



HAL
open science

Impact of age at diagnosis, sex, and immunopathological manifestations in 886 patients with pediatric chronic immune thrombocytopenia

Thomas Pincez, Helder Fernandes, Marlène Pasquet, Wadih Abou Chahla, Jérôme Granel, Sébastien Héritier, Mony Fahd, Stéphane Ducassou, Caroline Thomas, Nathalie Garnier, et al.

► To cite this version:

Thomas Pincez, Helder Fernandes, Marlène Pasquet, Wadih Abou Chahla, Jérôme Granel, et al.. Impact of age at diagnosis, sex, and immunopathological manifestations in 886 patients with pediatric chronic immune thrombocytopenia. *American Journal of Hematology*, 2023, 98 (6), pp.857-868. 10.1002/ajh.26900 . hal-04230544

HAL Id: hal-04230544

<https://hal.science/hal-04230544v1>

Submitted on 21 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

RESEARCH ARTICLE

Impact of age at diagnosis, sex, and immunopathological manifestations in 886 patients with pediatric chronic immune thrombocytopenia

Thomas Pincez^{1,2}  | Helder Fernandes^{1,3} | Marlène Pasquet⁴ |
 Wadih Abou Chahla⁵ | Jérôme Granel^{1,3} | Sébastien Héritier⁶  | Mony Fahd⁷ |
 Stéphane Ducassou^{1,3}  | Caroline Thomas⁸ | Nathalie Garnier⁹ |
 Vincent Barlogis¹⁰ | Eric Jeziorski¹¹ | Sophie Bayart¹² | Pascal Chastagner¹³ |
 Nathalie Cheikh¹⁴ | Corinne Guitton¹⁵ | Catherine Paillard¹⁶ | Julien Lejeune¹⁷ |
 Frédéric Millot¹⁸ | Valérie Li-Thiao Te¹⁹ | Coralie Mallebranche²⁰ |
 Isabelle Pellier²⁰ | Bénédicte Neven²¹ | Corinne Armari-Alla²² | Liana Carausu²³ |
 Christophe Piguet²⁴ | Joy Benadiba²⁵ | Claire Pluchart²⁶ | Jean-Louis Stephan²⁷ |
 Marianna Deparis²⁸ | Claire Briandet²⁹ | Eric Doré³⁰ | Aude Marie-Cardine³¹ |
 Thierry Leblanc⁷ | Guy Leverger⁶ | Nathalie Aladjidi^{1,3}

Correspondence

Thomas Pincez, Service d'Hématologie-Oncologie Pédiatrique, Centre de Cancérologie Charles-Bruneau, CHU Sainte-Justine, Montréal, QC, Canada.
 Email: thomas.pincez@umontreal.ca

Nathalie Aladjidi, Unité d'hématologie pédiatrique, Centre de référence national des cytopénies auto-immunes de l'enfant CEREVANCE, Hôpital des Enfants, Hôpital Pellegrin, Place Amélie Raba Léon, 33000 Bordeaux, France.
 Email: nathalie.aladjidi@chu-bordeaux.fr

Funding information

Ministère des Affaires Sociales et de la Santé, Grant/Award Number: CHUBX 2005/18

Abstract

Pediatric chronic immune thrombocytopenia (cITP) is a heterogeneous condition in terms of bleeding severity, second-line treatment use, association with clinical and/or biological immunopathological manifestations (IMs), and progression to systemic lupus erythematosus (SLE). No risk factors for these outcomes are known. Specifically, whether age at ITP diagnosis, sex, or IMs impact cITP outcomes is unknown. We report the outcomes of patients with pediatric cITP from the French nationwide prospective cohort OBS'CEREVANCE. We used multivariate analyses to investigate the effect of age at ITP diagnosis, sex, and IMs on cITP outcomes. We included 886 patients with a median (min-max) follow-up duration of 5.3 (1.0–29.3) years. We identified an age cutoff that dichotomized the risk of the outcomes and defined two risk groups: patients with ITP diagnosed <10 years (children) and ≥ 10 years (adolescents). Adolescents had a two to four-fold higher risk of grade ≥3 bleeding, second-line treatment use, clinical and biological IMs, and SLE diagnosis. Moreover, female sex and biological IMs were independently associated with higher risks of biological IMs and SLE diagnosis, second-line treatment use, and SLE diagnosis, respectively. The combination of these three risk factors defined outcome-specific risk groups. Finally, we showed that patients clustered in mild and severe phenotypes, more frequent in children and

Thomas Pincez and Helder Fernandes are co-first authors.

Thierry Leblanc and Guy Leverger are co-penultimate authors.

For affiliations refer to page 866

adolescents, respectively. In conclusion, we identified that age at ITP diagnosis, sex, and biological IMs impacted the long-term outcomes of pediatric cITP. We defined risk groups for each outcome, which will help clinical management and further studies.

1 | INTRODUCTION

Pediatric immune thrombocytopenia (ITP) is a rare autoimmune disorder characterized by a low platelet count ($<100 \times 10^9/L$) in the absence of other causes of thrombocytopenia and occurring before 18 years.¹ Chronic ITP (cITP) refers to ITP persisting for >12 months; ~30% of patients with pediatric ITP develop cITP.^{1,2} Age is a well-known important risk factor for cITP development, with the risk of cITP development being highest in adolescents with ITP.³⁻⁵

Although bleeding is the main complication of cITP, life-threatening bleeding is rare.⁶ Pediatric cITP is associated with poor health-related quality of life,^{7,8} and second-line treatments (i.e., other than corticosteroids and intravenous immunoglobulins) are required in up to 55% of patients.⁹ Disease remission is common and almost 75% of cITP patients with pediatric-onset seem to undergo spontaneous remission during 5 years of follow-up.^{6,10,11}

Some patients with cITP have associated immunopathological manifestations (IMs), clinical IMs (such as lymphoproliferative disorder and organ autoimmunity), and/or biological IMs (such as antinuclear antibodies [ANA] and hypogammaglobulinemia).⁹ However, the prevalence and spectrum of IMs in pediatric cITP are unknown. As in Evans syndrome,^{12,13} the occurrence of IMs suggests an underlying condition, classically systemic lupus erythematosus (SLE) or primary immunodeficiency (PID).¹³⁻¹⁵ A retrospective study identified a high rate of SLE in older female children at ITP onset.¹⁶ However, the incidence of SLE and PID in pediatric cITP patients has not been prospectively evaluated and can vary with the inclusion criteria and the follow-up duration. IMs can occur after ITP onset, and the underlying cause may only be identified several years afterward.

Thus, pediatric cITP is a heterogeneous condition regarding disease course in terms of hematological outcomes, second-line treatment use, IM incidence and type, and underlying diagnosis. Critically, there are no factors currently known to be associated with cITP outcomes. Whether age impacts cITP outcomes and could allow a risk stratification is unknown. Likewise, the effect of sex on cITP outcomes has not been prospectively evaluated, and whether IMs modify the cITP courses is unknown.

Here, we report a comprehensive long-term evaluation of 886 patients with pediatric cITP from the French nationwide prospective OBS'CEREVANCE cohort. We investigated whether the age at ITP diagnosis and sex impacted seven cITP outcomes. Then, we analyzed whether clinical and biological IMs allow us to refine the risk models. Finally, we integrated the risk factors identified to define risk groups for each outcome as well as cITP phenotypes.

2 | METHODS

2.1 | OBS'CEREVANCE cohort

Since 2004, French patients with cITP diagnosed before 18 years of age have been included in the prospective OBS'CEREVANCE cohort.^{9,17} The inclusion and exclusion criteria for the cohort are presented in Table S1. Written informed consent was obtained from all participants. The OBS'CEREVANCE cohort was approved by the Institutional Ethics Committee (CPRB-A; Bordeaux, France). The database was registered with the National Data Protection Authority (CNIL, 1396823V0).

