Adolescents and young adults with newly diagnosed primary immune thrombocytopenia

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Abstract

Current immune thrombocytopenia (ITP) guidelines target children and adults, leading to oversimplification. Adolescents and young adults (AYAS) comprise a separate group with distinct health and psychosocial issues. This study aimed to describe the clinical presentation and therapeutic strategies of ITP among AYAS. We analyzed data from two large ITP registries (PARC-ITP; CARMEN-France) and included newly diagnosed ITP patients (aged 12–25 years) with an initial platelet counts of $<100\times10^9$/L. Patients with secondary ITP or non-immune thrombocytopenia (n=57) and pregnant women (n=10) were excluded. Of the 656 cases of AYAS with primary ITP registered from 2004 up to 2021, 12-month follow-up data were available for 72%. The initial median platelet count was 12×10^9/L. In 109 patients (17%), the diagnosis was incidental, without documented bleeding. Apart from gynecological bleeding, the clinical and therapeutical characteristics of females and males were similar. Platelet-enhancing drugs were reported in 66%, 45%, and 30% of patients at diagnosis, 1–6 months, and 6–12 months after diagnosis, respectively. Corticosteroids were the preferred treatment at all time points. At 12 months, 50% of all patients developed chronic ITP. In the subgroup of patients with initial severe thrombocytopenia ($<20\times10^9$/L), those receiving frontline treatment had a higher remission rate at 1 year than those who followed an initial watch-and-wait strategy (53% and 32%; $P<0.05$). Our analysis indicates that the remission rate at 1 year may be associated with the initial treatment strategy. This hypothesis must be confirmed in prospective studies.

Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disease characterized by increased platelet destruction and impaired production. Most textbooks and practice guidelines describe pediatric ITP as acute and profound but self-limiting, with a low risk of life-threatening bleeding in the majority of patients.[1-4] In contrast, adult ITP is a chronic disease with an insidious onset of bleeding that is sometimes diagnosed incidentally. Adult ITP carries a high risk of severe bleeding in patients with a platelet count of $<20–30\times10^9$/L, with increased morbidity and mortality, particularly in patients aged >60 years.[5] Platelet-enhancing therapy is usually advised for adults with severe thrombocytopenia, especially the elderly or those with comorbidities.[6,7] In contrast, a watch-and-wait strategy is recommended for children with non-severe bleeding.[2,3] Recently, comparative studies in children and adults demonstrated unexpected similarities in the clinical and laboratory findings of both groups, particularly at disease onset, although differences in long-term prognosis and some aspects of patient management have been confirmed.[8-10]

Adolescents and young adults (AYAS) are recognized as a specific age group with symptoms, disease course, treatment goals, side effects, needs, and expectations that differ from children and adults. AYAS are of particular interest in oncology and transition medicine.[11,12] Characteristic features of AYAS include a high disease burden and poor compliance. The disease and treatment may negatively affect their personal development.[11,12] Some treatment difficulties in this age group can be partly attributed to their physiological development. Adolescents have rapid hormonal, behavioral, and social changes, all of which can potentially modify the disease or symptoms. There is no international consensus on the definition of AYAS. In the literature, age differs from 12–16 years at the lower and 25–40 years at the upper limit.[11]

AYAS are poorly studied in ITP-related literature[13,14] and clinical studies in this specific age group are lacking. Recommendations for AYAS with ITP are usually not covered by practice guidelines; therefore, the institutions providing care guide treatment options, are often designed exclusively for children or adults. However, in most ITP studies, the median age of patient cohorts is >40–50 years for adults[13,15] and <10 years for children. Thus, treatment goals and guidelines for AYAS are biased.

Many pediatric studies have revealed that children over the age of 10 years are at risk for chronic ITP.[16] Therefore, it is reasonable to suppose that AYAS have a major risk of developing chronic ITP. However, assuming that the immune system of AYAS has a high potential to reverse immune dysregulation and restore self-tolerance, we hypothesize that therapeutic strategies involving immunomodulation should result in better long-term outcomes in these individuals than in adults. Most ITP treatment strategies currently focus on preventing premature platelet destruction (immunosuppression and splenectomy) and promoting platelet production (thrombopoietin-receptor agonist [TPO-RA] treatment).

It is unclear whether the initial presentation, risk of chronicity, and response to ITP treatment in AYAS are more similar to adults or children. It is important to understand the disease characteristics in AYAS to use appropriate diagnostic tools, treatment strategies, and goals. This study aimed to describe the clinical and laboratory presentation of ITP and its corresponding treatment approach for AYAS.

Methods

Data source

We extracted data of AYAS from the Pediatric and Adult Registry on Chronic ITP (PARC-ITP) registered between May 2004 and May 2021 and CARMEN-France registry (Cytopénies Auto-immunes Registre Midi-Pyrénéen) between January 2013 and May 2021. Data extraction from PARC-ITP and CARMEN registries was approved by the local Review Boards and national or regional Ethics Committees. Informed consent was obtained from all participants registered in PARC-ITP. All of the patients in the CARMEN-France registry were informed; no one opposed data collection. See the *Online Supplementary Appendix* for more information.

Inclusion criteria were: patients aged between 12 and 25 years at the time of diagnosis of primary ITP as defined by international guidelines, i.e., an initial platelet count of $<100\times10^9$/L and no other conditions that may cause thrombocytopenia.[4] Patients with a subsequent diagnosis of secondary ITP or of non-immune thrombocytopenia and pregnant women in the study period were excluded.

