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Immune Thrombocytopenia Purpura in Children in Lebanon: Prevalence, Treatment Modalities, and Clinical Outcomes in a Retrospective Study

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Abstract

Background: Immune thrombocytopenia purpura (ITP) is one of the most common autoimmune diseases in children characterized by a decreased number of circulating platelets combined with impaired platelet production. There is limited literature data on the prevalence and treatment modalities, and outcome of ITP in children from Lebanon. *Methods:* We retrospectively reviewed the demographic and clinical data of 59 patients aged 0–18 years diagnosed with ITP between January 2007 and April 2016 in different hospitals in Beirut and the south of Lebanon. *Results:* ITP patients represented 2.5% of the total number of children admitted to these hospitals during this period. Among the ITP children, 55.93% were male and 44.07% were female. The greatest number of ITP children were in the 1–4 year group, followed by the 5–9 year group. As for the clinical course of the disease, 40.68% of the ITP children presented acute ITP, whereas 59.32% presented chronic ITP. Among the different therapeutic approaches adopted to treat these ITP children, intravenous immunoglobulin was the most commonly used, followed by steroids, a combination of these both agents, cyclosporine, and splenectomy. Interestingly, these therapeutic modalities induced a statistically significant increase in the patients' platelet count. In addition, the clinical course of ITP was not significantly associated with each of the age group, the platelet count at diagnosis, and gender of patients. *Conclusion:* This study showed the prevalence of ITP among children from Lebanon, where more than half of ITP children presented a chronic disease. Further studies are needed to evaluate additional predictors of chronic ITP among children from Lebanon and help medical providers make informed decisions about treating childhood ITP.

Keywords: Immune Thrombocytopenia Purpura; Children; Lebanon; Treatment.

1. Introduction

Immune thrombocytopenia purpura (ITP) is defined as an acquired blood autoimmune disorder characterized by the destruction of normal platelets coupled with defective platelet production [1]. Two forms of ITP have been reported: primary and secondary [2]. Primary ITP is characterized by isolated thrombocytopenia that is not triggered by other

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causes of thrombocytopenia, including drugs, infections, neoplasia, or other autoimmune diseases [3], while secondary ITP is associated with other disorders [1]. This disease can arise at any age, and its incidence, prevalence, and natural history differ significantly between children and adults [3]. This disorder is more frequent in children than in adults, with an estimated incidence of ITP in children of 4.0–5.3 per 100,000 compared with 1.6–2.6 per 100,000 in adults [3]. It is more common in children aged 2 to 5 years old but also occurs in other age groups [4].

The most important criterion for the diagnosis of ITP is an abnormal platelet count in peripheral blood of $<100\times10^9$/L [5]. Most ITP patients are asymptomatic for platelet counts greater than 50×10^9/L [6]. Clinical manifestations of ITP include localized hemorrhaging in the skin or gingival bleeding that usually leads to little to no clinical consequence, such as petechiae, purpura, ecchymoses, and epistaxis [6]. ITP can be classified as either acute or chronic based on thrombocytopenia duration. Patients with acute ITP often develop the disease after an infection and usually recover spontaneously within 12 months. However, chronic ITP lasts longer than 12 months without a specific cause [4].

Many clinicians reported that ITP has a significant impact on health-related quality of life. Being embarrassed by the large skin bleeds, children may not feel free to participate in their activities, and parents may be afraid of severe bleeding [7]. To treat ITP, prophylactic therapy is adopted since ITP patients recover spontaneously in many cases, while medical intervention is required when the low platelet count may cause life-threatening spontaneous bleeding [4]. Corticosteroids, intravenous immunoglobulin (IVIG), and anti-D immune globulin have been recommended as first-line treatment options, whereas rituximab and splenectomy have been recommended as second- and third-line treatment options, respectively. In addition, immunosuppressive agents like mycophenolate, azathioprine, and cyclosporine may be used to treat ITP [8].