2.2 | Patient selection

We included in this study all cohort patients with cITP, defined as ITP lasting >12 months.¹ We excluded patients with cITP secondary to transplantation, SLE, or PID known at ITP diagnosis, as well as those who developed Evans syndrome during follow-up. Data collection was completed on January 15, 2022.

2.3 | Definitions

We assessed bleeding severity (grade) using the Buchanan score.¹⁸ Bleeding sites were retrospectively reviewed from the charts of female adolescents older than 12 years old at ITP diagnosis. Hematological status was categorized as follows: non-remission (platelet count $<30 \times 10^9/L$, with or without treatment), partial remission (platelet count $\geq 30 \times 10^9/L$, with or without treatment), and complete remission (platelet count $\geq 100 \times 10^9/L$, with or without treatment).¹

We predefined the IMs associated with cITP (Table S1) and categorized them as clinical (lymphoproliferation and/or autoimmune/autoinflammatory organ disease) or biological (hypogammaglobulinemia, SLE biomarker, autoimmune lymphoproliferative syndrome [ALPS] biomarker and/or isolated autoantibodies). ANA was considered positive at a titer of $\geq 1/160$. The patients were monitored for clinical and biological IMs every 6-12 months according to the CEREVANCE guidelines.¹⁷

We used the Systemic Lupus International Collaborating Clinics Classification (SLICC) criteria to diagnose SLE.¹⁹ We used international classification criteria to diagnose PID,²⁰ as well as eventual criteria when existing (e.g., for ALPS).²¹ Genetics analyses for PID diagnosis were performed upon evocative IM, a molecular

technique used varied according to clinical context and date of analysis.

We defined second-line treatments as those other than corticosteroids and intravenous immunoglobulins.

2.4 | Identification of an age cutoff

For each of the seven outcomes analyzed (grade ≥ 3 bleeding, CR at 5 years after ITP diagnosis, IM, biological IM, clinical IM, SLE, and second-line treatment use), we fitted 17 multivariate models with age group (as a categorical variable with two groups) and sex as covariates. We used each entire age from 1 to 17 years as the age cutoff for age groups. To assess whether an age cutoff was present, we visually assessed the p -value distribution and required the lowest p -value to be $<.005$.

2.5 | Statistical analysis

We compared continuous and categorical variables using non-parametric Wilcoxon–Mann–Whitney and Fisher's exact tests, respectively. We used the Kaplan–Meier method to calculate the cumulative incidences and treatment-free estimates. We used the log-rank test to compare the survival curves.

We used multivariate logistic and Cox regressions to assess the independent effects of age group and sex. We reported the effects of age and sex with respect to the adolescent and female categories, respectively. We used logistic regression to analyze categorical variables, including bleeding grade ≥ 3 , bleeding grade ≥ 4 , and specific treatments received. We used Cox proportional hazards method to analyze time-dependent variables, including the cumulative incidences of IMs, clinical IMs, biological IMs, SLE diagnosis, and second-line treatment use. The proportionality of hazards was confirmed for each variable.

To investigate whether IMs were also associated with outcomes, we fitted multivariate models with age group, sex, clinical IMs, and biological IMs as covariates. For second-line treatment and SLE diagnosis analyses, we included clinical and biological IMs diagnosis as time-dependent covariates, to consider only IMs diagnosed before the first second-line treatment initiation or SLE diagnosis.

We performed a sensitivity analysis to investigate whether the year of ITP diagnosis represented a confounding factor of our results, as cITP management and follow-up evolved during the long timespan of our study. In each of our models, we added the year of ITP diagnosis as a third covariable (with age group and sex) as well as the interaction term between the year of ITP diagnosis and age group as a fourth covariate in models with a nominal ($p < .05$) effect of year of ITP diagnosis.

Statistical analyses were performed using RStudio (version 1.2.5033; R version 4.1.3, R Development Core Team) and Prism (ver. 9.1; GraphPad Software Inc., San Diego, CA) software. We considered

a p -value $<.005$ as statistically significant to consider multiple testing performed. All tests were two-sided.

3 | RESULTS

3.1 | Population

We included 886 patients diagnosed with cITP between 1990 and 2020 at 29 different French centers (Figure S1). The study participants consisted of 388 males (44%) and 498 (56%) females. The median (min-max) follow-up duration was 5.3 (1.0–29.3) years, which corresponded to a total of 5901 patient-years of observation. The number of patients still followed 5 and 10 years after ITP diagnosis was 481 and 177, respectively (Figure S2). No patient died during the follow-up. The median age at the final follow-up was 14.6 (1.3–35.3) years and 208 (23%) patients were >18 years and followed by an adult team at the last follow-up.

3.2 | cITP outcomes in the 886 patients

The OBS'CEREVANCE cohort allows the collection of prospective data on bleeding grade, hematological status, IMs, SLE diagnosis, thrombosis, and second-line treatment use.

Two-hundred thirty-seven (27%) and 21 (2%) patients experienced grade ≥ 3 and ≥ 4 bleeding during follow-up, respectively. Seven patients (0.8%) had grade 5 bleeding (Table S2). For three of the seven patients, these severe hemorrhages had occurred during the first 12 months after ITP diagnosis, thus four patients (0.6%) experienced grade 5 bleeding that occurred more than 12 months after ITP diagnosis. During the cITP course of the 120 female adolescents ≥ 12 years old at ITP diagnosis, 109 (91%) had bleeding of any grade and 95 (79%) had grade ≥ 3 bleeding. Specifically, 98 (82%) had cutaneous bleeding, 74 (62%) had abnormal uterine bleeding, 67 (56%) had oral bleeding, 49 (41%) had epistaxis, 6 (5%) had hematuria, and 5 (4%) had gastrointestinal bleeding. Only four of the 74 patients (5%) with abnormal uterine bleeding did not have another site of bleeding.

Hematological status at 5 and 10 years after ITP diagnosis is shown in Table 1. At the last follow-up, 197 patients (23%) were in CR without second-line treatment for more than 1 year.

IMs were diagnosed in 322 of 886 patients (36%) during follow-up (Table S3). Clinical IMs were diagnosed in 71 of 886 patients (8%), of whom 54 (76%) also developed a biological IM. The two most frequent types of clinical IMs were lymphoproliferation ($n = 27$ [3%]) and rheumatologic ($n = 25$ [3%]; Figure 1A). Biological IMs were diagnosed in 276 of 886 patients (31%). Among them, 222 (80%) did not develop any clinical IMs. The two most frequent biological IMs categories were SLE biomarker positivity ($n = 195$ [22%]), including 185 (21%) cases of positive ANA, and isolated autoantibodies ($n = 55$ [6.2%]; Figure 1B). None of the patients developed a malignancy.

TABLE 1 Patient characteristics.

