RETROSPECTIVE EVALUATION OF THE OUTCOME OF IMMUNE THROMBOCYTOPENIA IN CHILDREN AND ADOLESCENTS: SINGLE CENTER EXPERIENCE

By

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ABSTRACT

Background: *Primary immune thrombocytopenia (ITP) represents the commonest cause of isolated thrombocytopenia among children & adolescents; that's characterized by variable presentations and varied outcomes of disease differentiated into; acute, persistent, or chronic depending upon illness duration; with efforts made to increase knowledge about possible outcome predictors.*

Aim: *we aimed to study disease characteristics & outcome predictors among 50 enrolled patients.*

Methods: *This retrospective cohort study included collection of; demographic data, bleeding phenotype, Buchanan bleeding score onset of symptoms prior to diagnosis, proceeding viral infection or vaccination, initial platelet count & bone marrow finding, received treatment as well as; response to treatment among 50 patients already diagnosed as primary ITP child and adolescent which followed up since 2012 till 2020 in pediatric hematology clinic, Ain Shams University. Patients were further subdivided into acute, persistent & chronic ITP groups.*

Results: *Among included cohort; 38 (76.0%) were males of median (IQR) age of 5.25 (2.5-8.5) years. Chronic ITP represented the most prevalent outcome in the cohort 58.0%(n=29), with acute ITP 32.0%(n=16) & persistent ITP 10.0% (n=5). Among the chronic ITP group in comparison to other groups; female was more than third the patients 34.5% (n=10), 72.4%(n=21) reported >2weeks disease related symptoms with no seasonal peaks of diagnosis, 10%(n=1) presented initially with menorrhagia, Yet no statistical differences between groups regarding associated autoimmune symptoms, bleeding score, nor initial platelet count (p= 0.91, p=0.078, p=0.955) respectively. All chronic ITP groups required steroids in initial treatment with significant difference in*

response to treatment & recurrence of the disease (p=0.00) as none showed complete remission and all patients experienced disease recurrence.

Conclusion: *Different presentation of primary ITP. e.g. gender, bleeding symptoms, treatment among children can potentially serve as clinical predictors of outcome.*

Key words: *Chronic ITP, bleeding score.*

INTRODUCTION

Primary immune thrombocytopenia (ITP) constitutes the most diagnosed acquired pediatric bleeding disorder with an approximate annual incidence of almost 5 in each 100 children **Neunert et al. (2019)**. To date little is known about the precise etiology of primary ITP; with the most assumed cause; being self-production of auto-generating antiplatelet autoantibodies **Cooper and Ghanima. (2019)** mediating a subsequent macrophage induced platelet destruction in the liver & spleen through Fc receptor activation. This process is thereafter followed by phagocytic presentation of engulfed platelet antigens to T helper cells subtype 1 & 17, with the concurrent inhibition of the T regulatory (T Reg) cells leading to a pathologic T cell response **Lee JM. (2023)**.

In pediatric population, typical primary ITP occurs at ages between 2 to 7 years, mostly preceded by the reported history of viral infection 2–4 weeks before initial presentation, Yet there are also older ages at initial presentation, with a different autoimmune predisposition **Segal and Fogarty (2007)**.

ITP is generally characterized by a benign course of the disease with the most frequent sites of bleeding are the skin and superficial oral mucous membrane, epistaxis, and non-life-threatening menorrhagia **Makis et al. (2017)**. While spontaneous life-threatening intracranial bleeding rarely occurring in less than 1% of children, with critical levels of thrombocytopenia **Arnold DM. (2015)**. Treating children with acute ITP rests primarily upon treating bleeding phenotypes, were children with no symptoms or mild bleeding are for initial active observation, regardless the platelet count, while patients with symptomatic severe forms of bleeding require treatment in the form of, intravenous immunoglobulin (IVIG), anti-D immunoglobulin, or corticosteroids **Provan et al. (2010)**.

Managing children with persistent/chronic ITP holds same

concepts & indications for treatment start as in acute ITP, yet taking into consideration that the longer the duration, the less chances of spontaneous rise in platelet count, for which management should also relay on the platelet count impact over their quality-of-life **Provan et al. (2019)**.

