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CLINICAL PREDICTORS OF CHRONIC IMMUNE THROMBOCYTOPENIA ITP AMONG ADULTS AND CHILDREN

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Abstract:

Introduction: Immune thrombocytopenia (ITP) is defined as an isolated platelet count lower than $100 \times 10^9/L$ in the absence of preexisting diseases or conditions that could lead to thrombocytopenia (1,2). Although several factors influence the outcome, it is difficult to predict at diagnosis which patients will have the acute or chronic form of the disease (3,4). Therefore, we aim in this study to identify the clinical presentation of the disease, predictors of chronicity, and modalities of treatment given in the child and adult population at King Abdulaziz Medical City, Jeddah.Methods: We retrospectively reviewed the records of patients diagnosed with ITP between 1993 and 2017. Files were collected from a total of 185 patients, of whom 94 with primary ITP were included in the study.Results: Most patients were females (58.5%). Median age at diagnosis of ITP for patients above 14 years old was 29 years (IQR 32) and for pediatrics (≤14 years old) was 4 years (IQR 6). Mean platelet count at presentation was $20.02 \times 10^9/L$ (SD 23.270). The most common presentation was skin manifestation (51.1%) followed by bleeding (17% epistaxis, 13.8% bleeding gums, 3.2% gastrointestinal bleeding, 5.3% menorrhagia, 2.1% hematuria, 2.1% subconjunctival hemorrhage, 31.9% were asymptomatic). Acute ITP was seen in 24 patients (25.5%) and chronic in 70 (74.5%). Patients with chronic ITP had higher mean age at diagnosis (P=0.001). However, other predictors including gender, skin manifestation, incidental, and platelet count at diagnosis were not statistically significant.
Conclusion: Majority of the cases showed complete response to the first-line treatment (steroid, IVIG, anti-D). Adult age was the only predictor factor associated with chronic ITP.

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BACKGROUND:
Immune thrombocytopenia (ITP), previously known as idiopathic thrombocytopenia purpura, is uniformly defined as an isolated platelet count lower than 100×10^9/L in the absence of preexisting diseases or conditions that could lead to thrombocytopenia (1). The pathogenesis of ITP is still incompletely understood. However, ITP is believed to be an autoimmune meditated disorder in which autoantibodies are directed against the platelet membrane. Thus, platelet lifespan is reduced as a consequence of antibody-mediated clearance by macrophages in the spleen (2). In addition, platelet production is inhibited by the same antibodies (3,4). ITP may occur in the absence of an apparent predisposing etiology (primary ITP) or as a sequela of an associated condition (secondary ITP) (2,3). Several studies have estimated the annual incidence to be between 1 and 6.4 cases per 100,000 children (3,5). In adults, the annual ITP incidence is approximately 1–3 per 100,000 persons (6,7). Because ITP assumes a chronic course in most adults, prevalence estimates are somewhat higher (9.5–23.6 per 100,000 persons). The clinical manifestations vary from incidental findings to life-threatening bleeding. In general, IPT manifests in the following ways: cutaneous bleeding (86%), oral (19%), nasal (20%), and no bleeding (9%) (8). Major gastrointestinal hemorrhage and hematuria are less frequent. Intracranial hemorrhage (ICH), the most severe complication of ITP, is rare (9).

Recent guidelines have helped to clarify and classify the disease as follows: newly diagnosed patients are those who remain thrombocytopenic for 3 months; patients who are thrombocytopenic for more than 3 months are classified as having persistent ITP; and chronic ITP lasts for more than 12 months (3). Several papers have identified multiple predictors of chronic ITP in children, including age ≥11 years at presentation, female sex, no preceding infection or vaccination, absence of bleeding symptoms at diagnosis, insidious onset, and platelet count $\geq 20 \times 10^9$ at diagnosis (10,11). Although several factors influence the outcome, it is difficult to predict at diagnosis which patients will have newly diagnosed ITP or the chronic form of the disease.

In ITP, the first line of management is steroid with adjuvant intravenous immunoglobulin (IVIG). Multiple second-line regimens exist, including rituximab, immunosuppressive therapy, thrombopoietic agonists, and splenectomy. Thus we have several reasons to conduct this study. Firstly, ITP has a considerable impact on patients' lives.