	Total n = 886	Children (aged <10 years at ITP diagnosis) n = 591 (67%)	Adolescents (aged ≥10 years at ITP diagnosis) n = 295 (33%)	p-value
Sex ratio (males/females)	0.78 (388/498)	0.90 (280/311)	0.58 (108/187)	.003
IMs in first-degree relative, n (%)	122/311 (39%)	71/186 (38%)	51/125 (41%)	.72
Median age at ITP diagnosis, years (min-max)	7.3 (0.03–17.86)	4.3 (0.03–9.99)	13.1 (10.00–17.61)	–
First IM before or at ITP diagnosis, n (%)	40/886 (5%)	23/591 (4%)	17/295 (6%)	.23
Hematological status at 5 years after ITP diagnosis				
NR	113/474 (24%)	86/313 (27%)	27/161 (17%)	.01
NR without second-line treatment	55/474 (12%)	42/313 (13%)	13/161 (8%)	.1
PR	135/474 (28%)	91/313 (29%)	44/161 (27%)	.75
PR without second-line treatment	102/474 (22%)	68/313 (22%)	34/161 (21%)	.91
CR	224/474 (47%)	135/313 (43%)	89/161 (55%)	.02
CR without second-line treatment	189/474 (40%)	118/313 (37%)	71/161 (44%)	.20
Hematological status at 10 years after ITP diagnosis				
NR	30/205 (15%)	24/162 (15%)	6/43 (14%)	.99
NR without second-line treatment	16/205 (8%)	13/162 (8%)	3/43 (7%)	.99
PR	48/205 (23%)	44/162 (27%)	4/43 (9%)	.01
PR without second-line treatment	42/205 (20%)	39/162 (24%)	3/43 (7%)	.01
CR	129/205 (62%)	95/162 (59%)	34/43 (64%)	.01
CR without second-line treatment	114/205 (56%)	84/162 (52%)	30/43 (79%)	.04
Continuous complete remission at the last follow-up	197/846 (23%)	135/574 (24%)	62/272 (23%)	.86
Median follow-up after ITP diagnosis, years (min-max)	5.3 (1.0–29.3)	5.9 (1.0–29.3)	4.8 (1.0–25.2)	1.1×10^{-5}
Median age at last follow-up, years (min-max)	14.6 (1.3–35.3)	11.6 (1.3–33.4)	18.0 (11.8–35.3)	3.0×10^{-62}

Note: Denominators include only patients with available data. CR: complete remission (platelet count $\geq 100 \times 10^9/L$, with or without treatment), IMs: immunopathological manifestations, ITP: immune thrombocytopenia, NR: non-remission (platelet count $< 30 \times 10^9/L$, with or without treatment), PR: partial remission (platelet count $\geq 30 \times 10^9/L$, with or without treatment).

SLE (based on SLICC criteria) was diagnosed in 38 of 886 patients (4%), whereas no patient was diagnosed with a PID during follow-up. Among patients with SLE, 33 (87%) were females, all developed biological IMs (all had positive ANA $\geq 1/160$), and 22 (58%) developed clinical IMs. The median time from ITP to SLE diagnosis was 2.81 (0.1–15.5) years and the median age at SLE diagnosis was 15.40 (5.8–21) years.

Two (0.2%) patients were diagnosed with thrombosis. One patient had corticosteroid-induced hypertension and was diagnosed with leg distal deep vein thrombosis following leg lipoma surgery and the other had pulmonary arterial hypertension. Both had undergone splenectomy before thrombosis and were previously described.¹⁷

Second-line treatments were used in 396 of 886 patients (45%). The median number of treatments received was 2 (1–14) and the median time to first second-line treatment use was 3.1 (0–27) years. Two-hundred and three patients (23%) received immunosuppressors (azathioprine, mycophenolate mofetil, cyclosporine, sirolimus), 129 patients (15%) underwent splenectomy, 127 (14%) received hydroxychloroquine, 126 (14%) received thrombopoietin receptor agonists (TPO-RA), and 113 (13%) patients received rituximab.

3.3 | Identification of an age cutoff

We investigated whether we could identify an age at ITP diagnosis that dichotomized cITP outcomes and allowed us to define two age groups with different outcomes risks. We reasoned that, if such a binary category exists, it would provide meaningful insights into cITP pathophysiology and would be more helpful in a clinical setting than considering age as a continuous variable. We analyzed seven outcomes: grade ≥ 3 bleeding, CR at 5 years after ITP diagnosis, IM, clinical IM, biological IM, SLE, and second-line treatment use.

Among the seven outcomes analyzed, we could identify an age cutoff for all excepted CR at 5 years after ITP diagnosis (Figure 1C). The age cutoffs for the six outcomes ranged from 8 to 12 years (mean 9.67 years). The cutoff values being close to each other, we defined two age categories for all the following analyses: patients aged <10 years at ITP diagnosis (hereafter named children) and patients aged ≥ 10 years at ITP diagnosis (hereafter named adolescents). Of note, the cutoff age of 10 years corresponds to the beginning of adolescence according to the World Health Organization definition.²² This age threshold was also previously reported by several studies as predictive of ITP chronicity.^{4,5,23} The sensitivity analysis confirmed