Given this heterogeneity among minority of ITP patients in presentation, disease course & severity; as well as disease duration; several studies have been evolving to determine disease features as predictor for outcomes among children with primary ITP **Heitink-Pollé et al. (2014)**. in which the Intercontinental Cooperative ITP Study Group Registry II determined suggested; younger initial age of presentation, mild bleeding phenotype, and 1st line treatment with combination of steroids & IVIG; were predictors of the disease recovery during the initial 12 months since diagnosis **Bennett et al. (2018)**.

With more understanding of the primary ITP landscape among children & adolescents; we aimed to thoroughly examine disease characteristics, course, treatment response and disease outcome.

Ethical consideration:

1. An approval of the Ethical Committee of Faculty of Medicine, Ain Shams University under acceptance number 9iFMASU MS 84/ 2023 was obtained.
2. An Informed consent was taken from parents or care givers before getting involved in study.
3. Financial disclosure: The author received no financial support for the research.
4. The authors declared no potential conflicts of interest with respect to the research and publication of the research.
5. The data of the study are confidential and the patient has the right to keep it.
6. The patient has the right to refuse.

Methodology:

This retrospective cohort study was carried out during the period from February 2023 till December 2023 at the Pediatric Hematology department, Ain Shams University. Data of Pediatrics and adolescent patients diagnosed & following up as primary ITP in the period between 2012 till 2022 were included.

Inclusion Criteria:

- Already diagnosed pediatric primary ITP patients.

- The age of >6months<18 years.
- Both sexes.

Exclusion criteria:

Patients with; Evan's syndrome, hereditary platelet deficiency, or uncertain diagnosis of isolated thrombocytopenia.

Study Tools:

Data collected from already diagnosed ITP. patients' records during the period from 2012 to 2020 including:

1. Demographic data: age, gender, consanguinity, family history of any similar conditions or related conditions, sibling death or abortions.
2. Disease presentation and status: age at disease presentation, type of treatment, reported treatment related adverse events& 12 months follow up disease outcome.
3. Possible predictors of outcome including seasonal variation, symptoms and disease progression, preceding history of infection (within 2-4 weeks prior to the initial presentation), presence of any autoimmune symptoms, any life-threatening bleeding, need for hospital admission, initial platelet count & bone marrow (BM) aspiration & trephine findings, surveillance of viral etiology (cytomegaly-virus (CMV) & Epstein-bar virus (EBV) IgM), response to treatment (clinicalo-laboratory), & recurring episodes of the disease.

For disease status and response, we followed the criteria of the American Society of Hematology 2019 guidelines for immune thrombocytopenia **(Neunert et al. (2019)**. Defining patients' outcome according to time to remission: "Patients who entered in remission within 3 months of initial diagnosis were defined as acute ITP; within 3 to < 12 months as persistent ITP, while those with thrombocytopenia lasting > 12 months were defined as chronic ITP". Recurrent ITP defined as: "The patients who had a short transient response to treatment with drop of the platelet count to less than 100 x109/L after entering remission 3 months later were defined as recurrent ITP:

4. Lines of management: All enrolled patients were managed according to the local institute protocol for management of newly diagnosed children & adolescents with primary ITP adopting active observation in patients' with no or minimal

bleeding, **Neunert et al. (2019)**.

1st line therapy: with corticosteroids &/or IV IG in patients with life-threatening or nonlife-threatening extensive cutaneous or oral mucosal bleed,

2nd line therapy: with thrombopoietin receptor agonists (TPO-RAs) or mycophenolate mofetil (MMF) in patients without complete response to 1st line therapy after 3 months from initial diagnosis.

Regarding response to treatment, **Provan et al. (2019)** definition based upon achieved platelet increment after the 1st or 2nd line of treatment, with increment of platelet counts to ≥100 x 109/L is defined as complete response (CR), platelet count of <100 x 109/L≥20 x 109/L is identified as partial response (PR) and platelet count of <20 x 109/L despite treatment is described as unresponsiveness.