Outcomes and definitions

Treatment-free remission at 1-year FU was defined as a platelet count $\geq100\times10^9$/L at the 12-month FU without treatment for 6 months before, around, or after this FU. This definition was chosen in order to ensure the trueness of remission and not to include patients with prolonged response to treatment, rather than real remission. Chronic disease was defined as a platelet count of $<100\times10^9$/L at the 12-month FU or platelet count of 100×10^9/L under therapy at this time point. For patients with borderline platelet counts ($100–149\times10^9$/L), all available FU were studied to identify patients with relapse and reclassify them as chronic disease. Accurate diagnoses of remission versus chronic ITP were achieved through a precise decision tree (*Online Supplementary Figure S1*). See the *Online Supplementary Appendix for further details*.

Statistical analyses

Initial clinical data and FU information up to 12 months were analyzed. Continuous variables are reported as medians with the corresponding interquartile range (IQR). We analyzed the different subgroups based on sex, age (adolescents, 12–18 years *vs*. young adults, 18–25 years), and remission status at 12 months. We performed a multivariable logistic regression analysis to predict remission using sex, age, initial platelet count, and initial treatment at diagnosis (first-line drugs *vs*. watch-and-wait approach) as predictors. We hypothesized that initial treatment depends on initial platelet counts, and this possible interaction was considered in the model. Additionally, continuous data (age and initial platelet count) were modeled non-linearly using a three-knot restricted cubic spline. Since the non-linear contribution was not significant, these predictors were modeled linearly. We also tested whether initial bleeding moderated the effect of the above predictors on remission after 1 year. Comparing the two models (the initial model and the model with initial bleeding as a covariate) with the likelihood ratio test

shows that adding initial bleeding does not improve the model fit (χ^2 test value =0.99; *P*=0.32). Thus, initial bleeding was not included as a predictor. Odds ratios for selected initial platelet counts were reported with their corresponding 95% confidence interval (CI). For better understanding, the results of the logistic regression are presented as the probability of remission after 1 year.

P values were calculated with the χ^2 test , Fisher's exact test, or the Mann–Whitney U test. Fisher´s exact test was used when the expected frequency of one or more cells was < 5. A *P* value <0.05 was significant. All analyses were performed using R version 4.1.2.

Results

A total of 652 AYAS with initial diagnoses of primary ITP were recorded in the PARC-ITP and 71 in the CARMEN-French registries. Overall, 67 patients were excluded due to secondary ITP or non-immune thrombocytopenia (initially misdiagnosed) (n=57) or pregnancy (n=10). Finally, 656 AYAS with primary ITP were selected for analysis.

The AYAS were predominantly females (61%), particularly in the 18–25-year subgroup (70%). However, clinical characteristics were similar among the sexes. Males and females shared similar initial diagnostic procedures, comorbidities, bleeding symptoms (other than gynecological bleeding), median platelet counts, percentages of severe thrombocytopenia (<20×10^9/L), treatment requirements (except for red blood cell transfusion), and drug choices. Bone marrow puncture was performed at the time of diagnosis in 291 patients (44%), which supported the diagnosis of primary ITP. Comorbidities were reported in only 100 patients (15%), and two women but no men reported a thromboembolic event. At diagnosis, red blood cell transfusion rates differed between sexes (7% in females *vs*. < 1% in males). Females receiving a blood transfusion (n=27) had a mean hemoglobin of 7.5 g/dL, and 67% suffered active gynecological bleeding. Antiphospholipid antibodies were positive in 11 of 179 patients (7 females and 4 males, rate of positivity 6% for both). The initial positive results for ANA were higher in females (66/236; 28%) than in males (13/132; 10%). Similarly, the rate of reported thyroid disease was higher in females (2·2%) than in males (0.4%). The initial median platelet count for all AYAS was 12×10^9/L (interquartile range [IQR], 5-28). ITP was diagnosed as incidental (no reported bleedings) in 109 (17%) patients, whereas 538 (82%) suffered from bleeding symptoms at diagnosis; no information was provided for nine patients. AYAS without bleeding symptoms at diagnosis had a median platelet count of 38×10^9/L (IQR, 16-61) (Figure 1), whereas those with cutaneous and wet or internal bleeding had counts of 15×10^9/L (IQR, 7-26) and 8×10^9/L (IQR, 4-17), respectively. The initial clinical characteristics of patients are shown in Table 1. Intracranial hemorrhage occurred in four patients; two were diagnosed with ITP at the initial visit and two within the first 6 months of the disease. None of these patients reported hematuria, but it is unclear if microhematuria was tested. Their clinical descriptions and treatment approaches are

