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RESEARCH ARTICLE

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A comparative prospective observational study of children and adults with immune thrombocytopenia: 2-year follow-up

Alexandra Schifferli[1] | Andreas Holbro[2] | Meera Chitlur[3] | Michael Coslovsky[4] | Paul Imbach[5] | Hugo Donato[6] | Mohsen Elalfy[7] | Elena Graciela[8] | John Grainger[9] | Susanne Holzhauer[10] | Cecilia Riccheri[11] | Francesco Rodeghiero[12] | Marco Ruggeri[13] | Hannah Tamary[14] | Tatjana Uglova[15] | Runhui Wu[16] | Thomas Kühne[1,5], for The Intercontinental Cooperative ITP Study Group (ICIS)

[1]Department of Hematology/Oncology, University Children's Hospital Basel, Basel, Switzerland; [2]Department of Hematology, University Hospital Basel, Basel, Switzerland; [3]Carmen and Ann Adams Department of Pediatrics, Division of Hematology/Oncology, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan; [4]Clinical Trial Unit, University Hospital Basel, Basel, Switzerland; [5]Chairperson Intercontinental Cooperative ITP Study Group (ICIS), Basel, Switzerland; [6]Hematology/Oncology, Hospital del Niño de San Justo, San Justo, Buenos Aires, Argentina; [7]Pediatric Hematology and Oncology, Pediatric Hospital Ain Shams University, Cairo, Egypt; [8]Department of Hemalogy-Oncology Pedro de Elizalde, Children Hospital Buenos Aires, Buenos Aires, Argentina; [9]Department of Haematology, Royal Manchester Children's Hospital, Manchester, United Kingdom; [10]Department of Pediatric Hematology and Oncology, Charité, Berlin, Germany; [11]Servicio de Pediatria Hospital Alejandro Posadas Buenos Aires, Buenos Aires, Argentina; [12]Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; [13]Hematology Department, San Bortolo Hospital, Vicenza, Italy; [14]Hematology Unit, Schneider Children's Medical Center of Israel, Petah Tikva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [15]Department of Clinical Research, Belarusian Research Center of Pediatric Oncology, Hematology and Immunology, Minsk, Belarus; [16]Hematology Oncology Center, Beijing Children's Hospital Capital, Beijing, China

Correspondence
Alexandra Schifferli, Department of Oncology/Hematology, University Children's Hospital Basel, Spitalstrasse 33, 4031 Basel, Switzerland.
Email: alexandra.schifferli@ukbb.ch

Abstract

Comparative clinical studies of children and adults with immune thrombocytopenia (ITP) are poorly covered in the literature. However, the accepted classification of ITP—childhood ITP and adult ITP—results in considerable differences in treatment protocols and practice guidelines. The analysis of the Pediatric and Adult Registry on Chronic ITP (PARC-ITP) of patients at first presentation demonstrated fewer differences in clinical and laboratory findings at initial diagnosis between children and adults than expected. The present report of 2-year follow-up data supports the hypothesis that there are common aspects of childhood and adult ITP. Data of 3360 children and 420 adults were collected during the time of 2004 until 2015 at initial diagnosis. Follow-up information was available for 51% and 33% of children and 66% and 49% of adults at 12- and 24-months, respectively. Similarities were found in unexpected areas of ITP, such as the rate of late remission at 12 and 24 months, reported bleeding sites, platelet count in bleeders, and the frequency of treated patients with persistent or chronic ITP. Differences were confirmed for the overall rate of remission and treatment modalities. Unexpected differences were found in the percentage of nonbleeders, with more adults in the nonbleeder group. More studies are needed to investigate different age groups with the aim to optimize their management.

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is a diagnosis of exclusion and can be caused by multiple disease mechanisms including a variety of antiplatelet autoantibodies, cytotoxic T lymphocyte-mediated platelet

A complete list of members of the ICIS appears in the Appendix.

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destruction, T- and B-cell abnormalities with disturbed cytokine profiles, and impaired megakaryopoiesis.[1–5] Clinically, ITP of children differs from that of adults in spontaneous remission rate, bleeding pattern, and treatment need.[6–10] While approximately 80% of children are disease-free within 1 year, most adults (70%-80%) show a chronic course.[11] Adults have a higher bleeding risk; thus, pharmacological treatment and splenectomy are more often required in adults than in children,[9,10] whereas a watch and wait strategy is a standard approach for children with no or mild bleeding.[9,10] However, some of these clinical presumptions are limited by inconsistent study designs, study populations, collected information (e.g., bleeding assessment tools), definitions, study objectives, and end-points. Initial data of the Pediatric and Adult Registry on Chronic ITP (PARC-ITP) were previously published and demonstrated considerably smaller differences in clinical and laboratory findings at disease onset between children and adults than expected.[12] Moreover, recent studies showed that the severity of thrombocytopenia at diagnosis was a predictor of recovery from ITP in both children and adults.[13,14] The classification of pediatric and adult ITP may not adequately reflect clinical requirements. Sub-classifying patients based on phenotypic characteristics, including insidious or abrupt onset and grade of bleeding, describe ITP more accurately and consequently affect management decisions and probably better predict persistent or chronic ITP.

