Initial lymphocyte count's predictive value in immune thrombocytopenic purpura

Salwa S. El-Din El-Gendi, Wael A. Abbas, Dolagy N. Naguib

Department of Internal Medicine, Assuit University, Assuit, Egypt

Correspondence to Dolagy N. Naguib, MSc, Department of Internal Medicine, Assuit University, Assuit, Egypt
Tel: +20 128 549 4662;
e-mail: dolagynabil7@yahoo.com

Received 23 December 2018
Accepted 10 June 2019

Journal of Current Medical Research and Practice
September-December 2019, 4:362–367

Objective
The objective of this study was to examine whether absolute lymphocyte count (ALC) at diagnosis correlates with the course of immune thrombocytopenia purpura (ITP) and could be considered as a prognostic factor in adults and children.

Patients and methods
A retrospective study of 250 patients diagnosed as having primary ITP, including 150 adult patients and 100 children, was conducted between July 2013 and July 2018 at Hematology Department and outpatient clinic.

Results
A highly significant decrease in mean ALC was noted in chronic ITP adult cases (1.55 ± 0.69) compared with newly diagnosed ITP cases (2.99 ± 1.23) (P = 0.000). Moreover, ALC less than 2.050/mm^3 was associated with a significant risk for developing chronic ITP (P = 0.000), as only eight (26.7%) cases with ALC less than 2050/mm^3 developed newly diagnosed ITP, whereas 97 cases with ALC less than 2050/mm^3 (80.8%) developed chronic ITP. Thus ALC less than 2050/mm^3 is considered a significant risk factor for developing chronic ITP in adults. In contrast, mean ALC in pediatric cases showed a significant decrease in chronic ITP cases (2.55 ± 1.01) compared with newly diagnosed cases (3.68 ± 1.34) (P = 0.000). Moreover, ALC less than 2050/mm^3 was associated with a significant risk for developing chronic ITP (P = 0.001), as only one case less than 2050/mm^3 (2.5%) developed newly diagnosed ITP, whereas 17 cases less than 2050/mm^3 (28.3%) developed chronic ITP.

Conclusion
ALCs at diagnosis is statistically a strong predictor of the development of chronic ITP in adult and pediatric patients. ALC at cutoff less than 2050/mm^3 is considered a significant risk factor for developing chronic ITP in adults and pediatric cases (P = 0.000 and 0.001, respectively).

Keywords:
immune thrombocytopenic purpura, Initial lymphocyte counts, prognostic factors

J Curr Med Res Pract 4:362–367

2357-0121

Introduction

Immune thrombocytopenia purpura (ITP) is an acquired autoimmune disorder characterized by increased platelet destruction and decreased platelet number [1].

Primary immune thrombocytopenia is an acquired immune disorder characterized by an isolated thrombocytopenia owing to pathogenic antiplatelet autoantibodies, T-cell-mediated platelet destruction, and impaired megakaryocyte function [2,3].

It is associated with the production of autoantibodies directed against platelet glycoprotein complex IIb/IIIa and Ib/Ix, resulting in accelerated destruction of platelets by the reticular endothelial system via the activity of Fcγ- receptor-bearing phagocytic cells [4].

Studies have demonstrated that the pathogenesis of ITP involves multifactorial autoimmune mechanisms of both humoral and cellular immunity and that acute and chronic forms may represent two distinct immunopathological disorders [1,5].

It can be observed in both adults and children, with both sexes being affected [6]; however, the underlying mechanisms of pediatric ITP compared with adult ITP may be different [4,7,8].

There are three phases of the disease [9]:
(1) Newly diagnosed ITP: for all cases at diagnosis.,
(2) Persistent ITP: for patients with ITP between 3 and 12 months
(3) Chronic ITP: for patients with ITP lasting more than 1 year.

ITP is usually chronic in adults, and the probability of durable remission is 20–40% [10,11].

At least 70% of childhood cases will end up in remission within six months, even without treatment [12–14].

The treatment strategies consist of stimulating platelet production to increase the platelet counts, increasing platelet half-life, and decreasing the autoreactive nature of the immune response by targeting the autoreactive antibody production and the platelet destruction. [15,16].

Although lymphocytopenia is a commonly reported feature of many chronic autoimmune disorders, differential white cell counts at presentation have seldom been evaluated as predictors for development of chronic ITP [17,18].

