Original Research Report

THE DIFFERENCES BETWEEN PRE- AND POST-THERAPY LEVELS OF PLATELET COUNT AND PLATELET INDICES IN CHILDREN WITH IMMUNE THROMBOCYTOPENIA PURPURA

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ABSTRACT

Immune Thrombocytopenia Purpura (ITP) is an autoimmune disorder triggered by antiplatelet autoantibodies. Clinically, ITP is classified into three phases including Newly-Diagnosed ITP, Persistent ITP, and Chronic ITP, each with distinct durations and therapy implications. Patients with ITP who do not receive appropriate or optimal treatment are at a heightened risk of morbidity and mortality related to bleeding complications, the condition could worsen, potentially resulting in fatal consequences. In ITP patients, platelet counts decrease, accompanied by abnormal shifts in platelet indices, including Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Platelet Large Cell Ratio (P-LCR), and Plateletcrit (PCT). Thus, therapeutic response in ITP patients can be evaluated through increased platelet counts and normalization of platelet indices. This study aimed to assess the therapeutic response of platelet counts and platelet indices in pediatric ITP patients by comparing pre- and post- therapy levels overall by category, across all medication types administered, and according to the specific medication used within each category. The result of this study are expected to provide an overview of the most effective treatments across all ITP categories in order to prevent severe complications and reduce the risk of mortality. This retrospective study included ITP patients under 18 years old at Dr. Soetomo General Academic Hospital, Surabaya, conducted from September 2023 to March 2024. Platelet count and platelet indices pre- and post-therapy levels were analyzed using the Paired T-test for normally distributed data and the Wilcoxon test for non-normally distributed data, with significance set at $p < 0.05$. In summary, there were notable changes in the pre- and post-therapy levels of platelet, MPV, PDW, P-LCR, and PCT in each ITP category and for all therapies. Platelet count and PCT increased, while MPV, PDW, and P-LCR decreased. Patients treated with prednisone exhibited the best therapeutic response. Among the categories, Newly Diagnosed ITP demonstrated the most optimal therapeutic response. Overall, ITP therapy led to significant differences between pre- and post-therapy levels, marked by an increase in platelet counts and normalization of platelet indices.

Keywords: Immune Thrombocytopenia Purpura; Therapy; Response; Platelet; Child Health

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Highlights:

1. This study was the first to analyze the therapeutic response in children with ITP at Dr. Soetomo General Academic Hospital, Surabaya.
2. This study analyzed the response of platelet count and indices, including MPV, PDW, P-LCR, and PCT to therapy, which provides a more comprehensive perspective on therapy response in children with ITP.
3. This study explored the effectiveness of various therapeutic approaches based on ITP categories, offering new insights into the most effective treatment options for children with ITP.

INTRODUCTION

Immune Thrombocytopenia Purpura (ITP) is an autoimmune condition marked by the generation of autoantibodies against platelets, resulting in a decrease in platelet counts and bleeding manifesting as reddish skin patches (Pietras et al., 2024). These autoantibodies increase platelet destruction, disrupting hemostasis and resulting in bleeding, thrombocytopenia, and blood imbalances. ITP can arise due to viral infections, tumor malignancies, and other autoimmune or immunodeficiency conditions. Based on data from the World Health Organization (WHO) in 2018, the reported case of ITP was approximately 66 cases per

1.000.000 people annually, with higher rates observed in females and increasing with age. The Maryland Health Care Commission reports ITP prevalence in the United States as 9.5 cases per 100.000 children aged 1-5, 7.3 cases per 100.000 for ages 6-10, and 4.1 cases per 100.000 for ages 11-14. In Northern Europe, the annual incidence is 2.68 cases per 100.000 people (Wijaya, 2019). In Indonesia, although exact incidence data are not available, estimates indicate that the annual incidence ranges from 2 to 6 cases per 100.000 individuals (Sari, 2018). Immune Thrombocytopenia Purpura is typically categorized into three clinical phases: Newly Diagnosed ITP, Persistent ITP, and Chronic ITP, each defined by the duration of the condition. Newly Diagnosed ITP may resolve within three months, while Persistent ITP persists for 3-12 months. Chronic ITP is diagnosed if symptoms last beyond 12 months.

ITP leads to platelet depletion as antiplatelet autoantibodies target the GPIIb/IIIa glycoprotein on platelet surfaces, facilitating their destruction through interaction with Fc receptors on macrophages in the reticuloendothelial system (RES) of the spleen (Saeidi et al., 2014). Additionally, these autoantibodies attach to the GPIb-IX-V glycoprotein on megakaryocytes, reducing platelet production (Perera & Garrido, 2017). In response, the body enhances thrombopoiesis by the bone marrow, resulting in increased of immature platelets with a giant morphology. This causes an increase in several parameters, including the Mean Platelet Volume (MPV), measuring the average platelet size; Platelet Distribution Width (PDW), quantifying the variability in platelet size and reflects morphological heterogeneity; and Platelet Large Cell Ratio (P-LCR), evaluating the proportion of larger circulating platelets and is used to assess platelet activity by determining the ratio of larger platelets to the total platelet count (Saran et al., 2022). Conversely, Plateletcrit (PCT), as a parameter that detects the proportion of the total blood volume occupied by platelets, decreases due to platelet destruction (Subramaniam et al., 2014). Since platelet count and indices are interrelated, effective ITP therapy should ideally normalize these indices alongside platelet levels.