Understanding differences and similarities between children and adults with ITP will improve individual diagnosis and management. We aimed to assess and interpret comparative follow-up (FU) PARC-ITP Registry data in children and adults with ITP.

2 | METHODS

The PARC-ITP is an international multi-center registry designed to collect data prospectively in children and adults with newly diagnosed ITP. The registry is a project of the Intercontinental Cooperative Immune Thrombocytopenia Study Group (ICIS, www.itpbasel.ch) and is based on voluntary participation of pediatricians and adult hematologists worldwide. ICIS was founded in 1997 by pediatric hematologists to analyze multiple diagnostic and therapeutic aspects of ITP. Over the years, it was realized that a joint database for children and adults may facilitate better understanding of ITP. In May 2004, PARC-ITP was initiated to study the natural history of ITP in all age groups and develop and coordinate new hypotheses and projects.

ICIS is meanwhile well-established and active at various scientific congresses, and holds expert meetings every 3 years.[15–19]

The protocol, registration of data, and all registry documents are available via secure internet access (www.parc-itp.net). Data acquisition by investigators was performed by direct internet access into a database that is administered in the ICIS office in Basel, Switzerland (www.itpbasel.ch). Data are continuously registered at the time of diagnosis, at 6 and 12 months, and then yearly and include demographics, diagnostics, clinical data, and safety data of treatments. The questionnaires' structure is limited by a certain number of questions to maintain feasibility data transfer and collaboration of investigators. Data quality controlling and cleaning is performed at the office in Basel. ITP was defined according to the International Working Group (IWG) definitions.[20] Patients with missing FU data at certain time points (6, 12, and 24 months) were included in the analysis (Supporting Information Figure S1A). Secondary ITP was excluded from registration; patients in whom the diagnosis was revised from primary to secondary ITP or thrombocytopenia of other cause during FU were prospectively identified, and not excluded from the analysis. Ethical committee approval and informed consent were received from all patients.[12,21]

Data are reported using descriptive statistics. Frequencies and percentages are reported for counts and categorical variables. Continuous variables are reported as mean ± standard deviation (SD). Median and interquartile range (IQR) are reported for age and platelet count in Table 1.

Categorical variables were analyzed using Chi-square tests. Continuous variables between groups were compared using the nonparametric Wilcoxon's test. Cumulative incidences between groups were compared using the nonparametric log-rank test. A P-value of $<.05$ was considered statistically significant. Analyses were performed using R Development Core Team, version 3.4.0.[22]

2.1 | Definitions

If not mentioned otherwise, the definitions of the IWG were used.[20]

Patients were divided into two groups according to age at initial diagnosis. *Children* were defined as 3 months to 16 years of age, and *adults* as >16 years. For certain analyses, the adult group was divided into three subgroups including *young adults* (16–40 years), *midlife adults* (40–60 years), and *seniors* (> 60 years). *Age* refers to the age at first presentation of ITP, equating to the initial visit.

FU data at 6 months summarize the clinical course (e.g., bleeding and management) of the disease in the first 6 months (excluding information at initial diagnosis); *FU data at 12 months* summarize the clinical course during >6–12 months, and *FU data at 24 months* include the time during >12–24 months. Platelet counts were registered as a single value (mean ± SD) at approximately 6 (175 ± 47 days), 12 (365 ± 66 days), and 24 months (722 ± 59 days).

Remission of ITP: "Remission" in an autoimmune disease refers to the reoccurrence of tolerance and is difficult or even impossible to measure. We used the term "remission" to define ITP activity as assessed by the platelet count irrespective of prior or ongoing therapy. According to our definition, a platelet count of $>100 \times 10^9$/L at 6, 12, and 24 months of follow-up visits is considered a "remission." *Persistent ITP* was defined as a platelet count $<100 \times 10^9$/L at 6 months, and *chronic disease* as a platelet count $<100 \times 10^9$/L at 12 and/or 24 months. According to the IWG, the definition of persistent ITP covers the period between 3 and 12 months. The registry only records data at 6 months. *Ongoing ITP* was defined as patients with persistent or chronic ITP. *Late remission at 12 months* characterized patients with ongoing disease at 6 months but who were in remission at 12 months. *Late remission at 24 months* characterized patients with

TABLE 1 Initial characteristics of patients with early lost to Follow-up (without 6 month Follow-up data) compared to patients with FU data

	With FU[a]	Lost to FU at 6 mo	*P*-value
Total patients			
Children	2317	1043	
Adults	333	87	
Mean age (SD)/Median (IQR)			
Children	5.5 (4.3)/4.2 (2–8.5)	4.5 (3.7)/3.4 (1.6-6.6)	**<.001**
Adults	38.6 (19.3)/34.3 (20.3–53)	35.4 (18.1)/31.1 (20–49.1)	.19
F/M (%)			
Children female	1102(48)	507 (49)	.57
Adults female	229 (69)	43 (49)	**<.001**
Mean platelet count, initial (SD)/Median (IQR)			
Children	17 (18)/11 (5–21)	25 (25)/16 (6–36)	**<.001**
Adults	24 (24)/14 (5–36)	22 (21)/14 (5–35)	.81
No bleedings initial (%)			
Children	160 (7)	289 (28)	**<.001**
Adults	99 (30)	23 (26)	.55
Therapy initial yes (%)			
Children	1703 (74)	628 (60)	**<.001**
Adults	220 (66)	60 (69)	.61

(% refers to the total number of patients, platelet count $\times 10^9$/L).
[a]With FU: characterizes patients with Follow-up (FU) information at 12 and/or 24 months.

ongoing disease at 6 and/or 12 months but who were in remission at 24 months.

