

Clinical Outcome and its Predictors in Children With Newly Diagnosed Immune Thrombocytopenia

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ABSTRACT

Objective: To determine the predictors for chronic and/or persistent immune thrombocytopenia (ITP) among children with newly diagnosed ITP.

Methods: Ours was a mixed-design study (prospective: January 2020 to March 2022 and retrospective: January 2014 to December 2019), wherein we enrolled children, aged 1 month to 18 years presenting with newly diagnosed ITP.

Results: Of the 64 enrolled participants, 58 were followed up for atleast 1-year duration and 6 children were followed up for 3 to 12 months' duration. The median (IQR) age of the cohort was 8 (5, 11) years with a female preponderance (62.5%). Wet bleeding was seen in 56%; 6.25% developed intracranial bleeding. 67.2% (43/64) and 41.4% (24/58) children developed persistent and chronic ITP, respectively. Of the 34 children who achieved complete response at 12-months follow up, 21 (62%) achieved complete response by 3 months and the rest achieved complete response over the next 9 months. Development of overall response (complete or partial) at 3 and 12 months, was associated with a higher absolute lymphocyte count (ALC) at admission. The median ALC ($\times 10^3/\mu\text{L}$) at admission was 3.77 and 2.87 in children who had overall response and no response at 3 months, respectively ($P=0.03$). The median ALC ($\times 10^3/\mu\text{L}$) at admission was 3.99 and 2.96 in children who had overall response and no response at 12 months, respectively ($P=0.04$). Response rate was lesser in the treated group by approximately 10% compared to the non-treated group.

Conclusion: The rate of chronicity and intracranial bleeding in our cohort is more than the reported rates in literature. Higher ALC was found to be associated with response.

Keywords: Childhood, Chronic, ITP, Persistent, Platelet, Response

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INTRODUCTION

Immune thrombocytopenia (ITP) is the most common acquired cause of thrombocytopenia in children. Although childhood ITP is considered to have a benign course without any significant bleeding, rarely it may result in significant morbidity and mortality [1]. The restrictions imposed on the daily activities of children to avoid trauma contribute significantly to reduced quality of life [2]. It is usually a self-limiting disorder. But in 25-30% of the children, it might progress to become persistent or chronic ITP [3]. The risk factors for persistence or chronicity or significant bleeding are still unclear [4]. Studies on outcomes of childhood ITP are available from the Western world, but supporting literature from developing countries

is scant [5-12]. Hence, studying the outcome of ITP in our population will be of vital importance to understand the pathological, clinical and laboratory factors which predispose to persistence or chronicity. Our objective was to determine the proportion of children with newly diagnosed ITP who develop chronic or persistent ITP and risk factors for the same.

METHODS

We conducted a mixed design (prospective and retrospective) study, including all children aged 1 month to 18 years with newly diagnosed ITP. Children who had presented from January 2014 to December 2019 constituted the retrospective cohort. Those presenting between January 2020 and March 2022 were recruited consecutively and comprised the prospective cohort. The study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from parents/legally accepted representatives of children. Written assent was obtained from children between 12 and 18 years of age.

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We planned to enroll 96 children with ITP in the study to achieve 5% level of significance and 20% relative precision with a presumption that 50% will achieve remission at 1 year [12]. Children were diagnosed with ITP clinically if they had presented with platelet count $<100 \times 10^3/\mu\text{L}$ with normal peripheral smear examination except thrombocytopenia in the absence of any organomegaly, significant lymphadenopathy, joint pain, fever, significant family history for familial thrombocytopenia and abnormal phenotype findings (absent radius, features of Fanconi anemia etc). Bone marrow examination was performed as a part of initial evaluation whenever inherited marrow failure syndrome or congenital thrombocytopenia was suspected or if the patient presented in infancy. The clinical details including presenting complaints, examination findings, treatment details and follow-up reports were collected in a structured proforma. Children with ITP were generally observed without offering immunomodulatory therapy if they had presented with dry bleeding, irrespective of platelet count. Children who had wet bleeding any time during the study period, or when parents refused observatory treatment, were treated with immunomodulatory treatment. The drug used was left to the discretion of the treating pediatric hematologist. Children were followed up monthly for first 3-months and then every 3 months until 12-months in the pediatric hematology clinic. Clinical details were collected from hospital records in the retrospective cohort. The platelet counts at 3 months and 1 year from diagnosis were recorded to define the outcome.

