


# Newly diagnosed immune thrombocytopenia adults: Clinical epidemiology, exposure to treatments, and evolution. Results of the CARMEN multicenter prospective cohort

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## Abstract

The clinical epidemiology of immune thrombocytopenia (ITP) is not well known in adults. This study was aimed at assessing the clinical epidemiology of incident ITP adults, the factors associated with chronicity and exposure to treatments. This study was conducted in the CARMEN registry, a multicentric prospective cohort aimed at including all newly diagnosed ITP adults in the French Midi-Pyrénées region, South of France (3 million inhabitants) from June 2013. Descriptive analyses and multivariate logistic regression models were conducted. Out of 121 newly diagnosed ITP until December 2014, 113 patients were followed in the region and gave informed consent. Median age was 65 years. Half of the patients were female, 20.3% had a secondary ITP, 50.4% had a Charlson's score  $\geq 1$ , median platelet count was  $17 \times 10^9/L$ ; 50.9% had bleeding symptoms, including 2 severe gastrointestinal tract and 1 intracranial bleedings; 21.4% had another autoimmune disease and 20.3% experienced an infection within the six weeks before ITP onset. Persistency and chronicity rates were 68.2% and 58.7%, respectively. Antinuclear antibodies were associated with chronicity (OR: 2.89, 95% CI: 1.08-7.74). Sixty-eight (60.2%) patients were treated during the week following the diagnosis. Factors associated with the use of intravenous corticosteroids were secondary ITP and high bleeding score. Those associated with the use of intravenous immunoglobulin (IVIg) were a high bleeding score and low platelet count. In conclusion, severe bleeding is rare at ITP onset. Associated autoimmune diseases and recent infections were frequent. Antinuclear antibodies seem predictors of chronicity. Intravenous corticosteroids and IVIg were frequently used.

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## 1 | INTRODUCTION

Immune thrombocytopenia (ITP) is a rare autoimmune disorder due to peripheral platelet destruction and impaired platelet production, leading to thrombocytopenia and spontaneous bleeding.<sup>1</sup> It is said primary when not associated with another systemic disease.<sup>2</sup> ITP diagnosis relies upon the exclusion of other causes of thrombocytopenia. ITP first-line treatment is based on oral corticosteroids, plus intravenous immunoglobulin (IVIg) in case of severe bleeding.<sup>3,4</sup> In France, IVIg are added in case of Khellaf's bleeding score  $>8$ .<sup>5</sup> This score is based on the age of the patient and its bleeding symptoms.<sup>6</sup> In about 70% of adult cases, ITP becomes persistent (lasting  $>3$  months) or chronic (lasting  $>12$  months).<sup>2</sup> In these cases, various corticosteroid-sparing agents are used such as splenectomy, rituximab or thrombopoietin-receptor agonists (TPO-RA).<sup>3-5,7</sup> Splenectomy is usually considered in the chronic phase only.<sup>3-5</sup>

The clinical epidemiology of adult ITP is not well known. The classical feature of a disease concerning preferentially young women<sup>8</sup> has been challenged by population-based studies.<sup>9-11</sup> The frequency and pattern of secondary ITPs has been assessed by expert-opinion<sup>1</sup> or population-based studies<sup>11</sup> only. Similarly, the frequency of the various bleeding symptoms is not well-known.<sup>12</sup> Some data potentially related to ITP pathophysiology such as the frequency of autoimmune background (concurrent or personal history of other autoimmune disease), as well as the frequency of infection preceding ITP onset have not been systematically assessed in adult ITP cohorts. The estimated frequency of ITP becoming persistent or chronic stems from ancient series<sup>13-15</sup> or population-based study.<sup>11</sup> Recently, 115 newly diagnosed primary ITP patients included in a multicentric cohort stemmed from referral centers in France were prospectively followed during 12 months: 37.4% had recovered at 12 months spontaneously and 12.2% after treatment.<sup>16</sup> However, the rate of persistent ITP patients recovering before the chronic phase (ie, active ITP at 3 months but with normal platelet count without treatment before 12 months), on which is based the rationale for treatment choice since new standardization guidelines,<sup>2</sup> is not well-known in adults.