The management of ITP requires appropriate and effective therapy for each ITP category. In patients with ITP who do not receive appropriate treatment, the risk of both morbidity and mortality due to bleeding is significantly elevated. Bleeding may occur at various sites, including the skin, mucosal membranes, gastrointestinal tract, and intracranial regions. Intracranial hemorrhage is considered the most severe complication of ITP, affecting approximately 1% of patients with severe thrombocytopenia. The mortality rate associated with bleeding in ITP patients is estimated to be around 1% in children and 5% in adults (Hallan et al., 2022).

The management of Immune Thrombocytopenia Purpura generally aims to prevent serious bleeding during the thrombocytopenic period, which is phase-dependent. In patients with Newly-Diagnosed ITP, treatment options including high doses of corticosteroids such as prednisone and methylprednisolone, or a single dose of Intravenous Immunoglobulin (IVIg) or Anti-D Immunoglobulin (IV Anti-D). In contrast, for Persistent and Chronic ITP, treatment may involve corticosteroids such as prednisone and methylprednisolone, thrombopoietin receptor agonists (TPO-RA) like romiplostim and eltrombopag, as well as other agents such as rituximab and mycophenolate mofetil (MMF) (Provan et al., 2019).

This research aimed to evaluate the effectiveness of therapies administered to ITP patients across different categories, different medications, as well as the specific medication used within each category by analyzing the differences in pre- and post-therapy platelet counts and their indices, including MPV, PDW, P-LCR, and PCT, using both parametric and non-parametric statistical techniques. These parameters serve as indicators of therapeutic efficacy. The findings of this study are expected to inform the most effective treatment options for ITP patients, with the goal of preventing bleeding complications and reducing mortality rates. Effective management not only improves survival rates but also enhances the quality of life for these patients. However, thus far, no research has compared platelet count and indices levels by specific therapy types and ITP categories.

MATERIALS AND METHODS

This study employed an analytical, retrospective cohort design performed at Dr. Soetomo General Academic Hospital, Surabaya from September 2023 to March 2024. The subjects were pediatric patients with Immune Thrombocytopenia Purpura (ITP) treated at both the

outpatient clinic and inpatient ward from 2019 to 2023. Patients aged under 18 years diagnosed with ITP and with no history of other autoimmune diseases were enlisted in the study. Patients with inconsistent treatment or incomplete medical records were excluded. In this study, patients were categorized into three different groups: Newly Diagnosed ITP, encompassing those with ITP for up to three months; Persistent ITP, including patients with ITP lasting between three until twelve months; and Chronic ITP, referring to patients with ITP for more than twelve months (Sari, 2018).

The data collected included pre- and post-therapy levels of platelet, MPV, PDW, P-LCR, and PCT measured from complete blood count (CBC) tests (Saran et al., 2022). Pre-therapy levels were recorded at the patient's initial visit, while post-therapy levels were obtained from the latest CBC test results. Data were classified by component type, ITP category, and therapy type then analyzed using IBM SPSS Statistics for Mac, version 29.0 (IBM Corp., Armonk, N.Y., USA). The Shapiro-Wilk test was employed to assess the normality of the data. For comparison between pre- and post-therapy levels, the Paired T-test was used for normally distributed data as well as the Wilcoxon test for abnormally distributed data, with significance set at $p<0.05$. Ethical approval was obtained from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya No. 1419/LOE/301.4.2/VIII/2023 dated 18/8/2023.

RESULTS

A total of 35 data consisting children with Immune Thrombocytopenia Purpura were involved in this study.

Table 1. Characteristics of ITP Patients

Characteristics (n=35)	n (%)
Gender	
Male	16 (45.7)
Female	19 (54.3)
Age	
< 1	2 (5.7)
1-5	16 (45.7)
6-10	6 (17.1)
11-14	10 (28.6)
15-17	1 (2.9)
ITP Category	
Newly-Diagnosed	12 (34.3)
Persistent	5 (14.3)
Chronic	18 (51.4)
Total of Bleeding Manifestation	
1 bleeding manifestation	7 (20)
2 bleeding manifestation	6 (17.1)
3 bleeding manifestation	4 (11.4)
4 bleeding manifestation	5 (14.3)
6 bleeding manifestation	1 (2.9)
7 bleeding manifestation	1 (2.9)
No bleeding manifestation	11 (31.4)
Complication	
Hepatosplenomegaly	1 (2.9)
Anemia	5 (14.3)
No complication	29 (82.8)
Therapy	
Prednisone	21 (60)
Methylprednisolone	5 (14.3)
Eltrombopag	4 (11.4)
Prednisone changes to Eltrombopag	5 (14.3)

Table 1 displays the characteristics of ITP patients. Most individuals diagnosed with Immune Thrombocytopenia Purpura (ITP) in the Outpatient and Inpatient Departments of Dr. Soetomo General Academic Hospital, Surabaya from 2019 to 2023 are female (54.3%). The data indicate that the predominant age group for children diagnosed with ITP is 1-5 years (45.7%), and the most common ITP category is Chronic ITP (51.4%). A total of 68.6% of patients exhibit bleeding manifestations of varying severity, with the most frequent being one manifestation (20%). Additionally, almost all patients did not experience complication of ITP (82,8%). Furthermore, most patients received prednisone as part of their treatment (60%).

