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Prognosis and risk factors of chronicity in childhood idiopathic thrombocytopenic purpura: a single-center experience

Hatice Mine Çakmak[1], Kenan Kocabay[2]

[1] Duzce University, Faculty of Medicine, Department of Pediatrics, Department of Pediatric Hematology-Oncology, Duzce, Türkiye
[2] Duzce University, Faculty of Medicine, Department of Pediatrics, Duzce, Türkiye

Abstract

Objective: In previous studies, chronicity risk factors for idiopathic thrombocytopenic purpura (ITP) are unclear. This study aimed to evaluate the outcome of children with ITP and determine the chronicity risk factors.
Methods: This study retrospectively examined the demographics, laboratories, outcome, and chronicity risk factors among sixty children with ITP and obtained the data from the computer system. We analyzed demographics, treatment, and laboratory risk factors for chronic ITP by IBM SPSS and used binary logistic regression analysis.
Results: Of 60 children with ITP, 32 (53.3%) had acute, 25 (41.7%) had chronic, and 3 (5%) had persistent ITP. Demographics, laboratories (age <4 years, thrombocyte count at diagnosis, serum LDH, neutrophil count, mean platelet volume, status and grade of bleeding, infection in the last month) were unrelated to chronic ITP. As a new finding, loss of treatment response rates predicts chronicity in both univariate OR [2.56 (1.25 – 5.25)](p=0.01) and multivariate analysis OR [3.873 (1.488–10.08](p=0.006). Among second-line therapies, eltrombopag (n=6) achieved a durable response of thrombocyte count for more than 50.000/mm³ in five. However, two required the cessation of treatment two due to renal failure. Of two splenectomized patients, one could not achieve remission.
Conclusion: Lower platelet counts (<20.000/mm³), younger age, male gender, and initial treatment regimens (IVIG, steroid, IVIG plus steroid) did not influence chronicity in our study. We suggest that loss of response rates predicts chronicity as a new factor.
Keywords: Idiopathic Thrombocytopenic Purpura, Chronic, Children

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disease with increased thrombocyte destruction and decreased production. The condition resolves spontaneously (1).

First-line treatment includes steroids (high-dose dexamethasone or prednisone), IV immunoglobulin (IVIG), or both for selected cases. The second-line therapies are thrombopoietin reseptör agonists (eltrombopag, romiplostim), rituximab, and splenectomy. Immunosuppressive agents (e.g., azathioprine, cyclosporine, mycophenolate mofetil, etc.) are rarely used (1).

Risk factors for chronic ITP are age, thrombocyte level, insidious symptoms, no history of vaccination or infection, or chronic diseases at diagnosis. As a chronicity risk factor, age >4 years (2,3,4), thrombocyte count <20.000/mm³ at diagnosis and male sex are defined in other studies (5,6,7). However, male sex predominance is frequent at younger ages. Finally, the thrombocyte count at diagnosis was not associated with chronicity in ITP (8). Low white blood cell count, which differs according to age, was related to chronicity in ITP. However, it was not considered an independent variable. IVIG treatment was found to lower the risk of chronic ITP. However, IVIG is associated with lower thrombocyte counts and symptomatic illness at

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Corresponding Author: Hatice Mine Çakmak, Duzce University, Faculty of Medicine, Department of Pediatrics, Duzce, Türkiye
Email: h.m.tokuc@hotmail.com
ORCID iD: 0000-0003-3730-0982

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diagnosis (9). A randomized control trial found that IVIG was not an independent risk factor for chronic ITP (10).

In this retrospective study, we aim to report the outcomes of children with ITP. In addition, chronicity risk factors (age, neutrophil level, sex, the severity of bleeding, treatment with IVIG, steroid, or both, and rate of loss of response to treatment) were also investigated.

METHOD

In this study, the University computer database is retrospectively examined, and the data of children with primary ITP is recorded. This data included age at diagnosis, sex, infection in the last month, type and severity of bleeding, treatments and their cycles, thrombocyte levels at diagnosis, and the sixth month, first, and second year of diagnosis. In addition, each patient's disease course was evaluated. The subjects were diagnosed from 2010 to 2021 in our University Pediatrics Clinic. We followed all for more than or equal to one year. The exclusion criteria were inadequate follow-up (<1 year), having secondary ITP like collagen tissue disorders and malignancies.