Statistical analysis:

Data was analyzed using the Statistical Package for Social Science (IBM SPSS) version 27. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, and inter-quartile range (IQR) when data was non-parametric. Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent t-test while with non-parametric distribution done by using Mann-Whitney test. The comparison between more than two groups regarding quantitative data and parametric distribution was done by using One Way ANOVA test while with non-parametric distribution was done by using Kruskall-Wallis test. So, the p-value was considered significant as the following: P-value > 0.05: Non-significant (NS), P-value < 0.05: Significant (S), P-value < 0.01: Highly significant (HS).

RESULTS

Our results will be demonstrated in the following tables:

Table (1): Demographic data & clinical- characteristics of the disease

Demographic and clinical data		**Total no.=50**
Age at diagnosis (years)	Median (IQR)	5.25 (2.5-8.5)
	Range	1.25 – 14
Gender	male	12 (24%)
	female	38 (76%)
Presenting bleeding		
Non-life threatening mucocutaneous bleed		34 (68%)
Life threatening Hematemesis		1 (2%)
Life threatening Hematuria		3 (6%)
Menorrhagia		1 (2%)
Condition prior to diagnosis		
Preceded viral infection		17 (34%)
Onset of the symptoms prior to diagnosis	<2week >2week	18 (36%) 32 (64%)

This table shows demographic data & clinical- characteristics of the studied patient.

Table (2): Seasonal variation at time of disease diagnosis

	Months	**Total no.=50**
time of disease diagnosis	January	1 (2%)
	February	7 (14%)
	March	1 (2%)
	April	4 (8%)
	May	6 (12%)
	June	5 (10%)
	July	6 (12%)
	August	1 (2%)
	September	4 (8%)
	October	14 (28%)
	November	1 (2%)

This table shows that most of the studied patients were admitted in October [14 patients (28.0%)] followed by February [7 patients (14%) and followed by May and July [6 patients (12.0%) for each of them.

Table (3): Comparison of the studied group with different disease status regarding initial laboratory data

		Chronic ITP No. = 29	Acute ITP No. = 16	Persistent ITP No. = 5	Test value	P-value
Initial PLT	**Median (IQR)**	14 (7 - 33)	10 (8 - 28)	5 (5 - 61)	0.092≠	0.955
	Range	3 - 68	2 - 75	5 – 80		
Initial HGB	**Median (IQR)**	9 (7.4-11.2)	11(10.4 -12.2)	11(10.4 -12.2)	0.973•	0.615
	Range	6.1 - 14.6	9.3 - 14.5	8.6 - 11.2		
Initial TLC	**Median (IQR)**	6.5 (5.5 - 9.7)	7.9 (5 - 10.7)	9 (8.5 - 10.5)	2.113≠	0.348
	Range	4 - 15.9	4.3 - 21.2	6 - 14.3		
BM aspirate or trephine	**Not done**	2 (6.9%)	2 (12.5%)	0 (0%)	0.923*	0.630
	Done	27 (93.1%)	14 (87.5%)	5 (100%)		
BM megakaryocyte percentage	**Slightly increase**	24 (88.9%)	14 (100%)	5 (100%)	2.258*	0.688
	Normocellular BM	2 (7.4%)	0 (0%)	0 (0%)		
	Moderately increase	1 (3.7%)	0 (0%)	0 (0%)		

Table (3) shows that there was no statistically significant difference found between chronic, acute and persistent ITP groups regarding laboratory parameters, BM aspiration.

Table (4): Disease outcome at the end of diagnosis

		Total no.=50
Currant diseases status	Chronic ITP	29 (58.0%)
	Acute ITP	16 (32.0%)
	Persistent ITP	5 (10.0%)

The table shows that 29 patients (58.0%) were diagnosed as chronic ITP, 16 patients (32.0%) were diagnosed as acute ITP and 5 patients (10.0%) were diagnosed as persistent ITP.

