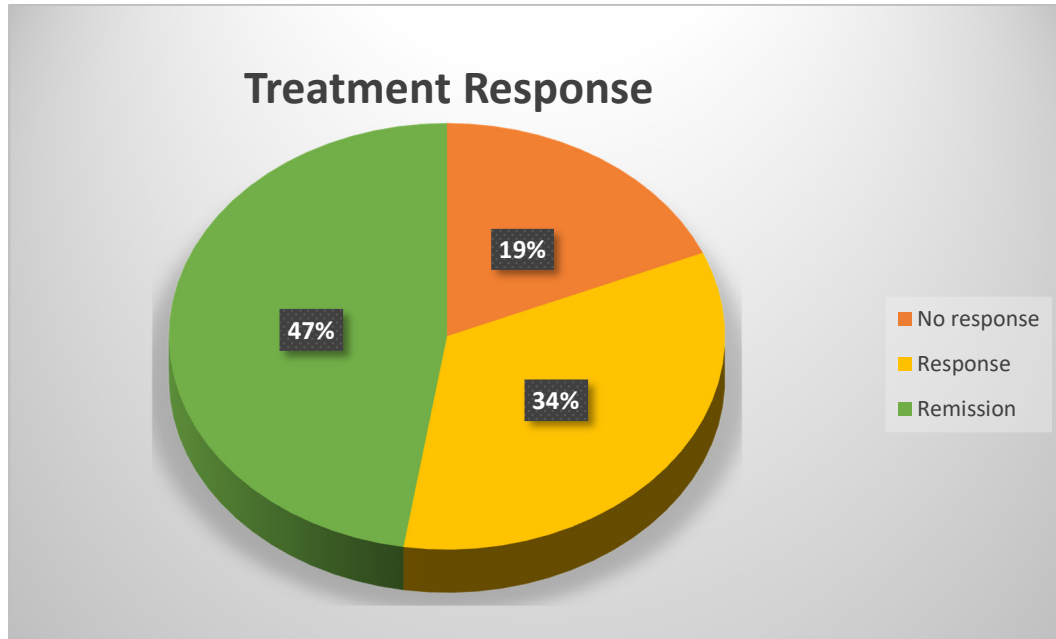


Table 2 Summary of current state of disease

Current state of disease	Frequency	(%)
Newly diagnosed	14	11.9
Persistent ITP	26	22.0
Chronic ITP	56	47.5
Relapse	14	11.9
Steroid dependent	8	6.8

5.2 Baseline platelet count and treatment related variables

The median time of treatment was 1.5 years. The average baseline platelet count was 10000 (Range =1-116000); hemoglobin 13.5 (Range = 2.79-16mg/dl) and WBC 8500 (Range= 4800-23000). At initial presentation, peripheral morphology was seen on 47.9% of patients. The commonest (44.9%) finding was isolated thrombocytopenia on the background of normal appearing platelets, red blood cells, and white blood cells. Five patients had associated IDA and three patients had features of megaloblastic anemia. Majority (91.5%) of patients were started on high dose (1-1.5 mg/kg) Prednisone; one patient was started on Dexamethasone and nine patients (7.6 %) did not need any treatment.

At one week assessment of platelet count, 23 patients had no records; 28.4 % had early response and 71.3% of them had no response. The minimum platelet count was 30,000 and the maximum 126,000. At one months, 71.5 % of patients had initial response. At six months 90.8 % had a durable response; platelet count ranged from 169-262000. At twelve months 71.2% had remission; 22.7 % had response, and 6.1% had no response (Table 3).

In an analysis to see factors that affect response significant positive association was found between duration of treatment and peak platelet count at one week, one month and 12 months but not at 6 months. There was also significant association between platelet count at one month, six months and 12 months. Significant association with one week peak platelet count was found only with one month count.

Table 3 Summary of peak platelet counts (N=118)

	N	Minimum	Maximum	Mean	Std. Deviation
WBC	118	4.8	23100.0	9296.781	4292.9555
Hemoglobin	118	2.79	16000.00	283.2854	2072.50974
Platelet	118	1	116000	22916.75	26191.781
Peak platelet count at one week	95	30	126000	27023.45	26424.105
Peak platelet count at one month	116	3000	177000	52885.34	35912.094
Peak platelet count at six month	118	5000	262000	79432.20	54565.698

Peak platelet count at 12 month	118	10000	262000	78478.81	53196.366
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In the assessment of treatment compliance, 33(28 %) patients had high compliance; 32(27.1%) had moderate compliance; 3 (2.5%) had low compliance, and 50 (42.4%) were not assessed.