The disease course lasted <3 months is defined as acute, 3-12 months as subacute, and >12 months as chronic. Chronic ITP has a prevalence of 10%-20%. Response to treatment was having a thrombocyte count ≥ 30.000/mm³ or two-fold the baseline level without bleeding. Complete loss of response to treatment is defined as having a thrombocyte count <100.000/mm³ or bleeding. Partial loss of response treatment is having a thrombocyte count of <30.000/mm³ or less than the basal thrombocyte count or bleeding. Recovery was defined as having a thrombocyte count over 150.000/mm³ for at least one month without any treatment. Corticosteroid dependency was the continuation of steroid treatment to avoid bleeding and maintain a platelet count above 30.000/mm³. Corticosteroid resistance is defined as having thrombocyte levels below 30.000 or bleeding or below the two hold of the beginning thrombocyte level despite adequate corticosteroid treatment. First-line therapies were IVIG, corticosteroid, IVIG plus corticosteroid. Second-line treatment included eltrombopag, mycophenolate mofetil, and splenectomy (11).

Statistical Analysis

This study analyzed demographics, treatment, and laboratory risk factors for chronic ITP by IBM SPSS and used binary logistic regression analysis. Categorical variables are represented as absolute numbers and percentages. Mean and standard deviation represented typically distributed quantitative variables. Not usually, allocating variables were expressed as medians and ranges. For example, a $p<0.050$ was reported as significant. The local ethics committee approved the study on 09.05.2022 with the approval number 2022/85. Informed consent was obtained.

RESULTS

Of sixty children diagnosed between 2010-2021 with primary ITP in our university pediatrics clinic, 32 (53.3%) had acute, 25 (41.7%) had chronic, and 3 (5%) had persistent ITP. Most of them, 38 (63.3%), were male. Skin manifestations included children with petechia, purpura, and ecchymosis 31 (52.5%). In forty-three (86%), the severity of bleeding was mild (Table 1).

Table 1. Demographics of children with *ITP

Variables	mean	SD
Age year)	7.1	4.74
	n	**(%)**
Sex		
Male	38	63.3
Female	22	36.7
Disease course		
Acute	32	53.3
Chronic	25	41.7
Subacute	3	5
Bleeding type		
none	9	15.3
Skin	31	52.5
Epistaxis	10	16.9
All	7	11.9
Mucosal	2	3.4
Bleeding severity		
Mild	43	86
Moderate	5	10
Severe	2	4
Treatment		
¶ IVIG alone	18	30
Corticosteroid alone	19	31.6
IVIG plus corticosteroid	19	31.6
Corticosteroid dependency	11	19
Corticosteroid resistance	3	5
Eltrombopag	6	10
╬MMF	2	3.3
Splenectomy	3	5
Remission		
Not in remission	14	24.1
In remission	44	75.9

Abbreviations: *ITP (immune thrombocytopenia), ¶IVIG (intravenous immunoglobin), ╬MMF (mycophenolate mofetil)

Table 2. Thrombocyte levels during the follow-up and first-line treatments

	Median	[minimum – maximum]
Thrombocyte count at 6th month (/mm³)	155000	[200 - 603000]
Thrombocyte count in the first year (/mm³)	213000	[5000 - 389000]
Thrombocyte count in the second year (/mm³)	201000	[4000 - 459000]
The last thrombocyte count (/mm³)	232000	[18390 - 543000]
IVIG cycles	1	[1 - 33]
IVIG cycles in the first year	1	[1 - 9]
Steroid cycles	1	[1 - 10]
IVIG plus steroid cycles	1	[1 - 6]

Abbreviations: ¶IVIG (intravenous immunoglobin)

First-line treatment included IVIG alone in 18 (30%), corticosteroid alone in 19 (31.6%), and IVIG plus corticosteroid in 19 (31.6%). Eleven (19%) had corticosteroid dependency. Three (5.2%) had corticosteroid resistance. In addition, mycophenolate mofetil was administered in two (3.4%), resulting in an inadequate response (Table 1). As a second-line treatment, eltrombopag (n=6), (10%) achieved platelet count response >50.000/mm³ in 5 (8.6%). However, in two cases, treatment resulted in a cessation of eltrombopag due to adverse reactions. These adverse events were renal failure (n=1), renal failure, elevated transaminases, vomiting, and diarrhea (n=1)]. Three (2 chronic, one acute) patients had undergone splenectomy. Of three (5%) splenectomized cases, one recovered. However, one had persistent thrombocytopenia, and the other's prognosis was unknown. Six (24%) of 25 chronic patients received eltrombopag; two (8%) had undergone splenectomy, and two (8%) took mycophenolate mofetil. Additionally, acute and persistent cases all recovered. Ten chronic issues achieved remission, and thirteen chronic patients had persistent thrombocytopenia. The current status of two children with chronic ITP is unknown.