The phase of the disease/outcome (newly diagnosed, persistent and chronic ITP) and response criteria were defined as per the International Working Group definition for ITP in Children and Adults, 2009 [13]. Newly diagnosed ITP was defined as from the time of diagnosis to 3 months from diagnosis. Persistent ITP was defined as platelet count $< 100 \times 10^3/\mu\text{L}$ lasting between 3 to 12 months from diagnosis and not reaching spontaneous remission or not maintaining complete response off therapy. Chronic ITP was defined as ITP lasting for more than 12 months. Complete response was defined as any platelet count of at least $100 \times 10^9/\text{L}$ and absence of bleeding. Partial response was defined as platelet count between 30 and $100 \times 10^9/\text{L}$ and at least two-fold increase in baseline platelet count and absence of bleeding. No response was defined as platelet count $< 30 \times 10^9/\text{L}$. Loss of response was defined as a platelet count $< 30 \times 10^9/\text{L}$ or platelet count less than two-fold increase from baseline or presence of clinical bleeding after achieving a complete or partial remission. Refractory ITP was defined as failure to achieve response or developing loss of response after splenectomy. Dry bleeding was defined as when bleeding

was confined to the skin. Wet bleeding was defined as when bleeding involved mucous membranes and/or internal organs.

Children who developed chronic ITP underwent detailed evaluation including serological testing for hepatitis B and hepatitis C virus, antinuclear antibody (ANA), immunoglobulins and thyroid hormones. Children who were tested positive for ANA were tested with extractable nuclear antigen (ENA) blot test to establish the diagnosis of systemic lupus erythematosus. Bone marrow examination was not performed for children who did not show response at 3 months and 12 months of follow up.

Statistical analysis: The collected data were entered in MS excel spreadsheet and analyzed using SPSS software version 16.0. The association between nominal variables was evaluated by Chi-square/ Fischer exact test and between continuous and nominal variables were assessed using Student-t test or Mann-Whitney U test. $P < 0.05$ was regarded as statistically significant. Odds ratio with 95% confidence interval was determined.

RESULT

Sixty-six children were recruited in the study. Two children were lost to follow-up (**Fig. 1**). Of the 64 children, 37 (57.8%) were recruited prospectively. Microcytic hypochromic anemia was observed in 28.2% children on peripheral smear examination. None of the patients enrolled in the study underwent bone marrow examination at enrollment.

The median (IQR) age of the cohort was 8 (5-11) years (range 16 months to 17 years) with a female preponderance (62.5%). Preceding history of infection was observed in 43.8% children; all were diagnosed with possible viral fever. Wet bleeding was noted in 37 (57.8%); intracranial bleeding was seen in 4 (6.25%), epistaxis in 20 (31.25%), oral bleeding in 10 (15.6%), hematuria in 1 (1.56%) and hematemesis in 2 (3.12%) children.

Fifty percent of children were not offered any form of immunomodulatory treatment. Oral prednisolone (1 mg/kg) alone for 14 days, intravenous immunoglobulin (IVIG) alone (1 gm/kg single dose), methylprednisolone (MP) alone (30 mg/kg for 3 days), combination of MP and IVIG and combination of prednisolone (1 mg/kg for 28 days) with either azathioprine (1-2 mg/kg for 6-12 months) or dapsone (1-2 mg/kg for 6-12 months) were prescribed to 9 (14.1%), 10 (15.6%), 3 (4.6%), 4 (6.25%) and 6 (9.4%) children, respectively. Evaluation for secondary etiology was performed in children who developed chronic ITP. All the children had normal immunoglobulin profile and tested negative for hepatitis B and C viral serologies. Anti-