Table (5): Predictors of outcome among acute, persistent & chronic ITP

		Chronic ITP	Acute ITP	Persistent ITP	Test value	P-value
		No. = 29	N=16	N=5		
Age at diagnosis (years)	Median (IQR)	6 (3 - 8.5)	4.5 (2 - 6.5)	4 (3 - 9)	1.995≠	0.369
	Range	1.5 – 14	1.25 – 13	2.5 – 12		
Gender	Female	10 (34.5%)	1 (6.2%)	1 (20%)	4.555*	0.103
	Male	19 (65.5%)	15 (93.8%)	4 (80%)		
Onset of Symptoms prior to diagnosis	>2weeks	8 (27.6%)	7 (43.8%)	3 (60%)	2.558*	0.278
	<2weeks	21 (72.4%)	9 (56.2%)	2 (40%)		
Mucocutaneous manifestation		17 (58.6%)	15 (93.8%)	2 (40%)	7.849*	0.020
Proceeding viral infection		7 (24.1%)	8 (50%)	2 (40%)	3.162*	0.206
Other autoimmune symptoms		4 (13.8%)	2 (12.5%)	1 (20%)	0.180*	0.914
Observation		2 (6.9%)	3 (18.8%)	0 (0%)	2.227*	0.328
Oral steroid		29 (93.1%)	14 (81.2%)	5 (100%)	4.813*	0.307
Intravenous Pulse steroids		16 (48.3%)	6 (37.5%)	1 (20%)	12.704*	0.013
Number of steroid courses	Once Twice	24 (82.8%) 5 (17.2%)	13 (81.2%) 1 (6.2%)	4 (80%) 1 (20%)	5.288*	0.259
TPO-RAs		19 (65.5%)	3 (18.8%)	4 (80%)	10.780*	0.005
IVIG		6 (20.7%)	6 (37.5%)	1 (20%)	1.618*	0.445
MMF		11 (37.9%)	1 (6.2%)	3 (60%)	7.309*	0.026
Response	Partial Complete	29 (100%) 0 (0%)	0 (0%) 16 (100%)	5 (100%) 0 (0%)	50.000*	0.000
Recurrence		24 (82.8%)	0 (0%)	0 (0%)	33.422*	0.000

(TPO-RAs): Thrombopoietin receptor agonist, (IVIG): Intravenous Immunoglobulin,

This table shows that there was statistically significant increase in the percentage of patients receiving TPOs in chronic and persistent groups [(65.5%) and (80%)] than acute ITP group (18.8%) with p-value = 0.005, and increase response in Acute ITP with p-value (000), increase mucocutaneous symptoms in acute ITP with p-value (0.020).

DISCUSSION

Though reported as the most common acquired bleeding disorder among children **Orkin et al. (2015)** primary ITP represents a heterogeneous disease entity of varying etiologic and clinical outcomes. **Cines et al. (2009)** More than 80% of acute primary ITP recover spontaneously, yet 20% develop persistently low platelet counts, diagnosed as chronic ITP, **Cheng et al. (2023)** with the lack of early clinical predictors of this variable outcome that can aid with the treatment decisions **Cooper N. (2014)**.

In the current study, a male to female ratio was 3:1, with median age at time of diagnosis of 5.25 years, presenting initially in more than 90% of the cohort with nonlife-threatening bleeding related to the skin &/or superficial oral and nasal mucosa, though the median initial platelet count was substantially low (12.5 x109/L). One of the largest studies of pediatric ITP natural disease history including 2031 children; by the Intercontinental Childhood ITP Study Group (ICIS) **Kühne, et al. (2001)**, the male-to female ratio was 1.2:1, and the mean age at diagnosis was 5.7 years, with a mean initial platelet count of 15x109/L & rarely presenting life-threatening bleeds.

Among the enrolled cohort none developed ICH, which coincides with the previous Egyptian multi-center report of 0.63% of ICH among included 4340 pediatric ITP patients over 2 decades reflecting the benign disease course and presentation **Elalfy et al. (2021)**.