Patients and methods

A retrospective study was performed at Hematology Unit of Internal Medicine Department and outpatient clinic, Assiut University Hospital, and Hematology Department and outpatient clinic, Assiut University Children Hospital, to assess the role of absolute lymphocyte counts (ALCs) at diagnosis as a prognostic factor in the course of ITP.

Data sheets of 250 patients diagnosed as having primary ITP between July 2013 and July 2018 at Hematology Department and outpatient clinic were retrospectively evaluated.

Inclusion criteria

The following were the inclusion criteria: primary ITP cases with full datasheet recorded, including age, sex, clinical presentation, complete blood count at diagnosis, bone marrow aspirate (BMA) if done, serology and autoimmune profile, and available follow-up data to determine whether the patient is newly diagnosed or has chronic ITP.

Exclusion criteria

The following were the exclusion criteria:

(1) Secondary ITP cases, secondary to the following:
   (a) Infectious diseases (hepatitis B or C, cytomegalovirus, HIV, and *Helicobacter pylori*)
   (b) Immune disorders (systemic lupus erythematosus)
   (c) Lymphoproliferative diseases (non- Hodgkin's lymphoma and chronic lymphoid leukemia)
(2) Cases without recorded enough data or without follow-up data.

Methodology and data collection

On reviewing the medical records of 600 patients with ITP admitted at the ward or followed up at the outpatient clinic of Hematology Department at Assiut University Hospital and Assiut University Children Hospital from 2013 to 2018 and excluding 350 cases according to the exclusion criteria, a total of 250 primary ITP cases were retrospectively evaluated and included in our study, which comprised 150 adult patients and 100 children.

The following data were collected and recorded:

(1) Demographic data: age, sex, and residence (if recorded)
(2) Clinical presentation: purpura, easy bruising, epistaxis, bleeding per gum, menorrhagia (in adult female), and intracranial hemorrhage
(3) Complete blood count at diagnosis, including total leukocytic count (TLC), ALC, platelet count, mean platelet volume (MPV), and hemoglobin (HB) level
(4) Autoimmune profile: antinuclear antibody and anti-double stranded DNA
(5) Serology for hepatitis B and C viruses
(6) BMA if done
(7) Duration of illness to determine whether the patient is newly diagnosed or has chronic ITP.

Statistical analysis

Data were collected and analyzed using statistical package for the social science, version 20 (IBM Corp., Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD, whereas nominal data were expressed in the form of frequency (%). χ^2-test was used to compare the nominal data of different groups in the study, whereas Student's *t*-test was used to compare mean of different two groups. *P* value was significant if less than 0.05.

Results

A total of 250 patients with primary ITP were included in our study, comprising 150 adult patients and 100 children, after reviewing more than 600 medical records of patients with ITP and excluding approximately 350 cases according to the exclusion criteria.

Adult cases data

Of 150 adult cases, 30 (20%) were newly diagnosed and 120 (80%) were chronic. There were 27 (18%) males and 123 (82%) females. Their age ranged from 19 to 73 years, and median age at diagnosis was 30 years. The mean age was 30.2 ± 6.71 years for newly diagnosed ITP and 34.1 ± 12.5 years for chronic ITP cases. Among the newly diagnosed ITP cases, 26 (86.7%) were younger

than 50 years old and four (13.3%) were 50 years or older, whereas among chronic ITP cases, 100 (83.3%) were younger than 50 years and 20 (16.7%) were 50 years or older. According to WHO classification of age in Africa (2002), old age starts from 50 years or above.

Clinical presentation of cases is shown in Figs. 1 and 2.

BMA was done in 82 (54.7%) cases, revealing 10 (33.3%) as newly diagnosed ITP cases and 72 (60%) as chronic.

Data about TLC, ALC, platelet count, HB level, and MPV are mentioned in Tables 1–3.

Pediatric cases data

Among the 100 pediatric cases, 40 (40%) were newly diagnosed and 60 (60%) were chronic. There were 53 (53%) males and 47 (47%) females. Their age ranged from 1 to 18 years, with median age at diagnosis of 6 years. The mean age was 4.2 ± 2.83 years for newly diagnosed ITP patients and 8.13 ± 4.08 years for chronic ITP patients. Among the newly diagnosed cases, 33 (82.5%) were younger than 6.75 years and 7 (17.5%) were 6.75 years or older, whereas among chronic ITP cases, 24 (40%) were younger than 6.75 years and 36 (60%) were 6.75 years or older.

