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RESEARCH ARTICLE

Pediatric refractory chronic immune thrombocytopenia: Identification, patients' characteristics, and outcome

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Abstract

Refractory chronic immune thrombocytopenia (r-cITP) is one of the most challenging situations in chronic immune thrombocytopenia (cITP). Pediatric r-cITP is inconsistently defined in literature, contributing to the scarcity of data. Moreover, no evidence is available to guide the choice of treatment. We compared seven definitions of r-cITP including five pediatric definitions in 886 patients with cITP (median [min-max] follow-up 5.3 [1.0–29.3] years). The pediatric definitions identified overlapping groups of various sizes (4%–20%) but with similar characteristics (higher proportion of immunopathological manifestations [IM] and systemic lupus erythematosus [SLE]), suggesting that they adequately captured the population of interest. Based on the 79 patients with r-cITP (median follow-up 3.1 [0–18.2] years) according to the CEREVANCE definition (≥ 3 second-line treatments), we showed that r-cITP occurred at a rate of 1.15% new patients per year and did not plateau over time. In multivariate analysis, older age was associated with r-cITP. One patient (1%) experienced two grade five bleeding events after meeting r-cITP criteria and while not receiving second-line treatment. The cumulative incidence of continuous complete remission (CCR) at 2 years after r-cITP diagnosis was 9%. In this analysis, splenectomy was associated with a higher cumulative incidence

Thomas Pincez and Helder Fernandes contributed equally as first authors.

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Pédiatriques (ABASP); Association pour la Recherche et les Maladies Hématologiques de l'Enfant (RMHE); Association Française du Syndrome d'Evans (AFSE); O-CYTO Patients' Association; GlaxoSmithKline; AMGEN; Novartis

of CCR (hazard ratio: 5.43, 95% confidence interval: 1.48–19.84, $p = 7.8 \times 10^{-4}$). In sum, children with cITP may be diagnosed with r-cITP at any time point of the follow-up and are at increased risk of IM and SLE. Second-line treatments seem to be effective for preventing grade 5 bleeding. Splenectomy may be considered to achieve CCR.

1 | INTRODUCTION

In children and adolescents, immune thrombocytopenia (ITP) frequently evolves toward spontaneous resolution, but it persists for >12 months in ~20% of cases, defined as chronic ITP (cITP).¹ cITP still has a high chance of spontaneous remission with a rate of almost 75% at 5 years.^{2–4} Around 55% of children with cITP will require second-line therapies (i.e., treatments other than corticosteroids or immunoglobulins),⁵ because of severe or repeated bleeding, severe thrombocytopenia, or alteration of quality of life.⁶ The most frequently used second-line treatments, thrombopoietin receptor agonists (TPO-RA) and rituximab, have response rates of >60% and ~60%, respectively.^{7–11} Therefore, a subset of patients with cITP require several second-line treatments and have a prolonged bleeding risk in addition to impaired quality of life and fatigue.^{12,13}

The identification of these high-risk children with refractory cITP (r-cITP) is critical both in clinical practice to improve management and in research to design specific clinical and biological studies. However, there is no consensual definition of r-cITP in pediatrics and a recent review highlighted the inconsistency of the definitions used in the literature.¹⁴ The historical definition used in adults (splenectomy failure with persistent severe ITP or bleeding risk requiring treatment)^{15,16} is too restrictive in pediatrics as splenectomy is rarely used given the possibility of spontaneous remission and the lifelong risk associated with asplenia.^{3,17–19} Therefore, the Intercontinental ITP Study (ICIS) group and the pediatric ITP Consortium of North America (ICON) have recently identified a critical need to harmonize the definition of r-cITP in children.¹⁴ One major limitation to eventually achieving a specific definition of r-cITP is that the different definitions have not been directly compared in the same cohort to assess the characteristics of the patients that are identified.

Another major challenge in pediatric r-cITP is that long-term data analysis on risk factors, frequency of underlying diagnoses, outcomes, and optimal therapeutic management are lacking.²⁰ The bleeding risk of these patients is unknown and whether some patients still achieve continuous complete remission (CCR) has not been investigated. Moreover, this category of patients represents the most difficult type of cITP to treat but no evidence is available to favor any second-line therapy over another.²¹

Based on a large prospective national cohort of pediatric cITP, we pragmatically compared several definitions of r-cITP to identify the best definition. We then investigated the risk factors, outcomes, and efficacies of second-line treatments based on the r-cITP definition retained. Finally, we investigated a previously published adult definition of multirefractory cITP.

2 | METHODS

2.1 | Population

OBS'CEREVANCE is a prospective cohort that began in 2004 and includes French patients with cITP diagnosed before 18 years of age (registered at www.clinicaltrials.gov as #NCT05937828).⁵ The inclusion and exclusion criteria for the cohort are presented in Table S1. Written informed consent was provided by all participants. The cohort was validated by the French National Data Protection Authority (CNIL, V2.0 10/03/2022) and the appropriate ethics committee.

We included in this study all patients in the cohort with cITP, defined as ITP lasting >12 months,¹⁵ without systemic lupus erythematosus (SLE) or primary immunodeficiency (PID) known at initial ITP diagnosis. We have also excluded patients with ITP secondary to transplantation and those who developed Evans syndrome during follow-up. Patients with SLE or PID diagnosed during follow-up were not excluded from the analyses. We have previously reported the characteristics of these patients.²² Data collection was completed on January 15, 2022.