First-line treatment has not been assessed in real-life practice since the publication of new ITP management guidelines.<sup>3-5</sup> Whether intravenous corticosteroids and IVIg are used in accordance with these guidelines is unknown.

In a methodological point of view, few prospective cohort studies have been conducted in ITP adults, including up to 340 patients.<sup>16-20</sup> However, these cohorts stemmed from reference centers, and were not dedicated at capturing all new cases of ITP in a given area. Drug exposures were rarely detailed.

The objectives of this study were (1) to detail the clinical epidemiology of ITP in newly diagnosed adults in a registry aimed at capturing all incident patients in a given region (namely, the Midi-Pyrénées region, South of France); (2) to identify the frequency of persistent ITP patients who achieved normal platelet count without treatment before the chronic phase; (3) to identify the factors associated with chronicity, (4) to assess in the real-life setting the use of first-line treatments as well as the exposure to non-corticosteroid treatment before the

chronic phase of the disease; and (5) to assess the factors associated with the use of intravenous corticosteroids and of IVIg at ITP onset.

## 2 | METHODS

### 2.1 | Data source: The CARMEN registry

*Cytopénies Auto-immunes: Registre Midi-PyréEN* (CARMEN) is a multi-center registry aimed at the prospective follow-up of all newly diagnosed ITP adults in the French Midi-Pyrénées region, South of France (near 3 million inhabitants) since June 2013, with detailed recording of clinical data and ITP treatment exposures.<sup>21</sup> All the internal physicians and hematologists in charge of ITP patients in the region belonging to public hospitals participate to the study, plus 3 private hospitals (22 centers in total). In France, 96% of ITP patients are treated in public hospitals.<sup>22</sup> This is the first clinical prospective registry aimed at including all newly diagnosed ITP in a given area.

Inclusion criteria in the registry are: (1) age  $\geq 18$  years, (2) newly diagnosed ITP, (3) follow-up in the Midi-Pyrénées region, and (4) written informed consent to data collection.<sup>21</sup> ITP is defined according to French guidelines: abnormal platelet count ( $<150 \times 10^9/L$ ) and exclusion of other causes of thrombocytopenia.<sup>5</sup> Follow-up is based on the real-life practice, with data recording at each visit (on an indicative basis, at diagnosis, 1, 3, 6 months and then every 6 months). Patients will be followed 10 years.

This multicenter registry is carried out on behalf of the French referral center for autoimmune cytopenia and the French national center for rare diseases in immunohematology (MaRIH). The Toulouse University Hospital Ethic Committee gave its approval (n°27-0512). Authorization for data collection were obtained from the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (n°12.067) and from the *Commission Nationale de l'Informatique et des Libertés* (N° 2012-438).

### 2.2 | Study population

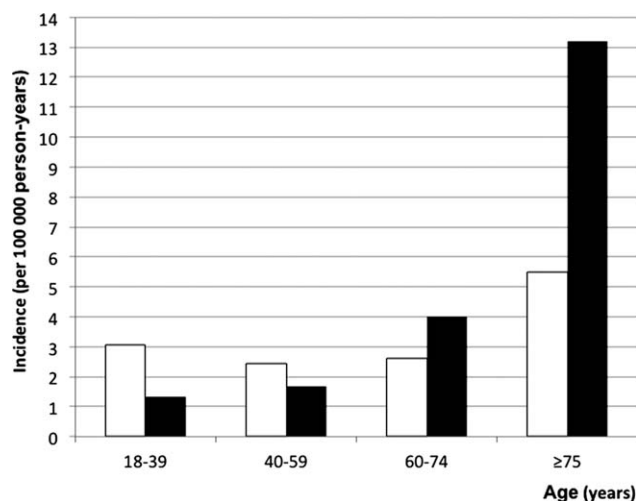
Study population included all the patients registered in the CARMEN registry between June 2013 and December 2014, to have a  $>12$ -months follow-up for all patients.

### 2.3 | Outcomes

All the epidemiological (clinical and lab tests) data described in this study are prospectively recorded in the registry. We assessed the frequency of patients entering the persistency and the chronic phase of the disease.<sup>2</sup> This was defined as the absence of recovering 3 and 12 months after ITP onset, respectively. Recovering was defined by normal platelet count on at least 2 tests at least 7 days apart, absence of bleeding signs and absence of ITP treatment. We defined ITP treatment at disease onset as ITP treatments used in the week following the diagnosis.