Therefore, the ability to predict the clinical course at the time of diagnosis could improve the quality of patients' lives and guide the management process. Secondly, the predictors of chronic ITP have mainly been studied in children and rarely in adults (4). For these reasons, we aim in this study to identify the clinical course of the disease in King Abdulaziz Medical City (KAMC), Jeddah, and predictors of chronicity in the child and adult populations.

METHODS:
This study was approved by the international review board at KAMC in Jeddah, Saudi Arabia. It included review of patient records from 1993 to 2017. Data were retrospectively collected from patients' files in the medical records and electronic medical record system (BestCare©). We included any child and adult patients diagnosed with ITP at KAMC-Jeddah. The exclusion criteria were: (1) thrombocytopenia secondary to systemic disease or medication; (2) patients <3 months old born to mothers with thrombocytopenia, in order to avoid inclusion of patients with thrombocytopenia secondary to maternal autoantibodies; (3) patients with incomplete clinical data or discontinued follow-up. Information were collected on demographic data (age, sex, age at diagnosis, and date of diagnosis), clinical manifestations at presentation, laboratory data at presentation (complete blood count, serology, autoimmune profile, bone marrow aspiration), treatment peak response and complications of the treatment, and the course of the disease (acute, persistent, chronic). The response criteria used were those adopted by the international working group: complete remission (platelet count: $>100 \times 10^9$/L); partial response (platelet count: 30×10^9/L and at least 2-fold increase from baseline count); no response (platelet count: 30×10^9/L or less than 2-fold increase from baseline, or bleeding). Corticosteroid dependence was defined as the need for ongoing administration or repeated doses of corticosteroids for at least 2 months to maintain a platelet count at or above 30×10^9/L and/or to avoid bleeding (3).

RESULTS:
We retrospectively reviewed the records of patients diagnosed with ITP from 1993 to 2017. In total, files were collected from 185 patients, of whom 91 were excluded for the following reasons: secondary ITP (e.g. associated with systemic lupus erythematosus, gestational thrombocytopenia, and lymphoma), misdiagnosed as ITP, or insufficient data.

We included 94 patients with primary ITP; 57 (60.6%) were above 14 years old and 37 (39.4%) were children (≤14 years old)).

Demographic features
The study included 17 adult men, representing 29.8% of the adult population, while the 40 adult women represented the majority (70.2%) of the adult patients. The median age at diagnosis of ITP was 29 years with an interquartile range (IQR= 32).
Among pediatrics, The median age of pediatric diagnosis was 4 years, with an IQR of 6. The study included 22 boys (59.5%) and 15 girls (40.5%).

Clinical manifestations
Among adults, the most common presentation in our study was a skin manifestation in 20 patients (35.1%). Other symptoms were epistaxis in 9 (15.8%); gum bleeding in 7 (12.3%); gastrointestinal bleeding in 2 (3.5%); menorrhagia in 4 (7%); hematuria in 2 (3.5%); subconjunctival hemorrhage in 1 (1.8%); and headache in 1 patient (1.8%). However, 25 out of 57 adult patients (43.9%) were asymptomatic and diagnosed incidentally. The presentation was preceded by infection in 13 patients (22.8%) and 1 patient had a history of recent vaccination (1.8%), which was hepatitis B vaccine. The median platelet count was 44×10^9/L (IQR=52).
Among pediatrics, The majority of patients had skin manifestations (28; 75.7%), while only 7 had epistaxis (18.9%); 6 had gum bleeding (16.2%); 2 had fever (5.4%); 1 had gastrointestinal bleeding (2.7%); 1 had menorrhagia (2.7%); 1 had headache (2.7%); and 5 had incidental findings (48.6%). Out of 37 patients, 18 (48.6%) had a history of infection and 2 (5.4%) had recent vaccination. The median platelet count was 10×10^9/L (IQR=26).

Treatment
Spontaneous remission was seen in 16 individuals while 82 were treated with one or more lines of treatment. First line treatment (steroid, IVIG, anti-D) was given to 81 patients (86.2%), of whom showed a complete response (Figures 2 and 3).