2.2 | Definitions

We analyzed a total of seven definitions for r-cITP and one for multirefractory cITP. We analyzed three main definitions proposed for pediatric r-cITP: the recently proposed definitions of the ICIS,²⁰ the definition published in an adolescent/young adults (AYAS) cohort,²³ and the definition proposed by the Centre de Référence des Cytopénies Auto Immunes de l'Enfant (CEREVANCE) at the 2022 ICIS meeting (Table 1). We also analyzed modified CEREVANCE and ICIS definitions derived from the main definitions described. In addition, we analyzed three definitions used in adults: the International Working Group (IWG) definition,¹⁵ the recently proposed Cytopénies Auto-immunes: Registre Midi-Pyrénées (CARMEN) definition,²⁴ and the previously published Centre de Référence des Cytopénies Auto-immunes de l'adulte (CERECAL) definition of multirefractory cITP.²⁰ We separately analyzed this last definition for multirefractory ITP, which includes failure to respond to splenectomy, to investigate whether this subgroup of patients have specific characteristics. Of note, all the definitions examined considered the total number of treatments regardless of whether they were given simultaneously or successively. The CEREVANCE practice is to use second-line treatments as successive monotherapies rather than simultaneously.

We assessed bleeding severity (grade) using the Buchanan score.²⁵ We categorized hematological status as follows: non-remission (NR, platelet count $<30 \times 10^9/L$, with or without treatment), partial remission

TABLE 1 Definitions of refractory chronic immune thrombocytopenia investigated in this study.

Definition (year of proposal)	Criteria	Ref
Pediatric definitions		
ICIS (2023)	Failure to respond to ≥ 2 second-line therapies from different categories of treatment modality (i.e., immunomodulatory therapies directed against B cells or T cells, and/or TPO-RA; introduction of a new second-line treatment considered as a failure in this study)	20
ICIS modified (2023)	Same criteria as the ICIS definition but with anti-CD20 therapies as a category distinct from the other immunosuppressive drugs	
AYAS (2023)	≥ 3 different lines of therapy given that two different first-line treatments (e.g., corticosteroids and IVIG) were considered as only one line of therapy	23
CEREVANCE (2022)	Administration of ≥ 3 second-line treatments considering the nine main second-line treatments (eltrombopag, romiplostim, rituximab, cyclosporine, sirolimus, azathioprine, mycophenolate mofetil, hydroxychloroquine, and splenectomy)	
CEREVANCE modified (2023)	≥ 4 second-line treatments considering the nine main second-line treatments as described in the CEREVANCE definition	
Adult definitions		
Carmen (2022)	Introduction of a new second-line treatment after eltrombopag and romiplostim (the two TPO-RA licensed for use in France)	24
CERECAL (2016)	cITP symptomatic and in NR after splenectomy, rituximab, eltrombopag, and romiplostim	26
IWG (2009)	Failure to respond to splenectomy (introduction of a new second-line treatment considered as a failure in this study)	15

Abbreviations: AYAS, Adolescent Young Adults; CARMEN, Cytopénies Auto-immunes: Registre Midi-Pyréenne; CERECAL, Centre de Référence des Cytopénies Auto-immunes de l'adulte; CEREVANCE, Centre de Référence des Cytopénies Auto-Immunes de l'Enfant; cITP, chronic immune thrombocytopenia; ICIS, Intercontinental ITP Study; IVIG, intravenous immunoglobulins; IWG, International Working Group; Ref, reference.

(PR, platelet count $\geq 30 \times 10^9/L$, with or without treatment), complete remission (platelet count $\geq 100 \times 10^9/L$, with or without treatment), and continuous complete remission (CCR, platelet count $\geq 100 \times 10^9/L$ without treatment for >12 months).¹⁵ The definitions of immunopathological manifestations (IM, clinical, and biological), SLE, and PID are described in Table S1. For the 79 refractory patients according to the CEREVANCE definition, we individually confirmed that the indication for the second-line treatments received was cITP and not an associated clinical IM.

2.3 | Statistical analysis

We used the nonparametric Wilcoxon–Mann–Whitney test and Fisher's exact test for comparison of continuous and categorical variables, respectively.

We used forward selection to analyze the factors associated with r-cITP diagnosis. We fitted univariate Cox proportional hazard regression models for sex, age at ITP diagnosis, IM diagnosed before development of refractoriness, bleeding grade at diagnosis, and platelet count at diagnosis. We then fitted a multivariate model with all covariates having p -value $< .35$ in univariate analysis.

We used the Kaplan–Meier method to calculate the cumulative incidences and the log-rank test to compare the cumulative incidence curves. We also fitted a linear regression model to analyze the cumulative incidence of r-cITP.

We used RStudio (version 2023.03.1 + 446; R version 4.1.3, R Development Core Team) and Prism (version 10.1; GraphPad

Software Inc., San Diego, CA) software for statistical analyses. We considered a p -value $< .05$ as statistically significant and all tests were two-sided.

3 | RESULTS

3.1 | Population

We included 886 patients with cITP (388 females, 498 males) from 29 centers (Table S2). Patients had a median age of 7.3 (0.03–17.86) years at ITP diagnosis and a median follow-up duration of 5.3 (1.0–29.3) years. A total of 225 (25%) were adults (>18 years old) at the last follow-up. In total, 237 patients (27%) experienced grade ≥ 3 bleeding, 21 (2%) experienced grade ≥ 4 bleeding, and seven (1%) experienced grade 5 bleeding at any time point during follow-up. At the last follow-up, 23.3% of patients were in CCR and 16.5% were in NR.