With regard to overall health status perception majority 53(44.9%) had very good health status perception towards themselves; 9(7.6%) patients rated themselves as having good health status; 1(0.8%) rated themselves as fair and 55(46.6%) were not assessed.

Table 4 Disease related characteristics and comparison of proportions based on treatment response (n=118)

Variable	No response (%)	Response (%)	Remission (%)	Total (%)
Treatment duration				
Not on treatment	4 18.2%	2 5.0%	0 0.0%	6 5.1%
Less than 6 months	7 31.8%	12 30.0%	10 17.9%	29 24.6%
Six month to 1 year	7 31.8%	7 17.5%	6 10.7%	20 16.9%
1 year-2 years	3 13.6%	12 30.0%	7 12.5%	22 18.6%
Above 2 years	1 4.5%	7 17.5%	33 58.9%	41 34.7%
Treatment at diagnosis				
No treatment	5	3	1	9

needed	22.7%	7.5%	1.8%	7.6%
Dexamethasone	1 4.5%	0 0.0%	0 0.0%	1 0.8%
High dose prednisone	16 72.7%	37 92.5%	55 98.2%	108 91.5%
Age category				
<= 25 years old	5 22.7%	13 32.5%	23 41.1%	41 34.7%
26-35 years old	9 40.9%	13 32.5%	21 37.5%	43 36.4%
36-45 years old	5 22.7%	6 15.0%	7 12.5%	18 15.3%
46-55 years old	1 4.5%	6 15.0%	5 8.9%	12 10.2%
above 55 years old	2 9.1%	2 5.0%	0 0.0%	4 3.4%
Current treatment				
Second-line treatment	2 9.1%	3 7.5%	2 3.6%	7 5.9%
Prednisone	20 90.9%	37 92.5%	54 96.4%	111 94.1%
Gender				
Male	4 18.2%	12 30.0%	14 25.0%	30 25.4%
Female	18 81.8%	28 70.0%	42 75.0%	88 74.6%

5.3 Factors associated with treatment response at 12 months in ITP patients

Based on the result of the Univariate analysis at 25% level of significance treatment at diagnosis, duration of treatment comorbidity, patients' current treatment and platelet count at one month were found to be significantly associated with treatment outcome of ITP patients at 12 months. However, on the multinomial logistic regression test at 5 % level of significance platelet count at 6 months and duration of treatment were found to be significantly associated. Accordingly after adjusting for other covariates the odds of having Response at 12 month is 10 times more likely than having No response if platelet count is between 30,000 and 100,000 relative to platelet count < 30,000 at 6 month(AOR= 10.4,95% CI =1.12,96.62, p-Value = .039). Similarly, for having platelet count above 100,000 at 6 months relative to non-response, the relative risk for Remission at 12 months would be expected to increase by 7.33 given the other variables are held constant the (AOR=7.339,95% CI=1.28,42.07, p-Value =.025). On the other hand, the odds of having remission decreases by 96% if treatment duration is between 6 months and 1 year as compared to those with more than 2 years treatment duration(AOR= .04 95% CI= 0.004-0.409 , p- Value= .007).

Table 5 Result for the multinomial logistic regression test

		Response		Remission	
Variable	Category	AOR	p-Value	AOR	p-Value
Platelet	< 30,000	1		1	
	30,000-100,000	10.4(1.12,96.62)	.039	.22(.02,1.96)	.178
	>100,000	7.33(1.28,42.07)	.025	.18(.04,.75)	.019
Duration of	> 2 years	1	.	1	

treatment	1- 2 years	.12(.01,1.54)	.105	.09(.009,1.003)	.050
	6 month-1 year	.09(.007,1.12)	.062	.04(.004,.40)	.007
	< 6 months	.26(.01,3.70)	.326	.15(.01,1.91)	.145