Clinical presentation of cases is shown in Figs. 3 and 4.

BMA was done in 28 (28%) cases, among which seven (17.5%) were newly diagnosed and 21 (35%) were chronic.

Data about TLC, ALC, platelet count, HB level, and MPV are mentioned in Tables 1–3.

Discussion

A total of 250 primary ITP cases were retrospectively evaluated and included in our study, comprising 150 adult patients and 100 children. In adult cases, 20% were newly diagnosed and 80% were chronic. This was consistent with the study by Stevens *et al.* [11] who stated that ITP is usually chronic in adults, and the probability of durable remission is 20–40%.

In children, 40% were newly diagnosed and 60% were chronic. Treutiger *et al.* [14], stated that at least 70% of childhood cases will end up in remission within six months, even without treatment. Moreover, Akbayram *et al.* [19], in their study revealed that 74% of the patients had acute ITP and 26% had chronic ITP, which was inconsistent with our study.

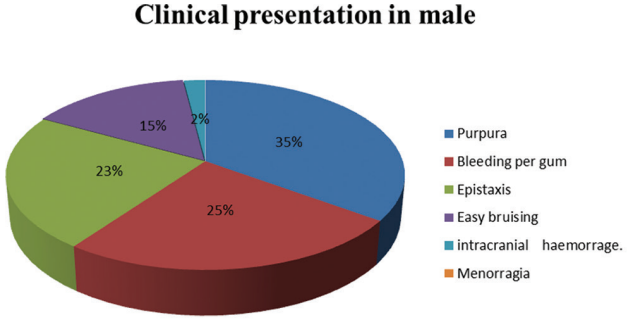
This can be explained by the fact that our study is a retrospective study based on patients' data sheets of ward admission and outpatient clinic visits. Number of newly diagnosed cases is not indicative of the true incidence of cases, this is attributed to the fact that the nature of our study is retrospective and that data

Table 1 Comparison between sex, age groups and cutoff points in total number of adult cases

Parameters	*n* (%)			*P*
	Newly diagnosed (*n*=30/150)	Chronic (*n*=120/150)	Total (*n*=150)	
Sex				
Male	10 (33.3)	17 (14.2)	27 (18)	**0.015**
Female	20 (66.7)	103 (85.8)	123 (82)	
Age (years)				
<50	26 (86.7)	100 (83.3)	126 (84)	0.180
≥50	4 (13.3)	20 (16.7)	24 (16)	
ALC (mm^3)				
<2050	8 (26.7)	97 (80.8)	105 (70)	**0.000**
≥2050	22 (73.3)	23 (19.2)	45 (30)	
TLC (mm^3)				
<6250	12 (40)	28 (23.3)	40 (26.7)	0.065
≥6250	18 (60)	92 (76.7)	110 (73.3)	
Platelet (mm^3)				
<6950	11 (36.7)	29 (24.2)	40 (26.7)	0.166
≥6950	19 (63.3)	91 (75.8)	110 (73.3)	
BMA				
	10 (33.3)	76 (63.3)	86 (57.3)	**0.003**

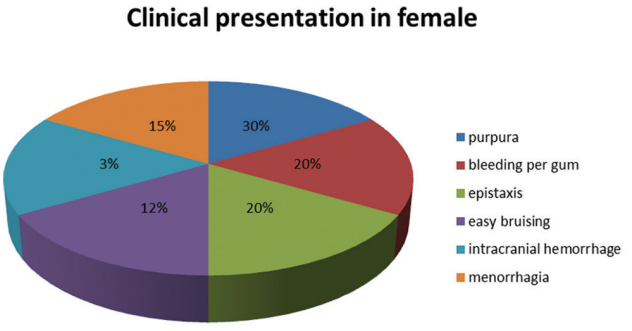
ALC, absolute lymphocyte count; BMA, bone marrow aspirate; TLC, total lymphocyte count. *P*<0.05, significant on comparison between sex, age groups, and cutoff points. Bold: Adult females developed chronic ITP more than males with significant difference (*P*=0.015).