Thrombocyte counts were recorded in the sixth month, first, and second year of diagnosis. The median IVIG cycle was 1 [1-33] (Table 2).

Table 3. Demographics, clinic status, laboratories, and chronicity

	Chronicity				Univariate			Multivariate		
	Non-chronic (n=35)		Chronic (n=25)				p	OR	(%95 CI)	p
Age at diagnosis (year)	**n**	**%**	**n**	**%**	**OR**	**(%95 CI)**				
≥4	24	55.8	19	44.2	**Reference**					
<4	11	64.7	6	35.3	0.689	(0.215– 2.204)	0.53	0.214	(0.027– 1.703)	0.145
Infection in the last month	n	%	n	%						
Absent	26	59.1	18	40.9	**Reference**					
Present	9	60	6	40	0.963	(0.29– 3.18)	0.95	0.692	(0.117– 4.093)	0.684
Bleeding	n	%	n	%						
Absent	4	44.4	5	55.6						
Present	30	60	20	40	0.533	(0.127– 2.232)	0.39	0.104	(0.01– 1.115)	0.061
Severity of bleeding	**n**	**%**	**n**	**%**						
Mild	24	55.8	19	44.2	---		---	---		---
Moderate	4	80	1	20	---		---	---		---
Severe	2	100	0	0	---		---	---		---
Thrombocyte count at diagnosis (/mm³)	**n**	**%**	**n**	**%**						
≥20000	9	60	6	40	**Reference**					
<20000	24	58.5	17	41.5	1.062	(0.318– 3.547)	0.92	1.5	(0.181– 12.418)	0.707
Neutrophil count at diagnosis (/mm³)	**n**	**%**	**n**	**%**						
≥1000	23	56.1	18	43.9						
<1000	1	100	0	0						
Laktat dehidrogenase at diagnosis (U/L)	**mean**	**SD**	**mean**	**SD**	0.995	(0.987– 1.004)	0.32			
	326.3	87	289.9	102.3						
Mean Platelet volume at diagnosis (fl)	**n**	**%**	**n**	**%**						
<11	11	50	11	50	---		---	---		---
≥11	4	100	0	0	---		---	---		---

OR (%95 CI): Odds ratio (%95), SD: Standard deviation

Among 60 patients with ITP, the chronicity risk factors were investigated. Age ≥ 4 years since diagnosis, presence of infection, bleeding and its severity, thrombocyte count ≥20.000/mm³, neutrophil count <1000/ mm³, mean platelet volume (>11 fL) diagnosis did not increase the risk for chronic ITP (Table 3). Treatment cycles also did not affect the chronicity. However, loss of response rates is strongly associated with chronic ITP and can be a good predictor of chronicity. Loss of response rates increased chronicity 2.56 times (p=0.010) and 3.87 times (p=0.005), respectively (Table 4).

Table 4. Treatment and chronicity

					Univariate			Multivariate		
IVIG treatment	**Non-chronic**		**Chronic**		**OR**	**(%95 CI)**	**p**	**OR**	**(%95 CI)**	**p**
	n	**%**	**n**	**%**						
Absent	15	65.2	8	34.8	**Reference**					
Present	20	54.1	17	45.9	1.594	(0.54-4.67)	0.395	5.223	(0.58- 46.9)	0.140
Steroid cycles										
	n	**%**	**n**	**%**						
Absent	14	66.7	7	33.3	**Reference**					
Present	21	55.3	17	44.7	1.619	(0.53-4.91)	0.395	2.871	(0.38- 21.56)	0.305
IVIG plus steroid										
	n	**%**	**n**	**%**						
Absent	26	63.4	15	36.6	**Reference**					
Present	9	47.4	10	52.6	1.926	(0.6–5.8)	0.244	0.158	(0.015-1.721)	0.130
	Mean	**SD**	**Mean**	**SD**						
Loss of response (n)	0.2	0.58	3.72	4.51	2.563	(1.25-5.25)	0.010	3.873	(1.49- 10.1)	0.006

OR (%95 CI): Odds ratio (%95), SD: Standard deviation

DISCUSSION

Children with ITP achieve remission spontaneously; only 20% develop chronic disease (1). However, our study reports a 40 % chronicity rate, higher than expected. The higher rates of our center may be associated with the fact that our center is nearly in the middle of Istanbul and Ankara; the chronic patients of Istanbul visit our center temporarily on holidays when they probably visit their relatives. Predictors for chronic ITP were investigated in several studies. Unfortunately, not many studies examined the variables of chronic ITP. Therefore, there are inconsistent results on this topic. Bennet et al. reported that at diagnosis younger age (<1 year, 1-6 years), the severity of bleeding and the treatment decreased the risk of chronicity for ITP. Sex and thrombocyte levels <20.000/mm³ did not affect chronicity in ITP (2). On the other hand, Jaime-Pérez et al. carried out a study that showed that children of older ages (≥ six years) male sex, infection history, and leukocyte level <6.25x10⁹/L were at higher risk for chronic ITP (3).