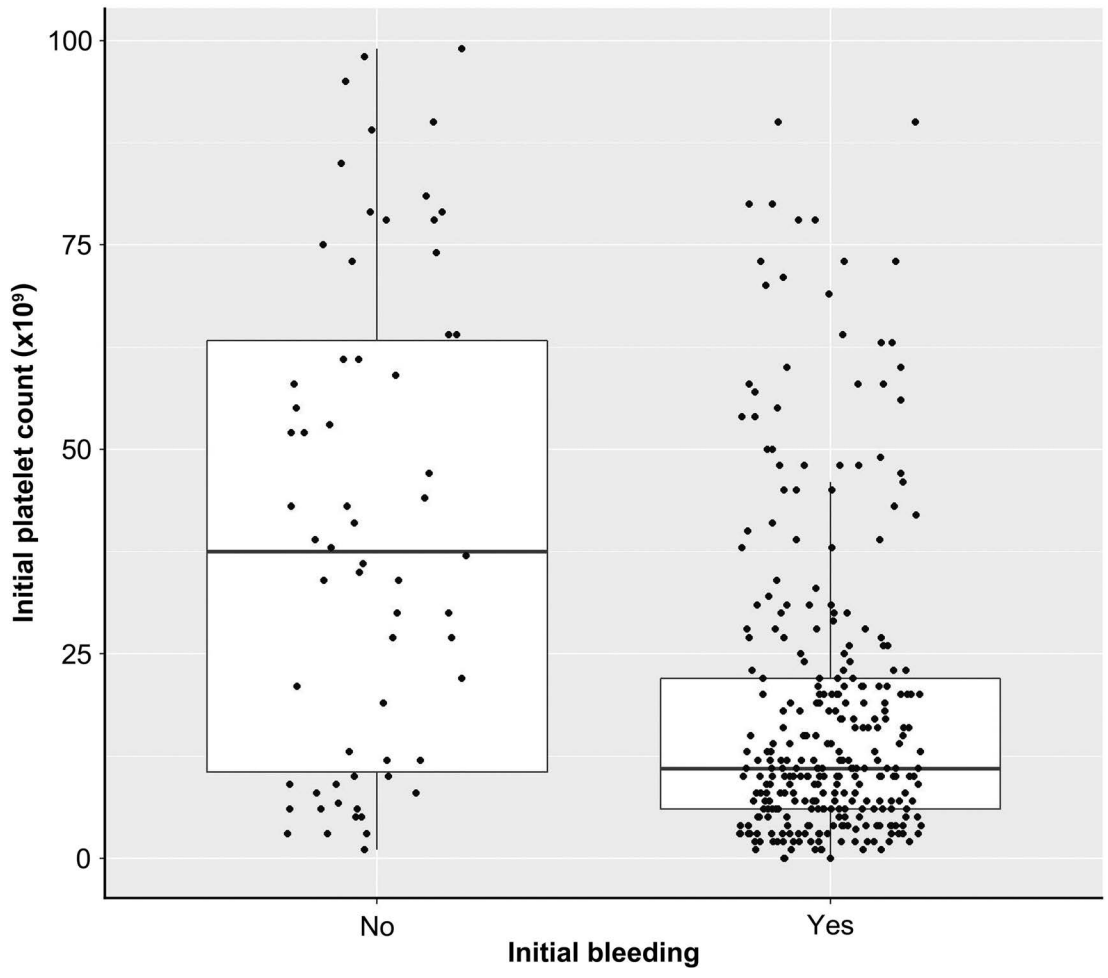


Figure 1. Occurrence of bleeding symptoms at diagnosis in patients with initial profound *versus* moderate thrombocytopenia. Median platelet count for patients without bleeding at initial diagnosis was 37.5×10^9/L and 11×10^9/L for patients with some bleeding symptoms (*P*<0.001).

shown in the *Online Supplementary Table S1*.

FU data was available for 547 (83%) patients at 6 months and 470 (72%) at 12 months. The median platelet counts and the distribution of severity (severe, moderate, and mild thrombocytopenia) at 6 and 12 months of FU were similar. Platelet counts <100×10^9/L were present in 49% of patients at 6 months and 42% at 12 months. However, bleeding propensity and treatment requirements decreased equally (Table 1).

We found only minor clinical differences between adolescents (12–18 years; 59% girls) and young adults (18–25 years; 70% women), with young adults presenting more mild-to-moderate thrombocytopenia (platelet count between 20–99×10^9/L) at diagnosis than adolescents (47% and 32%, respectively) and less initial bleeding (70% and 85%, respectively). However, the remission rate was identical in both age groups (57%). The higher median platelet count at 6 months FU in young adults compared to adolescents (114×10^9/L; IQR, 55-222 and 93×10^9/L, IQR 40-197, respectively) could be the result of a higher treatment rate at this time point (58% and 42%, respectively) (Table 2).

Drug treatments were reported for 66% at diagnosis, 45% after initial treatment until 6 months, and 30% at 6–12 months after diagnosis. Corticosteroids were most fre-

Table 1. Characteristics and treatment of adolescents and young adults with primary immune thrombocytopenia.

Characteristic	Initial	6-month FU	12-month FU
Total patients, initial N Female, N (%)	656 402 (61)	547 337 (62)	470 291 (62)
Mean age in years, initial (SD)	15.3 (2.5)	-	-
Platelet count ×10^9/L, median (IQR)* (no information about platelet count in 22 patients and 45 patients at 6- and 12-month FU)	12 (5-28)	97 (42-203)	107 (53-205)
Patients with platelet count, N (%) <20×10^9/L 20–49×10^9/L 50–99×10^9/L >100×10^9/L	 422 (64) 152 (23) 82 (13) -	 50 (9) 100 (18) 118 (22) 257 (47)	 37 (8) 62 (13) 98 (21) 228 (49)
Bleeding, yes, N (%)[f] Skin Oral Epistaxis Gastrointestinal and/or hematuria Gynecological (% female) Intracranial hemorrhage	538 (82) 470 (72) 158 (24) 140 (21) 35 (5) 88 (22) 2 (0·3)	223 (41) 182 (33) 49 (9) 65 (12) 10 (1·8) 57 (17) 2 (0·4)	139 (30) 107 (23) 29 (6) 39 (8) 10 (2) 33 (11) -
Platelet count ×10^9/L, median (IQR) for patients with bleeding Only skin Wet bleeding or internal bleeding	10 (5-21) 15 (7-26) 8 (4-17)	-	-
Platelet count ×10^9/L, median (IQR) for patients NOT bleeding	38 (16-61)	-	-
Patients with platelet-enhancing treatment, N (%)[†]	431 (66)	248 (45)	142 (30)
Drug used, N (% of treated) Corticosteroid IVIG (or Anti-D) Second-line and/or third-line	 285 (66) 225 (52) **	 182 (73) 100 (40) 46 (19)	 96 (68) 47 (33) 39 (28)
Platelet transfusion, N (%)	42 (6)	6 (1)	7 (2)
Blood transfusion, N (%)	28 (4)	NK	NK
Splenectomy, N (%)[ff]	0	5 (1)	8 (2)