There is a dearth of data in the literature on ITP in children from Lebanon. It is crucial to generate demographic and clinical data about this disease in children from Lebanon to determine whom is most likely impacted by ITP, help in diagnostic decision-making, and ultimately ensure effective forward planning for the health care needs of ITP patients in this country. Therefore, this retrospective study was carried in different hospitals in Beirut and south of Lebanon to investigate ITP in children from 0 to 18 years old in addition to the treatment modalities used and their outcome.

2. Methods and Subjects

This retrospective study was conducted in different hospitals in Beirut and the south of Lebanon from January 2007 to April 2016. The work was approved by the research ethics boards at each hospital and carried out in accordance with the 1964 Helsinki Declaration.

The target population includes children under 18 years old diagnosed with ITP. A designed questionnaire was used to gather demographic and clinical data from the children's medical records. Data about the therapeutic agents prescribed to the patients and treatment outcomes was collected from the physicians' logbooks.

The diagnosis of ITP was determined based on the medical history of the child, a physical examination, and a complete blood count. An ITP patient presents with a platelet count $< 100\times10^9$/L and normal hemoglobin concentration, white blood cell count, and peripheral blood smear in the absence of the known causes of thrombocytopenia. Bone marrow aspiration was carried out in children with acute ITP to exclude other causes of thrombocytopenia. The ITP was considered chronic when thrombocytopenia persists for more than 12 months after the initial diagnosis.

2.1. Statistical Analysis

The Kolmogorov-Smirnov test was performed to assess the normality of the data distribution. The Chi-Square test (X^2 test) of independence was used to test whether there is a significant relationship between two categorical variables. The student's t-test or Wilcoxon rank sum test were used to evaluate the statistical significance of differences for continuous variables. Data are presented as means ± SEM. Statistical significance was set at *p <0.05, **p <0.01, and ***p < 0.001. The statistical analysis was performed using GraphPad Prism.

3. Results

59 ITP patients were involved in this study, representing a total of 2.5% of all patients admitted to the studied hospitals during the years from 2007 to 2016; the total number of patients admitted during this period was 2360. While 55.93% of the ITP children were male, 44.07% of them were female (Figure 1 and Table 1). There was no significant association between ITP development and gender (X^2=0.1388, p>0.05) reflecting that ITP affects both sexes equally (Table 1). The percentage of ITP children admitted to hospitals in the south of Lebanon (74.58%) was significantly higher than those admitted to hospitals in Beirut (25.42%) (Table 2).

Among the ITP children involved in this study, 40.68 % had acute ITP while 59.32% had chronic ITP. The mean age of patients with acute ITP was 3.87±0.56 years which was significantly different than that of patients with chronic ITP 5.38±0.75 years (Table 3). On the other hand, the highest number of children with acute and chronic ITP was among those who are 1-4 years old (45.83 and 45.71%, respectively), followed by 5-9 years old children (29.17 and 25.71 %, respectively; Table 3 and Figure 2-a). No significant association was found between the clinical course of ITP and the age group (X^2=0.328; p=0.987; Figure 2-a).

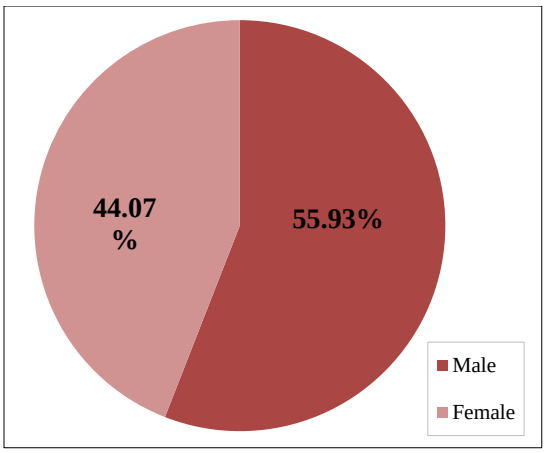

Figure 1. Distribution of ITP children admitted to different hospitals of Beirut and the south of Lebanon according to the gender

Table 1. Distribution of children admitted to different hospitals of Beirut and the south of Lebanon according to the ITP disease and gender