In another study, leukocyte levels above 6250/mm³ decreased, and thrombocyte levels above 20.000/mm³ increased the risk of chronic ITP. In addition, older age (>4 years) increased the risk of chronic ITP in another study(4). However, this study found no relationship between chronicity in ITP and older age (>4 years). They also reported age that ≥ five years is a risk factor. Treatment with IVIG (Intravenous Immunoglobulin) did not affect the chronicity rate in that study (4).

In previous studies and meta-analyses, lower thrombocyte counts have been associated with chronic ITP (4,5,6,7). However, Italian AIEOP studies found no relationship with platelet count (8). Opposing the previous studies, except for Italian AIEOP studies, we found that thrombocyte levels ≤20.000/mm³ didn't decrease the risk of chronic ITP.

The male gender decreased the risk of chronic ITP in various studies. Finally, this relation was related to the fact that the male gender is predominant in younger patients (4, 7). Our study supports the results that gender does not influence the chronicity of ITP.

Deel et al. and Ahmed et al. suggested low leukocyte counts predicted chronic ITP. However, leucocyte count that differs according to age is not an independent variable (13, 14). Therefore, we didn't find infection status in the last month, bleeding level, or neutrophil count predictive for chronic ITP.

IVIG treatment decreased chronic ITP rates in a few previous studies due to the lower platelet counts and an acute presentation (9,15). However, Heitink-Polle et al. concluded that immunoglobulin treatment is not associated with chronicity (10). Additionally, we investigated steroid and IVIG plus steroid effects, and none of the initial therapies was related to chronicity. In logistic regression analysis, loss of response rates significantly predicted this study's chronicity (2.56-fold and 3.87-fold).

Second-line treatments for chronic and persistent ITP include thrombopoietin receptor agonists, rituximab, and splenectomy. Additionally, mycophenolate mofetil and 6-mercaptopurine are other second-line drugs (16). Unfortunately, two of the six patients in our study needed to stop the treatment due to renal failure despite the eltrombopag's efficacy. In addition, one of the splenectomized patients couldn't achieve remission. Splenectomy in idiopathic thrombocytopenic purpura treatment doesn't always lead to a cure for the disease.

Limitations of the Study

The limitations of our study are that more patients should be followed to reach more objective results, and the local factors (being a small city near big cities) did not let to increase the number of patients. Also, due to the rarity of pediatric hematology-oncology specialists, more than one hospital doctor followed the patient. In addition, data is heterogenous

due to different doctors' treatment approaches. Finally, this study is retrospective. Therefore, randomized control trials will show more accurate results.

CONCLUSION

Lower platelet counts (<20.000/mm³), younger age, male gender, and initial treatment regimens (IVIG, steroid, IVIG plus steroid) did not influence chronicity in our study. Therefore, different studies have different results in the literature, depending on the independent variables (gender, leukocyte counts, treatment regimens) (4-15). We suggest that loss of response rates predicts chronicity as a new factor.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Ethical permission was obtained from the Duzce University Medical Faculty Clinical / Human Research Ethics Committee for this study with the date 09.05.2022 and number 2022/85, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: HMÇ, K.K., Design: HMÇ, K.K., Supervising: HMÇ, K.K., Financing, and equipment: HMÇ, KK, Data collection and entry: HMÇ, Analysis, and interpretation: HMÇ, K.K., Literature search: HMÇ, Writing: HMÇ, Critical review: KK