Bleeding was defined as any bleeding event in the last recorded time period, independently of intensity or frequency. *Location of bleeding* was recorded for all bleeding events in the last time period and not per event.

Corticosteroid therapy was defined as any form of corticosteroids irrespective of dosage or administration route. Hence, high-dose and pulsed therapies were included in this definition. *Seconda and third-line treatment was defined as* drugs other than corticosteroids, IVIG and Anti-D. *Relevant co-medication* was defined as drugs with known effects on hemostasis [anti-inflammatory drugs (NSAID), anticoagulants, and platelet antagonists].

Co-morbid conditions were defined as one or more of the following conditions at initial registration: arterial hypertension, diabetes mellitus, gastrointestinal disease, thyroid disease, cancer, alcohol abuse, cardiovascular disease, rheumatoid arthritis (RA), psoriasis, systemic lupus erythematosus, recent major general surgery, acute respiratory failure, chronic obstructive pulmonary disease, infectious disease, obesity, recent knee or hip replacement surgery (<1 year), and splenomegaly.

Patients lost to FU at a specific visit were defined as patients who missed the relevant visit and all following visits, including those who have been discharged because of improvement of thrombocytopenia.

3 | RESULTS

In total, 3780 evaluable patients with primary ITP were included between May 2004 and November 2015 (Supporting Information Figure S1A). Data were provided by 84 investigators of 74 participating sites in 31 countries. The 10 most active centers are listed according to total patient number: China, Argentina, United Kingdom, Egypt, Israel, Italy, and Germany and together registered 2101 patients (56%). Number of countries, institutions, and patients registered in the PARC-Registry are demonstrated in Supporting Information Table S1. FU information was available for the 6-, 12-, and 24-month evaluations in 68%, 51%, and 33% of children and 79%, 66%, and 49% of adults, respectively (Supporting Information Figure S1B).

3.1 | Initial patient characteristics

Data at the time of first presentation included 3360 children (89%) and 420 adults (11%). The adult subgroups consist of 250 young adults, mean age 24.2 years (SD 7.3), 101 midlife adults, mean age 50.2 years (SD 5.4), and 69 seniors, mean age 60.8 (SD 7.2). The age distribution of young adults, midlife adults, and seniors at the 12-month visit was similar to that at baseline. The male:female ratio was in favor of male patients in children (1.09:1) and female patients in adults (0.54:1). Mean age of all children was 5.2 ± 4.1 years and that of adults was 38 ± 19 years.

"Relevant co-medication" was reported in 10.7% (45) of adults and in 2% (68) of children. However, young adults showed a low relevant

TABLE 2 Follow-up data of patients with/without remission at 12 month

	All		Remission		Ongoing disease	
	Children	Adult	Children	Adult	Children	Adult
Total patients (%)	**1639**	**271**	**1160 (71)**	**133 (49)**	**479 (29)**	**138 (51)**
Female (% of total female)	776	189	521 (67)	96 (51)	255 (33)	93 (49)
Male	863	82	639 (74)	37 (45)	224 (26)	45 (55)
Mean age (SD)	**5.7 (4.4)**	**39.4 (19.5)**	**5 (4.1)**	**39.6 (19.5)**	**7.4(4.5)**	**39.2 (19.7)**
Female	6.2 (4.5)	38.3 (19.2)	5.3 (4.3)	38.2 (19.3)	7.9 (4.5)	38.5 (19.2)
Male	5.3 (4.2)	41.8 (20.2)	4.7 (4)	43.1 (19.8)	6.8 (4.4)	40.7 (20.6)
No bleeding (%)[a]	**1215 (74)**	**205 (76)**	**1039 (90)**	**110 (83)**	**176 (37)**	**95 (69)**
Female (% of total female)	560 (72)	137 (73)	463 (89)	79 (82)	97 (38)	58 (62)
Male	655 (76)	68 (83)	576 (90)	31 (84)	79 (35)	37 (82)
Platelet count (SD)[b]	**191 (126)**	**122 (94)**	**250 (99)**	**197 (80)**	**46 (29)**	**51 (26)**
Female	183 (125)	123 (91)	250 (97)	193 (78)	46 (28)	52 (26)
Male	198 (126)	120 (100)	251 (101)	207 (86)	46 (30)	49 (25)
Platelet enhancing treatment (%)[a]	**307 (19)**	**109 (40)**	**86 (7.4)**	**37 (28)**	**221 (46)**	**72 (52)**
Female (% of total female)	170 (22)	82 (43)	45 (8.6)	28 (29)	125 (49)	54 (58)
Male	137 (16)	27 (33)	41 (6.4)	9 (24)	96 (43)	18 (40)

(% refers to the total number of patients if not other mentioned, platelet count $\times 109$/L).
[a]In the period of time between 6 and 12 months.
[b]At 12 month.
Data of patients with known remission state only are demonstrated.

co-medication rate (3.6%) similar to that of children compared with midlife adults (10.9%) and seniors (36.2%). Anti-inflammatory drug use only (e.g., NSAIDs) was reported in 60% of adults and 97% of children in whom relevant co-medication was reported.