	Gender		
	Female N° (%)	**Male N° (%)**	**Total**
ITP	26 (2.58%)	33 (2.43%)	59
Non ITP	980 (97.41%)	1321 (97.5%)	2301
Total	1006 (100%)	1354 (100%)	2360
X^2=0.1388, p>0.05			

Table 2. Distribution of ITP children admitted to different hospitals of Beirut and the south of Lebanon according to the gender and region

	Female	**Male**	**Total**
South of Lebanon	19 (32.2%)	25 (42.37%)	44 (74.58%)
Beirut	7 (11.86%)	8 (13.56%)	15(25.42%)
Total	26 (44.07%)	33 (55.93%)	59 (100%)

Table 3. Distribution of ITP children admitted to different hospitals of Beirut and the south of Lebanon according to the age, gender, and clinical course of the disease (acute/chronic)

	ITP				
	Acute (24)		**Chronic (35)**		**Total (59)**
Age in years, mean (SE)	3.87 (0.56)		5.38 (0.75)		
Age group	No	%	No	%	
< 1 year	2	8.33	3	8.57	5
1-4 years	11	45.83	16	45.71	27
5-9 years	7	29.17	9	25.71	16
10-14 years	2	8.33	4	11.43	6
15-18 years	2	8.33	2	5.71	4
Gender					
Male	14	58.33	19	54.29	33
Female	10	41.67	16	45.71	26
Platelet count					
$< 10\times10^9$/L	1	4.17	3	8.57	4
$10\text{-}19\times10^9$/L	6	25	9	25	15
$20\text{-}49\times10^9$/L	8	33.33	15	42.86	23
$>50\times10^9$/L	7	29.17	8	22.86	15