Adult ITP data consistently suggests against seasonal trends in ITP diagnosis **Giri et al. (2015)** which comes in contrast with pediatric ITP whom data confirms seasonal peaks of the disease diagnosis **Moussalem and Yassine et al. (2003)**, in the current cohort we observed a strikingly sharp peak of 36% of the patients' disease presentation during autumn months of September & October, along with another minor peak of 14% of the patients' diagnosed in rainy months of February. Those seasonal trends follow the highest peaks of viral respiratory tract infection in children, that's' have been reported to proceed the ITP diagnosis in up to (79%) of children with acute/persistent ITP **Makis et al. (2017)**.

In the current study, 92% of the patients had a BM examination done, this practice tends to change with time where less patients are having this study recently. BM evaluation is considered

recommended initially only if other abnormalities co-occurring including boney-aches, hepatosplenomegaly, presence of other cytopenia, &/or before starting a 2nd line therapy after failure of response to the 1st line therapy for exclusion of other causes of thrombocytopenia as inherited/acquired bone marrow failure **Provan et al. (2010)**.

No doubt, the general concepts of ITP treatment are notably differing between adult & pediatric population, with the active observation being the most adopted 1st line in pediatric ITP; unlike the higher risk of severe bleeding & the less likelihood of achieving spontaneous remission in adult ITP, making the start of medical treatment among adults mandatory in the setting of low platelet count less than 30x109/L regardless of the associated bleeding manifestations **Kim and Despotovic, (2021)** in contrast, only 10% of our reported cohort were offered active observation.

In the studied cohort, adopted second line therapies included TPO-RAs 52.0% of the patients & MMF in 30.0%, reflecting the paradigm shift in 2nd line therapies in ITP from previously adopted immunosuppressive therapy to the growing use of TPO-RAs.

Eltrombopag & romiplostim gained the US Food and Drug Administration in 2008 for treating adult chronic ITP, which was followed in 2015; by Eltrombopag approval for treating pediatric chronic ITP .,Both drugs are now being increasingly used in the pediatric and adult ITP owing to their efficacy, safety along with the reported health related quality of life improvement among patients with ITP **Wong et al. (2017)** By the end of 12 months of follow up, 58% of the patients were labelled as chronic ITP patients. In an Egyptian single center report, out of 308 children with ITP, chronic ITP was the reported outcome in 71.4% **Diab et al. (2021)**, also reported among 343 children with ITP by the ICIS group, 36% were reporting platelet count <100x109/L by the end of the 12th months from diagnosis **Neunert et al. (2013)**.

Focusing into clinical and laboratory factors that can serve as a possible outcome predictor, we observed no age difference among patients with chronic as well as; patients with acute/persistent ITP, yet 83% of the enrolled females were among the chronic ITP group. Similar trends shown in a systematic review and meta-analysis by Katja et al., 2014, including 54 studies about possible chronic ITP predictors the

authors concluded that chronic ITP patients was significantly observed among older children and involving females more than acute/persistent ITP patients **Heitink-Polle et al. (2014)**. In the Intercontinental Childhood ITP Study Group, chronic ITP occurrence was concluded being more among older children > 10 years, & females **Kühne et al. (2003)**.

In our analysis highest reports of preceding viral infection was among patients with acute & persistent ITP (50% & 40% respectively), unlike 24% of chronic ITP patientss. In an analysis targeting chronic ITP children in Japan, it was concluded that absence of a reported preceding viral infection shortly before the initial ITP presentation can serve as a strong chronicity predictor **Kubota et al. (2010)** The initial platelet count showed no significant difference between chronic & acute/persistent ITP patients (p=0.95), there was differing presenting bleeding phenotypes among the patients, with 93% of acute ITP group presenting with mild mucocutaneous bleed. **Glanz et al., 2008** reported no difference in the initial bleeding severity between acute & chronic ITP patients, yet significantly higher initial platelet counts among patients with chronic ITP, concluding that among their cohort a 4 folds increase in risk of chronicity among females with initial presenting higher platelet counts **Glanz et al. (2008)**.