Co-morbidities were reported in 360 children, 32 young adults, 42 midlife adults, and 55 seniors (10.7%, 12.8%, 41.6%, and 79.7%, respectively).

3.2 | Lost to FU

Lost to FU was significantly higher in patients achieving remission of ITP. At 6 and 12 months, remission rates in children subsequently lost to FU were 87% and 82%, respectively (chi-square test comparing remission state of patients with and without FU, $P < .001$ at both time points). In adults, remission rates were 64% ($P = .008$) and 56% ($P = .15$), respectively. Among all patients with persistent ITP at 6 months, FU information at 12 and/or 24 months was provided for 90% of children and adults. Comparison of the initial characteristics between patients with FU data and patients lost to FU at 6 months found that children lost to FU had a lower age, higher initial mean platelet count, lesser initial bleeding, and lesser initial drug treatment (Table 1).

3.3 | Natural history: Remission and ongoing disease

The characteristics of patients in remission and with ongoing disease at 12 months are shown in Table 2 and mean platelet counts at all FU are depicted in Figure 1A. Patients in remission at 6, 12, and 24 months consisted of 70%, 71%, and 71% of children and 45%, 49%, and 56% of adults, respectively. Among the patients with persistent ITP, 212/592 (36%) children and 42/155 (27%) adults achieved remission at 12 months. Late remission at 24 months was reported in 83/298 (28%) and 26/87 (30%) adults. The cumulative incidence of remission was significantly different between children and adults ($P < .001$) and is demonstrated in Figure 2. For this analysis, patients achieving remission at 6 and/or 12 months and consequently lost to FU were presumed to be still in remission at the 24-month FU.

In children, mean age of patients with late remission at 12 and 24 months was higher (6.9 ± 4.7 years) than that of children with reported early remission at 6 months (4.8 ± 4 years) ($P < .001$). Children with persistent ITP had a mean age of 7.2 ± 4.6 years. Adults with early remission at the 6-month FU had a mean age of 37.9 ± 18.5 years and those with a late remission at 12 and 24 months had a mean age of 40.4 ± 20.4 years, which was not significant ($P = .45$).

Mean platelet count in patients with ongoing ITP was very similar in children and adults at the 12-month FU: $46 \pm 29 \times 10^9$/L and $51 \pm 26 \times 10^9$/L, respectively. Children in remission showed a higher platelet count at all FU examinations compared with adults (Figure 1A).

3.4 | Bleeding manifestations

Approximately 37% and 36% of children diagnosed with chronic ITP reported no bleeding at 12 and 24 months, respectively. A higher percent

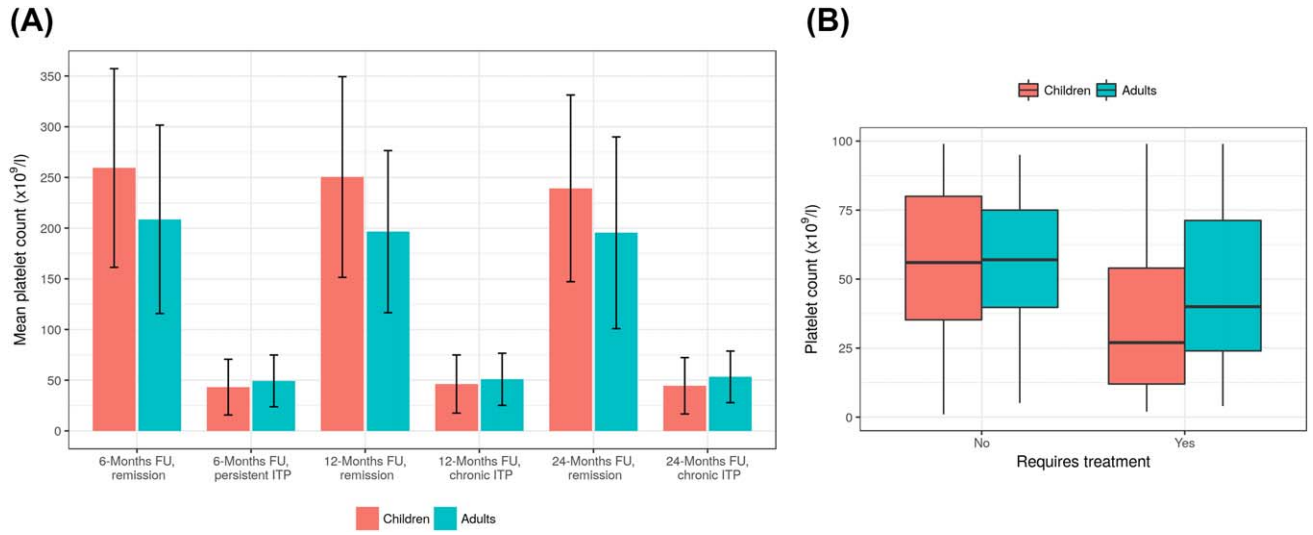

FIGURE 1 Platelet counts at FU. (A) Mean platelet counts in patients with ongoing ITP was similar in children and adults at all FU. Children in remission showed a higher platelet count at all FU examinations compared with adults. (B) Distribution of platelet count in patients with a chronic ITP at 12 month FU requiring or not requiring treatment [Color figure can be viewed at wileyonlinelibrary.com]