REFERENCES

1. Miltiadous O, Hou M, Bussel J.B. Identifying and treating refractory ITP: difficulty in diagnosis and role of combination treatment. Blood. 2020;135(7):472-490. https://doi.org/10.1182/blood.2019003599.
2. Bennett CM, Neunert C, Grace RF, Buchanan G, Imbach P, Vesely SK, et al. Predictors of remission in children with newly diagnosed immune thrombocytopenia: Data from the Intercontinental Cooperative ITP Study Group Registry II participants. Pediatr Blood Cancer. 2018;65(1). https://doi.org/10.1002/pbc.26736.
3. Jaime-Pérez JC, Aguilar-Calderón P, Jiménez-Castillo RA, Ramos-Dávila EM, Salazar-Cavazos L, Gómez-Almaguer D. Treatment outcomes and chronicity predictors for primary immune thrombocytopenia: 10-year data from an academic center. Ann Hematol. 2020;99(11):2513-2520. https://doi.org/10.1007/s00277-020-04257-2.
4. Fernández-Plaza S, González de Pablo J, Gálvez E, Zubicaray J, Guillén M, Sevilla J, et al. Variables related to chronic immune thrombocytopenia: experience from a single center and comparison to a meta-analysis. Eur J Pediatr. 2021;180(7):2075-2081. https://doi.org/10.1007/s00431-021-03990-8.
5. Glanz J, France E, Xu S, Hayes T, Hambidge S. A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. Pediatrics. 2008;121: e506–e512 https://doi.org/10.1542/peds.2007-1129.
6. Bruin M, Bearings M, Uiterwaal C, Révész T, Bode L, Wiesman ME et al. Platelet count, previous infection and FCGR2B genotype predict development of chronic disease in newly diagnosed idiopathic thrombocytopenia in childhood: results of a prospective study. Br J Haematol. 2004; 127:561–567. https://doi.org/10.1111/j.1365-2141.2004.05235
7. Heitink-Pollé KM, Nijsten J, Boonacker CW, de Haas M, Bruin MC. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. Blood. 2014; 124:3295–3307. https://doi.org/10.1182/blood-2014-04-570127.
8. Emilia Parodi, Giovanna Russo, Piero Farruggia, Lucia D Notarangelo, Maria T Giraudo, Margherita Nardi, "AIEOP-ITP Study Group". Management strategies for newly diagnosed immune thrombocytopenia in Italian AIEOP Centres: do we overtreat? Data from a multicentre, prospective cohort study. Blood Transfus 2020;18(5):396-405. https://doi.org/10.2450/2020.0041-20.
9. Tamminga R, Berchtold W, Bruin M, Buchanan GR, Kühne T. Possible lower rate of chronic ITP after IVIG for acute childhood ITP an analysis from registry I of the Intercontinental Cooperative ITP Study Group (ICIS). Br J Haematol 2009; 146:180–184. https://doi.org/10.1111/j.1365-2141.2009.07743.x.
10. Heitink-Pollé KMJ, Uiterwaal CSPM, Porcelijn L, Tamminga RYJ, Smiers FJ, van Woerden N, et al. Investigators Intravenous immunoglobulin versus observation in childhood immune thrombocytopenia: a randomized controlled trial. Blood 2018;132: 883–891. https://doi.org/10.1182/blood-2018-02-830844.
11. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, Cuker A, Despotovic JM, George JN, Grace RF, Kühne T, Kuter DJ, Lim W, McCrae KR, Pruitt B, Shimanek H, Vesely SK. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019 Dec 10;3(23):3829-3866. https://doi: 10.1182/bloodadvances.2019000966.
12. Donato H, Picón A, Rapetti MC, Rosso A, Schvartzman G, Drozdowski C, Di Santo JJ. Splenectomy and spontaneous remission in children with chronic idiopathic thrombocytopenic purpura. Pediatr Blood Cancer. 2006 Oct 15;47(5 Suppl):737-9. https://doi: 10.1002/pbc.20982.

13. Deel M, Kong M, Cross K, Bertolone S. Absolute lymphocyte counts as prognostic indicators for immune thrombocytopenia outcomes in children. Pediatr Blood Cancer 2013; 60:1967–1974. https://doi.org/10.1002/pbc.24628.

14. Ahmed I, Rajpurkar M, Thomas R, Chitlur M. Initial lymphocyte count and the development of persistent/chronic immune thrombocytopenic purpura. Pediatr Blood Cancer. 2010; 55:508–511. https://doi.org/10.1002/pbc.22570.

15. Demircioglu F, Saygi M, Yilmaz S, Oren H, Irken G. Clinical features, treatment responses, and outcome of children with idiopathic thrombocytopenic purpura. Pediatr Hematol Oncol. 2009;26(7):526–532. https://doi.org 10.108/08880010903044540.

16. Grace RF, Despotovic JM, Bennett CM, Bussel JB, Neier M, Neunert C, Crary SE, Pastore YD, Klaassen RJ, Rothman JA, Hege K, Breakey VR, Rose MJ, Shimano KA, Buchanan GR, Geddis A, Haley KM, Lorenzana A, Thompson A, Jeng M, Neufeld EJ, Brown T, Forbes PW, Lambert MP. Physician decision making in selection of second-line treatments in immune thrombocytopenia in children. Am J Hematol. 2018;93(7):882-888. https://doi: 10.1002/ajh.25110.