Addressing ITP treatment regimens among acute and chronic ITP pediatric patients, report by the ICIS Group demonstrated children with 32% of acute ITP received IV IG in contrast to 13% among chronic ITP patients, Likewise, though statistically not significant (p=0.78) higher rates of IVIG use among patients with acute ITP in Makis et al., 2017 study). Similarly in our cohort IV IG & active observation have been used mainly among acute ITP patients in 37.5% & 18.8% respectively, with increased steroids (oral &/or IV) use, among all chronic & persistent patients, and in 80% of acute ITP patients. Interestingly, regarding the initial type of treatment received & its impact on the disease course, the meta-analysis by **Katja et al., 2014** reported that combining corticosteroids with the IVIG in the initial treatment regimen to be significantly associated with higher chronic outcome (OR 2.67) **Heitink-Polle et al. (2014)**.

As for 2nd line therapies among the current studies; TPO-RAs showed statistically significant

(p=0.005) higher use among persistent & chronic ITP patients. TPO-RAs &/or immunosuppressive use is increasingly addressed not only in the setting of chronic/persistent ITP, but recently in acute ITP in recent pediatric clinical trials which shall add to the knowledge about their possible impact over the course of the disease **Grace and Lambert, (2022)**.

Initial response to treatment is among the strongest predictors of disease outcomes in the setting of variable hematologic disorders, given the lack of similar evidence among pediatric ITP patients, the current study confirmed a statistically significant response to 1st line therapies (p=0.00) among different ITP groups, with all of the chronic ITP groups achieving only PR, unlike CR seen in all acute ITP patients.

Disease recurrence was statistically higher among females, the chronic ITP group, patients receiving TPO-RAs. In a similar study reporting outcome of 71 pediatric ITP patients treated with 1st line therapy IV IG, steroids, & anti-D, 68.9% showed a response following initiation of therapy with 33 % of the patients confirmed chronic ITP after the initial 12 months follow up, recurrences were observed in both acute and chronic ITP patients (45% vs 55% respectively) **Grace and Lambert, (2022)**.

CONCLUSION

Typical pediatric ITP is usually a disease of young age<10years, of slight male predominance, with mild initial disease presentation in spite of low platelet counts. Variable disease outcomes were encountered with gender, history of preceding viral illness, bleeding phenotype, & initially adopted treatment line and response, thus serving as a possible outcome predictor.

RECOMMENDATION

- Mandatory identification of ITP natural history, outcome predictor among the studied patient.
- Further studies are needed to confirm these results.

STUDY LIMITATIONS

- Refusal of some parents.
- Withdrawal of some cases.

REFERENCES

1. **Neunert C, Terrell DR, Arnold DM, et al. (2019):** American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv; 3:3829-66.
2. **Cooper N, Ghanima W. (2019):** Immune thrombocytopenia. N Engl J

Med; 381:945–55.