of adults with chronic ITP had no bleeding manifestations (69% and 64% at 12 and 24 months, respectively) ($P < .001$ at both time points). Children and adults achieving remission showed very similar percentages of nonbleeders at all reported FU examinations (e.g., Table 2).

The bleeding sites showed similarities in children and adults at all FU examinations (Supporting Information Table S2). Cutaneous bleeding, oral cavity bleeding, and epistaxis were the main bleeding sites. No major difference in bleeding sites was found between patients achieving remission and patients with chronic ITP. Occurrence of menorrhagia

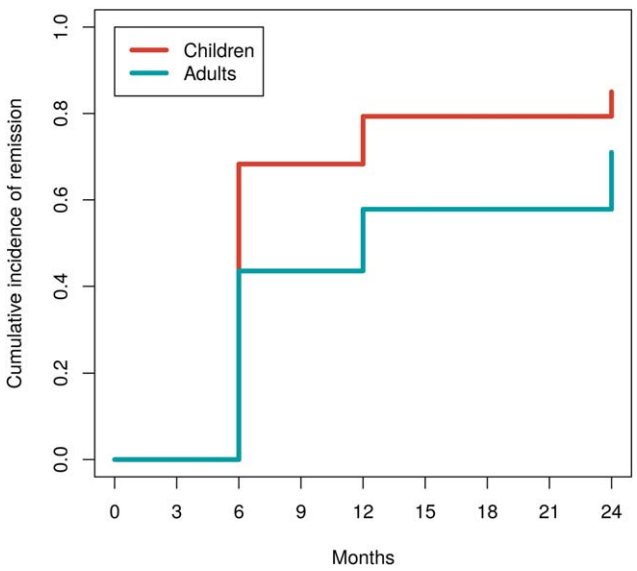

FIGURE 2 Cumulative incidence of remission. The cumulative incidence of remission was significantly different between children and adults (log-rank test, $P < .001$). For this analysis it was assumed that patients achieving remission at 6 or12 months and consecutively lost to FU were still in remission at 24 months FU. It is of note that patients lost to FU at 12 and 24 months had a higher remission rate in the previous FU than patients with FU data [Color figure can be viewed at wileyonlinelibrary.com]

was similar in adults (16–50 years) and adolescents (13–16 years) in patients with ongoing ITP at 6 months (12.2% and 13.8%, respectively) and 12 months (7.8% and 4.9%, respectively). Information about actual numbers of bleeding events and their severity was not recorded. Mean platelet count in bleeders with chronic ITP (at the12-month FU) was $36 \pm 26 \times 10^9$/L in children and $40 \pm 25 \times 10^9$/L in adults and in non-bleeders, $63 \pm 25 \times 10^9$/L and $56 \pm 25 \times 10^9$/L, respectively.

During the overall study period, intracranial hemorrhage (ICH) was reported in 20 children (0.6%) and seven adults (1.7%). Characteristics of patients with ICH are shown in Supporting Information Table S3.

Co-morbidities did not appear to affect bleeding in children or adults; approximately 69% and 66% of children and 44% and 43% of adults with and without co-morbidities with persistent ITP at 6 months reported bleeding, respectively. This was also observed in adults on relevant co-medication; only 22% of adults diagnosed with chronic ITP and taking relevant co-medication reported a bleeding event compared with 32% of those without co-medication. The group of children on relevant co-medication was too small for a detailed analysis.

3.5 | Management

Platelet-enhancing drug treatment was reported at the 6-month FU (initial treatment not included), 12- and 24-month FU in 30%, 19%, and 19% of children and in 59%, 40%, and 33% of adults, respectively. However, for patients with ongoing ITP, treatment did not differ between children and adults (58%, 46%, and 47%; and 58%, 52%, and 40% at the three FU examinations, respectively). Women with ongoing disease were more often treated than men (Table 2). The platelet counts of treated and untreated patients with chronic ITP are shown in Figure 1B.

3.6 | First-line treatment (corticosteroids and IVIG)

Corticosteroids were prescribed in 19% of children and 49% of adults during the first 6 months of the disease (initial treatment excluded).

Corticosteroid use decreased in both children and adults over time, with 12% and 11% of children and 33% and 21% of adults receiving corticosteroids at 12 and 24 months, respectively. However, the proportion of patients receiving corticosteroids in the group of patients requiring treatment remained high at all three FU examinations (adults, 83%, 81%, and 65%; and children, 65%, 63%, and 56%, respectively). Immunoglobulin (IVIG and anti-D) use was higher in children than in adults at all three FU examinations (e.g., Table 2).