Figure 1



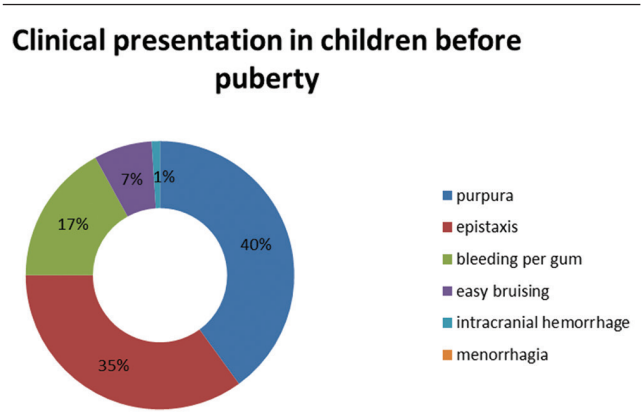
Clinical presentation in male.

Figure 2



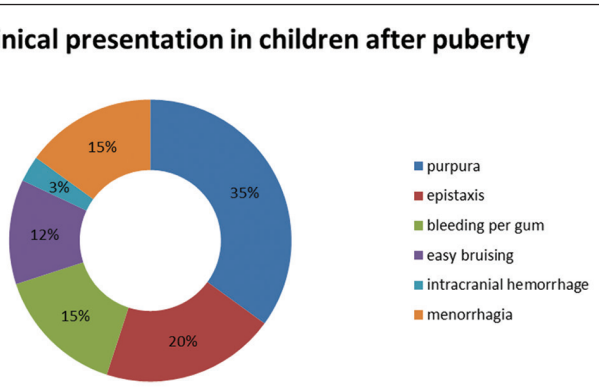
Clinical presentation in female.

Figure 3



Clinical presentation in children before puberty.

Figure 4



Clinical presentation in children after puberty.

Table 2 Comparison between sex, age groups, and cutoff points in total number of pediatric cases

Parameters	*n* (%)			*P*
	Newly diagnosed (*n*=40/100)	Chronic (*n*=60/100)	Total (*n*=100)	
Sex				
Male	24 (60)	29 (48.3)	53 (53)	0.252
Female	16 (40)	31 (51.7)	47 (47)	
Age (years)				
<6.75	33 (82.5)	24 (40)	57 (57)	**0.000**
≥6.75	7 (17.5)	36 (60)	43 (43)	
ALC (mm^3)				
<205	1 (2.5)	17 (28.3)	18 (18)	**0.001**
≥2050	39 (97.5)	43 (71.7)	82 (82)	
TLC (mm^3)				
<6250	8 (20)	15 (25)	23 (23)	0.561
≥6250	32 (80)	45 (75)	77 (77)	
Platelet (mm^3)				
<6950	5 (12.5)	7 (11.7)	12 (12)	0.900
≥6950	35 (87.5)	53 (88.3)	88 (88)	
BMA				
	7 (17.5)	21 (35)	28 (28)	0.056

ALC, absolute lymphocyte count; BMA, bone marrow aspirate; TLC, total lymphocyte count. *P*<0.05, significant on comparison between sex, age groups, and cutoff points. Bold: Highly significant difference between ages of children of newly diagnosed and chronic ITP according to incidence above and below cuttoff age and mean age (*P*=0.000). Older children tends to develop chronic ITP.

Table 3 Comparison between newly diagnosed versus chronic ITP cases in children and adults according to various parameters

Parameters	Newly diagnosed	Chronic	*P*
Age (years)			
Children	4.2±2.83	8.13±4.08	**0.000**
Adults	30.2±6.71	34.1±12.5	0.180
ALC (mm^3)			
Children	3.68±1.34	2.55±1.01	**0.000**
Adults	2.99±1.23	1.55±0.69	**0.000**
TLC (mm^3)			
Children	8.23±2.45	7.74±2.3	0.310
Adults	7.9±2.98	9.19±3.63	0.074
Platelet (mm^3)			
Children	23.68±17.16	23.37±16.06	0.927
Adults	21.67±19.48	16.37±14.49	0.098
HB level (g/dl)			
Children	10.23±1.53	11.14±1.72	**0.008**
Adults	10.9±2.04	11.65±1.88	0.055
MPV (fl)			
Children	9.75±1.21	9.87±1.37	0.664
Adults	8.9±1.4	9.75±1.25	**0.001**