Table 2. Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices

Components	N	Pre-therapy		Post-therapy		P
		Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Platelet	35	27.5 ± 25.83		236.22 ± 145.89		<0.001**
MPV	26	11.67 ± 2.63		9.65 ± 2.12		<0.001**
PDW*	25		17.1 (8.5-24.9)		10.6 (7.6-24.71)	<0.001**
P-LCR	19	36.14 ± 11.11		23.44 ± 9.27		<0.001**
PCT	12	0.08 ± 0.06		0.2 ± 0.1		0.002**

Notes: MPV=Mean Platelet Volume; PDW=Platelet Distribution Width; P-LCR=Platelet Large Cell Ratio; PCT=Plateletcrit; *Abnormal data distribution; **Significant p<0.05

Table 2 compares the pre- and post-therapy levels of all components. The result shows an increase in platelet and PCT levels, while MPV, PDW, and P-LCR levels decrease. Statistical analysis using Paired T-tests and Wilcoxon tests reveal significant changes in platelet, MPV, PDW, and P-LCR levels ($p < 0.001$), as well as a significant change in PCT ($p = 0.002$)

Components	ITP Category	N	Pre-therapy		Post-therapy		P
			Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Platelet	Newly-Diagnosed	12	27.75 ± 25.41		346.04 ± 88.51		<0.001**
	Persistent	5	43.4 ± 34.03		199.2 ± 92.02		0.024**
	Chronic*	18		10.23 (1-63)		111 (15-576)	<0.001**
MPV	Newly-Diagnosed	9	10.39 ± 2.55		8.08 ± 1.76		0.004**
	Persistent	5	11.08 ± 1.41		9.68 ± 0.64		0.045**
	Chronic	12	12.89 ± 2.68		10.83 ± 2.08		0.001**
PDW	Newly-Diagnosed	8	17.96 ± 5.89		11.78 ± 4.49		0.010**
	Persistent	5	15.3 ± 3.78		10.16 ± 1.19		0.033**
	Chronic*	12		18.45 (8.5-24.9)		12.05 (7.6-24.71)	0.003**

P-LCR	Newly-Diagnosed	5	34.56 ± 14.49	16.84 ± 5.86	0.040**
	Persistent	5	36.42 ± 11.43	22.44 ± 5.25	0.016**
	Chronic	9	36.86 ± 10.27	27.67 ± 10.7	0.001**
PCT	Newly-Diagnosed	4	0.10 ± 0.09	0.31 ± 0.049	0.049**
	Persistent	4	0.06 ± 0.047	0.18 ± 0.095	0.056
	Chronic	4	0.08 ± 0.049	0.13 ± 0.069	0.172

Table 3. Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices according to ITP Category

Notes: MPV=Mean Platelet Volume; PDW=Platelet Distribution Width; P-LCR=Platelet Large Cell Ratio; PCT=Plateletcrit; *Abnormal data distribution; **Significant p<0.05

Table 3 presents the analysis of pre- and post-therapy of platelet count and indices levels across ITP categories. In Post-therapy, each category exhibits an increase in platelet and PCT levels, while MPV, PDW, and P-LCR levels decrease. Statistical analysis indicates significant differences in all components in each ITP category (p<0.05), except for PCT levels in the Persistent ITP (p=0.056) and Chronic ITP categories (p=0.172).

Table 4. Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices according to the Therapy

Components	**Therapy**	**N**	**Delta**	**Pre-therapy**		**Post-therapy**		**P**
			(10^3/µL)	**Mean ± SD**	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**	
Platelet	Prednisone	21	237.22	33.48 ± 27.64		270.71 ± 123.36		<0.001**
	Methylprednisolone	5	224.6	38.4 ± 22.49		263 ± 135.34		0.020**
	Eltrombopag	4	67.41	5.33 ± 3.49		72.75 ± 40.31		0.046**
	Prednisone changes to Eltrombopag	5	186.2	9.2 ± 9.49		195.4 ± 222.12		0.122
MPV	Prednisone	19	2.02	11.43 ± 2.59		9.40 ± 1.97		<0.001**
	Methylprednisolone	3	3.2	12.96 ± 1.7		9.76 ± 2.71		0.058
	Eltrombopag*	2	1.4		13.39 (9.6-17.19)		11.99 (9.2-14.78)	0.180
	Prednisone changes to Eltrombopag*	2	0.8		10.4 (9.4-11.4)		9.6 (9.3-9.9)	0.180
PDW	Prednisone	18	5.62	17.69 ± 5.19		12.07 ± 4.06		<0.001**
	Methylprednisolone	3	8.89	20.99 ± 5.62		12.1 ± 6.35		0.105
	Eltrombopag*	2	0.02		16.63 (8.5-24.76)		16.6 (8.5-24.71)	0.317
	Prednisone changes to Eltrombopag*	2	3.3		13.1 (13.1-13.1)		9.8 (9.6-10)	0.180

Notes: MPV=Mean Platelet Volume; PDW=Platelet Distribution Width; *Abnormal data distribution; **Significant p<0.05

Table 4 compares pre- and post-therapy of platelet count and indices levels according to the therapy administered. In Post-therapy, all therapies led to an increase in platelet levels, while MPV and PDW levels decrease. P-LCR and PCT levels cannot be analyzed due to incomplete data. Statistical analysis

revealed significant differences in platelet levels across all therapies ($p<0.05$), except for prednisone switched to eltrombopag therapy ($p=0.122$). MPV and PDW levels show significant changes only with prednisone therapy ($p<0.001$).