FU: follow-up; IQR: interquartile range ; NK: not known; SD: standard deviation; IVIG: intravenous immunoglobulin. *Platelet counts are values recorded at diagnosis and follow-up visits. The platelet count at 6 months was defined as the value at 3–9 months; platelet count at 12 months was defined as the value at 11–18 months. [f]Information about bleeding is clinical data between follow-up visits (6 or 12 months). [†]"Initial" treatment is the treatment lasting over a maximum of 4 weeks; "6-mo FU" treatment is the treatment lasting until 6 months, excluding initial therapy; "12-mo FU" treatment is the treatment between 6 and 12 months. Patients with a combination of different corticosteroids are counted once. Patients treated with a combination of different second- or third-line treatments are counted once. Patients treated with a combination of different immunoglobulins are counted once. **Seven patients received recombinant thrombopoietin-receptor agonists, probably as part of a study (China, Egypt). [ff]Splenectomy are only counted once during follow-up. At 12 months FU, in total 13 patients were splenectomized.

quently used at all time points. Among the treated patients, 74% received corticosteroids during the first 6 months (excluding initial treatment) and 68% between 6 and 12 months. Second-line treatments were heterogeneous and administered to 28% of patients receiving treatment beyond 6 months (Table 3).

At the 12-month FU 236 of 470 patients (50%) suffered from chronic disease, 38% were in remission, and 12% had an unclear status. Chronic disease at 12 months was identical for both sexes, and the median platelet count in chronic ITP was 57×10^9/L (IQR, 31-85). Asymptomatic chronic ITP (no bleeding between 6 and 12 months) characterized 109 of 236 (46%) patients with chronic disease, irrespective of the treatment strategy. At 12 months, 56 patients not undergoing treatment in the last 6 months had borderline platelet counts ranging from 100×10^9/L to 149×10^9/L. Of these, at least 16 (29%) had a relapse (platelet count $<100\times10^9$/L) at a later date, with seven of 16 harboring platelets $<50\times10^9$/L (available FU differed greatly in this group of patients).

The characteristics of patients in remission compared to those with chronic ITP are shown in Table 4. Overall, 23% of chronic ITP and 15% of patients in remission tested positive for ANA at their initial visit. However, this blood test was performed in only half of the cohort, and definition of positivity may show strong variation. An initial diagnosis of severe thrombocytopenia was more prevalent among patients in remission at 12 months than those

Table 2. Comparison of characteristics between adolescents and young adults (within the group of all adolescents and young adults).

Characteristic	Adolescent	Young Adult
Subgroup age in years, range	12-18	18-25
Total patients, initial N Female, N (%)	517 306 (59)	139 97 (70)
Total FU at 6 months, N (%)	427 (83)	120 (86)
Total FU 12 at months, N (%)	361(70)	109 (78)
Median platelet count $\times10^9$/L, (IQR)* Initial FU at 6 months FU at 12 months	 11 (5-25) 93 (40-197) 105 (51-195)	 18 (8-38) 114 (55-222) 114 (63-232)
Patients with platelet count < 20×10^9/L, N (%) Initial FU at 6 months FU at 12 months	 349 (68) 44 (10) 32 (9)	 73 (53) 6 (5) 5 (4)
Tested patients ANA-positive, N (%)	53/272 (20)	26/98 (27)
Antiphospholipid antibody status pos of tested patients, N (%)	7/115 (6)	4/64 (6)
Chronic disease at 12-month FU, N (%) Unclear N=55	183/323 (57)	52/92 (57)
Patients with bleeding, N (%)[ƒ] Initial Until 6-month FU 6–12-month FU	 441 (85) 180 (42) 115 (32)	 97 (70) 43 (36) 24 (22)
Percentage of patients with platelet-enhancing treatment,[†] N (%) Initial Until 6-month FU % patients receiving coticosteroids % patients receiving IVIG % patients receiving second- or third- line** 6–12-month FU % patients receiving corticosteroids % patients receiving IVIG % patients receiving second/third line[†]	 338 (65) 178 (42) 70 51 15 107 (30) 67 37 26	 93 (67) 70 (58) 83 13 27 35 (32) 69 20 31

FU: follow-up; IQR: interquartile range; IVIG: intravenous immunoglobulin; ANA: antinuclear antibody. *Platelet count at 6 months was defined as the value at 6±3 months; platelet count at 12 months was defined as the value at 11–18 months. [ƒ]No information for 40 and 49 patients at 6-month FU and 12-month FU, respectively. [†]Initial treatment is treatment lasting a maximum of 4 weeks; 6-month follow-up treatment is defined as the treatment lasting until the 6-month follow-up, excluding initial therapy. No information for 25 and 36 patients at 6-month and 12-month FU, respectively. **Patients with a combination of different second- or third-line treatments are counted once.

with chronic ITP (69% *vs*. 56%). However, patients with initial platelet counts <20×10^9/L (n=256) showed a similar tendency to develop chronic disease (51%) as to go into remission (49%) at 12 months. In contrast, among the 159 patients with an initial platelet count ≥20×10^9/L, only 55 (35%) were in remission at 12 months (Figure 2). The initial platelet count was a significant factor of remission in the analysis of predictors presented further down. Adolescents (12–18 years) and young adults (18–25 years) showed identical remission rates (43%). Further analyses of the different age groups (12–<15, 15–<18, and 18–<21, 21–<25 years) are shown in Figure 2A. The worst outcome, i.e., the lowest remission rate of 28%, was observed in the 15–<18-year subgroup with an initial platelet count of ≥20×10^9/L.