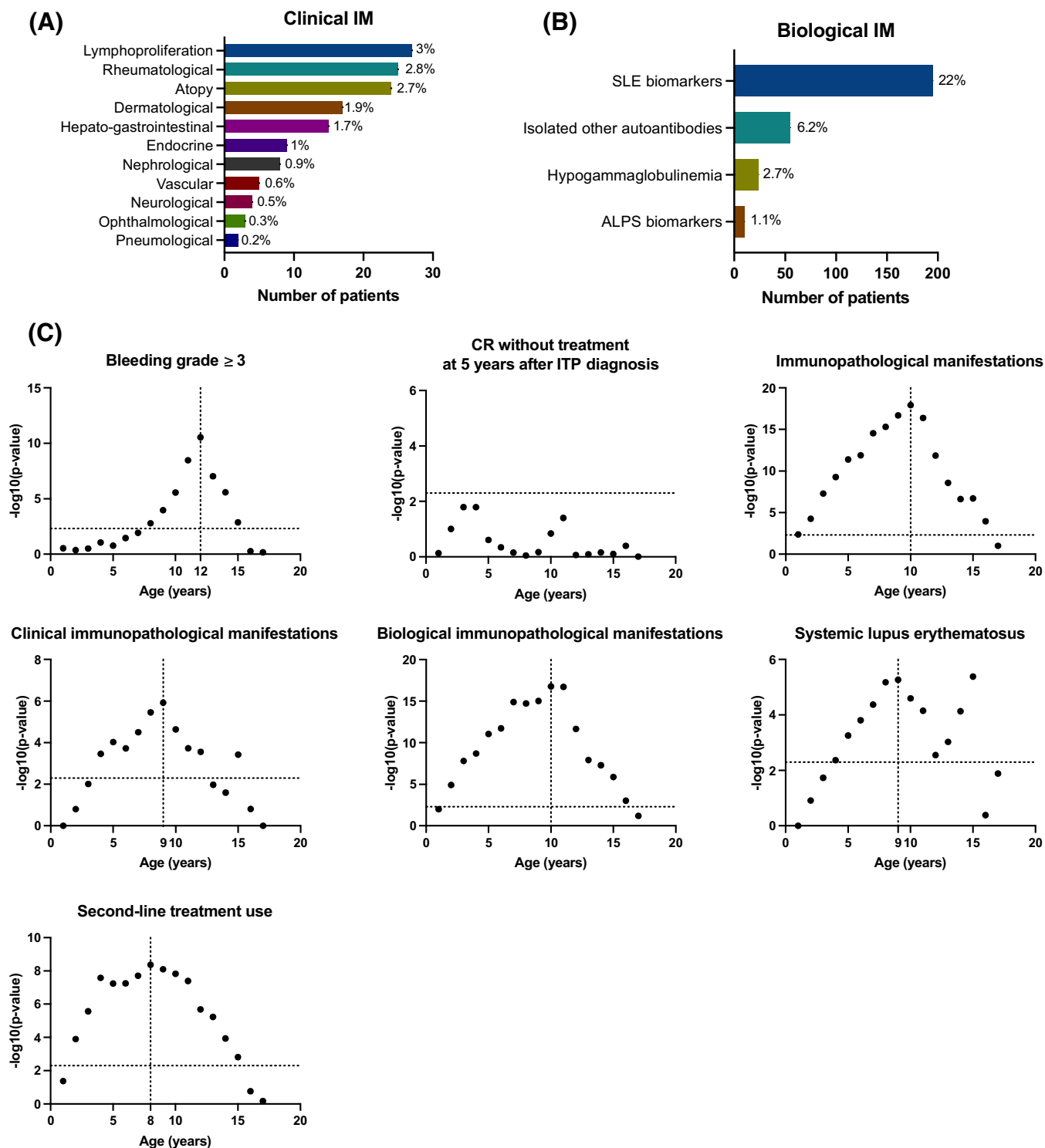


FIGURE 1 Immunopathological manifestations (IMs) associated with chronic immune thrombocytopenia (cITP) and identification of age cutoff across outcomes. (A–B) Distribution of clinical (A) and biological (B) IMs in the entire cohort ($n = 886$), based on data at the last follow-up. (C) Identification of age cutoff across outcomes. For each outcome, we modeled the effect of age group (as a categorical variable with two groups and adjusted for sex) using iteratively all integers ranging from 1 to 17 years as age cutoff. We show the $-\log_{10}(p\text{-value})$ for the age group. Horizontal dotted line represents the multiple-testing corrected p -value threshold of $p < .005$ and the vertical dotted line represents the cutoff with the higher p -value. For complete remission (CR) without treatment at 5 years after ITP diagnosis, we could not identify a cut-off reaching statistical significance. [Color figure can be viewed at wileyonlinelibrary.com]

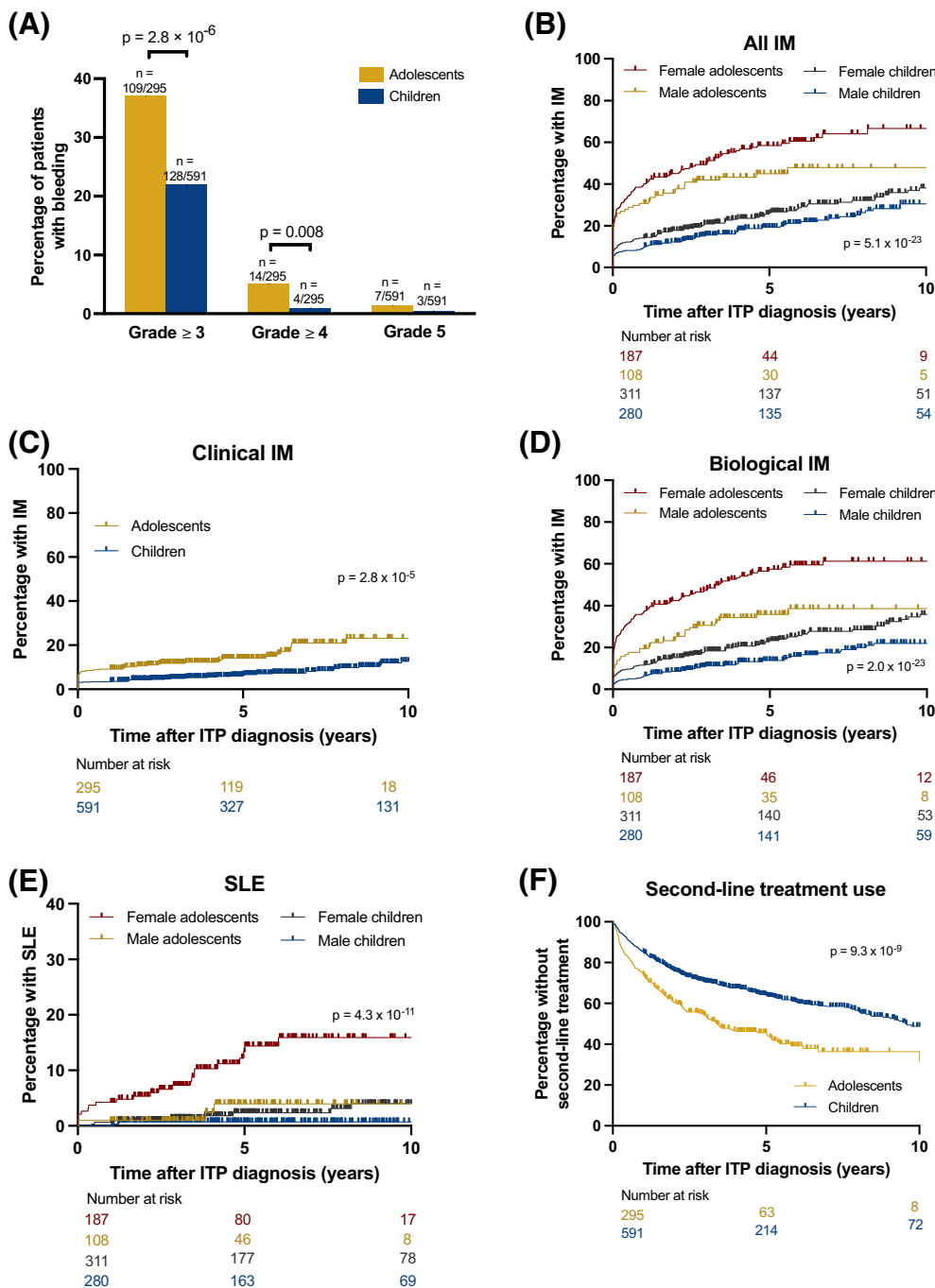


FIGURE 2 Effect of age group and sex on chronic immune thrombocytopenia (cITP) outcomes. (A) Bleeding grade ≥ 3 , grade ≥ 4 , and grade 5 according to age group. (B–E) Cumulative incidence of all immunopathological manifestations (IMs, clinical and biological, (B), clinical IMs (C), biological IMs (D), and systemic lupus erythematosus (SLE, E) according to age group +/- sex. (F) Proportion of patients who did not receive second-line treatment (other than corticosteroids or intravenous immunoglobulins) according to age group. We only present the variables associated with outcomes in multivariate models. [Color figure can be viewed at wileyonlinelibrary.com]

that the potential practice evolution during the follow-up period did not affect our results (Table S4).

In the entire cohort, 591 (67%) and 295 (33%) patients were aged <10 (i.e., children) and ≥ 10 years (i.e., adolescents) at ITP diagnosis, respectively (Table 1). There were more female than male adolescents (187/295 [64%] vs. 311/591 [53%]; $p = .003$). The median follow-up duration was longer for children than for adolescents (5.9 [1.0–29.3] vs. 4.8 [1.0–25.2]; $p = 1.1 \times 10^{-5}$).

In summary, we identified that age at ITP diagnosis impacted six of the seven cITP outcomes and defined two risk groups: patients aged <10 and those ≥ 10 years at ITP diagnosis. Having identified that

age dichotomized the outcomes, we then investigated the effect of age group at ITP diagnosis and sex on these outcomes.

3.4 | Effect of age at ITP diagnosis and sex on cITP outcomes

For the six outcomes, we investigated the independent effects of age group and sex in multivariate models (see Methods).