Table 5. Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices of each Category according to the Therapy

Components	ITP Category	Therapy	N	Pre-therapy		Post-therapy		P
				Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Platelet	Newly-Diagnosed	Prednisone	8	25.24 ± 28.2		367.93 ± 67.83		<0.001**
		Methylprednisolone	4	32.75 ± 21.48		302.25 ± 118.97		0.014**
	Persistent	Prednisone	5	43.4 ± 34.03		199.2 ± 92.02		0.024**
	Chronic	Prednisone	8	35.53 ± 23.93		218.18 ± 128.19		0.006**
		Metilprednisolone	1	61		106		---
		Eltrombopag	4	5.33 ± 3.49		72.75 ± 40.31		0.046**
		Prednisone change to Eltrombopag	5	9.2 ± 9.49		195.4 ± 222.12		0.122
MPV	Newly-Diagnosed	Prednisone	7	9.9 ± 2.68		8.05 ± 2.03		0.025**
		Methylprednisolone*	2		12.09 (11.3-12.89)		8.2 (8.1-8.3)	0.180
	Persistent	Prednisone	5	11.08 ± 1.41		9.68 ± 0.64		0.045**
	Chronic	Prednisone	7	13.2 ± 2.28		10.55 ± 1.89		0.009**
		Eltrombopag*	2		13.39 (9.6-17.19)		11.99 (9.2-14.78)	0.180
		Prednisone change to Eltrombopag*	2		10.4 (9.4-11.4)		9.6 (9.3-9.9)	0.180
PDW	Newly-Diagnosed	Prednisone	6	17.51 ± 6.18		12.89 ± 4.71		0.038**
		Methylprednisolone*	2		19.34 (14.5-24.18)		8.45 (7.8-9.1)	0.180
	Persistent	Prednisone	5	15.3 ± 3.78		10.16 ± 1.19		0.033**
	Chronic	Prednisone	7	19.57 ± 5.09		12.73 ± 4.8		0.016**
		Eltrombopag*	2		16.63 (8.5-24.76)		16.6 (8.5-24.71)	0.317
		Prednisone change to Eltrombopag*	2		13.1 (13.1-13.1)		9.8 (9.6-10)	0.180
P-LCR	Newly-Diagnosed	Prednisone	3	40 ± 13.71		20.3 ± 4.67		0.124
		Methylprednisolone*	2		26.4 (15.4-37.4)		11.65 (10.2-13.1)	0.180
	Persistent	Prednisone	5	36.42 ± 11.43		22.44 ± 5.25		0.016**
	Chronic	Prednisone	5	39.86 ± 9.04		28.02 ± 9.54		0.001**

Notes: MPV=Mean Platelet Volume; PDW=Platelet Distribution Width; P-LCR=Platelet Large Cell Ratio; *Abnormal data distribution; **Significant $p<0.05$

Table 5 compares pre- and post-therapy of platelet count and indices levels within each ITP category

according to the therapy administered. All therapies in each ITP category led to an increase in post-therapy platelet levels, accompanied by decrease in MPV, PDW, and P-LCR levels. PCT levels could not be analyzed due to incomplete data. Statistical analysis shows significant differences in platelet levels of each therapy ($p<0.05$), except for the transition from prednisone to eltrombopag therapy in Chronic ITP ($p=0.122$). MPV, PDW, and P-LCR levels show significant changes only with prednisone therapy ($p<0.001$), except for Newly Diagnosed ITP patients receiving prednisone ($p=0.124$).

DISCUSSION

Characteristics of Children with Immune Thrombocytopenia Purpura

This study found that female children were more likely to be diagnosed with Immune Thrombocytopenia Purpura (ITP) during the 2019 to 2023 period, with a male-to-female ratio of 1:1.2. This aligns with the findings from Al-Suheel et al. (2014), which suggest a higher prevalence of ITP in female children compared to males. This is likely because females are more susceptible to autoimmune diseases due to various factors, including immune, hormonal, and chromosome differences (Kronzer et al., 2021). However, the findings of this study differ from those reported by Alwadi et al. (2020), who investigated 95 pediatric ITP cases in Riyadh, Saudi Arabia, and observed a higher case of ITP in male children compared to females.

This study also revealed that the majority of pediatric patients were within the age range of 1 to 5 years, accounting for 45.7% of the cases. This is consistent with the study conducted by Friedman & Beck (2019), which states that cases of ITP most commonly occur in children aged 2-5 years because children's immune systems are still developing, leading to an exaggerated response to an antigen or platelet, as ITP in children is often triggered by viral or bacterial infections or immunization. Furthermore, the majority of the studied population was dominated by the Chronic ITP category (51.4%). This may be due to the fact that many cases of Newly Diagnosed ITP or Persistent ITP progress to Chronic ITP, it is estimated that 20-25% of pediatric ITP cases develop into Chronic ITP over time (Lee, 2023).