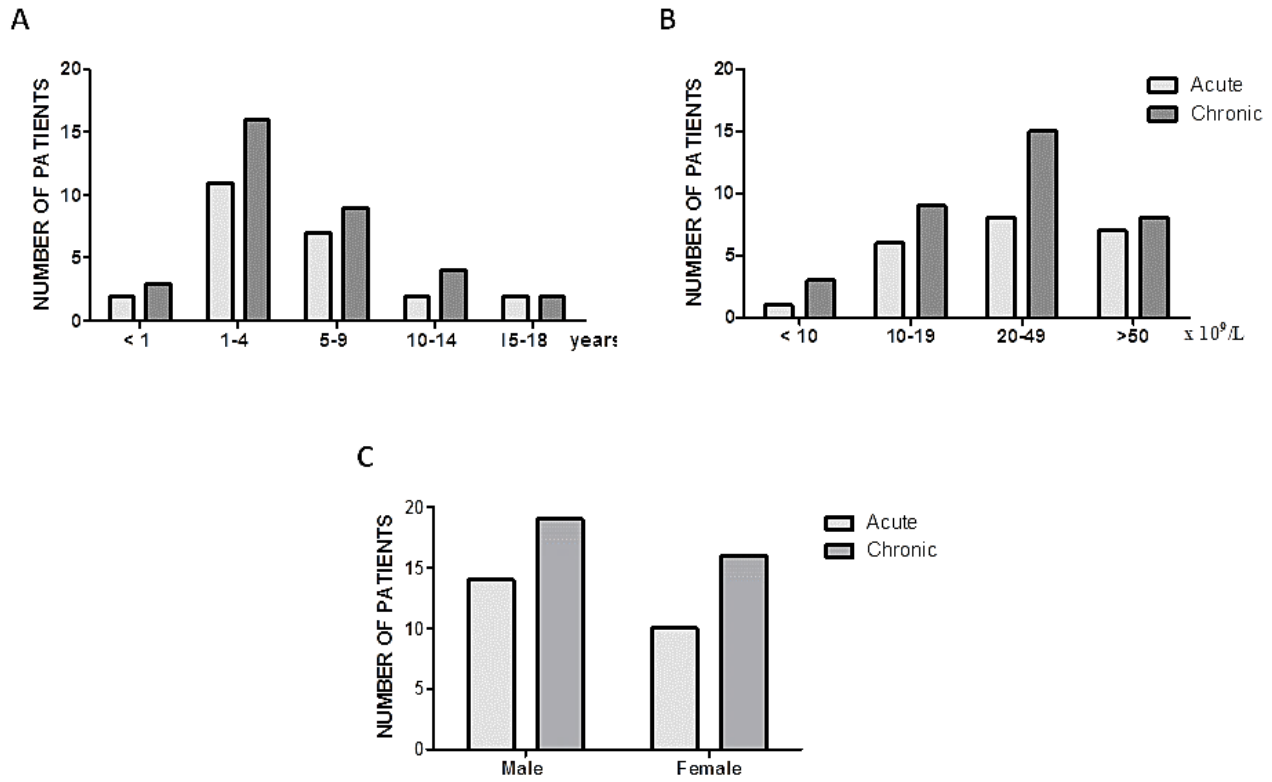

Figure 2. Distribution of ITP children admitted to different hospitals of Beirut and the south of Lebanon: A. According to the ITP clinical course and age group of patients (X^2=0.328; p=0.987). B. According to the ITP clinical course and number of platelets at diagnosis (X^2=0.09; p=0.758). C. According to the ITP clinical course and gender of patients (X^2=0.877; p=0.83).

The platelet count at diagnosis was significantly elevated in chronic ITP compared to that in acute ITP (Table 3 and Figure 2-b). No significant association was found between the clinical course of ITP and the platelet count at diagnosis (X^2=0.09; p=0.758; Figure 2-b).

Acute ITP and chronic ITP were more prevalent in male (58.33% and 54.29%, respectively) than in female (41.672% and 45.71%, respectively; Table 3 and Figure 2-c). The clinical course of ITP was not significantly associated with the gender of patients (X^2=0.877; p=0.83; Figure 2-c).

Four different types of treatment were adopted against ITP, as shown in Table 4. The most commonly used therapeutic drug was IVIG (37.29%), followed by steroids (23.73%), the combination of both therapeutic agents (18.64%), cyclosporine (5.08%), then splenectomy (5.08%), while 10.17% of the ITP patients were only observed without treatment (Table 4). Splenectomy and treatment with cyclosporine were used as second-line therapy in patients that did not respond to treatment with IVIG and steroids. Interestingly, all treatment modalities resulted in a statistically significant platelet increase (p <0.01; p <0.001; Figure 3). Although the small number of patients treated with cyclosporine did not allow the performance of a statistical test, the results clearly showed an increase in the number of platelets posttreatment (Figure 3-d).

Table 4. Distribution of ITP children admitted to different hospitals of Beirut and the south of Lebanon according to the type of treatment and the clinical course of the disease (acute/chronic)

Treatment	Number of Patients (%)	Platelets at diagnosis		Acute	Chronic
		Mean $\times 10^9$	SD	No (%)	No (%)
IVIG	22 (37.29%)	102.3	21.87	8 (33.33%)	14 (40%)
Steroids	14 (23.73%)	88.86	16.68	6 (25%)	8 (22.86%)
IVIG+Seroids	11 (18.64%)	44.09	17.93	3 (12.5%)	8 (22.86%)
Splenectomy	3 (5.08%)	82.6	30.03	0 (0%)	3 (8.57%)
Cyclosporine	3 (5.08%)	37.67	23.17	1 (4.17%)	2 (5.71%)
Observation alone	6 (10.17%)	360.8	72.47	6 (25%)	0 (0%)
Total	59 (100%)			24 (100%)	35 (100%)