3.2 | Comparison of refractory chronic immune thrombocytopenia definitions

We compared the AYAS, CEREVANCE, and ICIS definitions of pediatric r-cITP, as outlined in the Methods section. These definitions accounted for 179 (20%), 79 (9%), and 37 (4%) patients in our cohort, respectively (Table 2). There was no patient identified by a more stringent definition that was not included in a broader definition: all patients

TABLE 2 Characteristics of refractory patients according to the three main pediatric definitions.

Definition Category	AYAS		CEREVANCE		ICIS		p-value
	Refractory	Non-refractory	Refractory	Non-refractory	Refractory	Non-refractory	
Number (%)	179 (20.2)	707 (79.8)	79 (8.9)	807 (91.1)	37 (4.2)	849 (95.8)	
Sex ratio, F/M (ratio)	99/80 (1.2)	399/308 (1.3)	45/34 (1.3)	453/354 (1.3)	20/17 (1.2)	478/371 (1.3)	.87
Age at diagnosis, median (min-max), years	7.8 (0.4–15.6)	7.0 (0.0–17.6)	8.3 (0.7–15.2)	7.1 (0.0–17.6)	10.1 (1.0–15.2)	7.1 (0.0–17.6)	.017
Presentation at ITP diagnosis							
Bleeding grade, median (min-max)	2 (0–5)	2 (0–5)	2 (0–5)	2 (0–5)	2 (0–5)	2 (0–5)	.008
Platelet count, median (min-max), 10 ⁹ /L	8 (1–80)	11 (1–97)	8 (1–80)	11 (1–97)	9 (1–56)	11 (1–97)	.04
Follow-up, median (min-max), years	6.8 (1.0–29.3)	5.1 (1.0–27.2)	7.8 (1.0–25.2)	5.2 (1.0–29.3)	8.8 (2.2–25.2)	5.3 (1.0–29.3)	4.9E-04
Age at last follow-up, median (min-max), years	15.9 (4.4–35.3)	14.2 (1.3–34.9)	16.8 (5.6–35.3)	14.5 (1.3–34.9)	17.9 (7.0–35.3)	14.5 (1.3–34.9)	1.67E-05
Underlying diagnosis							
Primary (i.e., no IM), n (%)	92 (51.4)	472 (66.8)	36 (46.6)	528 (65.4)	15 (40.5)	549 (64.7)	.005
IM (clinical or biological), n (%)	87 (48.6)	235 (33.2)	43 (53.4)	279 (34.6)	22 (59.5)	300 (35.3)	.005
Clinical IM, n (%)	33 (18.4)	67 (9.5)	19 (24.1)	81 (10.0)	6 (16.2)	94 (11.1)	.30
Biological IM, n (%)	77 (43.0)	205 (29.0)	39 (49.4)	243 (30.1)	22 (59.5)	260 (30.6)	4.5E-04
SLE, n (%)	14 (7.8)	24 (3.4)	8 (10.1)	30 (3.7)	2 (5.4)	36 (4.2)	.67
Bleeding at any time point during follow-up							
Grade ≥3, n (%)	75 (41.9)	162 (22.9)	39 (49.4)	198 (24.5)	22 (59.5)	215 (25.3)	2.62E-05
Grade ≥4, n (%)	14 (7.8)	7 (1.0)	10 (12.7)	11 (1.2)	4 (10.8)	17 (2.0)	.009
Grade = 5, n (%)	6 (3.4)	1 (0.1)	5 (6.3)	2 (0.2)	2 (5.4)	5 (0.6)	.03
Hematological status ^a							
CCR at 5 years of follow-up, n/n total (%)	24/112 (21.4)	165/362 (45.6)	7/49 (14.3)	182/425 (42.8)	2/24 (8.3)	187/450 (41.5)	9.1E-04
CCR at last follow-up, n/n total (%)	41/176 (23.0)	156/670 (23.2)	13/78 (16.7)	184/768 (24.0)	8/37 (21.6)	189/809 (23.4)	1
NR at last follow-up, n/n total (%)	35/175 (20.0)	104/655 (15.9)	21/77 (27.3)	118/753 (15.7)	9/36 (25.0)	130/794 (16.4)	.17

Abbreviations: CCR, continuous complete remission; IM, immunopathological manifestations; NR, no remission; SLE, systemic lupus erythematosus.

^aDenominator includes only patients for whom data were available.