3.7 | Second (third)-line treatment

Second (third)-line drug treatment was reported in 38%, 47%, and 44% of treated children and 67%, 74%, and 72% of adults at 6-, 12-, and 24-month FU, respectively. The modality of treatment was not analyzed for this report. Splenectomy was performed in 4 children and 23 adults within the first 6 months (0.2% and 7.1% of children and adults). In 2/4 children, the reason for performing splenectomy was not obvious in the questionnaire. Splenectomy was performed in 13 (0.8%) and 13 (1.2%) children and in 14 (5.2%) and 8 (4.1%) adults during 6–12 months and 12–24 months, respectively. The female:male ratio of splenectomized patients was in favor of females in adults (67%) and also in children to a lesser extent (57%). Between May 2004 and January 2008, 35 splenectomies (0.8 total cases/month; adults, 0.5/month; children, 0.3/month) were performed; between 2008 and November 2015 39 splenectomies were performed (0.4 total cases/month; adults, 0.2/month; children, 0.2/month). Remission rate after splenectomy (at 6 or 12 months) was 54% in children and 70% in adults at the next FU, with no difference between the two FU times. In 4 children (13%) and 6 adults (14%), the remission state was unknown.

4 | DISCUSSION

Comparative clinical studies of pediatric and adult ITP are rare and based on retrospective data.[23,24] PARC-ITP represents the first prospective observational cohort of children and adults with ITP and allows direct comparison of children and adults.

Differences between pediatric and adult ITP have been traditionally emphasized[6] and appear to be opinion-based rather than evidence-based.[7–10] Incongruity of definitions and lack of comparative data might have further contributed to the separation of childhood and adulthood ITP.[25] In most textbooks,[26,27] pediatric ITP is described as an acute and profound but self-limiting thrombocytopenia following a viral infection, with a low life-threatening bleeding risk. In contrast, adult ITP is described as a chronic disease with an insidious onset and a moderate thrombocytopenia, sometimes detected as an incidental thrombocytopenia, a high bleeding risk for patients with a platelet count $<30 \times 10^9$/L (40), and increased morbidity and mortality, particularly in patients aged >60 years.[11,25,28,29] Current concepts of pediatric and adult ITP resulted in treatment protocols and practice guidelines with clinically relevant differences between these groups.[7–10]

PARC-ITP first data analysis of children and adults with newly diagnosed ITP revealed surprising similarities in presenting platelet count, likelihood of overall bleeding when platelets were $<20 \times 10^9$/L, and percentage of patients who remained untreated in both populations.[12] Patients differed with regard to co-morbidities and initial treatment modality. Pediatric and adult ITP seem to share more common clinical and laboratory aspects than previously presumed. This report is an analysis of FU data and supports the hypothesis of common aspects among children and adults. Similarities were found in many unexpected areas of ITP regarding natural history, including late remission rate at 12 and 24 months, reported bleeding sites, platelet count in bleeders, and need to treat patients with persistent or chronic ITP. Differences were confirmed for the overall remission rate and treatment modalities. Unexpected differences were found regarding the percentage of non-bleeders.Age group were arbitrary chosen. The age of thepediatric cohort corresponds to data previously reported in the literature,[30] the adult cohort was slightly younger than that reported, e.g., by Abrahamson and coworkers,[31,32] the difference here could be explained based on our definition of adults aged >16 years.

4.1 | Remission

Remission rate in adults (45% at 6-month FU) was higher than expected.[6,7] In adults, we could not differentiate patients in remission still receiving ITP treatment from those with sustained remission after discontinuing treatment. In children, remission rate was comparable to earlier reports,[33] so as differences in age between patients with early remission (until 6 months) and those with persistent or chronic disease (4.9 ± 4 years, 7.2 ± 4.6 years, and $7.4 + 4.5$ years, respectively).[33] Children with late remission (at 12 or 24 months) were older (6.9 ± 4.7 years) than patients with early remission in our cohort.

Late remission at 12- and 24-month FU examinations was very similar in children (36% and 28% of patients with ongoing ITP at the previous FU) and adults (28% and 30%). Late remission data in adults are scarce,[34] and this is neglected in some publications involving therapeutic recommendations, particularly the time point of splenectomy.[8,10] Sailer et al.[34] showed that between 6 months and 3 years after diagnosis, adults with severe ITP ($<20 \times 10^9$/L platelets) had a 0.5% chance per month of obtaining complete remission during treatment with or without low-dose steroids and reported a 61% cumulative probability of complete remission in not splenectomized patients. In children, ICIS reported a late remission rate of 16%-25% between 6 and 12 months[33,35] and 24% between 12 and 24 months[24]; however, the definition of remission was a platelet count $>150 \times 10^9$/L, which may explain the small difference with our study.