### 2.4 | Statistical analyses

For descriptive analyses, mean  $\pm$  standard deviation or median and range were used for quantitative variables, and percentages for



**FIGURE 1** Incidence rates of ITP by age and sex groups. Females are represented by white bars and males by black bars

qualitative ones. To calculate the incidence of ITP by age and gender group, we used as denominator regional demographic data from the National Institute for Statistics and Economics (*Institut national des statistiques et des études économiques, Insee*) at the 1st January of 2014.<sup>23</sup> The evolution of the disease was assessed in the whole cohort and in the subgroup of patients with primary ITP.

Logistic regression models were performed to assess the factors associated with chronicity as well as the factors associated with the use of intravenous corticosteroids and of IVIg at ITP onset. The following covariates were included to assess the risk of chronicity: age, gender, Charlson's comorbidity score,<sup>24</sup> secondary versus primary ITP, history of autoimmune disease, antinuclear antibody positivity (title  $\geq 1/160$ ), infection prior to ITP onset, Khellaf's bleeding score without the age, presence of mucosal bleeding and platelet count. The following covariates were included to assess the factors associated with intravenous corticosteroids and IVIg: age, gender, Charlson's comorbidity score,<sup>24</sup> secondary versus primary ITP, Khellaf's bleeding score and platelet count. The age was categorized as  $<65$  and  $\geq 65$  years due to nonlinear association in all models and because 65 years was the median age. There was also no linear association regarding the platelet count. Due to previous findings by Grimaldi-Bensouda et al.,<sup>16</sup> we tested several thresholds of platelet counts to assess the association with chronicity:  $\leq 10$ ,  $\leq 20$ ,  $\leq 30$ , and  $\leq 50 \times 10^9/L$ . Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. All variables significant at the threshold of 20% in univariate analysis were included in the multivariate model ( $\alpha = 5\%$ ).

Statistical analyses were carried out using SAS V9.4<sup>TM</sup> software (SAS Institute, Cary, NC).

### 3 | RESULTS

#### 3.1 | Selection of the population

Out of 121 newly diagnosed ITP patients identified between June 2013 and December 2014, 7 did not give written informed consent

and 1 was not followed in the Midi-Pyrénées region. Consequently, 113 adult patients were included in the study.

#### 3.2 | Clinical epidemiology at ITP diagnosis

Median age was 65 years (range: 18-95) and 57 patients (50.4%) were female; 57 patients (50.4%) had a Charlson's score  $\geq 1$  (9.7% had a Charlson's score  $\geq 3$ ). Median platelet count at ITP diagnosis was  $17 \times 10^9/L$  (range: 1-126). Eight patients had a platelet count between 100 and  $150 \times 10^9/L$  at ITP diagnosis.

Incidence rates by age and sex groups are shown in Figure 1. The incidence increased after 60 year-old and was the higher in  $\geq 75$  years. There was a female predominance in younger patients and a clear male predominance in older patients.

Twenty-three patients (20.3%) had secondary ITP (detailed in Supporting Information Table S1). Five Evans syndromes were identified, in the context of Sjögren syndrome, systemic lupus erythematosus, hepatitis C virus infection, myelodysplastic syndrome and sarcomatoid carcinoma ( $n = 1$  each).

Fifty-seven patients (50.4%) had bleeding symptoms, including 2 severe gastrointestinal tract bleedings, 2 hematuria and 1 intracranial bleeding (Supporting Information Table S2). Median Khellaf's bleeding score<sup>6</sup> was 5 (range: 0-35).