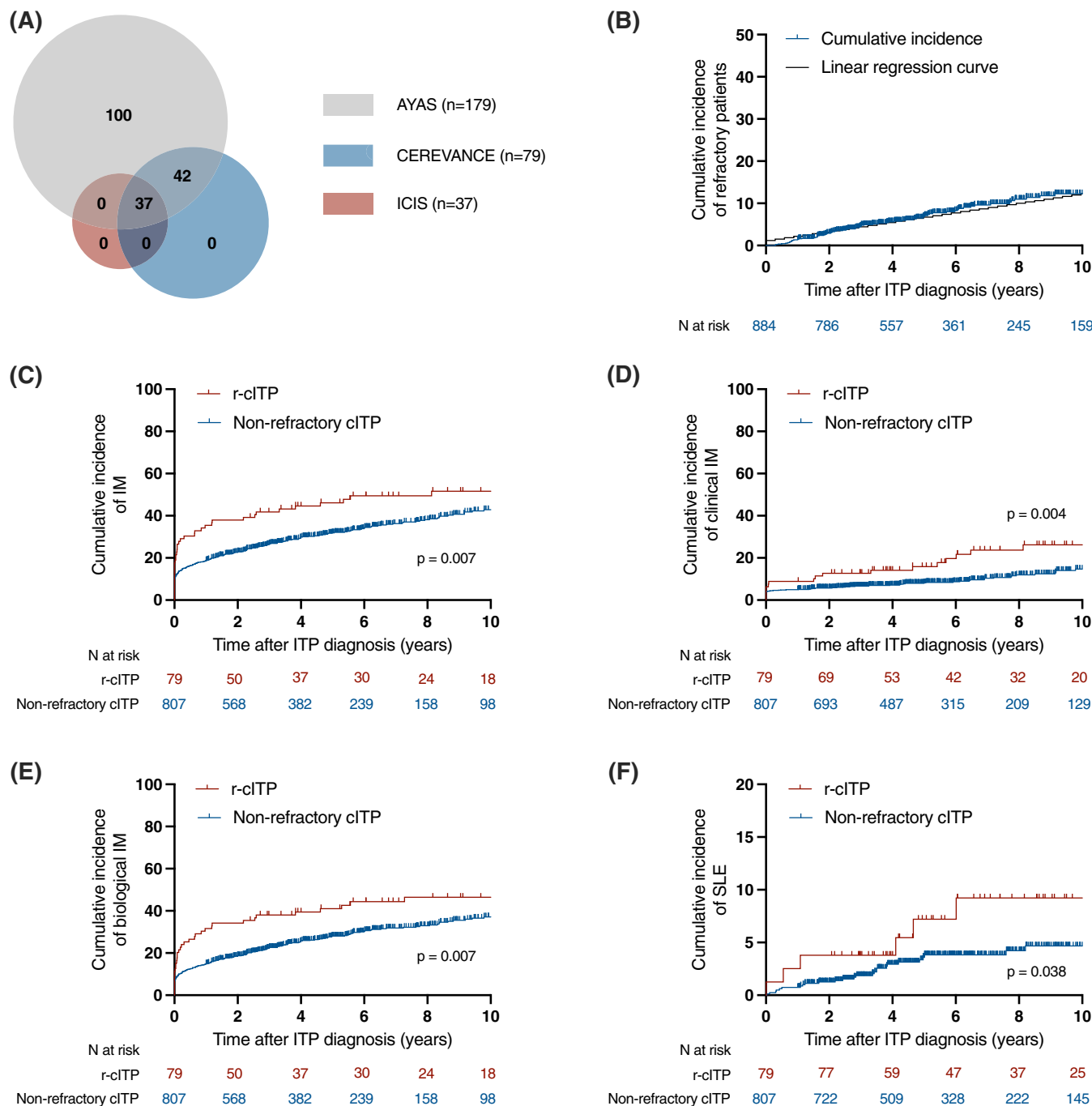


FIGURE 1 Epidemiology of patients with refractory chronic immune thrombocytopenia (r-cITP). (A) Venn diagram of the three main pediatric definitions included in the study. The circle sizes are proportional to the number of patients with r-cITP according to each definition. (B) Cumulative incidence of patients with r-cITP using the CEREVANCE definition. The dates at which refractoriness criteria were met were available for only 77 of the 79 patients with r-cITP. Linear regression formula: $y = 1.115X + 1.190$. (C) Cumulative incidences of immunopathological manifestations (IM, clinical or biological) in patients with and without r-cITP according to the CEREVANCE definition. The median times to IM diagnosis were 8 and 14 years, respectively. (D) Cumulative incidences of clinical IM in patients with and without r-cITP according to the CEREVANCE definition. (E) Cumulative incidences of biological IM in patients with and without r-cITP according to the CEREVANCE definition. The median times to biological IM diagnosis were 12 and 19 years, respectively. (F) Cumulative incidences of systemic lupus erythematosus (SLE) in patients with and without r-cITP according to the CEREVANCE definition. N, number; ITP, immune thrombocytopenia. [Color figure can be viewed at wileyonlinelibrary.com]

included in the ICIS definition were included in the CEREVANCE definition and all patients included in the CEREVANCE definition were included in the AYAS definition (Figure 1A). Those three definitions

effectively identified patients with more frequent severe (grade ≥ 3) bleeding at any time point of follow-up than non-refractory patients ($p < 2.6 \times 10^{-5}$, Table 2). The other characteristics of the refractory

population were also similar for the three subgroups with a higher proportion of patients with IM ($p < .005$) and a lower proportion of patients in CCR at 5 years of follow-up ($p < 9.4 \times 10^{-4}$) for all three definitions. The AYAS and CEREVANCE definitions also identified a higher proportion of patients with SLE in the refractory group ($p \leq .015$). The more stringent modified CEREVANCE definition identified 4% of patients classified as refractory, and these patients had similar characteristics than those identified by the other definitions (Table S3). The modified ICIS identified 7% of patients as refractory, and these patients were similar to those identified by the CEREVANCE definition with an overlap of 80% (Figure S1A and Table S3).

We then analyzed the definitions proposed for adults with cITP. Using the recent CARMEN definition that did not consider splenectomy,²⁴ we identified only 14 patients (1.6%) in our cohort (Table S3). Apart from more frequent grade ≥ 3 and grade ≥ 4 bleeding events, the patients identified with this definition did not present characteristics different from those with non-refractory cITP. Finally, we examined whether using the historical definition of r-cITP (refractory to splenectomy) identified a population with similar characteristics as the other initially assessed definitions. The 29 patients (3%) meeting these criteria had partially similar characteristics as they had higher prevalence rates of grade ≥ 4 bleeding and clinical IM ($p < .04$) but were not different regarding grade ≥ 3 bleeding or overall IM (Table S3).