The study shows that 68.6% of patients experienced bleeding manifestations, with the majority having one bleeding manifestation (20%). Based on the sign and symptoms, petechiae, ecchymosis, epistaxis, gum bleeding, and genital tract bleeding are the most common initial manifestations of ITP (Omar et al., 2018). The bleeding manifestations experienced by the 35 patients include ecchymosis (15/35), petechiae (13/35), oral mucosal bleeding (8/35), epistaxis (6/35), hematemesis (4/35), menometrorrhagia/abnormal uterine bleeding (2/35), hematoma (2/35), subconjunctival hemorrhage (1/35), hematuria (1/35), and purpura (1/35). This result is aligned with the study conducted by Neunert et al. (2015) that most patients with ITP exhibit a range of bleeding manifestations because platelet levels influence the amount and severity of bleeding, where lower platelet level correlate with more frequent bleeding, thus impacting the disease severity (Frelinger III et al., 2015). According to the study results, two classes of medications were administered as therapy for pediatric patients with ITP, namely corticosteroids and Thrombopoietin Receptor Agonists (TPO-RA). Corticosteroid medications included prednisone used by 60% of patients and methylprednisolone used by 14.3% of patients. The TPO-RA medication, such as eltrombopag was administered to 11.4% of patients, while 14.3% of patients were switched from prednisone to eltrombopag at different intervals. This treatment approach is consistent with both international consensus from the American Society of Hematology and the national Clinical Practice Guidelines for ITP patients at Dr. Soetomo General Academic Hospital Surabaya, which recommend corticosteroids as the first-line treatment and TPO-RA as the second-line therapy for ITP (Provan et al., 2019).

Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices

In this study, the effectiveness of therapy evaluated by analyzing changes in platelet count and indices towards normal ranges. Generally, effective therapy is associated with an increase in platelet count and normalization of platelet indices, characterized by a decrease in MPV, PDW, and P-LCR levels while PCT is expected to increase. This is consistent with the findings of this study which demonstrated an overall increase in platelet counts among the 35 (thirty-five) patients following

therapy, with a statistically significant difference ($p<0.05$). This finding suggests that the administered therapy effectively inhibited platelet destruction and stimulated platelet production through various mechanisms, leading to a positive therapeutic response as evidenced by the increase in mature circulating platelets (Negash et al., 2016).

This study analyzed 26 (twenty-six) patients for MPV levels, 25 for PDW, 19 for P-LCR, and 12 for PCT. The results showed a decrease in MPV, PDW, and P-LCR levels post-therapy, while PCT levels increased. The analysis indicates a significant difference between pre- and post-therapy levels for each component ($p<0.05$), with platelet counts, MPV, PDW, and P-LCR showing the most notable differences. Similar to the findings of Frelinger III et al. (2015), this study indicates that ITP treatment results in an increase in platelet counts and a normalization of platelet indices. This effect is attributed to the reduction in platelet destruction and controlled the increase in platelet production, resulting in a greater, more balanced proportion of mature platelets, which tend to be smaller in size, and fewer immature or giant platelets. This stabilization and reduced variability in platelet size contributed to the concurrent decreases in MPV, PDW, and P-LCR. Moreover, increased platelet production resulted in a higher blood volume proportion occupied by platelets, as reflected in the higher PCT levels, indicating an increased platelet count in circulation post-therapy (Walle et al., 2023).

Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices according to ITP Category

The analysis reveals that all three ITP categories started with low mean platelet levels, which increased significantly post-therapy ($p<0.05$), especially in the Newly Diagnosed and Chronic ITP categories. This indicates effective responses to therapy, with higher mature platelet production and more stable platelet levels. The highest mean platelet increase was seen in Newly Diagnosed ITP, with a delta of 318.89 x $10^3/\mu L$. Statistical analysis revealed significant differences in MPV, PDW, and P-LCR levels pre- and post-therapy levels in all categories ($p<0.05$), with Chronic ITP showing the most pronounced differences. These findings suggest that each ITP category responded well to therapy, as evidenced by reductions in MPV, PDW, and P-LCR levels towards normal ranges due to reduced platelet destruction and increased production of small, mature platelets, resulting in a more homogenous and orderly platelet distribution in the blood (Xu et al., 2023). In addition, Plateletcrit (PCT) level showed an increase in post-therapy. Statistical analysis presents a meaningful distinction between pre- and post-therapy in the Newly Diagnosed ITP ($p<0.05$), but not in Persistent and Chronic ITP ($p>0.05$).

Analysis of pre- and post-therapy levels in platelet count and indices shows that patients in the Newly Diagnosed ITP category exhibited significant differences in all blood parameters. Compared to other ITP categories, patients with Persistent and Chronic ITP showed significant differences in most blood components, except for PCT. Chronic ITP patients frequently exhibited significant changes across all blood components, except PCT. These findings suggest that patients with Newly Diagnosed ITP respond positively to treatment, achieving increased platelet levels and normalization of platelet indices. In case of Persistent and Chronic ITP categories, therapy improves platelet indices but may not sufficiently increase blood volume platelet proportion, as reflected in PCT levels. The effectiveness of treatment for ITP categories can vary depending on factors, such as the specific therapy used, its duration, and patient adherence. The study conducted by Liu et al. (2023) indicate that Newly Diagnosed and Persistent ITP patients often show better responses due to an active immune phase, while Chronic ITP patients may respond less effectively due to immune modulation and reduced activity. Furthermore, Chronic ITP patients tend to have elevated TFH cells, enhancing B-cell differentiation and antiplatelet antibody production (Yao et al., 2016). Although previous research indicated a reduced therapeutic response in Chronic ITP, this study observed favorable responses in platelet levels and normalization of MPV, PDW, and P-LCR, potentially due to differences in sample size, which the prior study involved 85 (eighty-five) pediatric ITP patients, while this study analyzed only 35 (thirty-five) cases, which may account for some variations in findings.

Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices according to the Therapy

The study results indicate a meaningful

distinction in platelet levels before and after therapy across all medication types, with platelet levels increasing post-therapy. The highest platelet delta was observed with prednisone, at 237.22 x $10^3/\mu l$. Statistical analysis revealed significant differences in platelet levels before and after therapy in patients treated with prednisone, methylprednisolone, and eltrombopag ($p<0.05$), with the most significant change observed in the prednisone group. However, patients with switched therapy from prednisone to eltrombopag did not show a meaningful distinction in platelet levels ($p>0.05$). This suggests that prednisone, methylprednisolone, and eltrombopag all produce a favorable therapeutic response by reducing platelet destruction and enhancing controlled platelet production, with prednisone showing the greatest average platelet increase. The lack of statistical significance in the prednisone to eltrombopag switched therapy could be associated to the limited sample and high variability in the data. Additionally, the short duration of eltrombopag administration in some patients may have influenced the results, as eltrombopag typically increases platelet levels within a period of 2 to 24 weeks (Kim et al., 2018).

The study also showed a decrease in MPV and PDW levels post-therapy, in line with the expected therapeutic response. Notable difference in MPV and PDW before and after therapy were detected in patients undergoing treatment with prednisone ($p<0.05$), while no significant differences were established in patients receiving therapy with methylprednisolone, eltrombopag, or prednisone switched to eltrombopag ($p>0.05$). This could be correlated to the limited sample in this analysis. The corticosteroid group showed the highest delta values for MPV and PDW, indicating that prednisone and methylprednisolone effectively reduced platelet destruction and promoted more homogenous platelet production in terms of size and morphology (Negash et al., 2016).

These results imply that corticosteroids, specifically prednisone, provide a favorable therapeutic response in children with ITP. The study conducted by Mazzucconi et al. (2024) similarly concludes that the administration of prednisone as a therapeutic approach can increase platelet levels, restore the platelet indices to normal levels, and maintain it over an extended period. Prednisone works through multiple mechanism, as an immunosuppressant, it inhibits platelet destruction by autoantibodies, reduces antiplatelet antibody production, enhances platelet production, and decreases structural changes in the endothelium, leading to reduced bleeding and platelet consumption (Kim & Despotovic, 2021).

Comparison between Pre- and Post-therapy Levels of Platelet Count and Indices of each Category according to the Therapy

Based on platelet levels, all medications administered to patients across different ITP categories resulted in an elevation of platelet levels post-therapy. The analysis revealed a significant difference in platelet levels before and after therapy for prednisone and methylprednisolone in the Newly Diagnosed ITP category ($p<0.05$), with prednisone indicating the most significant effect. In the Persistent ITP category, significant differences were also observed in platelet levels before and after prednisone therapy ($p<0.05$). While in chronic ITP, a meaningful distinction in platelet levels were noted before and after therapy for both prednisone and eltrombopag ($p<0.05$), with prednisone showing the most pronounced effect. However, patients in the Chronic ITP category, switched from prednisone to eltrombopag, showed a tendency for platelet increases, though no meaningful distinction was found in pre- and post-therapy platelet counts ($p>0.05$). This could be associated to the limited sample and high variability (as reflected in the standard deviation). Regarding MPV and PDW levels before and after therapy, all medication types administered across different ITP categories resulted in a decrease in both parameters. The analysis showed significant differences in MPV and PDW levels before and after therapy in all ITP categories ($p<0.05$). This suggests that prednisone therapy provides a favorable response by gradually increasing platelet counts and ensuring that circulating platelets are predominantly mature, resulting in a decrease in mean platelet volume and size variation (Mazzucconi et al., 2024).

The study also found a decrease in P-LCR levels post-therapy. Newly Diagnosed ITP category showed no significant difference in P-LCR levels before and after prednisone or methylprednisolone therapy ($p>0.05$). However, in the Persistent and Chronic ITP categories, significant differences in P-LCR levels were observed after prednisone therapy ($p<0.05$). In contrast, switching from prednisone to eltrombopag did not result a significant difference ($p>0.05$). This indicates that in Persistent and Chronic ITP categories, prednisone therapy

effectively controls platelet production, leading to a higher number of smaller and mature platelets compared to immature platelets, resulting in a reduced ratio (Kuter, 2021). The absence of significant differences in some variables could be influenced by the small sample size, which may not fully represent the therapeutic response in the entire population.

The results suggest that in all three ITP categories, prednisone demonstrates higher effectiveness compared to other medications in providing a favorable therapeutic response in children because prednisone has multiple mechanisms of action in eliciting a therapeutic response, including reducing platelet destruction, rapidly altering endothelial cell integrity to facilitate primary hemostasis, modulating cytokine production and inflammatory process, as well as reducing bleeding and bruising (Yan et al., 2023). Additionally, the duration of therapy and patient adherence significantly affect the effectiveness of treatment.