Adolescents were more likely to experience grade ≥ 3 (aOR = 2.10, 95% CI = 1.54–2.85, $p = 2.8 \times 10^{-6}$, Figure 2A)

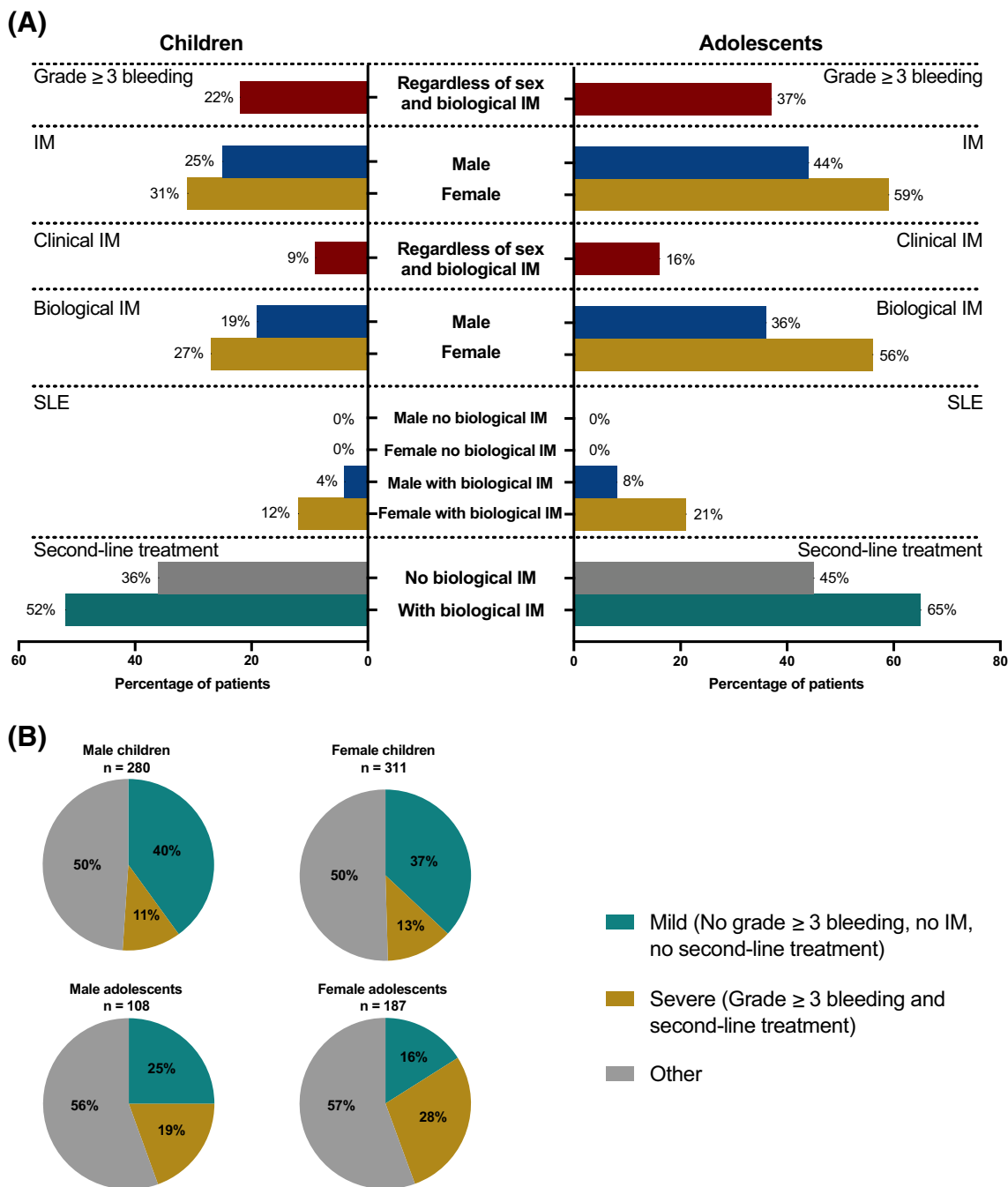


FIGURE 3 Risk groups and phenotypes within the OBS'CEREVANCE cohort. (A) Proportion of patients within each risk group for the six outcomes. Risk groups are defined based on the variables statistically significant in the multivariate models and percentages are based on data at the last follow-up. (B) Proportion of patients with mild and severe phenotypes is defined by a combination of outcomes, according to age group and sex, and based on data at the last follow-up. IMs: immunopathological manifestations, SLE: systemic lupus erythematosus. [Color figure can be viewed at wileyonlinelibrary.com]

bleeding, whereas sex was not associated with grade ≥3 bleeding (aOR = 1.15, 95% CI = 0.84–1.56, *p* = .39). Of note, the adolescent group was also nominally (*p* < .05) associated to grade ≥4 bleeding but did not reach multiple-testing corrected statistical threshold (aOR = 3.51, 95% CI = 1.42–9.48, *p* = .008). We could not investigate the effect of age at diagnosis and sex on grade 5 bleeding because of the low number of events.

Adolescence and female sex were independently associated with a higher cumulative incidence of IMs (clinical and/or biological; adjusted hazard ratio [aHR] = 2.73, 95% CI = 2.18–3.41, *p* = 1.2×10^{-18} and aHR = 1.32, 95% CI = 1.05–1.66, *p* = .018, respectively). Four risk subgroups were defined based on age and sex, and age had a greater impact than sex (Figure 2B). At the 5-year follow-up, the proportions of patients with IMs among female

adolescents, male adolescents, female children, and male children were 58%, 45%, 26%, and 19%, respectively. The median time from cITP to first IM diagnosis was longer in children than adolescents (2.2 [0–20.7] vs. 0.3 [0–14.7] years; $p = 3 \times 10^{-8}$).

Adolescents had a higher risk of clinical IMs than children (aHR = 2.40, 95% CI = 1.60–3.61, $p = 2.3 \times 10^{-5}$), whereas the risk did not differ between the sexes (aHR = 0.74, 95% CI = 0.49–1.10, $p = .14$; Figure 2C). The adolescent and female patients had a higher risk of biological IMs compared to children and male patients, respectively (aHR = 2.80, 95% CI = 2.21–3.55, $p = 1.7 \times 10^{-17}$ and aHR = 1.66, 95% CI = 1.23–2.12, $p = 7.6 \times 10^{-5}$, respectively; Figure 2D).

Adolescents and female patients had a higher risk of underlying SLE than children and male patients, respectively (aHR = 4.35, 95% CI = 2.20–8.62, $p = 2.5 \times 10^{-5}$ and aHR = 4.64, 95% CI = 1.81–11.91, $p = .001$, respectively). Three risk subgroups were defined based on age and sex; male adolescents and female children had a similar cumulative incidence of SLE (aHR = 1.18, 95% CI = 0.31–4.51, $p = .80$ for male adolescents; Figure 2E). At the 5-year follow-up, the proportions of SLE patients among female and male adolescents, and female and male children were 12%, 4%, 2%, and 1%, respectively.

Adolescents were more likely to receive second-line treatment than children (aHR = 2.12, 95% CI = 1.72–2.61, $p = 9.6 \times 10^{-13}$), whereas sex did not influence the likelihood of second-line treatment use (aHR = 1.19, 95% CI = 0.97–1.46, $p = .10$, Figure 2F). At the 5-year follow-up, 64% of children and 46% of adolescents had not received any second-line treatments, respectively. Specifically, adolescents were more often treated with hydroxychloroquine and splenectomy than children (Table S5).

In summary, the adolescent age group had uniformly less favorable outcomes with more grade ≥ 3 bleeding, clinical and biological IMs, SLE diagnosis, and second-line treatment use. Female sex was independently associated with more biological IMs and SLE diagnosis.

3.5 | Impact of IMs on cITP outcomes

We then investigated whether clinical and biological IMs also affected cITP outcomes which allowed us to refine risk modeling in addition to age group and sex. We fitted multivariate models with age group, sex, clinical IMs, and biological IMs as covariates (see methods).

Clinical IMs were not associated with any of the three outcomes analyzed: grade ≥ 3 bleeding, SLE diagnosis, and second-line treatment use (Table S6).