DISCUSSION:
The aim of this study was to identify the clinical and laboratory parameters that predict the chronicity of ITP. Age was determined as significant predictor of chronicity, however, other variables including gender, incidental findings and platelet count at initial diagnosis were not statistically significant. These findings were supported by other previous reports (4,12).
Among the pediatric population, studies

have reported several predictors for chronicity: an older age at diagnosis (>10 years), female sex, higher platelet count at presentation (10×10^9/L), and the lack of a preceding infection or vaccination (11,13,14). However, we were unable to replicate similar findings. This could be explained by the fact that the current study was conducted at tertiary center that deals most of the time with complicated chronic cases. Therefore, as most cases of ITP in children are acute and self-limiting in nature, we had a small pediatric population in our study. The median age in previous published studies is 5 years (mean 5.5 years), which is comparable to our study. ITP was more prevalent in boys, a finding supported by international and regional studies (15–17). In contrast, other publications have shown a predominance in girls (18). In the literature, a higher platelet count was found to be associated with chronic ITP (19); however, it is interesting that our study found that a higher platelet count was associated with acute ITP. Most of the children presented with cutaneous manifestations, while some presented with epistaxis, gastrointestinal bleeding, and menorrhagia (6).

In the adult population (>14 years), the median age at diagnosis in our study was 29 years, consistent with one study carried out in Oklahoma (8). However, the median age in other published studies ranges from 47 to 56 (4,6,8,20). This can be explained by the fact that, apart from the peak occurring in people over 70 years of age, ITP is thought to be a disease that affects young people. Thus the impact on the current study median was mainly due to the presence only of 2 patients over 70 years old.

Clinical presentation among adults tends to be mainly asymptomatic and diagnosed as incidental thrombocytopenia. If bleeding occurs, it is mostly platelet-dependent, whereby the lower the platelet count, the more likely the patient is to present with bleeding symptoms (20). Skin and mucous membrane bleeding represent the majority of bleeding symptoms, with a very low risk of severe bleeding such as intracranial hemorrhage (ICH) among adults (21,22). Our results support these findings, as skin bleeding was the most common presentation, followed by epistaxis and gum bleeding, respectively, while there was no major bleeding such as ICH among our adult population. However, the overall numbers with an incidental presentation were slightly lower than those presenting with clinical symptoms.

In this current study, ITP in adults was more common in women, with a female to male ratio of

2.3:1. Previous studies, both older and more recent, have led to a consensus of opinion that adult ITP is more common in women than men. The median platelet count was 29×10^9/L and the analysis did not demonstrate any association between the platelet count and chronic ITP. We subdivided the group using a platelet count of 20×10^9/L as a cut-off point, and had the same results. Our finding does not contradict other studies.

The limitations of our study are as follows. Firstly, although we used an extended period of data collection from 1993 to 2017, we had a small sample size for the pediatric population. Secondly, the majority of childhood ITP cases are acute and self-limiting; they usually present to primary health care and our data was collected from a tertiary center that commonly deals with advanced cases of ITP. Thirdly, this study was based on a retrospective review of medical records, and thus the quality of our data relies on the physician's documentation.

CONCLUSION:
In conclusion, clinical epidemiology showed that adult ITP generally affects young women and tends to be chronic in nature. In comparison, ITP in children had a slight predominance for boys over girls. Moreover, no risk of life-threatening bleeding such as intracranial hemorrhage (ICH) was reported in either adults or children. Regarding clinical predictors, adult age was associated with chronic ITP. No association was found between ITP outcome and following factors: gender, bleeding at presentation, or initial platelet count. While the lack of predictors for chronic ITP in adults is consistent with the literature, the absence of such predictors for children in our population needs to be validated by further research with a larger sample size.