Among patients with initial severe thrombocytopenia (< 20×10^9/L, n=256), the remission rate at 1 year depended on the initial treatment strategy, i.e., remission rates were 53% and 32% for patients receiving any frontline treatment and watch-and-wait treatment, respectively

Table 3. Treatment specification at 6- and 12-month follow-up.

Characterstic	6-month FU*	12-month FU*
Total patients at follow-up, N (female)	547 (337)	470 (291)
Patients with platelet-enhancing drugs, N (% of all)	248 (45)	142 (30)
Patients receiving corticosteroids, N (% of treated)	184 (74)	96 (68)
Patients receiving IVIG and/or anti-D, N (% of treated)	100 (40)	47 (33)
Patients receiving at least one second-line treatment, N (% of treated)[f] TPO-RA Rituximab Other[†] Azathioprin Vinca alkoaloids Interferon Mycophenolatmofetil Tacrolimus	46 (19) 16 10 17 6 2 2 5 1	39 (28) 13 6 10 6 1 2 6 0
Splenectomy, N (%)	5 (1)	8 (2)

FU: Follow-up; IVIG: intravenous immunoglobulin; TPO-RA: thrombopoietin receptor agonist. *Treatment "6-mo FU": until 6 months, excluding initial therapy; treatment "12-mo FU": between 6 and 12 months. [f]Patients may receive more than one second-line treatment. [†]e.g., Dapsone, hydroxychloroquine, belimumab, and probably more study drugs.

Table 4. Characteristics of patients in remission and chronic disease at 12 months (evaluated between 11–18 months).

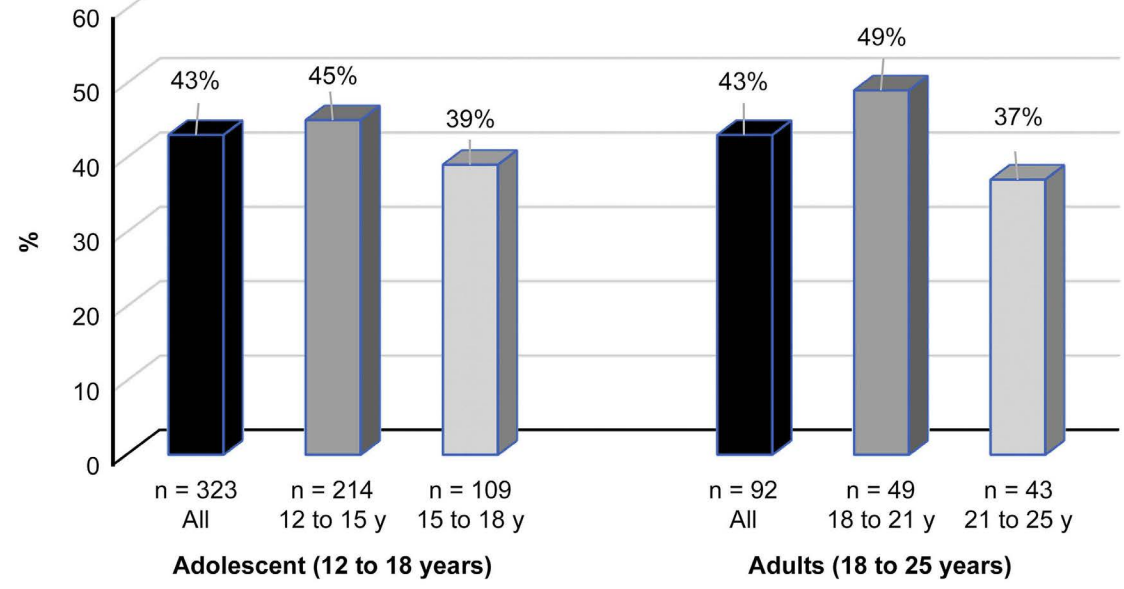
Characteristic	In remission*	Chronic ITP*
Total patients, N (female)	180 (112)	236 (149)
Median age in years, initial (IQR)	14 (13-17)	15 (13-17)
Median platelet count ×10^9/L, (IQR) Initial FU 12 months[f]	 11 (5-26) 206 (156-276)	 16 (7-34) 57 (31-85)
Patients with initial platelet count <20×10^9/L, N (%)	125 (69)	131 (56)
Tested patients ANA-postive, N (%)	13/87 (15)	32/142 (23)
Comorbidities, N (%)	137 (76)	211 (89)
Patients with bleeding, N (%) Initial Until 6-month FU 6–12-month FU	 154 (86) 60 (33) 20 (11)	 184 (78) 128 (54) 115 (49)
Patients with platelet-enhancing treatment, N (%) Initial Until 6-month FU 6–12-month FU	 127 (71) 69 (38) 20 (11)	 146 (62) 135 (57) 111 (47)

ITP: immune thrombocytopenia; FU: follow-up; IQR: interquartile range; ANA: antinuclear antibody. *Definition of remission at 12 months: platelet count > 100 × 10^9/L and no treatment at least for 6 months surrounding the 12-month FU (the time without treatment could be before or after the 12-month FU (see also *Online Supplementary Figure S1*). [f]The platelet count at 12 months was defined as the value at 11–18 months.