Biological IMs were independently associated with an increased risk of SLE diagnosis (aHR = 3.91, 95% CI = 2.60–5.87, $p = 5.5 \times 10^{-11}$, adjusted for age at diagnosis, sex, and clinical IM, Table S6). Female sex, biological IMs, and adolescence conferred a 5-fold, 4-fold, and 3-fold cumulative risk increase of SLE diagnosis, respectively. Biological IMs were also independently associated with an increased risk of second-line treatment use of the same magnitude as adolescents (aHR = 1.95, 95% CI = 1.56–2.43, $p = 4.6 \times 10^{-9}$, adjusted for age at diagnosis, sex, and clinical IMs). Specifically,

biological IMs were associated with higher use of hydroxychloroquine but with lower use of splenectomy (Table S5). This result suggests that hydroxychloroquine allows avoiding subsequent splenectomy in patients with biological IMs (consisting mainly of patients with ANA). Of note, biological IMs were also nominally associated with grade ≥ 3 bleeding but did not reach the multiple-testing corrected statistical threshold.

Thus, biological IMs were an additional risk factor, independent of age group and sex, associated with a higher risk of SLE diagnosis and second-line treatment use.

3.6 | cITP risk groups and phenotypes

Based on the three risk factors identified, we resumed the risk groups and their outcomes for the OBS'CEREVANCE cohort in Figure 3A. Risk groups were defined based on risk factors previously identified as statistically significant. In a clinical setting, the combination of age group, sex, and biological IMs allows one to estimate the absolute risk for each outcome. For example, 93/144 (65%) of adolescents with biological IMs (a group with the highest risk) had received a second-line treatment while only 164/453 (36%) of children without biological IMs (a group with the lowest risk) had received one.

Combining the outcomes, we could define two antagonist cITP phenotypes, mild and severe cITP, that together included 426 of the 886 patients (46%) reported (Figure 3B). Mild cITP represented patients without grade ≥ 3 bleeding nor second-line treatment received. Mild cITP was more frequent in children than adolescents (aOR = 2.55, 95% CI = 1.83–3.59, $p = 4.4 \times 10^{-8}$) and was not affected by sex (aOR = 0.79, 95% CI = 0.59–1.06, $p = .11$). At the opposite, severe cITP represented patients with grade ≥ 3 bleeding and second-line treatment use (with or without biological IMs). Severe cITP was more frequent in adolescents than children (aOR = 2.4, 95% CI = 1.68–3.49, $p = 2.0 \times 10^{-6}$) and was not affected by sex (aOR = 1.34, 95% CI = 0.93–1.97, $p = .12$).

4 | DISCUSSION

We reported the comprehensive outcomes of a large prospective observational national cohort of patients with unselected pediatric cITP, including the first systematic description of IMs in this population. Our data extend the encouraging findings from cohorts with shorter follow-up as with 5901 patients-years follow-up,^{2,6,10} only 27% of patients experienced grade ≥ 3 bleeding, no patient experienced lethal hemorrhage, and 5 years after diagnosis, 40% of the patients still followed were in CR without any treatment. We showed that age at ITP diagnosis was a major determinant of several outcomes and that adolescents had more frequent unfavorable events such as grade ≥ 3 bleeding, associated IMs, SLE diagnosis, and second-line treatment use. Moreover, sex and biological IMs independently influenced several outcomes. Those data deciphered the heterogeneity of pediatric cITP and provided for the first time clinically relevant

risk factors for almost all the outcomes analyzed. Collectively, these results have several implications regarding (1) clinical heterogeneity of patients with cITP, (2) cITP clinical course, (3) underlying etiology, (4) clinical counseling and management, and (5) design of further clinical and translational studies.

Regarding clinical heterogeneity, our study prospectively quantified the IMs associated with cITP and suggests that, with sufficient follow-up, autoimmunity in cITP is broader than the sole autoimmune thrombocytopenia in 36% of patients. This number greatly varies according to age at diagnosis and sex. Biological IMs were more frequent (31% of patients) than clinical IMs (8%). SLE biomarkers (22% of patients), and specifically ANA positivity (21%), were by far the most frequent IM reported in this study. The other IMs were rarely diagnosed. By contrast, clinical and biological IMs occurred in 66% and 67% of the Evans syndrome patients of the same OBS'CEREVANCE cohort, respectively, and the most common biological IM was hypogammaglobulinemia (36% of patients).¹³ Of note, these absolute numbers are influenced by follow-up duration. Biological IMs in patients with cITP were associated with clinical IMs in only 20% of cases, whereas biological IMs were diagnosed in 76% of patients with clinical IM. This suggests that biological IMs of clinical relevance (ANA, hypogammaglobulinemia, thyroid auto-antibodies...) should be regularly searched in patients developing a clinical IM.

Regarding cITP clinical course, we could identify a clear cutoff for six of the seven outcomes investigated regarding age at ITP diagnosis, suggesting the effect of age is not linear. Moreover, age cutoffs were remarkably closed (ranging from 8 to 12 years), suggesting that a change in cITP pathophysiology occurs at these ages. This result is in line with previous studies that investigated the risk of chronicity in pediatric ITP and that reported an age cutoff ranging between 8 and 11 years.^{3-5,23} Our study suggests that older age at ITP diagnosis, in addition to increase the risk of evolution toward cITP, is also associated with cITP outcomes. Together, these studies highlight the different clinical courses of both acute and chronic ITP in children and adolescents. Dedicated biological investigations are warranted to investigate whether the pathogenesis of ITP differed across age groups.

Regarding underlying etiology, SLE absolute risk was low (4%). Biological IMs, including ANA, mostly occur without an underlying SLE diagnosis. However, SLE diagnosis risk greatly differs based on the three risk factors identified. As it was previously known in individuals without cITP,²⁴ female adolescents, particularly those with biological IMs, represent a population with a high risk of SLE.

An important finding of our study was the absence of PID diagnosis. Importantly, genetic tests for PID were performed in patients with suggestive clinical presentations at ITP diagnosis, and patients with a PID diagnosed at or before ITP onset were not included in the present study. Therefore, we cannot exclude the possibility that some patients had undiagnosed monogenic PID. Some PIDs can have variable expressivity and remain paucisymptomatic, such as shown in ALPS, CTLA4 haploinsufficiency, and LRBA deficiency.²⁵⁻²⁷ Comprehensive genetic studies are required to definitively conclude whether an underlying PID is present. However, our findings suggest that,

contrary to multilineage hematological autoimmunity,¹³ cITP in isolation rarely precedes PID diagnosis in the routine clinical setting.

Finally, no cases of malignancy were diagnosed in this study, whereas 3% of patients with pediatric-onset Evans syndrome from the same cohort developed a hematological malignancy.¹³

Regarding clinical counseling and management, our results provide data for several clinical questions in the care of patients with pediatric cITP. As both children and adolescents in our cohort had some favorable long-term outcomes and still have a chance of spontaneous recovery, therapeutic escalation should be reserved for patients with clinical severity and/or with impaired quality of life. Clearly, adolescents had a different cITP course than children, with more frequent unfavorable events, including grade ≥ 3 bleeding, associated IMs, SLE diagnosis, and second-line treatment use. Moreover, the female sex was independently associated with biological IMs and SLE diagnosis, and biological IMs were independently associated with SLE diagnosis and second-line treatment use. Our results suggest that patient management can be tailored based on these three risk factors. Adolescents should deserve closer clinical follow-up and more frequent biological IM monitoring. It is probably wise to monitor IMs every 3-6 months, especially for at-risk manifestations such as nephrological or neurological. As well, intensified education regarding bleeding risk and early recognition of clinical immunopathological symptoms is warranted in this population. In presence of biological IMs, 52% of children and 65% of adolescents had received a second line-treatment use. Thus, patients with biological IMs, regardless of age group, warrant more frequent follow-up regarding IMs, SLE, and second-line treatment. Inversely, complete work-up for underlying etiology in children, especially males, without severe bleeding nor biological IM, could probably be reduced to every one or 2 years.