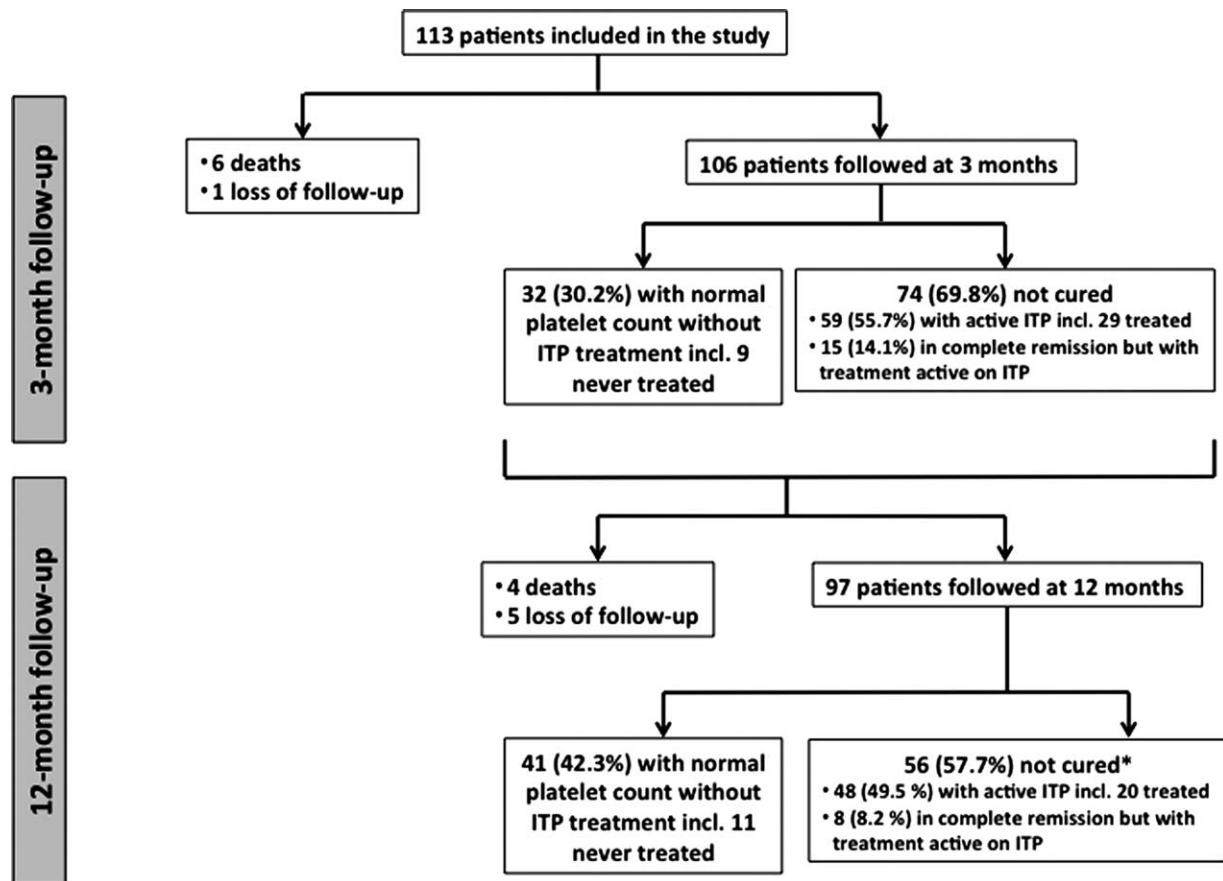
Twenty-five patients (21.4%) had a concurrent or a history of autoimmune disease (Supporting Information Table S3). Antinuclear antibodies were tested in 92 patients (86.8%) and positive in 36 (39.1% of tested patients). Twenty-three patients (20.3%) experienced an infection within the six weeks before ITP onset, including 12 viral lower respiratory tract infections and 3 gastroenterites. These viral infections were not documented microbiologically.

#### 3.3 | Frequency of patients entering the persistent and the chronic phases

ITP course at 3 and 12 months in the whole cohort is described in Figure 2. Out of the 113 included patients, 6 patients deceased (intracranial bleeding,  $n = 1$ , melanoma,  $n = 1$ , suicide,  $n = 1$ , unknown cause,  $n = 3$ ) and 1 was lost of follow-up before the third month after the first signs. Out of the remaining 106 patients, 32 (30.2%) had normal platelet count at 3 months without any treatment active on ITP, 15 (14.1%) had normal platelet count at 3 months with exposure to treatment active on ITP and 59 (55.7%) had persistent low platelet count (including 29 with exposure to ITP treatment).