(*P*<0.05) (Figures 2B, 3). These two treatment subgroups did not differ in age, sex, and bleeding occurrence. In contrast, among patients with initial moderate thrombocytopenia, those followed with the watch-and-wait approach had a higher remission rate (37/90, 41%) than those receiving any first-line treatment (18/69, 26%), particularly intravenous immunoglobulin (IVIG) (4/24, 17%) (Figure 2B). However, the size of the last subgroup was small. Figure 3 shows the probability of remission according to the initial platelet count and initial treatment strategy, with the curves crossing at a platelet count of 30×109/L (interaction). This means that the effect of initial treatment on remission depends on the magnitude of the initial platelet count.

Discussion

In our analysis, AYAS exhibited a clinical pattern that reflected overlapping characteristics of children and adults. As for children AYAS presented with infrequent comorbidities, high initial bleeding rate, and a very low initial platelet count. Conversely, and similar to adults we found more females, a high risk of chronicity >50%, and a prolonged need for treatment between 6-12 months in 30% of cases (*Online Supplementary Table S2*).[9] The AYAS group was clinically very homogenous, and we found no reason to clinically separate young adults from adolescents given that the course of disease and risk of chronicity are similar (Table 2). Our analysis highlights that AYAS are mainly treated with corticosteroids throughout the 1-year observation period, probably leading to considerable side effects (Table 1). However, we do not have information on dose and duration. The reason for this treatment may be drug convenience, offering the possibility of on-demand treatment (especially for menstruating women); moreover, the availability of alternative treatments such as TPO-RA was limited (especially for children aged <16 years) in the study period, and such treatments are costly. The high rate of chronic disease in AYAS confirms the poor recovery rates among older children. Many pediatric studies reveal that age >10 years is a major risk factor for chronicity.[16] According to the ICIS I registry, the remission rates of patients aged 10–16 and 1–10 years were 53% and 72%, re-



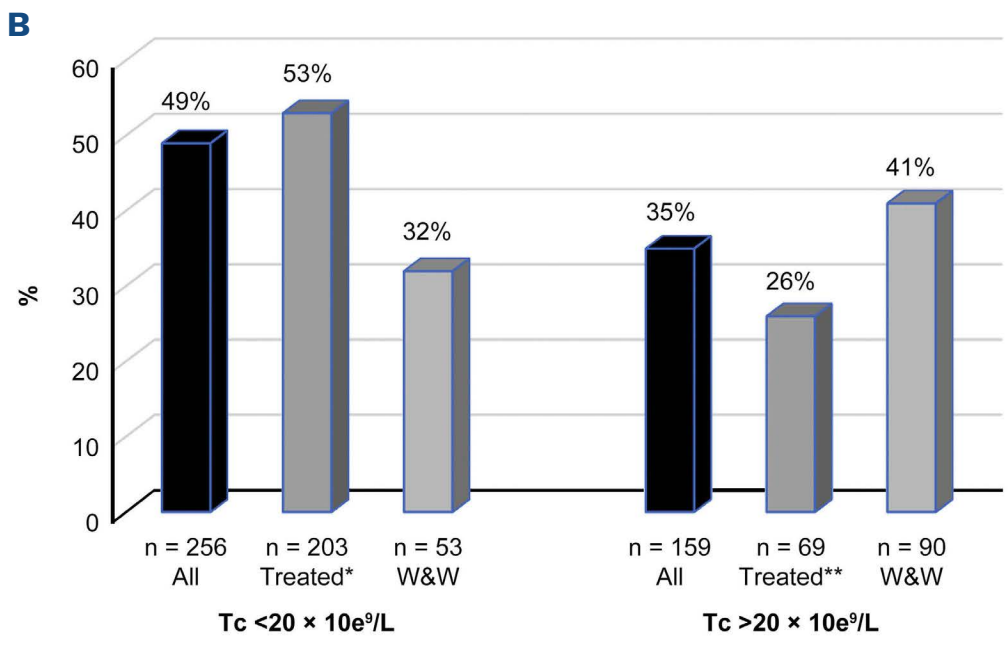
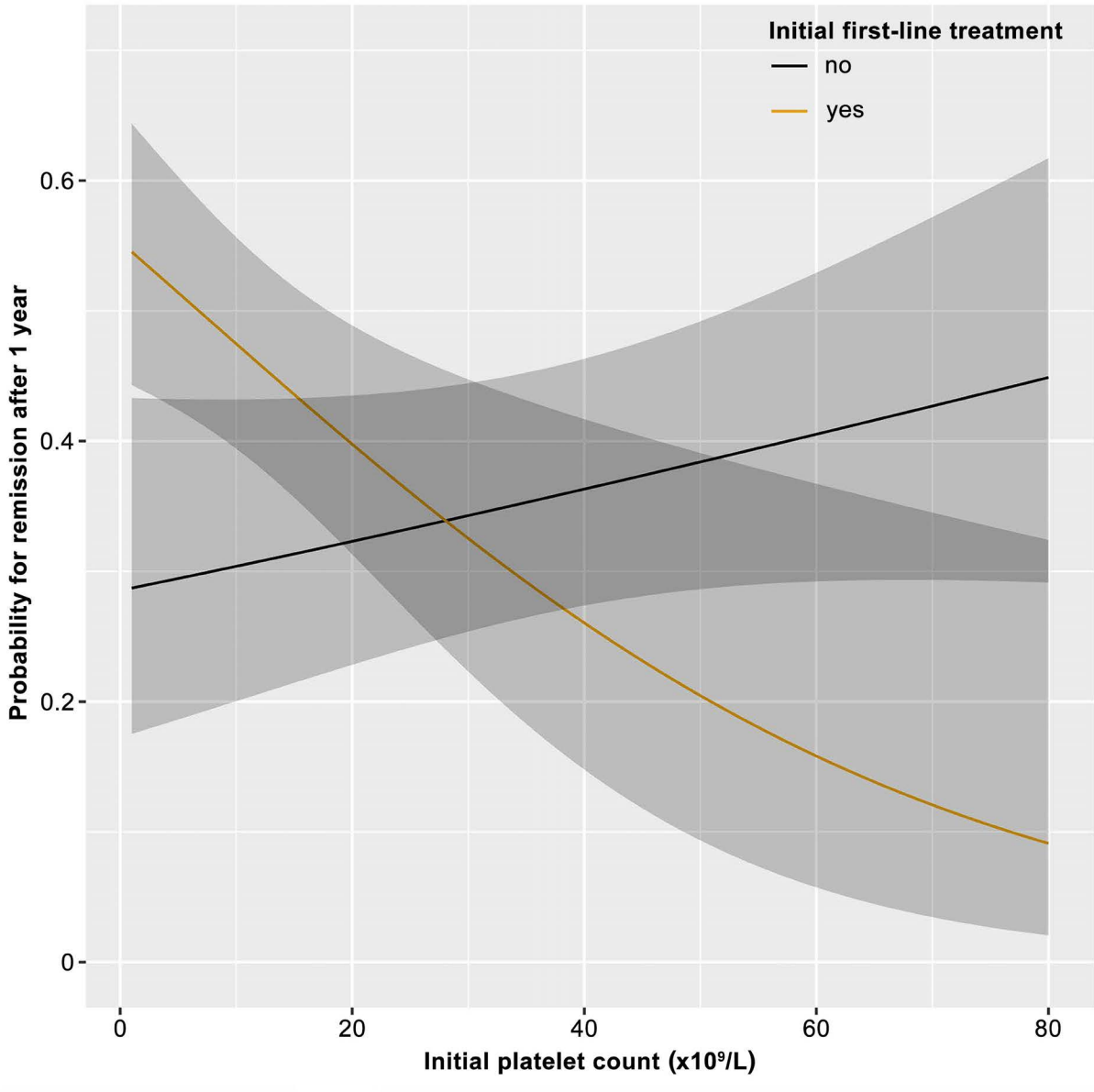