Regarding the design of further clinical and translational studies, our data suggest that age at ITP diagnosis, sex, and IMs are three risk factors that warrant consideration in study design. These studies should consider, at least, stratifying the population or adjusting the results based on age at ITP diagnosis. Furthermore, adolescents being a subgroup of grade ≥ 3 bleeding and second-line treatment use, they represent a population of interest to target clinical trials, with a cut-off of more than 10 years old at initial diagnosis of ITP.

To our knowledge, this study represents the largest observational long-term cohort of patients with pediatric-onset cITP. However, it has several limitations. The long timespan (30 years), nationwide and real-life conditions may have led to some heterogeneity in practices. To limit this bias, the CEREVANCE group developed national guidelines in 2004, and specifically in 2009, 2017, 2021.²⁸ As well, individual case-by-case multidisciplinary and nationwide meetings are organized by the reference center, and national annual meetings allow the present harmonization of clinical care and therapeutic strategies. For this study, the coordinating research team prompted all centers to update follow-up data and gathered data from adult teams when the patient had reached adulthood. We acknowledge that the follow-up length was influenced by age at ITP diagnosis, IMs diagnosis, and second-line treatment use (Table S7). Specifically, patients with IMs

had longer follow-up duration than those without any IM. However, our results are supported by the large number of patients included and the magnitudes of the differences found. As well, we found more events in adolescents despite a shorter follow-up than in children.

In conclusion, our data highlight the need for multidisciplinary care, long-term follow-up, and transition to care by adult specialists for patients with pediatric cITP. Particular attention should be paid to female adolescents; these patients are more likely to require input from non-hematological specialists, such as gynecologists, rheumatologists, nephrologists, or clinical immunologists. The long-term course of adult patients with pediatric-onset cITP is currently unknown and is under investigation in the OBS'CERE-VANCE cohort.

AUTHOR CONTRIBUTIONS

T.P., H.F., G.L., T.L., and N.A. designed the study, analyzed the data, and drafted the paper. T.P. and H.F. performed the statistical analyses. M.P., W.A.C., S.H., M.F., S.D., C.T., N.G., V.B., E.J., S.B., P.C., N.C., C.G., C.P., J.L., F.M., V.L.-T.T., C.M., I.P., B.N., C.A.-A., L.C., C.P., J.B., C.P., J.-L. S., M.D., C.B., E.D., A.M.-C., T.L., G.L., and N.A. participated in patient recruitment, prospective data collection, data interpretation, and manuscript revision.

AFFILIATIONS

- ¹Centre de Référence National des Cytopenies Auto-immunes de l'Enfant (CEREVANCE), Bordeaux, France
- ²Division of Pediatric Hematology-Oncology, Charles-Bruneau Cancer Center, Department of Pediatrics, Sainte-Justine University Hospital, Université de Montréal, Montréal, Québec, Canada
- ³Pediatric Hemato-Immunology, CIC1401, INSERM CICP, Bordeaux University Hospital, Bordeaux, France
- ⁴Pediatric Oncology Immunology Hematology Unit, Children's University Hospital, Toulouse, France
- ⁵Department of Pediatric Hematology, Jeanne de Flandre Hospital, Lille University Hospital, Lille, France
- ⁶Sorbonne Université, AP-HP, Armand Trousseau University Hospital, Pediatric Hematology Oncology Unit, Paris, France
- ⁷Pediatric Hematology Unit, Robert-Debré University Hospital AP-HP, Paris, France
- ⁸Pediatric Hematology Unit, Nantes University Hospital, Nantes, France
- ⁹Institute of Pediatric Hematology and Oncology, Hospices Civils de Lyon, Lyon, France
- ¹⁰Department of Pediatric Hematology, La Timone Hospital, Marseille University Hospital, Marseille, France
- ¹¹Pediatric Oncology Hematology Unit, Arnaud de Villeneuve University Hospital, Montpellier, France
- ¹²Pediatric Hematology Unit, Rennes University Hospital, Rennes, France
- ¹³Department of Pediatric Hematology and Oncology, Children's University Hospital, Nancy, France
- ¹⁴Department of Pediatric Hematology-Oncology, Besançon University Hospital, Besançon, France

¹⁵Department of Pediatrics, Bicêtre University Hospital, AP-HP, Le Kremlin-Bicêtre, France

¹⁶Department of Pediatric Hematology and Oncology, Haute-pierre University Hospital, Strasbourg, France

¹⁷Department of Pediatric Hematology-Oncology, Clocheville Hospital, Tours University Hospital, Tours, France

¹⁸Department of Pediatric Hematology, Poitiers University Hospital, Poitiers, France

¹⁹Department of Pediatric Hematology/Oncology, Amiens University Hospital, Amiens, France

²⁰Pediatric Unit, Angers University Hospital, Angers, France

²¹Pediatric Hematology-Immunology and Rheumatology Department, Necker-Enfants Malades Hospital, AP-HP, Paris, France

²²Pediatric Hematology-Oncology Department, Grenoble University Hospital, Grenoble, France

²³Department of Pediatric Hematology, CHU de Brest, Brest, France

²⁴Pediatric Oncology Hematology Unit, Limoges University Hospital, Limoges, France

²⁵Department of Hematology-Oncology Pediatrics, Nice University Hospital, Nice, France

²⁶Pediatric Hematology-Oncology Unit, Institut Jean Godinot, Reims University Hospital, Reims, France

²⁷Department of Pediatric Oncology, North Hospital, University Hospital of Saint Etienne, Saint Etienne, France

²⁸Pediatric Oncology- Hematology Unit Department, Caen University Hospital, Caen, France

²⁹Department of Pediatrics, Dijon University Hospital, Dijon, France

³⁰Pediatric Unit, Clermont-Ferrand University Hospital, Clermont-Ferrand, France

³¹Department of Pediatric Hematology and Oncology, Rouen University Hospital, Rouen, France

ACKNOWLEDGMENTS

This work was supported (since 2004) by the French Ministry of Health (Programme Hospitalier de Recherche Clinique [PHRC] 2005, Rare Disease Plan 2007 and 2017), Association Bordelaise pour l'Avancement des Sciences Pédiatriques (ABASP) research charity, Association pour la Recherche et les Maladies Hématologiques de l'Enfant (RMHE) research charity, Association Française du Syndrome d'Evans (AFSE), and O-CYTO patients' association. It was also partially supported by GlaxoSmithKline, AMGEN, and Novartis. T.P. is a recipient of a Charles Bruneau fellowship award and merit scholarship program for foreign students of the Ministry of Education and Higher Education of Quebec. The authors thank the patients, their families, and the medical and paramedical teams involved in the CEREVANCE prospective cohort study since 2004. We also thank the following pediatricians and their teams who contributed patient data: Guy Leverger (APHP - Trousseau, $n = 164$), Nathalie Aladjidi (Bordeaux, $n = 121$), Thierry Leblanc (APHP - Robert Debré, $n = 65$), Marlène Pasquet (Toulouse, $n = 46$), Wadih Abou Chahla (Lille, $n = 45$), Caroline Thomas (Nantes, $n = 45$), Nathalie Garnier (Lyon, $n = 44$), Vincent Barlogis (Marseille, $n = 43$), Eric Jeziorski (Montpellier, $n = 43$), Sophie Bayart (Rennes, $n = 40$), Pascal Chastagner (Nancy, $n = 29$), Nathalie

Cheikh (Besançon, $n = 26$), Corinne Guitton (APHP - Bicêtre, $n = 24$), Catherine Paillard (Strasbourg, $n = 16$), Julien Lejeune (Tours, $n = 16$), Frédéric Millot (Poitiers, $n = 14$), Valérie Li-Thiao Te (Amiens, $n = 13$), Isabelle Pellier (Angers, $n = 13$), Bénédicte Neven (APHP - Necker, $n = 13$), Corinne Armari-Alla (Grenoble, $n = 12$), Liana Carausu (Brest, $n = 10$), Christophe Piguet (Limoges, $n = 8$), Joy Benadiba (Nice, $n = 7$), Claire Pluchart (Reims, $n = 7$), Jean-Louis Stephan (Saint Etienne, $n = 7$), Marianna Deparis (Caen, $n = 5$), Claire Briandet (Dijon, $n = 4$), Eric Doré (Clermont Ferrand, $n = 3$), and Aude Marie-Cardine (Rouen, $n = 3$).