Strength and Limitations

This study presents the effectiveness of each therapy by providing a comparison of pre- and post-therapy of platelet counts and indices levels across the three ITP categories, as well as various therapeutic interventions. This research result may provide a valuable foundation for future research and may inform the selection of therapies for ITP patients. However, the small sample size and inadequate medical record data resulted in the inability to analyze certain platelet indices and other parameters, such as IPF, limiting the ability to fully assess the therapeutic response. Furthermore, several factors influencing the study outcomes including the duration of treatment, patient adherence to medication, patient immunity, disease onset, and disease recurrence are important factor that cannot be analyzed due to data limitations.

CONCLUSION

There are differences between the pre- and post-therapy levels of platelet count, MPV, PDW, P-LCR, and PCT in each ITP category and all therapy provided, where platelet counts and PCT increase, while MPV, PDW, and P-LCR decrease. Patients treated with prednisone demonstrates the most favorable therapeutic response. Similarly, patients with Newly Diagnosed ITP category also respond good to the therapy.

Acknowledgment

The authors express an intent to sincerely acknowledge and thank to the Faculty of Medicine Airlangga University and Dr. Soetomo General Academic Hospital Surabaya for their authorization and encouragement throughout the course of this research. Their collaboration and assistance are instrumental in facilitating the completion of this study.

Conflict of interest

None.

Ethical consideration

Ethical approval and research permission were secured from the Health Research Ethics Committee of the Dr. Soetomo General Academic Hospital Surabaya No. 1419/LOE/301.4.2/VIII/2023 dated 18/8/2023.

Funding disclosure

None.

Author contribution

RRCK contributed to the conceptualization and design of the study, data collection, analysis, and interpretation, as well as manuscript preparation. MRA, YH, and PZR participated in the study design, manuscript writing, and provided guidance and supervision throughout data collection, interpretation, and manuscript drafting.

REFERENCES

Al-Suheel, A., Alshehri, D., Alzahrani, M., Shati, A., Almedhesh, A., Dhafer, ;, Alshehri, B., & Alzahrani, M. (2014). Immune Thrombocytopenia among Children Living at a High Altitude Region A Hospital-Based Retrospective Study Immune Thrombocytopenia among Children Living at a High Altitude Region: A Hospital-Based Retrospective Study. *Cairo Univ*, *82*(2). www.medicaljournalofcairouniversity.net

Alwadi, K. W., Alomari, A., Alrugaib, A. K., Alrubayea, A., Alzoman, M., & Alkahtani, F. (2020). Clinical Characteristics and Outcomes of Pediatric Patients With Immune Thrombocytopenic Purpura in King Abdulaziz Medical City and King Abdullah Specialist Children's Hospital: A 10-Year Study. *Cureus*, *12*. https://doi.org/10.7759/cureus.11366

Frelinger III, A. L., Grace, R. F., Gerrits, A. J.,

Berny-Lang, M. A., Brown, T., Carmichael, S. L., Neufeld, E. J., & Michelson, A. D. (2015). Platelet function tests, independent of platelet count, are associated with bleeding severity in ITP. *Blood, The Journal of the American Society of Hematology*, *126*(7), 873–879. https://doi.org/10.1182/blood-2015-02

Friedman, J. N., & Beck, C. E. (2019). Diagnosis and management of typical, newly diagnosed primary immune thrombocytopenia (ITP) of childhood. *Paediatrics & Child Health*, *24*(1), 54–54. https://doi.org/10.1093/pch/pxy197

Hallan, D. R., Simion, C., Sciscent, B. Y., Lee, J., & Rizk, E. (2022). Immune Thrombocytopenic Purpura and Intracerebral Hemorrhage, Incidence, and Mortality. *Cureus*, *14*(4). https://doi.org/10.7759/cureus.24447

IBM Corporation. (2023). *IBM SPSS Statistics for Macintosh, Version 29.0.2.0*. IBM Corporation.

Kim, T. O., Despotovic, J., & Lambert, M. P. (2018). Eltrombopag for use in children with immune thrombocytopenia. *Blood Advances*, *2*(4), 454–461. https://doi.org/10.1182/bloodadvances.2017010660

Kim, T. O., & Despotovic, J. M. (2021). Pediatric immune thrombocytopenia (ITP) treatment. In *Annals of Blood* (Vol. 6, Issue 4). AME Publishing Company. https://doi.org/10.21037/aob-20-96

Kronzer, V. L., Bridges, S. L., & Davis, J. M. (2021). Why women have more autoimmune diseases than men: An evolutionary perspective. *Evolutionary Applications*, *14*(3), 629–633. https://doi.org/10.1111/eva.13167

Kuter, D. J. (2021). The treatment of immune thrombocytopenia (ITP)-focus on thrombopoietin receptor agonists. In *Annals of Blood* (Vol. 6, Issue March). AME Publishing Company. https://doi.org/10.21037/aob-21-23

Lee, J. M. (2023). Advances in management of pediatric chronic immune thrombocytopenia: a narrative review. In *Journal of Yeungnam Medical Science* (Vol. 40, Issue 3, pp. 241–246). Yeungnam University School of Medicine and College of Medicine. https://doi.org/10.12701/jyms.2022.00745

Liu, X. guang, Hou, Y., & Hou, M. (2023). How we treat primary immune thrombocytopenia in adults. In *Journal of Hematology and Oncology* (Vol. 16, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13045-023-01401-z