3.3 | Incidence and predictive factors of r-cITP according to the CEREVANCE definition

We retained the CEREVANCE definition for the remainder of the study because of the clinically adequate intermediate size of the population selected and its flexibility to the type of second-line treatments received (see Discussion for details) and we also performed several analyses with the ICIS definition.

The 79 patients with r-cITP according to the CEREVANCE definition had a median age of 8.3 (0.7–15.2) years at ITP diagnosis (Table 2). The most frequently received second-line treatment before meeting the r-cITP criteria were rituximab ($n = 31$ [39%]) and azathioprine ($n = 28$ [35%], Table S4).

The patients met the CEREVANCE r-cITP definition a median of 3.0 (0.3–20.0) years after ITP diagnosis. Twelve patients (15%) met the r-cITP definition within 1 year of ITP diagnosis. The median age at r-cITP diagnosis was 12.9 (3.3–31.2) years and 11 (14%) were adults. The cumulative incidence of r-cITP steadily increased almost linearly with time (Figure 1B). With each additional year after ITP diagnosis, 1.15% (95% confidence interval [CI]: 1.104–1.126) more patients fulfilled the r-cITP criteria. At 1, 5, and 10 years after ITP diagnosis, 1%, 7%, and 12% of patients had r-cITP, respectively. We found the same pattern using the ICIS definition (Figure S1B).

We used Cox regression to analyze the factors associated with refractoriness to consider longer follow-up of patients with r-cITP compared to the rest of the cohort (7.8 [1.0–25.2] vs. 5.2 [1.0–29.3] years, respectively, $p = 8.4 \times 10^{-5}$). In both univariate and multivariate analyses, older age at diagnosis was the only factor associated with r-cITP

occurrence (hazard ratio [HR]: 1.08 per year, 95% CI: 1.01–1.15, $p = .026$, adjusted for bleeding grade and platelet count at diagnosis, Table S5). Patients with r-cITP also received the first second-line treatment earlier than patients without r-cITP who received only 1 or 2 second-line treatments (0.85 [0.0–8.8] vs. 1.42 [0.0–16.8] years after ITP diagnosis, respectively, $p = .003$).

3.4 | Immunopathological manifestations and underlying diagnosis

The 79 r-cITP patients had a median follow-up of 3.2 (0–18.2) years after meeting the criteria for refractoriness. At the end of follow-up, 43 patients (53.4%) had a diagnosis of an associated IM, eight patients (10.1%) had a diagnosis of SLE, and none had a diagnosis of PID. Two patients who underwent genetic analyses and met multirefractoriness criteria are described below.

The cumulative incidence of IM was higher in patients with r-cITP than others (HR: 1.56, 95% CI: 1.13–2.16, $p = .007$). The cumulative incidences of IM at 5 years after ITP diagnosis in patients with and without r-cITP were 46% and 32%, respectively (Figure 1C). An increased risk was found for both clinical IM (HR: 2.10, 95% CI: 1.27–3.47, $p = .004$, Figure 1D) and biological IM (HR: 1.59, 95% CI: 1.14–2.24, $p = .007$, Figure 1E). We found the same trend for higher incidence of IM using the ICIS definition, but the association was statistically nonsignificant ($p = .05$, Figure S2A).

The cumulative incidence of SLE was higher in patients with r-cITP than others (HR: 2.49, 95% CI: 1.05–5.02, $p = .038$). The cumulative incidences of SLE at 5 years after ITP diagnosis in patients with and without r-cITP were 7% and 3% (Figure 1F). We also found the association using the ICIS definition ($p = .01$, Figure S2B).

3.5 | Outcomes of refractory patients

No patients died and only one patient (1%) experienced grade 5 bleeding after the diagnosis of r-cITP (intracerebral hemorrhages 4.7 and 6.8 years after meeting the r-cITP criteria). This patient had no ongoing second-line treatment at the time of grade 5 bleeding events and had not undergone splenectomy. We found no difference in the rate of grade 5 bleeding between refractory and non-refractory patients (1/79 [1.3%] vs. 6/807 [0.7%], respectively, $p = .48$).

The median total number of second-line treatments received by r-cITP patients was four (3–14). We investigated the joint failure to treatments for the four main second-line treatments received (TPO-RA, splenectomy, azathioprine, and rituximab). Despite all patients had a failure to at least two second-line treatments as per r-cITP definition, we found that only two (3%) failed to respond to both splenectomy and TPO-RA (Figure S3). The hematological status at the end of follow-up was NR, PR, CR, and CCR in 21 (27%), 16 (21%), 27 (35%), and 13 (17%) patients, respectively (CCR status and detailed hematological status available for 78 and 77 patients, respectively).