3. **Lee JM. (2023):** Advances in management of pediatric chronic immune thrombocytopenia: a narrative review. Yeungnam University Journal of Medicine.;40(3):241-246.
4. **Fogarty PF, Segal JB. (2007):** The epidemiology of immune thrombocytopenic purpura. Current opinion in hematology.; 14(5):515-519.
5. **Makis A, Gkoutsias A, Palianopoulos T, et al. (2017):** Prognostic factors for immune thrombocytopenia outcome in Greek children: A retrospective single-centered analysis. Advances in hematology.; 1-7.
6. **Arnold DM. (2015):** Bleeding complications in immune thrombocytopenia. Hematology 2014, the American Society of Hematology Education Program Book.; (1):237-242.
7. **Provan D, Stasi R, Newland AC, et al. (2010):** International consensus report on the investigation and management of primary immune thrombocytopenia. Blood, The Journal of the American Society of Hematology.; 115(2):168-186.
8. **Provan D, Arnold DM, Bussel JB, et al. (2019):** Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood advances.; 3(22):3780-817.
9. **Heitink-Pollé KM, Haverman L, Annink KV, et al. (2014):** Health-related quality of life in children with newly diagnosed immune thrombocytopenia. Haematologica.; 99(9):1525-1531.
10. **Bennett CM, Neunert C, Grace RF, et al. (2018):** Predictors of remission in children with newly diagnosed immune thrombocytopenia: Data from the Intercontinental Cooperative ITP Study Group Registry II participants. Pediatric blood & cancer.; 65(1): e26736.
11. **Orkin SH, Nathan DG, Ginsburg D, et al. (2015):** Nathan and Oski's Hematology of Infancy and Childhood. 8th ed. Philadelphia, PA: Saunders Elsevier.
12. **Cines DB, Bussel JB, Liebman HA, et al. (2009):** The ITP syndrome: pathogenic and clinical diversity. Blood.;113(26):6511-6521.
13. **Cheng CN, Yang YN, Yeh YH, et al. (2023):** Predictors of Remission in Severe Childhood Immune Thrombocytopenia. Diagnostics.; 13(3):341.
14. **Cooper N. (2014):** A review of the management of childhood immune thrombocytopenia: how can we provide an evidence-based approach? Br J. Haematol.;165(6):756-767.
15. **Kühne T, Imbach P, Bolton-Maggs PH, et al. (2001):** Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. The lancet.; 358(9299):2122-5.
16. **Elalfy MS, Eltonbary KY, El Ghamry IR, et al. (2021):** Intracranial hemorrhage in primary immune thrombocytopenia (ITP): 20 years' experience in pediatrics. European journal of pediatrics.;

180:1545-552.

17. **Giri S, Pathak R, Aryal MR, et al. (2015):** Seasonal variation of immune thrombocytopenic purpura related hospitalizations among adults in the USA: analysis of the nationwide inpatient sample database. Therapeutic Advances in Hematology.; 6(4):217-8.
18. **Moussalem M, Yassine N. (2003):** Immune thrombocytopenic purpura in childhood: a Lebanese perspective. Molecular immunology.; 39(17-18):1105-1107.
19. **Kim TO, Despotovic JM. (2021):** Pediatric immune thrombocytopenia (ITP) treatment. Ann Blood.; 6(4).
20. **US Food and Drug Administration (2018):** Eltrombopag. Available at www.accessdata.fda.gov/scripts/cder /daf/index.cfm?event5overview. process&applno5022291. Accessed 22 May.
21. **Wong RSM, Saleh MN, Khelif A, et al. (2017):** Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood.;130(23):2527-2536.
22. **Diab AM, Abouamer AA, Motaleb GS, et al. (2021):** Prognostic evaluation of immune thrombocytopenia outcomes in Egyptian children: a retrospective single-center experience. Вопросы гематологии/онкологии и иммунопатологии в педиатрии.; 20(3):26-30.
23. **Neunert CE, Buchanan GR, Imbach P, et al. (2013):** Bleeding manifestations and management of children with persistent and chronic immune thrombocytopenia: data from the Intercontinental Cooperative ITP Study Group (ICIS). Blood, The Journal of the American Society of Hematology.; 121(22):4457-4462.
24. **Heitink-Polle KM, Nijsten J, Boonacker CW, et al. (2014):** Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. Blood, The Journal of the American Society of Hematology.; 124(22):3295-307.
25. **Kühne T, Buchanan GR, Zimmerman S, et al. (2003):** A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. The Journal of pediatrics.; 143(5):605-608.
26. **Kubota M, Adachi S, Usami I, et al. (2010):** Characterization of chronic idiopathic thrombocytopenic purpura in Japanese children: a retrospective multi-center study. Int J Hematol.; 91(2):252-257.
27. **Glanz J, France E, Xu S, et al. (2008):** A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. Pediatrics.; 121(3): 506-612.
28. **Grace RF, Lambert MP. (2022):** An update on pediatric ITP: differentiating primary ITP, IPD, and PID. Blood, The Journal of the American Society of Hematology.; 140(6):542-555.
29. **Huma Z, Saadia A, Mahwish F, et**

al. (2018): Clinical features and outcome in paediatric newly diagnosed immune thrombocytopenic purpura in a tertiary care centre. Pak J Med Sci.; 34 (5).