Continuous data were expressed in the form of mean±SD, whereas nominal data in the form of frequency (%). ALC, absolute lymphocyte count; BMA, bone marrow aspirate; TLC, total lymphocyte count. *P*<0.05, significant on comparison between sex, age groups, and cutoff points. Bold: A significant difference between mean ages of children who were newly diagnosed and those who developed chronic ITP. Thus older children tends to develop chronic ITP.

collected depends on availability of sheets of admission or follow up at out patient clinic, while patients with newly diagnosed ITP make less visits to the hospital. This makes their number in our study less than its true incidence.

Our study included 18% males and 82% females. It was consistent with Schoonen *et al.* [20] and Moulis *et al.* [21] who stated that there is a predilection for female patients in younger adults, but prevalence in men and women is fairly even in the elderly (>65 years).

Male:female ratio in our study was almost 1: 4. However, Cines and Bussel [22] stated that the ratio is 1:1.2–1.7. This difference could be attributed to the fact that our study is a retrospective one, including patients with enough follow-up data recorded, and not including all patients who developed ITP.

In our study, females developed chronic ITP more than males (83.7 and 63%, respectively, $P = 0.015$). Katja *et al.* [23] declared that females developed chronic ITP significantly more often.

Children in our study represented 53% males and 47% females, without significant sex preference, which was consistent with Cines and Bussel [22], as they stated that childhood cases are roughly equal for both sexes.

Age of the adult cases ranged from 18 to 73 years, with median age at diagnosis of ITP was 30 years. The mean age was 32.03 ± 11.59 years for newly diagnosed

ITP and 35.61 ± 13.33 years for chronic ITP, with no significant difference in the mean age of cases, whether newly diagnosed and chronic ITP (P = 0.180). This was inconsistent with Cines and Bussel [22] and Abrahamson *et al*. [24], who considered median age at diagnosis of ITP was 55–60 years.

Age of the pediatric cases ranged from 1 to 17 years, with mean age of 4.2 ± 2.87 for newly diagnosed ITP and 8.12 ± 4.08 years for chronic ITP, with highly significant difference between newly diagnosed and chronic cases (P = 0.000). This was consistent with Katja *et al*. [23] whose study stated that chronic ITP cases were older than acute in pediatric study groups.

On examination of the marrow, an increase in the production of megakaryocytes may be observed and may help in establishing a diagnosis of ITP. On the basis of ASH 2011 guidelines, Neunert *et al*. [25] stated that BMA is not necessary done irrespective of age in patients presenting with typical ITP.

Our study focus was to determine the relation between ALC at diagnosis and the development of chronic ITP. A highly significant difference was found between means of ALC in adults, and also between ALC groups at cutoff 2050/mm^3. The same results were also found in pediatric cases; thus, ALC less than 2050/mm^3 is considered a major risk factor in developing chronic ITP in adults and children.

This was consistent with Akbayram *et al*. [19], whose study demonstrated that ALC values (ALC = or <2050/mm^3) at presentation were independently predictive of disease duration. Of patients with an ALC less than or equal to 2050/mm^3, 33.6% developed chronic ITP, whereas 22.4% of those with an ALC >2050/mm^3 followed a chronic course in children.

Our study also found a significant difference between means of MPV in adults only, with mean of 8.9 ± 1.42 for newly diagnosed ITP and 9.75 ± 1.25 for chronic ITP, with a statistically significant difference (P = 0.001). This was consistent with Yildirmak *et al*. [26], who found a significant higher mean MPV of 9.2 fl in patients developing chronic ITP compared with a mean of 8.1 fl in patients with recovered ITP (P = 0.04). However, in pediatric cases, it was calculated with mean of 9.75 ± 1.21 for newly diagnosed ITP and 9.87 ± 1.37 for chronic ITP, without significantly different means (P = 0.664).

HB level mean was significantly different between newly diagnosed and chronic groups in pediatric cases only (P = 0.008). No previous study had been done to determine the relation with HB level and chronic ITP development.

Recommendations

Physicians and pediatricians may elect to manage newly diagnosed cases of ITP, but there will be a need to refer their patients to a hematologist once initial ALCs are low.

It could guide the decision on therapeutic management of the disease, especially if treatment would prevent development of chronic disease.