Figure 2. Rate of remission. (A) Rate of complete remission off-treatment, depending on different adolescents and young adults (AYAS) age groups. (B) Rate of remission, depending on initial platelet count (×10^9/L) and initial choice of treatment strategy. Remission rate shows no significant differences among age groups within AYAS (A). Note: percentages are calculated for patients with known remission status. No or insufficient information about remission state for 124/338 (37%) of patients 12–<15years, 70/179 (39%) of patients 15–<18 years, and 47/139 (34%) of patients 18 years. Rate of complete remission (Tc >100×10^9/L, off-treatment) was calculated according to initial treatment and initial platelet count (B). Treated: initial treatment (intravenous immunoglobulin [IVIG] and/or corticosteroids), W&W: initial watch-and-wait strategy. * Remission rate for patients that initially received IVIG monotherapy (N=35/60) (58%), IVIG + corticosteroids (N=25/49) (51%), corticosteroid monotherapy (N=45/89) (51%), other (N=3/5). ** Remission rate for patients that initially received IVIG monotherapy (N=2/16) (13%), IVIG + corticosteroids (N=2/8) (25%), corticosteroid monotherapy (N=14/43) (33%), other (N=0/2).

spectively.[18] Similarly, Donato *et al*. reported recovery rates of 49% among children aged 9–18 years and 71% in those aged 1–8 years at diagnosis.[19] Among patients diagnosed with ITP at 10–18 years from 1976 to 2000, Lowe and Buchanan observed 57% with chronic disease, 27% in recovery, and 15% with unclear results.[14] These values are similar to our AYAS cohort aged between 12 and 25 years. However, it is to note that definition of remission and chronicity varies in the literature and in published guidelines. The term “chronic disease” was corrected in 2009 to designate a disease lasting ≥12 months and with a platelet count <100×10^9/L. In our analysis, adolescents aged 15–18 years had a slightly higher chronic disease rate (61%) than those aged 12–15 years (55%). We found no differences in the remission rates of males and females. This finding agrees with Lowe and Buchanan.[14]

Among the factors that can modify chronicity, we found that initial ANA was more frequently positive in patients with chronic disease (23%) than those in remission at 1 year (15%) (Table 4). However, interpretation is limited given the heterogeneous definition of ANA positivity among institutions and the low testing frequency. In the literature, initial ANA results have been reported as an indicator of ITP chronicity, although the data on children and adults remains controversial.[15,20-22] We also found that AYAS in remission had lower initial platelet counts than those with later chronic disease. These results are similar to previous publications of outcome predictors in children and adults.[16,21] Surprisingly, AYAS with severe thrombocytopenia who initially followed a watch-and-wait strategy had a higher rate of chronic disease (68%) than those initially treated with corticosteroids and/or IVIG (47%) (Figure 2B). Our results suggest that early treatment benefits AYAS suffering from "pediatric-like" severe ITP. However, data from a meta-analysis and a prospective trial yielded contradictory results regarding initial IVIG and long-term remission in children.[16,23] Our findings show that AYAS with moderate and mild thrombocytopenia who in-