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Figure 1. Flowchart illustrating patient selection
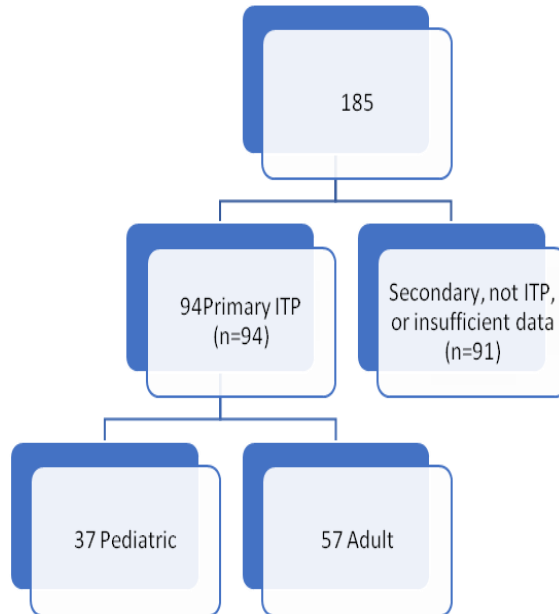
**Table 1:**

Presentation	Acute	Chronic	p Value
Demographic Data			

Characteristics of patients with ITP:

Pediatric (n=37)	11 (28.2%)	28 (71.8%)	
male (n=22, 59.5%)	9 (56.3%)	13 (61.9%)	
female (n=15, 40.5%)	7 (43.8%)	8(38.1%)	Ped: 0.729
Adult (n=57)	12 (21.8%)	43 (78.2%)	Adults: 1
Male (n=17, 29.8%)	2 (25%)	15(30.6%)	
Female (n=40, 70.2%)	6 (75.0%)	34 (69.4%)	
Clinical Manifestation			
Bleeding symptoms (n=58, 62%)	16 (27.6%)	42 (72.4%)	0.562
Pediatric (n=21)	11 (52.4%)	10 (47.6%)	0.19
Adult (n=37)	5 (13.5%)	32 (86.5%)	0.88
Incidental (n=36)	7 (19.4%)	29 (80.5%)	0.286
Pediatric (n=7)	4 (57.14%)	3 (42.9%)	0.437
Adult (n=29)	3 (10.3%)	26 (89.7%)	0.470
Laboratory Parameters			
PLT	26.79	26.47	0.866
Pediatric	7.5	10	1
Adults	50	44	0.412
MCV	81.5	75.1	0.355
Pediatric	78	72	0.044
Adults	81.67	81	0.176

Table 2: Multivariant analysis of risk factors of chronic ITP

	Odds Ratio	P-value	95% Confidence Interval
Age:			
Paediatrics	1	1	1
Adult (14-50)	3.9	0.016	(1.289, 11.65)
Adult (>50)	5.2	0.046	(1.033, 26.684)
Gender:			
Female	1	1	1
Male	0.934	0.954	(0.316, 2.879)
Incidental finding	0.920	0.931	(0.232, 3.743)
Platelet count	0.195	0.986	(0.965, 1.007)

Figure 2: Percentage of patients given different lines of treatment

Line of Treatment

- First-line treatment
- Second-line treatment
- Spontaneous remission
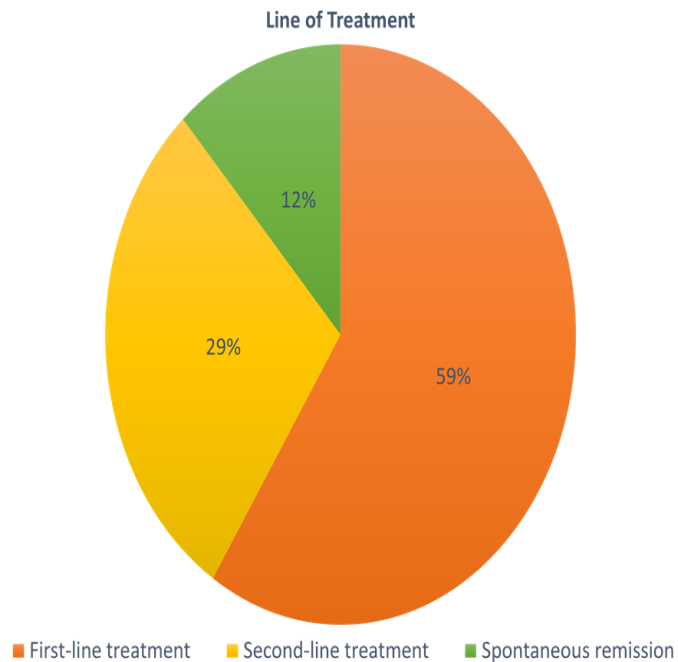
Figure 3: Response to different lines of treatment