Mazzucconi, M. G., Rodeghiero, F., Avvisati, G., De Stefano, V., Gugliotta, L., Ruggeri, M., Vianelli, N., Fazi, P., Paoloni, F., Sargentini, V., Baldacci, E., Ferretti, A., Martino, B., Vincelli, I. D., Carli, G., Fortuna, S., Ianni, M. Di, Ranalli, P., Palandri, F., … Santoro, C. (2024). Prednisone vs high-dose dexamethasone in newly diagnosed adult primary immune thrombocytopenia: a randomized trial. *Blood Advances*, *8*(6), 1529–1540. https://doi.org/10.1182/bloodadvances.2023010975

Negash, M., Tsegaye, A., & Medhin, A. G. (2016). Diagnostic predictive value of platelet indices for discriminating hypo productive versus immune thrombocytopenia purpura in patients attending a tertiary care teaching hospital in Addis Ababa, Ethiopia. *BMC Hematology*, *16*(1), 18. https://doi.org/10.1186/s12878-016-0057-5

Neunert, C., Noroozi, N., Norman, G., Buchanan, G. R., Goy, J., Nazi, I., Kelton, J. G., & Arnold, D. M. (2015). Severe bleeding events in adults and children with primary immune thrombocytopenia: A systematic review. *Journal of Thrombosis and Haemostasis*, *13*(3), 457–464. https://doi.org/10.1111/jth.12813

Omar, I. M., Abuelela, S., & Emam, N. (2018). Value of Pre- and Post-Treatment Platelet Indices in Patients with Immune Thrombocytopenic Purpura. *Journal of Biosciences and Medicines*, *06*(09), 11–24. https://doi.org/10.4236/jbm.2018.69002

Perera, M., & Garrido, T. (2017). Advances in the pathophysiology of primary immune thrombocytopenia. *Hematology*, *22*(1), 41–53. https://doi.org/10.1080/10245332.2016.1219497

Pietras, N. M., Gupta, N., Vaillant, A. A. J., & Pearson, A. L. (2024, May). *Immune Thrombocytopenia*. National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/books/NBK562282/

Provan, D., Arnold, D. M., Bussel, J. B., Chong, B. H., Cooper, N., Gernsheimer, T., Ghanima, W., Godeau, B., González-López, T. J., Grainger, J., Hou, M., Kruse, C., McDonald, V., Michel, M., Newland, A. C., Pavord, S., Rodeghiero, F., Scully, M., Tomiyama, Y., … Kuter, D. J. (2019). Updated international consensus report on the investigation and management of primary immune thrombocytopenia. In *Blood Advances* (Vol. 3, Issue 22, pp. 3780–3817). American Society of Hematology. https://doi.org/10.1182/bloodadvances.2019000812

Saeidi, S., Jaseb, K., Asnafi, A. A., Rahim, F., Pourmotahari, F., Mardaniyan, S., Yousefi, H., Alghasi, A., Shahjahani, M., & Saki, N. (2014). Immune Thrombocytopenic Purpura in Children and Adults: A Comparative

Retrospective Study in IRAN. *International Journal of Hematology-Oncology and Stem Cell Research*, *8*(3), 30–36.

Saran, K., Vidya, K., Seema, K., Prasad, A., & Prakash, J. (2022). Study of platelet indices and their role in evaluation of thrombocytopenia. *Journal of Family Medicine and Primary Care*, *11*(10), 6236–6242. https://doi.org/10.4103/jfmpc.jfmpc_460_22

Sari, T. T. (2018). Immune Thrombocytopenic Purpura. *Sari Pediatri*, *20*(1), 58–64. https://doi.org/10.14238/sp20.1.2018.58-64

Subramaniam, N., Mundkur, S., Kini, P., Bhaskaranand, N., & Aroor, S. (2014). Clinicohematological Study of Thrombocytosis in Children. *International Scholarly Research Notices Hematology*, *2014*, 1–4. https://doi.org/10.1155/2014/389257

Walle, M., Arkew, M., Asmerom, H., Tesfaye, A., & Getu, F. (2023). The diagnostic accuracy of mean platelet volume in differentiating immune thrombocytopenic purpura from hypoproductive thrombocytopenia: A systematic review and meta-analysis. *PLoS ONE*, *18*(11). https://doi.org/10.1371/journal.pone.0295011

Wijaya, S. (2019). Immune Thrombocytopenia. *Cermin Dunia Kedokteran*, *46*(11), 658–661. https://doi.org/10.55175/cdk.v46i11.402

Xu, P., Han, S., Hou, M., Zhao, Y., & Xu, M. (2023). The serum lipid profiles in immune thrombocytopenia: Mendelian randomization analysis and a retrospective study. *Thrombosis Journal*, *21*(1). https://doi.org/10.1186/s12959-023-00551-x

Yan, X., Zhang, Y., Lang, H., Huang, Z., Chen, X., He, H., Zhao, Q., & Wang, J. (2023). Research on the mechanism of prednisone in the treatment of ITP via VIP/PACAP-mediated intestinal immune dysfunction. *European Journal of Medical Research*, *28*(1). https://doi.org/10.1186/s40001-023-00987-x

Yao, X., Li, C., Yang, J., Li, C., & Xia, Y. (2016). Differences in frequency and regulation of T follicular helper cells between newly diagnosed and chronic pediatric immune thrombocytopenia. *Blood Cells, Molecules, and Diseases*, *61*, 26–36. https://doi.org/10.1016/j.bcmd.2016.06.006