At one year, 4 additional patients had deceased (cancer of unknown primitive,  $n = 1$ , lung infection  $n = 1$ , heart rhythm disease,  $n = 1$ , unknown cause,  $n = 1$ ) and 5 were lost of follow up. Out of the 97 remaining patients with follow-up  $>1$ year, 41 patients had normal platelet count at 12 months without any treatment active on ITP, 8 had normal platelet count at 12 months with exposure to treatment active on ITP and 48 had persistent low platelet count (including 20 with exposure to ITP treatment).

Seven patients (9.5%) with low platelet count at 3 months had normal platelet count at 12 months. Out of them, 4 had been exposed to



**FIGURE 2** ITP evolution at 3 and 12 months in the whole cohort. Four of the 32 patients with normal platelet count without ITP treatment at 3 months had relapsed at 12 months: 2 with platelet count between  $100$  and  $150 \times 10^9/L$  without ITP treatment, 1 treated patient achieving normal platelet count and 1 treated patient with platelet count  $< 100 \times 10^9/L$

an ITP treatment during the persistent phase of the disease. Five more patients with normal platelet count under treatment at 3 months after ITP onset at normal platelet count without treatment at 12 months. In total, 12 persistent ITP patients (16.2%) had normal platelet count without treatment at 12 months. In contrast, four patients with normal platelet count without treatment at 3 months had relapsed at 12 months: 2 secondary and 2 primary ITPs.

ITP course in the subgroup of patients with primary ITP ( $n = 90$ ) is shown in Figure 3. Results were similar except a lower rate of mortality. Ten patients (16.7%) with persistent ITP at 3 months (6 with low platelet count and 4 with normal platelet count but under ITP treatment) had normal platelet count without treatment at 12 months. As said previously, only 2 primary ITPs with normal platelet count without treatment at 3 months had relapsed at 12 months. These 2 relapses consisted in mildly decrease in platelet count (between  $100$  and  $150 \times 10^9/L$ ) without bleeding or ITP treatment.

Among primary ITP patients, the evolution toward persistency and chronicity was lower in patients never treated (respectively, 9 and 11 patients out of 27) in comparison with patients necessitating at least one second-line treatment (none out of 23 patients).

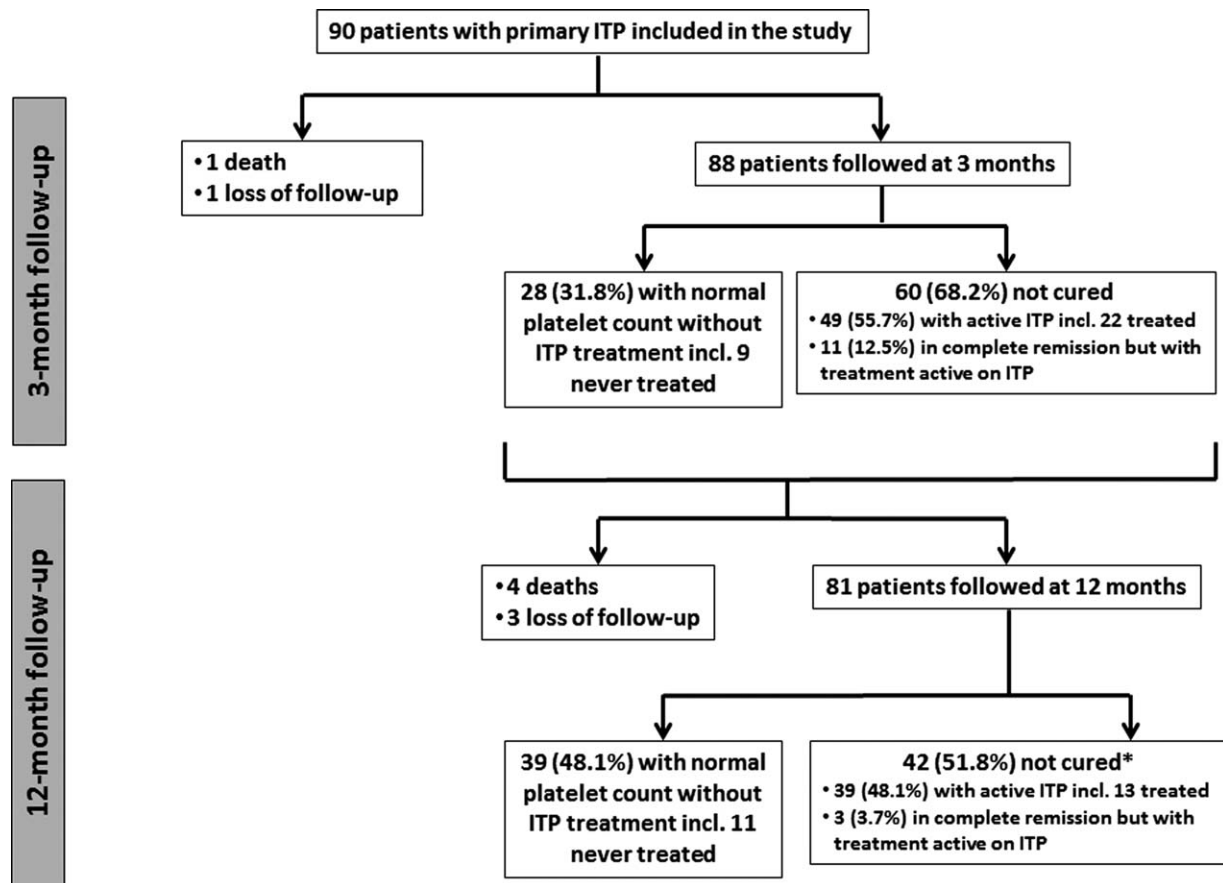
Among the eight patients with platelet count between  $100$  and  $150 \times 10^9/L$  at ITP diagnosis, one had stable platelet count at 3 and 12 months, one had platelet count  $< 100 \times 10^9/L$  at 3 and 12 months