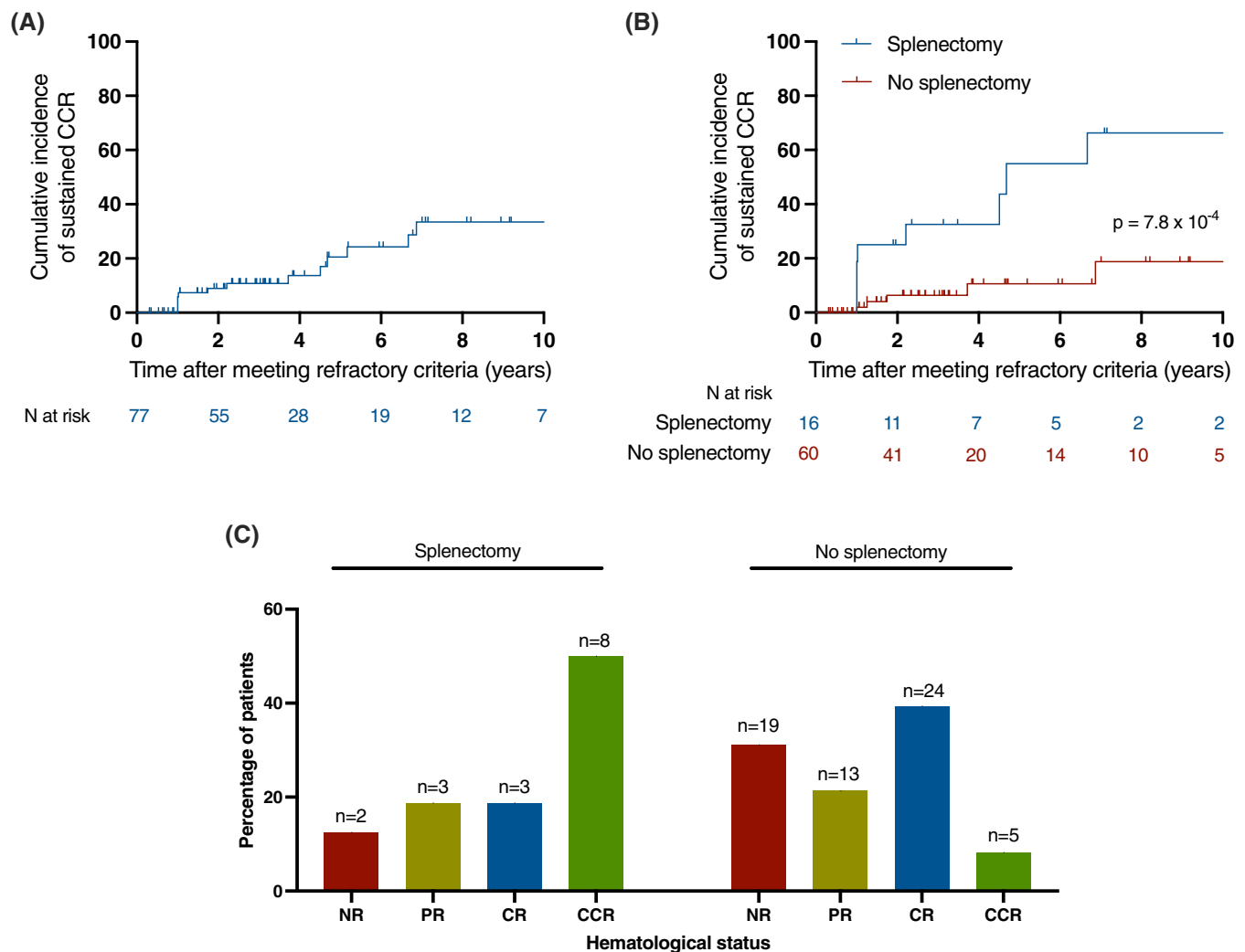


FIGURE 2 Outcomes of patients with refractory chronic immune thrombocytopenia (r-cITP). (A) Cumulative incidence of sustained continuous complete remission (CCR) in patients with r-cITP according to the CEREVANCE definition. (B) Comparison of cumulative incidences of sustained CCR in patients with r-cITP who did or did not undergo splenectomy (log-rank test). Sufficient data were available for the curves shown in A and B (dates at which refractoriness criteria were met and CCR status) for only 76 of the 79 patients with r-cITP. (C) Hematological status in patients with r-cITP who did or did not undergo splenectomy. Sufficient data were available for only 77 of the 79 patients. CR, complete remission; N, number; NR, no remission; PR, partial remission. [Color figure can be viewed at wileyonlinelibrary.com]

The cumulative incidences of CCR at 2 and 5 years after r-cITP diagnosis were 9% and 21%, respectively (Figure 2A). The patients in CCR at the last follow-up had a lower rate of clinical IM compared to the other groups, while there were no statistically significant differences in other characteristics (Table S6). The numbers of patients in CCR at last follow-up among those with and without clinical IM were 0/19 (0%) and 13/59 (22%, $p = .03$), respectively. The patients in CCR at the last follow-up had not received more second-line treatments than the others (3 [3–5] vs. 3 [3–8], respectively, $p = .35$) but had higher rate of splenectomy and lower rates of receiving TPO-RA and immunosuppressive drugs other than rituximab (Table S6). To consider the longer follow-up duration after meeting the refractoriness criteria of patients in CCR compared to the others (5.5 [1.7–18.2] vs. 3.0 [0–14.8] years, respectively, $p = .02$), we analyzed the effects of splenectomy on the cumulative incidence of sustained CCR (i.e., CCR persisting until the last follow-

up). Splenectomy was associated with a 5-fold increase in the cumulative incidence of sustained CCR (HR: 5.43, 95% CI 1.48–19.84, $p = 7.8 \times 10^{-4}$, Figure 2B). The numbers of patients in CCR at the last follow-up among those who did or did not undergo a splenectomy after r-cITP diagnosis were 8/16 (50%) and 5/62 (8%), respectively ($p = 4.1 \times 10^{-4}$, Figure 2C). This difference was still present after excluding patients who underwent splenectomy before having met the refractoriness criteria (8/16 [50%] vs. 2/46 [4%], respectively, $p = 1.3 \times 10^{-4}$). The refractory patients who underwent splenectomy were not older than the others (age at r-cITP diagnosis: 11.9 [3.3–17.7] vs. 13.1 [3.6–31.2] years, respectively, $p = .40$). No severe or recurrent bacterial infections were documented in these patients with a median follow-up of 4.6 (0.1–18.1) years after splenectomy. We found the same trend for higher incidence of CCR in patients who underwent splenectomy using the ICIS definition, but the association was statistically nonsignificant ($p = .07$, Figure S4).