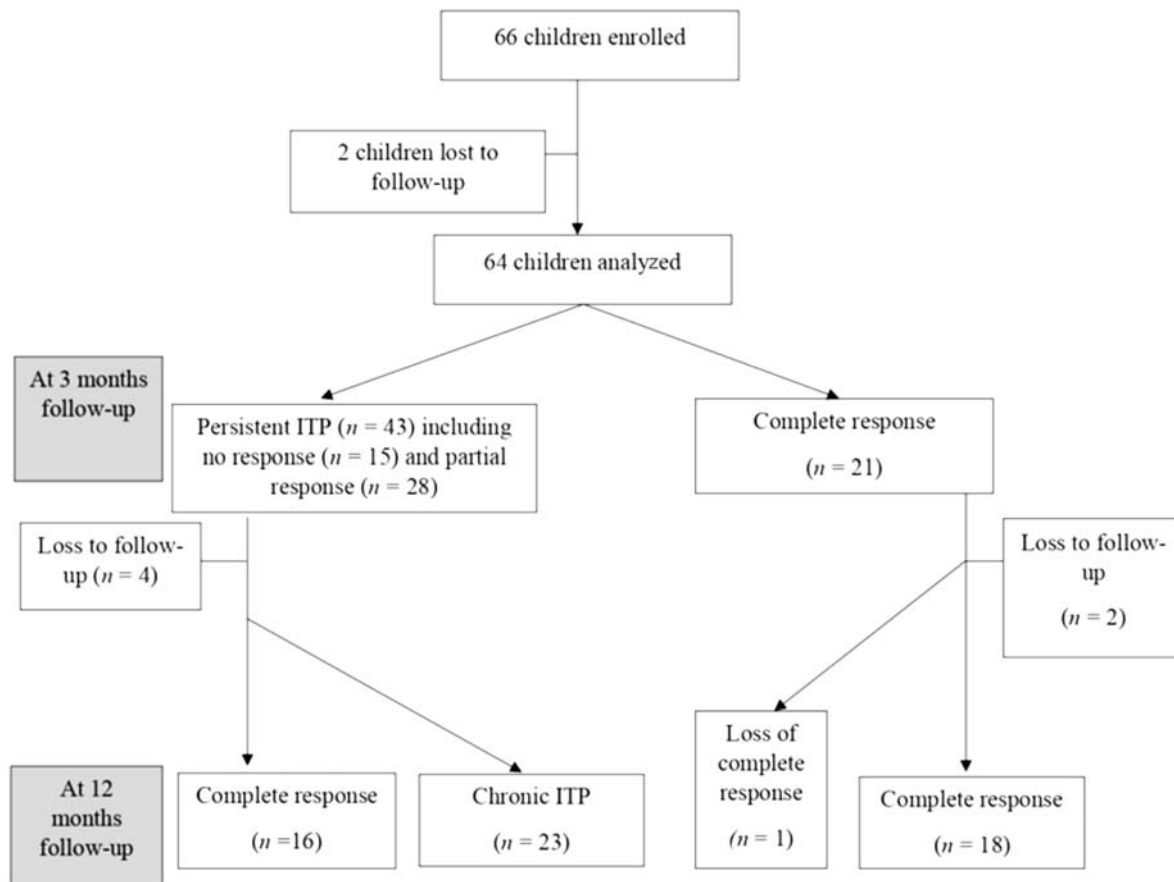


Fig. 1 The response rate of the study subjects

nuclear antibody tested positive in four children but ENA blot test was negative in all of them. Hypothyroidism (symptomatic) was identified in 8 children.

During follow-up, non-responders continued to have dry bleeding, although none of them developed wet bleeding. Consequently, the treatment plan was not revised for any of them. Genetic evaluation (next generation sequencing) or bone marrow examination for congenital thrombocytopenia was not performed for any child in the study. At end of 3-months follow-up, persistent ITP developed in 43 children (67.1%). At 12-months follow-up, 34 out of 58 children (58.8%) had complete response and 24 (41.2%) developed chronic ITP. No child developed refractory ITP. The outcome data is given in **Fig. 1**.

The clinical factors were assessed for its association with development of persistent ITP and chronic ITP (**Table I**). None of the factors were significantly associated with the development of chronic or persistent ITP. The median (IQR) ALC ($\times 10^3/\mu\text{L}$) at diagnosis was 3.77 (3.1, 4.5) and 2.87 (1.9, 4.6) in children who were in overall

response (complete or partial) and no response at 3 months, respectively. The median (IQR) ALC ($\times 10^3/\mu\text{L}$) at diagnosis was 3.99 (2.8, 4.9) and 2.96 (2.1, 4.3) $\times 10^3/\mu\text{L}$ in children who were in overall response (complete or partial) and no response at 12 months, respectively. ALC at diagnosis was significantly associated with overall response at 3 months ($P = 0.03$) and 12 months ($P = 0.04$). The association between other parameters of hemogram including hemoglobin level and white cell count at admission and overall response at 3 and 12 months were not significant ($P > 0.05$). The association of other clinical factors with overall response is given in **Table II**. The overall response rate (either partial or complete) at both time points (3 and 12 months) was higher in the group who were not offered any treatment in comparison to the group who were offered some form of treatment (**Table III**).