Initial platelet count x10^9/L	Odds ratio	Lower 95 CI	Upper 95 CI	*P*
10	2.07	1.15	3.74	0.02
12	1.91	1.08	3.39	0.03
30	0.92	0.50	1.70	0.80
60	0.28	0.08	0.91	0.03

Figure 3. Logistic regression predicting remission *versus* no remission. Logistic regression was performed to predict remission. Predictors were age, sex, initial platelet count, and initial therapy (presence or absence). The influence of age and sex was not significant (*P*=0.15; *P*=0.78, respectively). The interaction between treatment and platelet count was significant (*P*=0.002). The graph (on the probability scale) shows the curves crossing at about 30×10^9/L. As an example, a patient with an initial platelet count of 10× 10^9/L AND receiving upfront treatment has a 55% chance of remission (brown line), and the same patient receiving NO treatment has a 29% chance of remission (black line), (odds ratio=2.07, 95% 95% confidence interval [CI]: 1.15- 3.74; *P*=0.020). Conversely, a patient with an initial platelet count of 60×10^9/L AND receiving upfront treatment has a 12% chance of remission (brown line), and the same patient receiving NO treatment has a 44% chance of remission (black line) (odds ratio=0.28, 95% CI: 0.08-0.91; *P*=0.03). The odds ratios in the table below indicate the change of the risk dependent on therapy and platelet count. Odds ratios were calculated for several platelet count level.

itially received frontline treatment have a lower remission rate (26%) than the watch-and-wait subgroup (41%) (Figure 2B). Several hypotheses can be considered, such as the possibility that those patients requiring medical intervention for bleeding despite only moderate thrombocytopenia might have been misdiagnosed with ITP. They may have hereditary thrombocytopenia, secondary ITP, or a combination of pathologies with a higher propensity to bleed despite moderate thrombocytopenia. Therefore, this special subgroup would have high rates of "chronic disease," if the diagnosis was wrong and the treatment was inadequate. Further investigations are warranted to understand the underlying disease mechanism of these patients.

We found a high relapse rate among patients in remission at 12 months harboring borderline platelet values (100-149×10^9/L). This finding raises the question of whether the threshold of 100×10^9/L to define ITP remission is correct for AYAS.

Current practice guidelines do not address AYAS; diagnostic and therapeutic recommendations focus only on children and adults. According to the literature, ITP in children and adults presents clinical differences that give the impression of two different diseases, with adults presenting with more moderate thrombocytopenia and less initial bleeding.[10] However, using a temporal perspective, ITP may differ only in disease initiation and cessation, i.e., the trigger of the disease and the intrinsic capacity to induce tolerogenic mechanisms. Young children have "favorable pathophysiological and physiological features" at both time points, whereas adults have "unfavorable features." In most children, the trigger seems to be a viral infection that causes transient cross-reactivity with platelet antigens, ultimately corrected by the immune system. In adults, the trigger is less clear, and immune dysregulation progresses to a complex disease that is not easily or rapidly corrected, probably due to immunosenescence, comorbidities, and drugs.[24,25] Herein, we showed that the course of ITP in AYAS is similar to "adult-type" ITP. Nevertheless, AYAS may benefit from new treatment goals focusing on restoring a durable immune balance and curing the disease rather than a symptomatic strategy, e.g., elevating the platelet count, limiting patient activities, and risk management.[26]

Much interest remains in whether more aggressive therapy during the early phase of ITP mitigates persistent or chronic disease.[27] Novel approaches involving early combined therapies against T and B cells with and without TPO-RA have provided promising results.[28-30] Some small-scale trials focusing on young adults (iROM-study, *clinicaltrials gov. Identifier: NCT02760251*, and iROM2-study, *clinicaltrials gov. Identifier: NCT04812483*) are still ongoing. The use of rituximab early in the disease course, especially in young women, could be a promising strategy.[31] Restoring immune tolerance appears to be a promising early treatment goal for AYAS. However, intense therapies require early identification of those that elicit a refractory response.

The loss of FU and missing data may have biased our results, particularly the remission rate. In a previous analysis of the PARC, patients of all ages lost to FU were predominantly those with remission in the first months of the disease.[9] In addition, our efforts to accurately classify patients in remission and chronic disease have generated unequal observation periods. This could be another source of bias, especially for patients with relapses later at FU but missing data. Specific limitations of both registries have been published elsewhere[15,32] and will not be discussed in detail here; however, the difficulties of making an accurate diagnosis of primary ITP could be the explanation for some unexpected results.

Defining ITP in only two age categories - children and adults - seems inappropriate and oversimplifies the clinical characteristics and needs of AYAS. AYAS have a long life expectancy and high quality of life expectations; thus, treatment strategies and goals must be reconsidered for this age group. Upfront immune modulation could be a promising strategy for AYAS and an approach that requires further investigation. Future ITP trials should have the following aims: i) discern AYAS ITP as an entity distinct from pediatric and adult ITP, ii) adopt treatment goals that reduce the rate of chronic disease, and iii) dissuade the use of corticosteroids beyond initial management.

Disclosures

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Contributions

Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision and writing by AS. Conceptualization, methodology, review, and editing, investigation, data curation and supervision by GM. Conceptualization, review and

editing, and supervision by BG. Conceptualization, review, and editing by TL, NA and MM. Review and editing, investigation, and data curation by GL and JG. Review and editing, and investigation by ME, MC, AH and SH. Review and editing, and funding acquisition by GlG. Review and editing by PI. Conceptualization, methodology, supervision, review and editing, and funding acquisition by TK.

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