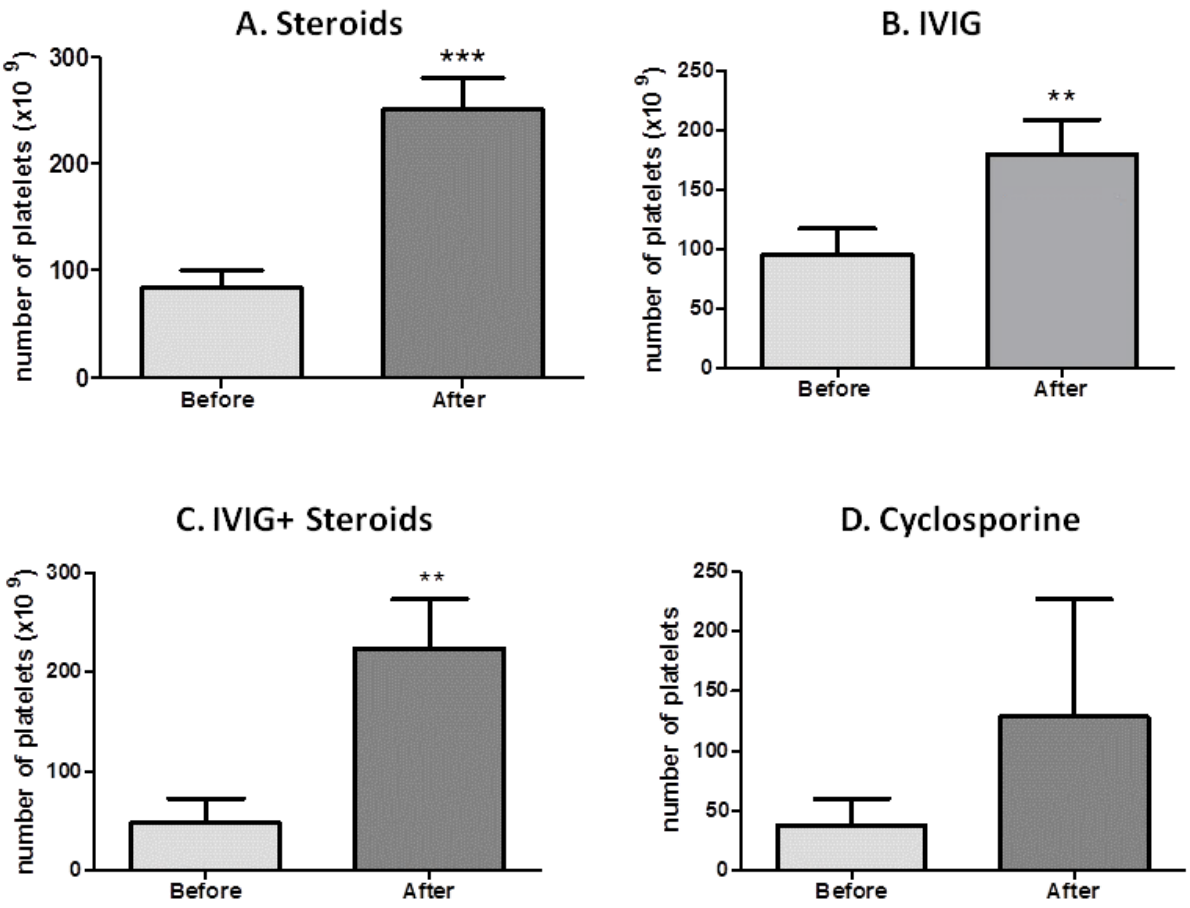

Figure 3. Effect of treatment on platelets number. The number of platelets of children with ITP was measured before and after treatment. A. Treatment with Steroids (n=14). B. Treatment with IVIG (n=22). C. Treatment with Steroids and IVIG (n=11). D. Treatment with Cyclosporine (n=3). Matched data for each patient were compared and subjected to one-tailed paired t-test analysis to determine significant differences. *** p value <0.001, ** p value <0.01.

4. Discussion

Immune thrombocytopenia purpura is the most prevalent acquired bleeding disorder in children, with an estimated incidence of 5 per 100,000 children every year [9]. In the present study, we analyzed the demographic characteristics of 59 ITP children from Lebanon and evaluated the ITP clinical course in addition to the treatment modalities and outcome.

The ITP patients in our study were younger at diagnosis than those involved in a similar study performed in Ankara, 3.87±0.56 years versus 4.8 ± 3.9 years for acute ITP and 5.38±0.75 years versus 6.8 ± 4.2 years for chronic ITP [10]. Similar to our study findings, a nearly equal distribution of ITP between both sexes was reported in South Africa [11]. As for the distribution of ITP children among the age groups, our findings are in line with those of ITP children from Qatar, where the highest percentage of ITP children were 1-4 years old [12].