FUNDING INFORMATION

This work was supported (since 2004) by the French Ministry of Health (Programme Hospitalier de Recherche Clinique [PHRC] 2005, Rare Disease Plan 2007 and 2017), Association Bordelaise pour l'Avancement des Sciences Pédiatriques (ABASP) research charity, Association pour la Recherche et les Maladies Hématologiques de l'Enfant (RMHE) research charity, Association Française du Syndrome d'Evans (AFSE), and O-CYTO patients' association. It was also partially supported by GlaxoSmithKline, AMGEN, and Novartis. T.P. is a recipient of a Charles Bruneau fellowship award and merit scholarship program for foreign students of the Ministry of Education and Higher Education of Quebec.

CONFLICT OF INTEREST STATEMENT

The authors have declared that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

Deidentified individual data along with data dictionary used for this study are available with publication on request to the corresponding authors upon a signed data access agreement.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all participants.

ORCID

Thomas Pincez  <https://orcid.org/0000-0002-9412-333X>

Sébastien Héritier  <https://orcid.org/0000-0003-0384-6370>

Stéphane Ducassou  <https://orcid.org/0000-0001-7736-0838>

REFERENCES

- Rodeghiero F, Stasi R, Gernsheimer T, 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(11):2386-2393.
- Schifferli A, Holbro A, Chitlur M, et al. A comparative prospective observational study of children and adults with immune thrombocytopenia: 2-year follow-up. *Am J Hematol*. 2018;93(6):751-759.
- Heitink-Pollé KMJ, Nijsten J, Boonacker CWB, de Haas M, Bruin MCA. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. *Blood*. 2014;124(22):3295-3307.
- Edslev PW, Rosthøj S, Treutiger I, et al. A clinical score predicting a brief and uneventful course of newly diagnosed idiopathic thrombocytopenic purpura in children. *Br J Haematol*. 2007;138(4):513-516.
- Revel-Vilk S, Yacobovich J, Frank S, et al. Age and duration of bleeding symptoms at diagnosis best predict resolution of childhood immune thrombocytopenia at 3, 6, and 12 months. *J Pediatr*. 2013;163(5):1335-1339.e2.
- Neunert CE, Buchanan GR, Imbach P, et al. Bleeding manifestations and management of children with persistent and chronic immune thrombocytopenia: data from the intercontinental cooperative ITP study group (ICIS). *Blood*. 2013;121(22):4457-4462.
- Flores A, Klaassen RJ, Buchanan GR, Neunert CE. Patterns and influences in health-related quality of life in children with immune thrombocytopenia: a study from the Dallas ITP cohort. *Pediatr Blood Cancer*. 2017;64(8):e26405.
- Grace RF, Klaassen RJ, Shimano KA, et al. Fatigue in children and adolescents with immune thrombocytopenia. *Br J Haematol*. 2020;191(1):98-106.
- Ducassou S, Gourdonneau A, Fernandes H, et al. Second-line treatment trends and long-term outcomes of 392 children with chronic immune thrombocytopenic purpura: the French experience over the past 25 years. *Br J Haematol*. 2020;189(5):931-942.
- Rosthøj S, Rajantie J, Treutiger I, et al. Duration and morbidity of chronic immune thrombocytopenic purpura in children: five-year follow-up of a Nordic cohort. *Acta Paediatr*. 2012;101(7):761-766.
- Bansal D, Bhamare TA, Trehan A, Ahluwalia J, Varma N, Marwaha RK. Outcome of chronic idiopathic thrombocytopenic purpura in children. *Pediatr Blood Cancer*. 2010;54(3):403-407.
- Hadjadj J, Aladjidi N, Fernandes H, et al. Pediatric Evans syndrome is associated with a high frequency of potentially damaging variants in immune genes. *Blood*. 2019;134(1):9-21.
- Pincez T, Fernandes H, Leblanc T, et al. Long term follow-up of pediatric-onset Evans syndrome: broad immunopathological manifestations and high treatment burden. *Haematologica*. 2022;107(2):457-466.
- Grace RF, Lambert MP. An update on pediatric immune thrombocytopenia (ITP): differentiating primary ITP, IPD, and PID. *Blood*. 2022;140(6):542-555.
- Saettini F, Cattoni A, Redaelli M, et al. Primary immunodeficiencies, autoimmune hyperthyroidism, coeliac disease and systemic lupus erythematosus in childhood immune thrombocytopenia. *Acta Paediatr*. 2021;110(2):643-651.
- Hazzan R, Mukamel M, Yacobovich J, Yaniv I, Tamary H. Risk factors for future development of systemic lupus erythematosus in children with idiopathic thrombocytopenic purpura. *Pediatr Blood Cancer*. 2006;47(S5):657-659.
- Pincez T, Aladjidi N, Heritier S, et al. Determinants of long-term outcomes of splenectomy in pediatric autoimmune cytopenias. *Blood*. 2022;140(3):253-261.
- Buchanan GR, Adix L. Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. *J Pediatr*. 2002;141(5):683-688.
- Petri M, Orbai A-M, Alarcón GS, et al. Derivation and validation of systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64(8):2677-2686.
- Bousfiha A, Moundir A, Tangye SG, et al. The 2022 update of IUIS phenotypical classification for human inborn errors of immunity. *J Clin Immunol*. 2022;42(7):1508-1520.
- Oliveira JB, Bleesing JJ, Dianzani U, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH international workshop. *Blood*. 2010;116(14):e35-e40.
- World Health Organization. Adolescent health. 2022 <https://www.who.int/health-topics/adolescent-health>
- Bennett CM, Neunert C, Grace RF, et al. Predictors of remission in children with newly diagnosed immune thrombocytopenia: data from the intercontinental cooperative ITP study group registry II participants. *Pediatr Blood Cancer*. 2018;65(1):e26736.
- Watson L, Leone V, Pilkington C, et al. Disease activity, severity, and damage in the UK juvenile-onset systemic lupus erythematosus cohort. *Arthritis Rheum*. 2012;64(7):2356-2365.

25. Neven B, Magerus-Chatinet A, Florkin B, et al. A survey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. *Blood*. 2011;118(18):4798-4807.
26. Hoshino A, Toyofuku E, Mitsui N, et al. Clinical courses of IKAROS and CTLA4 deficiencies: a systematic literature review and retrospective longitudinal study. *Front Immunol*. 2022;12:784901.
27. Jamee M, Hosseinzadeh S, Sharifinejad N, et al. Comprehensive comparison between 222 CTLA-4 haploinsufficiency and 212 LRBA deficiency patients: a systematic review. *Clin Exp Immunol*. 2021;205(1):28-43.
28. Haute Autorité de santé. Protocole national de diagnostic et de soins. Purpura thrombopénique immunologique de l'enfant et de l'adulte. 2022 https://www.has-sante.fr/upload/docs/application/pdf/2017-06/dir36/pnds-_purpura_thrombopenique_immunologique.pdf

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pincez T, Fernandes H, Pasquet M, et al. Impact of age at diagnosis, sex, and immunopathological manifestations in 886 patients with pediatric chronic immune thrombocytopenia. *Am J Hematol*. 2023;98(6):857-868. doi:10.1002/ajh.26900