Finally, we did not identify any characteristics associated with NR status at the last follow-up (Table S6). Patients in NR at the last follow-up had higher rate of receiving TPO-RA than the others, with no statistically significant difference in the total number of second-line treatments received (4 [3–8] vs. 3 [3–8], $p = .16$). The numbers of patients in NR at last follow-up among those who did and did not receive TPO-RA were 18/44 (41%) and 3/33 (9%), respectively ($p = .002$). We found no statistically significant differences regarding the other second-line treatments.

3.6 | Multirefractory patients

We identified five patients (0.6%) who fulfilled the multirefractoriness criteria. The median time to multirefractory diagnosis was 5.7 (3.7–23.0) years after ITP diagnosis (Table S7).²⁶ All had grade 3 bleeding during cITP course and two experienced frequent grade 4 bleeding events. With a median follow-up of 2.2 (0.2–5.0) years after meeting multirefractoriness criteria, they had received a median total of six (6–8) second-line treatments. At the end of follow-up, two patients were in NR, two in PR, and one in CR.

Two of those patients underwent genetic analyses to search for inherited thrombocytopenia. One patient was found to have a heterozygous pathogenic variant in *TUBB1* and the other had a heterozygous variant of unknown significance in *SLFN14*.

4 | DISCUSSION

Based on a large prospective pediatric cITP cohort, we showed that while the characteristics of patients identified with the different r-cITP definitions were similar, the size of the refractory population selected differed. Using the CEREVANCE definition, we showed a persistent and stable risk for r-cITP diagnosis throughout follow-up and identified older age at ITP diagnosis as a risk factor. Long-term follow-up of r-cITP patients showed a higher cumulative incidence of patients with IM and SLE diagnoses. The patients experienced an important treatment burden but only one patient experienced grade 5 bleeding. We showed that the treatments used had a major impact on hematological status and that resolution of r-cITP was still possible, but almost exclusively after splenectomy.

The term “refractory ITP” encompasses two distinct clinical situations as specified in the recent ICIS proposal: newly diagnosed refractory ITP and chronic refractory ITP.²⁰ As the patients included in the first category (defined as no response to ≥ 2 first-line treatments) may evolve or not toward cITP and r-cITP, the group of patients identified according to the two definitions may not overlap. Recently, we showed that newly diagnosed refractory ITP was rare within the CEREVANCE network,²⁷ and in the present study, only 15% of patients with r-cITP met the refractoriness criteria within 1 year after ITP diagnosis. Therefore, newly diagnosed refractory ITP and r-cITP seem to correspond to different groups of patients, suggesting differences in their underlying pathophysiology.

The definition of r-cITP should adequately identify the subset of patients with a more severe clinical course while avoiding too broad or too stringent inclusion criteria. A too broad definition would unwarrantedly include patients who would not benefit from being considered as refractory, whereas a too stringent definition would miss some patients who would require specific attention and care. Our study suggests that pediatric r-cITP and multirefractory cITP likely represents a continuum with non-refractory cITP rather than a completely distinct subgroup. Indeed, the several definitions analyzed were enriched for patients with similar characteristics. This suggests that these various definitions adequately captured the subgroup of interest and has important implications for the design of further biological and clinical studies. Using a broader definition would require a larger sample size to confer sufficient power, whereas a more stringent definition may be adequate for smaller, targeted studies. Therefore, the choice of a specific definition is based on finding the optimal balance between a too broad and a too stringent definition and may depend on the context and cohort studied. It is important to mention that all the definitions of r-cITP proposed are based on the number of treatments received, which is not always synonymous of severe bleeding. In our cohort, despite severe (grade ≥ 3) bleeding were more frequent in refractory than non-refractory patients, 40% to 58% of patients with r-cITP (depending on the definition) did not experience any severe bleeding. Of note, all patients in our study with r-cITP had received first-line treatment but the diagnosis of r-cITP should be considered with caution in patients that did not receive any first-line treatment because of a contraindication. Moreover, the decision to give a second-line therapy does not imply that the first-line or previous second-line treatment had no effect. Therapy may be effective but only transiently, or associated to side effects, or not the best approach considering quality of life. Overall, the concept of “difficult-to-treat ITP,” as suggested by some groups may be more suitable than “refractory ITP.”²⁴

We retained the CEREVANCE definition in the current manuscript for three reasons. First, the size of the population selected seemed more clinically meaningful and intermediate between the broader AYAS definition and the more stringent ICIS and modified CEREVANCE definitions. Second, the ICIS criteria which considered anti-CD20 therapies in the same category as T-cell-directed immunosuppressive treatments was not adapted to the clinical practice in the French CEREVANCE network that distinguishes B- from T-cell-directed therapy and uses anti-CD20 therapies earlier than other immunosuppressive treatments. Third, this definition was relatively flexible and allowed us to capture the great variability of practices in cITP management over time in our cohort. Our choice was consolidated by the fact that the definition chosen had prognostic and therapeutic implications. Notably, the CEREVANCE definition is very close to the one proposed by Miltiadous et al.,²¹ and was almost equivalent to a modified ICIS definition.