As for the clinical course of ITP, we found that it was not significantly associated with each of the age group, the platelet count at diagnosis, and gender of patients. In contrast, Grimaldi-Bensouda et al. (2016) showed that each of the female gender, older age (≥10 years old), and higher platelet count ($\geq 10 \times 10^9$/L) was associated with increased chances of developing chronic ITP in children from France [13]. Other predictors of chronic ITP in children have been identified, including the absence of preceding infection or vaccination, insidious onset, and anti-nuclear antibody positivity [14]. On the other hand, our findings are in agreement with those of Güngör et al. (2018), who showed that the mean age of patients and the mean platelet count at diagnosis were significantly higher in chronic ITP compared to that in acute ITP [10].

Treatment of ITP patients tends to ensure a safe platelet count that prevents severe bleeding rather than reaching a normal platelet count [5]. Selection of a therapeutic measure against ITP is hard due to the heterogeneity of this disease and lack of diagnostic markers [15]. In our study, several therapeutic measures were adopted, and they were effective in increasing the platelet count. Different therapeutic approaches were reported in a similar study conducted on ITP children diagnosed during the years 2008–2018 in northeast Mexico. ITP children were treated with steroids (40.4%), IVIG (15.4%), a combination of both agents (15.4%), rituximab at low doses plus steroids (7.7%), danazol plus steroids (3.8%) while 17.3% of ITP children were under clinical observation. The initial response to treatment included 30.2% complete response, 55.8% response and 14.0% non-response rates reflecting a heterogeneous response to therapy [16].

On the other hand, the American Society for Hematology (ASH) recommended in her guidelines of 2011 and 2019 that children who have no or mild bleeding should be managed with observation alone, irrespective of their platelet count, since the rates of actual bleeding in the pediatric population are low and the rates of remission are high [17, 18]. Regarding ITP children who have non-life-threatening mucosal bleeding and/or diminished health-related quality of life, the ASH guidelines of 2019 recommended courses of corticosteroids no longer than 7 days as first-line treatment rather than IVIG. As for the second line of treatment, it suggested the use of thrombopoietin receptor agonists rather than rituximab and splenectomy [18]. In 2018, the joint working group of several European hematology societies recommended that a low platelet count alone is not enough to give treatment to children with newly diagnosed ITP. It also stated that there were no standard treatments for chronic ITP in children and suggested to avoid performing splenectomy in children and keeping it as a last therapeutic option [18].

5. Conclusion

The prevalence of ITP among children in Lebanon is 2.5%. This disease affects both sexes equally and is more prevalent among children who are 1-4 years old. More than half of ITP children presented a chronic disease. The clinical course of ITP was not significantly associated with each of the age group, the platelet count at diagnosis, and gender of patients. Moving forward, additional predictors of chronic ITP should be analyzed in future studies to effectively predict the course of the disease at the time of diagnosis. Given the variety of the available therapeutic options, it is also important to conduct well-designed comparative effectiveness trials to assist medical providers in making informed decisions about the treatment of ITP in children.

6. Declarations

6.1. Author Contributions

Conceptualization, Has.K. and Hal.K.; methodology, Hal.K.; software, F.A.; validation, Hal.K.; formal analysis, F.A.; investigation, Hus.K. and K.S.; resources, Hus.K.; data curation, F.A..; writing—original draft preparation, Z.F.; writing—review and editing, Hal.K.; visualization, F.A.; supervision, Hal.K.; project administration, Has.k. and Hal.K.; funding acquisition, Not applicable. All authors have read and agreed to the published version of the manuscript.

6.2. Data Availability Statement

The data presented in this study are available on request from the corresponding author.

6.3. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

6.4. Ethical Approval & Institutional Review Board Statement

This retrospective study was conducted in different hospitals in Beirut and the south of Lebanon from January 2007 to April 2016. The work was approved by the research ethics boards at each hospital and carried out in accordance with the 1964 Helsinki Declaration.

6.5. Informed Consent Statement

Not applicable.

6.6. Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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