6 Discussion

In this cross-sectional study of ITP patients on treatment, the results shows that majority of our patients are treated with Prednisone and they have good response to the treatment. The study also found a relationship between duration of treatment, type and dose of steroid used at diagnosis and effect of initial and durable response on the overall remission rate. The overall response rate at 1 month, 6 months is 61.9% and 66.9 % respectively; remission rate at 12 month is 47.5%. The overall no response rate was 18.6%. This result is comparable to other studies but long term remission rate might be lower because studies in other countries showed a high relapse rate (70-90%) when steroid therapy is stopped or tapered (30). Another study in China showed an overall initial response of 40.4 % and sustained response of 26.8 % and long term response at 12 months was 33% (11) which is much lower when compared to this study. The reason for this variation could be due to larger number of sample size, baseline clinical profile (all patients with secondary ITP, patients with history of prior steroid treatment for any condition) which excluded patients from the study, lower baseline platelet count and severe bleeding manifestations at presentation (11). On the contrary, a British study where patients were followed for about 10 years showed a response rate of 93% with treatment and 85 % off treatment. However , on the average treatment duration was two years (20) where, as in this study, average treatment duration was 1.5 years. This study also supports the findings in this report where duration of treatment was found to be significantly associated with treatment outcome.

The study also showed female predominance and preponderance in young adult age group, which is comparable to worldwide studies. A study in Malaysia showed an incidence of 71.8% in females and a median age of 36 years old, which is comparable to our finding (30 vs 36 years old). The commonest bleeding presentation in this research was epistaxis, which is in contrary to the finding that cutaneous bleeding was the commonest. Corticosteroid was the commonest prescribed first line drug and splenectomy was rare, which is consistent with this researches finding. In this study majority (91.8 %) needed treatment at diagnosis Vs 80.6 % treated (35). The reason for the difference might be due to the larger sample size and a lower median threshold of platelet count at baseline used in the other study.

7 Strength of the study

The major strength of this study was the fact that hematologists were involved in the diagnosis, treatment, and follow-up of study subjects. In addition data was collected by experienced nurses and physicians. Finally, since there are limited studies in Ethiopia regarding ITP treatment, this study may serve as a basis for future prospective studies.

8 Limitation of the study

The design and site of the study had to be changed at last the minute due to some technical and procedural issues that could not be handled on time. Thus, the study was done on a small sample size which jeopardizes the generalizability of the study. There were also limitations in gathering and analyzing data due to the change in data collection procedure, which shifted and got limited to chart review only. Moreover, majority of the charts were incomplete and many variables with missed values made categorization inconsistent and some of the regression analysis results unrealistic which could not be interpreted or reported. So handling of missed values and re-categorization of variables further compromised the reliability of the results.

9 Conclusion

The study showed that there is a good treatment response rate among adults with ITP. Factors that significantly affect responses and remission of ITP were found to be durable response at six months of therapy and longer duration of treatment.

In general, this study only revealed an overview of treatment response pattern and factors associated with it, which may give an insight for future researchers, the department and the hospital as a Whole.

10 Recommendations

For future researchers and the department, I recommend multicenter study that includes additional clinical and laboratory data with a larger sample size.

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Annex I

Consent form

Title of the project:

I have been well aware of that this research to be undertaken is for the partial fulfillment of specialty certificate which is fully supported and coordinated by the Department of Internal Medicine, SPHMMC and the designate principal investigator is Dr. Haymanot Assefa. I have been fully informed in the language that I understand best about the research project objectives and all the information the observer take will be kept confidential. I understood that the research has no any risk. I have assured that the right to ask information that is not clear about the research before and or during the research work and to contact; SPHMMC IRB Office: Tel: (.....)

Principal Investigator: Dr. Haymanot Assefa; Tel: +251912058095

I have read this form, or it has been explained to me in the language I comprehend best and understood the condition stated above, therefore, I am willing and confirm the participation in the study by signing the consent.

Signature of the Patient/Guardian: _____ Date: _____

Signature of Investigator(s): _____ Date: _____

Annex II

Questionnaire

The checklists used to assess subjects by the investigator.

Section one: Socio-demographic characteristics

- Medical registration number
- Age in years
- Gender
 - Male
 - Female
- Religion
 - Orthodox
 - Islamic
 - Catholic
 - Protestant
 - If other specify.....