DISCUSSION

Immune thrombocytopenia, an autoimmune entity, is characterized by recurrent bleeding manifestations consequent to a low platelet count which affect their quality of life [1]. We evaluated 64 children with ITP for

Table I Association Between Clinical Factors and Development of Persistent and Chronic ITP

<i>Outcome at 3-months (n = 64)</i>				
<i>Clinical factor</i>	<i>Complete remission n (%)</i>	<i>Persistent ITP n (%)</i>	<i>P value</i>	<i>Odds ratio (95% CI)</i>
Age ≤ 10 years	13 (28.3)	33 (71.7)	0.21	0.54 (0.18, 1.76)
Female gender	14 (35.0)	26 (65.0)	0.63	1.70 (0.50, 5.72)
Duration of symptom < 14 days	19 (33.9)	37 (66.1)	1.00	0.89 (0.23, 3.45)
Wet bleeding	13 (35.1)	24 (64.9)	0.87	1.13 (0.36, 3.53)
History of fever	9 (32.1)	19 (67.9)	0.92	1.18 (0.35, 3.51)
Not treated	11 (34.4)	21 (65.6)	0.79	0.66 (0.21, 2.09)
<i>Outcome at 12-months (n = 58)</i>				
<i>Clinical factor</i>	<i>Complete remission n (%)</i>	<i>Chronic ITP n (%)</i>	<i>P value</i>	<i>Odds ratio (95% CI)</i>
Age ≤ 10 years	26 (59.1)	18 (40.9)	0.89	0.67 (0.21, 1.35)
Female gender	21 (58.3)	15 (41.7)	1.00	0.97 (0.33, 2.84)
Duration of symptom < 14 days	32 (61.5)	20 (38.5)	0.67	0.22 (0.21, 1.35)
Wet bleeding	21 (65.6)	11 (34.4)	0.28	0.52 (0.18, 1.51)
History of fever	16 (64.0)	9 (36.0)	0.46	0.67 (0.23, 1.96)
Not treated	19 (63.3)	11 (36.7)	0.45	0.66 (0.23, 1.90)

CI confidence interval, ITP Immune thrombocytopenia

their outcome. The rate of persistent ITP and chronic ITP in our cohort was 67.2% and 41.2% respectively. The median (IQR) age of our study cohort was 8 years (5, 11) with a female preponderance (62.1%). The average age of children with ITP in a majority of the studies was 5-6 years [5-12], which is much lower than that observed in our cohort in comparison to the literature. Like our study, most of these studies also observed a female preponderance.

Wet bleeding was observed in 55% of our cohort. Most common bleeding manifestation in literature has been dry bleeding in the form petechiae and ecchymosis [6,11]. The prevalence of intracranial bleed was 6.25% in our cohort which was much higher than the reported prevalence from other studies including the study from North India (4%) [5-12,15]. The reason for higher incidence of wet bleeding including intracranial bleeds was unclear in our study. The

Table II Association Between Clinical Factors and Overall Response

<i>Clinical factor</i>	<i>Overall responder n (%)</i>	<i>Non-responder n (%)</i>	<i>P value</i>	<i>Odds ratio (95% CI)</i>
<i>Outcome at 3-months</i>				
Age ≤ 10 y (n = 46)	13 (28.3)	23 (71.7)	0.21	0.54 (0.18, 1.76)
Females (n = 40)	14 (35.0)	26 (65)	0.63	1.70 (0.50, 5.72)
Duration of symptom < 14 days (n = 56)	19 (33.9)	37 (66.1)	1.00	0.89 (0.23, 3.45)
Wet bleeding (n = 37)	13 (35.1)	24 (64.9)	0.87	1.13 (0.36, 3.53)
History of fever absent (n = 36)	12 (33.3)	24 (66.7)	0.92	1.18 (0.35, 3.51)
Not treated (n = 32)	11 (34.4)	21 (65.6)	0.79	0.66 (0.21, 2.09)
<i>Outcome at 12-months</i>				
Age ≤ 10 y (n=44)	31 (70.5)	13 (29.5)	1.00	0.9 (0.21, 1.87)
Females (n = 36)	27 (75)	9 (25)	0.35	1.71 (0.54, 5.41)
Duration of symptom < 14 days (n = 52)	37 (71.2)	15 (28.8)	1.00	0.65 (0.13, 2.56)
Wet bleeding (n = 32)	24 (75.0)	8 (25)	0.42	0.63 (0.20, 1.96)
History of fever absent (n = 33)	23 (69.7)	10 (30.3)	0.84	0.89 (0.28, 2.81)
Not treated (n = 30)	24 (80)	6 (20)	0.10	0.38 (0.12, 1.24)

CI Confidence interval

Table III Comparison of Response Rate Between Groups Which Were Treated and Not Treated (n = 58)

Timeline	Group	Non-response n (%)	Partial response n (%)	Complete response n (%)
3 months (n = 64)	Treated (n = 32)	10 (32.2)	12 (37.5)	10 (31.2)
	Not treated (n = 32)	5 (15.6)	16 (50)	11 (34.4)
12 months (n = 53)	Treated (n = 28)	11 (39.3)	2 (7.1)	15 (53.6)
	Not treated (n = 30)	6 (20.0)	5 (16.7)	19 (63.3)

onset of illness was acute (< 14 days) in 90% of our population compared to 75% reported in a Nordic cohort [10]. These deviations may have been due to a referral bias or aggressive nature of this disease in our population and needs further evaluation.