4.2 | Bleeding

Definition, assessment, and grading of bleeding in patients with ITP has been developed with consensus conferences[20] and use of bleeding scores.[36,37] Unfortunately, there is no consensus on which bleeding assessment tool should be used in a routine clinical setting and at which time point or in which clinical situation bleeding should be assessed. Bleeding assessment is further hindered by the lack of clear inclusion criteria of study populations.[28,38–41] We focused on the analysis of nonbleeders because the definition is clearer. However,

diagnosing a "nonbleeder" requires a complete clinical assessment. More adults with persistent or chronic ITP exhibited a nonbleeding phenotype (e.g., 69% at the 12-month FU) than children (37%), despite similar platelet counts in both. However, bleeding sites were similar among them, particularly at 24 months of FU, with the same proportions of mucocutaneous bleeding and hematuria in the two age groups. In a systematic review of the literature, Neunert et al. revealed more severe bleeding events in children than in adults, excluding ICH.[41] This information together with our data contradicts the widely accepted paradigm that adults have a higher bleeding complication risk. Nevertheless, according to literature, elderly patients (>60 years) still have an increased bleeding risk.[11,28,29,42] The number of elderly patients in PARC-ITP (69) was too small to be analyzed separately. Overall ICH incidence in our cohort was 0.6% in children and 1.7% in adults, which is similar to the findings of a recent systematic review of severe bleeding of 0.4% and 1.4%, respectively, as well as the results of other reports.[25,41,43,44] ICH was reported during initial diagnosis of ITP in 14/20 (70%) of children and 7/7 (100%) of adults, corresponding to the results of a study of 40 children revealing that ICH occurred in 18 (45%) patients within the first 7 days.[43]

4.3 | Treatment

Drug treatment in children and adults with ongoing ITP was similar in both age groups. Indeed, 58% of patients with persistent ITP (at 6 months) received platelet-enhancing treatment independently of age group, with a small decrease over time in both groups. Therefore, children with ongoing disease are not treated less frequently than adults with platelet-enhancing drugs, despite the recommendation of a watch and wait strategy in pediatric patients with no or mild bleeding.[9,10] A possible bias could have been that children with active ITP were treated because of bleeding ("on-demand therapy") compared with a certain percentage of adults who probably received platelet-enhancing drugs as prophylaxis. However, the treatment rationale was not registered. Differences were seen in the choice of treatment modality. In adults, steroids were the preferred therapy at 6- and 12-month FU (84% and 81% of patients under treatment, respectively) and second (third)-line drugs at 24-month FU (72%). In children, steroids (65%, 63%, and 56%) and immunoglobulins (67%, 55%, and 55%) were similarly represented at all FU examinations. A decline of steroid use was seen at FU for all patients probably because of cumulative toxicity and poor drug acceptance. The percentage of children and adults using second (third)-line therapy was relatively stable over time.

The splenectomy rate was relatively low with a cumulative splenectomy rate until the 24-month FU of 30/3360 (0.9%) children and 44/420 (11%) adults. The monthly splenectomy rate decreased after 2008 in adults and, to a lesser extent, in children. For decades, splenectomy was the treatment of choice for patients with chronic ITP in case of corticosteroid failure[45,46]; however, recent data suggest that <25% of patients with ITP undergo splenectomy, mostly with a delay from second- to third-line treatment.[47] The reason for this decline are probably various, medical professionals recommend increasingly to delay splenectomy but also patients do not accept uncritically the procedure. The optimal role of splenectomy in chronic ITP treatment in the current era of TPO-RAs still has to be determined. Of concern was early splenectomy at the 6-month FU in 4 children and 23 adults. This is not in accordance with current guidelines.[9,10]

4.4 | Limitations

PARC-ITP is an international registry based on voluntary participation of investigators. Limitations include different data source levels including different countries, institutions, and investigators; voluntary basis of data registration; unbalanced number of children and adults; and high percentage of patients with loss to FU who were not further treated in a given institution. However among all patients with persistent ITP at 6 months, FU information at 12 and/or 24 months was provided for 90% of children and adults.In addition, some aspects of the registry questionnaire are defined according to a specific time point (e.g., platelet count) and others according to a time interval (e.g., bleeding and therapy). To better characterize patients lost to FU, an analysis was conducted to evaluate the effect of this bias. Demographic data and clinical characteristics (including initial platelet count, bleeders, and initial therapeutic approach) differed, particularly in children lost to FU at 6 months compared with those who were not lost. For the group of lost to FU at 12 and 24 months, we found a higher percentage of patients in remission at the previous FU in children and adults. In this analysis, we included all patients independently, even if FU data were missing at some time points, with the goal to describe the registered patients as a whole without artificially selecting a subpopulation of ITP. Following this strategy, we used statistical evaluation for selected and clearly defined issues only.

In conclusion, understanding differences and similarities among different age groups with ITP during FU may be valuable in characterizing study populations and in better defining inclusion criteria for trials and further individualizing diagnosis and management. Future studies will investigate criteria to better define age groups.

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CONFLICT OF INTERESTS

M.Chitlur, M.Coslovsky, P.I., H.D., M.E., G.E., S.H., C.R., M.R., H.T., T. U., and R.W. declare no competing financial interests. A.S. advisory

board for Novartis and received research funds of Amgen; A.H. consultancy for Novartis; J.G. advisory board for ITP Support Association, Novartis, GSK, Amgen; F.R. Board member for Amgen, Argenx, Novartis; T.K. advisory board UCB biosciences and received research funds of Amgen.