- Residency/location
 - Urban
 - Rural
 - Semi-urban
- Educational status
 - No education
 - Primary school completed
 - High school completed
 - Higher education
- Occupation
 - Unemployed
 - Government Employed
 - NGO
 - Self-employed
 - If other specify
- Income (monthly in Ethiopian Birr
.....
- Living arrangement
 - With parents
 - Alone
 - With siblings
 - With relatives
 - Other (specify)
- How do you perceive your overall health
 - Very good

- Good
- Fair
- poor

Section two: Clinical profile

- Date of diagnosis(Duration of illness) in years
.....
- What is the current state of the disease?
 - Newly diagnosed
 - Persistent ITP
 - Chronic ITP
 - Relapse
 - Steroid dependent
- Symptom at diagnosis
 - Incidental
 - Bleeding
 - Other
- If the Answer is 2 for the above question, please refer to the IBLS table below
 - Skin PE).....
 - Oral (PE)
 - Skin (Hx)
 - Oral (Hx)
 - Epistaxis
 - Gastrointestinal (GI)
 - Urinary (U)
 - Gynecological (GYN)

- Pulmonary
 - Intracranial hemorrhage
 - Subconjunctival hemorrhage
- Rescue treatment required at diagnosis (Rescue treatment include Blood/platelet transfusion, surgical/medical treatment other than Steroid to control overt bleeding)
 - a. Yes b. No
 - Do you have any known comorbid illness?
 - a. Yes b. No
 - If the answer is Yes for the above question, please specify
.....

Section four: Relevant baseline investigation results

- CBC at baseline
.....
- Peripheral morphology done
 - Yes b. No
- If peripheral morphology was done, what was the finding (i.e. conclusion)?
.....
- Hepatitis B surface Ag
 - Positive b. Negative c. Not known
- Hepatitis C antibody
 - Positive b. Negative c. Not known n
- H. pylori stool antigen
 - Positive b. Negative c. Not known
- HIV status

- Positive
- b. Negative
- c. Not known

Section 3: Treatment related factors

- Duration of treatment
.....
- What is the patient currently taking?(List type, duration and dose of all medications patient is taking)
.....
- What was the type and dose of steroid patient started at diagnosis?
.....
- Does the patient have history of splenectomy?
 - Yes
 - b. No
- Does the patient suffers or have any history of adverse medication effect?
 - a. Specified
 - b. Not specified
- If specified, please state the condition
.....

Section V: Treatment response assessment

- Peak Platelet count at
 - One week.....
 - One month.....
 - Six month.....
 - Twelve months

Section VI: Treatment compliance assessment

Table 6 Morisky Medication Adherence Scale (MMAS)

1. Do you sometimes forget to take your medications?	NO	YES
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medications? NO	NO	YES

YES		
3. Have you ever cut back or stopped taking your medications without telling your doctor, because you felt worse when you took it? NO YES	NO	YES
4. When you travel or leave home, do you sometimes forget to bring along your medications? NO YES	NO	YES
5. Did you take your medications yesterday? NO YES	NO	YES
6. When you feel like your health condition is under control, do you sometimes stop taking you medications? NO YES	NO	YES
7. Taking medications every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan? NO YES	NO	YES
8. How often do you have difficulty remembering to take all your medications?	Never/rarely 4 Once in a while 3 Sometimes 2 Usually 1 All the time 0	

Table 7 Immune thrombocytopenia bleeding assessment score (IBLS)

		Bleeding grade	
Site	0 (None)	1 (Minor bleeding)	2 (Marked bleeding)
Site	0(none)	1(Minor bleeding)	2(Marked bleeding)
Skin (PE)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	None	blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (Hx)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	None	1 blood blister or >5 petechiae and/or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min
Epistaxis	None	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal	None	Occult blood	Gross blood
Urinary	None	Microscopic (+ve dipstick)	Macroscopic
Gynecological	None (normal period)	Spotting not at time of normal period	Bleeding >spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial hemorrhage	None	N/A	Yes
Subconjunctival hemorrhage	None	Yes	N/A

Annex III

Declaration

We the undersigned agree to accept all responsibilities for the scientific and ethical conduct of the research project. We will provide timely progress report to my advisor and seek the necessary advice and approval from my primary advisors in the course of the research. We will communicate timely to my advisors all stakeholders involved in the study including any source of funding for this research.

Name of the student(s): _____

Signature: _____

Date: _____

Approval of the Advisor Name of the advisor: Mr. Simegnew Handebo

Signature: _____

Date: _____

Approval of the Advisor Name of the advisor: Dr. Helen Hilawi

Signature: _____

Date: _____

Approval of the Advisor Name of the advisor: Tirumebet Mezgebu

Signature: _____

Date: _____