Our data provided important information on the epidemiology of r-cITP. The almost linear cumulative incidence without any plateau over time showed that patients with cITP have a small ($\sim 1.15\%$ per year) but persistent risk of r-cITP diagnosis. Older age at diagnosis

was the only factor associated with r-cITP incidence in multivariate analysis and was associated with a 8% increase in yearly incidence.

Patients with r-cITP had higher cumulative incidence rates of IM and SLE. These observations suggest that some r-cITP patients may have distinct pathophysiological characteristics that can be present from the time of disease onset. Notably, the proportion of SLE diagnoses in patients with r-cITP (10.1%) was even higher than in our previous study of patients with pediatric-onset Evans syndrome from the same cohort (7.3%) despite a longer follow-up.²⁸ Among the few patients meeting the criteria for multirefractoriness published previously,²⁶ two who underwent genetic analysis had an identified or suspected inherited thrombocytopenia. Therefore, although the small sample size prevents definitive conclusions, a diagnosis of refractory (or particularly multirefractory) cITP warrants deeper investigation for underlying diagnosis, specifically SLE, PID, and inherited thrombocytopenia.

Severe bleeding, and specifically grade 5 bleeding, is the main concern in cITP, and the rate of severe bleeding manifestations in children with r-cITP is unknown. Our data showed that despite an increased frequency of severe bleeding over the overall course of cITP (consistent with escalation therapy) and the relatively high proportion (27%) of patients in NR at last follow-up, only one patient experienced grade 5 bleeding after r-cITP diagnosis and while off treatment. We found no statistically significant difference in grade 5 bleeding risk between refractory and non-refractory patients. However, the absolute number of grade 5 bleeding events in r-cITP was higher than those reported previously in cITP,^{2,22} and the small number of patients with r-cITP limited the power of the analysis. Nevertheless, this suggests that the second-line treatments retain their effectiveness in r-cITP to prevent the risk of grade 5 bleeding.

CCR is the ultimate goal and is still possible in patients with cITP, as described previously.²² Whether this goal is achievable in r-cITP remains unknown. We showed here that 73% of patients with r-cITP had some hematological remission at the last follow-up (PR or better), and 17% were in CCR. However, sustained CCR without splenectomy seems very rare in pediatric r-cITP as this outcome was seen in only 4% of patients in this subgroup.

Overall use of splenectomy in cITP has decreased over the last decades due to the emergence of effective alternative therapies that avoid the side effects of splenectomy, including lifelong risks of infection and thrombosis.^{17,18} Some clinicians may also be reluctant to perform splenectomy in patients with r-cITP based on the assumption that if a patient did not respond to previous second-line treatments, they may not respond well to splenectomy.²⁹ Indeed, some studies that mainly included adult patients suggested that a greater number of treatments before splenectomy is associated with a lower response rate.^{30,31} In addition, a longer course of cITP may be considered a negative prognostic factor for a response, as shown with fostamatinib.³² Recent data in adults suggest that splenectomy may still be effective in refractory patients.³¹ Our data suggest that splenectomy may be effective to obtain CCR in children with r-cITP. Moreover, only 2/16 patients (13%) were in NR at the last follow-up

after splenectomy, and we did not identify concerning events relating to the safety of the procedure in this population. Nevertheless, caution is still required with regard to the differential diagnosis before splenectomy, and our current recommendations are to perform genetic analysis looking for inherited thrombocytopenia and PID before splenectomy.¹⁹

Recently, we showed that IM were associated with increased risks of both splenectomy failure and complications.¹⁹ The number of patients with r-cITP who underwent splenectomy was too small to confirm this result in this population. However, no patients with r-cITP and clinical IM achieved CCR at the last follow-up in the present study. Therefore, IM diagnosis should be taken into account when considering splenectomy in patients with r-cITP.

Our data have several limitations. The cohort study design is not exempt from some selection bias, despite the network being deep-rooted for more than 10 years in the French pediatric hematologist network. As well, the real-life setting implies that information gathered may be affected by practice variability. To limit this bias, the CEREVANCE group recommends clinical and biological follow-up at least every 6–12 months.¹⁹ Finally, the non-randomized design has to be considered in the interpretation of the effect splenectomy seen in this cohort.

We also showed that patients with r-cITP in NR at the last follow-up had more frequently received TPO-RA. However, this association should be interpreted cautiously as confounding factors, such as discrepancies in treatment dosage, may be present. Moreover, TPO-RA use changed greatly during the study period as these treatments obtained regulatory approval in 2016.⁵ Furthermore, patients in NR had received more second-line treatments than those not in NR, although the difference was not statistically significant. Nevertheless, this result suggests that TPO-RA may not be the best strategy as monotherapy in this population, as used traditionally.⁵ Treatment combination with TPO-RA and immunosuppressive drugs should be considered and investigated further.^{26,33,34}

In conclusion, the small proportion of patients with cITP who will meet the criteria for r-cITP each year warrants specific investigations and follow-up for IM and SLE. Genetic analyses to screen for differential diagnoses as inherited thrombocytopenia or PID are recommended, especially in the case of multirefractory patients or before definitive treatments such as splenectomy. Patients and their parents should be informed that a sustained CCR is still possible. Treatment combination with TPO-RA and immunosuppressive drugs should be evaluated. Alternatively, splenectomy may be considered in selected children in whom differential diagnoses and IM have been excluded.

AUTHOR CONTRIBUTIONS

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

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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.

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SUPPORTING INFORMATION

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

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