Further studies should be done to differentiate between the pathogenesis of newly diagnosed and chronic ITP and to find the cause of decreased ALC in chronic ITP.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Cooper N, Bussel J. The pathogenesis of immune thrombocytopaenic purpura. Br J Haematol 2006; 133:364–374.

2 Olsson B, Andersson PO, Jernas M, Jacobsson S, Carlsson B, Carlsson LM, *et al*. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. Nat Med 2003; 9:1123–1124.

3 Khodadi E, Asnafi AA, Shahrabi S, Shahjahani M, Saki N. Bone marrow niche in immune thrombocytopenia: a focus on megakaryopoiesis. Ann Hematol 2016; 95:1765–1776.

4 Provan D, Newland AC. Current management of primary immune thrombocytopenia. Adv Ther 2015; 32:875–887.

5 Gernsheimer T. Chronic idiopathic thrombocytopenic purpura: mechanisms of pathogenesis. Oncologist 2009; 14:12–21.

6 Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR. Northern Region Haematology Group. Br J Haematol 2003; 122:966–974.

7 Schulze H, Gaedicke G. Immune thrombocytopenia in children and adults: what's the same, what's different? Haematologica 2011; 96:1739–1741.

8 Perera M, Garrido T.Advances in the pathophysiology of primary immune thrombocytopenia. Hematology. 2017; 22:41–53.

9 Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, *et al*. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009; 113:2386–2393.

10 Cines DB, Blanchette VS Immune thrombocytopenic purpura. N Engl J Med 2002; 346:995–1008.

11 Stevens W, Koene H, Zwaginga JJ, Vreugdenhil G. Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights. Neth J Med 2006; 64:356–363.

12 Watts RG. Idiopathic thrombocytopenic purpura: a 10-year natural history study at the children's hospital of Alabama. Clin Pediatr (Phila) 2004; 43:691–702.

13 Ou CY, Hsieh KS, Chiou YH, Chang YH, Ger LP. A comparative study of initial use of intravenous immunoglobulin and prednisolone treatments in childhood idiopathic thrombocytopenic purpura. Acta Paediatr Taiwan 2006; 47:226–231.

14 Treutiger I, Rajantie J, Zeller B, Henter JI, Elinder G, Rosthøj S. NOPHO ITP Study Group. Does treatment of newly diagnosed idiopathic thrombocytopenic purpura reduce morbidity? Arch Dis Child 2007; 92:704–707.

15 Lazarus AH. Monoclonal versus polyclonal anti-D in the treatment of ITP. Expert Opin Biol Ther 2013; 13:1353–1356.

16 Crow AR, Lazarus AH. Mechanistic properties of intravenous immunoglobulin in murine immune thrombocytopenia: Support for FcγRIIB falls by the wayside. Semin Hematol 2016; 53 (Suppl 1):S20–S22.

17 Deel MD, Kong M, Cross KP, Bertolone SJ. Absolute lymphocyte counts

as prognostic indicators for immune thrombocytopenia outcomes in children. Pediatr Blood Cancer 2013; 60:1967–1974.

18 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.

19 Akbayram S, Karaman K, Dogan M, Ustyol L, Garipardic M, Oner AF. Initial lymphocyte count as prognostic indicator for childhood immune thrombocytopenia. Indian J Hematol Blood Transfus 2017; 33:93–96.

20 Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F, *et al*. Epidemiology of immune thrombocytopenic purpura in the general practice research database. Br J Haematol 2009; 145:235–244.

21 Moulis G, Palmaro A, Montastruc JL, Godeau B, Lapeyre-Mestre M, Sailler L. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood 2014; 124:3308–3315.

22 Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). Blood 2005; 106:2244–2251.

23 Katja MJ, 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.

24 Abrahamson PE, Hall SA, Feudjo-Tepie M, Mitrani-Gold FS, Logie J. The incidence of idiopathic thrombocytopenic purpura among adults: a population-based study and literature review. Eur J Haematol 2009; 83:83–89.

25 Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011; 117:4190–4207.

26 Yildirmak Y, Yanikkaya-Demirel G, Palanduz A, Kayaalp N. Antiplatelet antibodies and their correlation with clinical findings in childhood immune thrombocytopenic purpura. Acta Haematol 2005; 113:109–112.