AUTHOR CONTRIBUTIONS

A.S., A.H., and T.K. analyzed and interpreted data, and wrote the article; A.H., M.Chitlur, H.D, M.E., G.E., J.G., S.H., C.R., F.R., M.R., H. T., T.U., and R.W. recruited patients and collected data; A.S., A.H., M.Chitlur, M.Coslovsky, P.I., H.D, M.E., G.E., J.G., S.H., C.R., F.R., M. R., H.T., T.U., R.W., and T.K. reviewed the manuscript and provided editorial input; M.Coslovsky, and A.S. performed statistical analysis; T.K., P.I., and A.S. designed and conducted the Registry, and all authors approved the final manuscript.

ORCID

Alexandra Schifferli http://orcid.org/0000-0001-9459-8709
Marco Ruggeri http://orcid.org/0000-0003-1557-0957

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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APPENDIX : MEMBERS OF THE ICIS

The list of participating physicians (Intercontinental Cooperative ITP Study Group (ICIS) investigators) is as follows:

Argentina: *Donato Hugo*, *Elena Graciela*, *Espina Bibiana*, *Graciera Alfonso*, *Kohan Regina*, *Lavergne Marta*, *Picón Armando Oscar*, *Pierdominici Marta*, *Rapetti Maria Cristina*, *Riccheri Cecilia*, *Schvartzman Gabriel*. Austria: *Minkov Milen*, *Trebo Monika*. Belarus: *Uglova Tatjana*. Cambodia: *Devenish Robyn*, *Sophâl Chean*. Canada: *Blanchette Victor*, *Cham Bonnie*, *Eisenstat David*, *Israels Sara*, *Klaassen Robert*, *Lee David*, *Lillicrap David*, *McCusker Patricia*, *Silva Mariana*, *Yanofsky Rochelle*. China: *Wu Runhui*, *Yu Ziqiang*. Croatia: *Roganovic Jelena*. Denmark: *Kjaersgaard Mimi*. Ecuador: *Sghirla Juan*. Egypt: *AL-Tonbary Youssef*, *Elalfy Mohsen*, *Fouda Ashraf*, *Khadiga Yehia*. France: *Lutz Patrick*. Germany: *Erkel Joseph*, *Groth Renate*, *Holzhauer Susanne*, *Hummler Markus*, *Janssen Gisela*, *Meyer Oliver*, *Salama Abdulgabar*, *Schütz Barbara*, *Taube Tillmann*, *von Stackelberg Arend*. Greece: *Aronis Sophie*, *Platokouki Helen*. Iran: *Faranoush Mohammad*. Israel: *Koren Ariel*, *Levin Carina*, *Revel-Vilk Shoshana*, *Shraga Aviner*, *Tamary Hannah*, *Yacobovich Joanne*. Italy: *Cattaneo Marco*, *Fortuna Stefania*, *Ruggeri Marco*. Japan: *Bessho Fumio*. *South* Korea: *Choe Byung-Kyu*, *Kim Heung-Sik*, *Kwon Ki-Young*, *Park Sang- Kyu*. Netherlands: *Koene Harry*. Pakistan: *Adil Salman Naseem*, *Alidina Amin*, *Fadoo Zehra*, *Farrukh Ali*, *Kakepoto Ghulam Nabi*, *Khurshid Mohammad*, *Naz Naveen*, *Sajida Ali Muhammad*, *Shaikh Mohammed Usman*, *Vaziri Irfan*. Poland: *Niewiadomska Edyta*, *Zawilska Krystyna*. Russia: *Abdukadyrov Kudrat*, *Chistyakova Vera*, *Pshenichnaya Ksenia*. Serbia and Montenegro: *Colovic Milica*, *Elezovic Ivo*, *Todorovic Milena*, *Vukovic Suvajdzic Nada*. South Africa: *Wainwright Linda*. Sri Lanka: *Vidyatilake Sudharma*. Switzerland: *Brazzola Pierluigi*, *Gratwohl Alois*, *Kühne Thomas*, *Rischewski Johannes*, *Tichelli André*. Thailand: *Chuansumrit Ampaiwan*. Turkey: *Aydinok Yesim*, *Balkan Can*, *Kavakli Kaan*. United Kingdom: *Grainger John*. USA: *Bennett Carolyn*, *Bergstrom Steven*, *Bottner Wayne A*, *Boudreaux Jeanne*, *Chitlur Meera*, *Cole Craig*, *Ettinger Robert S*, *Farnen John P*, *Felgenhauer Judy*, *Go Ronald*, *Green David*, *Guerrera Michael*, *Inoue Susumu*, *Jacobs Shana*, *Lockhart Sharon*, *Luchtman-Jones Lori*, *Michaels Lisa*, *Neier Michelle*, *Nugent Diane*, *Onwuzurike Nkechi*, *Ramdas Jagadeesh*, *Reynolds Frank*, *Shaffer Linda*, *Sharp James C*, *Sprehe Michael R*, *Stout Linda A*, *Tancabelic Jakica*, *Tarantino Michael D*, *Wells Donlad T*, *Zakarija Anaadriana*.