The proportion of children developing persistent ITP and chronicity in our study was 67.5% and 41.4% respectively. These rates were higher compared to outcome observed in other studies (Table IV). The overall response was associated with the ALC at diagnosis. Ahmed et al had observed ALC < 3.05 x 10³/μL was associated with the development of persistent ITP at 6 months [16]. It appears that the lymphocytes, especially the regulatory T-cells, have major impact in the pathogenesis of chronic ITP. Lower levels of regulatory T-cells and/or T-cell dysregulation breaching the self-tolerance mechanism is suspected to play a key role in pathogenesis of ITP and development of chronicity [17-19].

A total of 31 children (53.44%) were offered treatment in our cohort. But majority of the published studies had more than two-thirds of their cohort treated [5-12] (Table IV). The American Society of Hematology (ASH) Practice Guidelines 1996 was the principle guideline followed widely by hematologists during 2000-2010. This guideline recommended offering treatment for children with minor bleeding and platelet count < 10 x 10³/μL or in children < 3

years with platelet count < 20 x 10³/μL, irrespective of presence of bleeding [20]. However, the ASH Practice Guidelines in 2011 did not recommended treatment to children with minor bleeding, irrespective of their age or severity of thrombocytopenia. [21] A higher proportion of children offered treatment in these studies could be because these were performed more than a decade ago. Lesser rate of chronicity in these published studies in comparison to our cohort could be because of multiple factors including difference in ethnicity, age, sex, type of onset, pattern of bleeding and proportion with preceding illness [5-12]. The impact of treatment on outcome needs to be studied further. We did not find any difference in rate of chronicity on the basis of treatment. In fact, the complete response rate was higher in the subgroup which was not offered treatment possibly because lesser aggressive disease in the group that was not offered treatment.

To conclude, the disease was aggressive in our cohort with higher incidence of wet bleeding, including intracranial bleeding and higher rate of chronicity. Limitations of our study include a small sample size, single center origin of cases and partially retrospective nature of cases. We observed that a wait and watch policy had remission chances comparable to treated group. Studying in detail in a cohort of larger sample size is of paramount importance to understand the disease in a developing

Table IV Comparison of Clinical and Outcome Data of our Study with Existing Literature

Study	Sample size	Age (y)	Female (%)	Onset <14 days (%)	Dry bleeding (%)	History of preceding illness (%)	Complete response at 1 year (%)	Chronic ITP (%)
Our study	64	8 (5,11) ^a	62.1	89.7	44.8	43.1	58.8	41.4
Kocak et al [11]	162	6.4 (3.8) ^b	NA	NA	NA	NA	66	34
Gungor et al [6]	211	5.4 (4.1) ^b	50.7	53.6	89	53.6	71.5	29.5
Watts et al [8]	499	5.85 ^c	51	NA	NA	NA	76	24
Diab et al [7]	308	5 (3.4) ^b	46.8	NA	NA	17.5	71.4	28.6
Zeller et al [10]	506	0-7 ^d	43.7	74.9	59.1	57.7	75	25
Bansal et al [12]	270	6 ^c	NA	NA	NA	NA	43.2	56.8
Grace et al [9]	505	5.1 ^c	50.7	NA	NA	67.6	NA	24.5
Zafar et al [5]	103	4.5 (2.9) ^b	43.6	22.3	78.6	22.3	NA	33

^amedian (IQR), ^bmean (SD), ^cmedian, ^drange. ITP Immune thrombocytopenia, NA Not available

WHAT THIS STUDY ADDS?

- A high proportion of children (41.4%) presenting as newly diagnosed immune thrombocytopenia developed chronicity.
- The disease was aggressive in our cohort with a higher proportion presenting with wet bleeds including intracranial bleeding.
- A higher absolute lymphocyte count at admission is associated with response at 3 and 12 months.

country setting and the role of regulatory T-cells in the pathogenesis and outcome needs to be investigated.

Ethics clearance: Institutional Ethics Committee, JIPMER; No. JIP/IEC/2019/0136, dated Nov 11, 2019.

Contributors: JGR: Conceptualized and designed the study, analyzed the data and supervised the study; PS: Collected and analyzed data, drafted the manuscript; CGD: Managed the cases, analyzed the data and supervised the study; JGR: Guarantor of the paper. All authors approved the final version of manuscript and are accountable for all aspects related to the study.

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