and 6 had normalized platelet count ( $>150 \times 10^9/L$ ) at 3 and 12 months. All were primary ITPs and none required treatment.

Factors associated to chronicity without any exposure to ITP treatment are presented in the Table 1. In univariate analysis, two factors were significantly associated to chronicity: secondary ITP and antinuclear antibody positivity. There was a trend for a decreased risk in case of viral infection prior to ITP onset (OR: 0.55, 95% CI: 0.14-2.20), for bleeding symptoms at ITP onset (OR: 0.49 [0.22-1.12]) and for mucosal bleeding at ITP onset (OR: 0.66, 95% CI: 0.26-1.67). In multivariate analysis, only antinuclear antibody positivity was associated with chronicity (OR: 2.89, 95% CI: 1.08-7.74). The results were similar in post hoc sensitivity analysis restricted to primary ITP patients (data not shown).

### 3.4 | Exposure to ITP treatment at disease onset

Sixty-eight patients (60.2%) were treated during the week following ITP diagnosis. Among them, 66 (98.5%) received corticosteroids (median dose:  $0.99$  mg/kg/d, range: 0.31-2.00), including 21 (31.3%) intravenously (methylprednisolone; median dose:  $1.29$  mg/kg/d; range: 0.63-4.81) initially. Twenty-nine (43.3%) of the treated patients received IVIg, 8 (11.9%) platelet transfusion, 2 romiplostim and 1 rituximab.



**FIGURE 3** ITP evolution at 3 and 12 months in the cohort restricted to primary ITP patients. Two of the 28 patients with normal platelet count without ITP treatment at 3 months had relapsed at 12 months, consisting in a platelet count between  $100$  and  $150 \times 10^9/L$  without ITP treatment

In multivariate analysis, the factors associated with the use of intravenous corticosteroids were secondary ITP and Khellaf's bleeding score  $>8$  (Supporting Information Table S4). In multivariate analysis, the factors associated with the use of IVIg were Khellaf's bleeding score  $>8$  and platelet count  $<10 \times 10^9 G/L$  (Supporting Information Table S5).

### 3.5 | Exposure to non-corticosteroid treatment during the year after disease diagnosis

Among the 68 patients treated for ITP, 32 (47.1%) were exposed to non-corticosteroid treatments during the year after disease diagnosis. These treatments were TPO-RAs ( $n = 15$ ; eltrombopag alone,  $n = 9$ ; romiplostim alone,  $n = 7$ ; both,  $n = 1$ ), rituximab ( $n = 11$ ), danazol ( $n = 7$ ), dapsone ( $n = 6$ ), persistent use of IVIg (defined as 3 consecutive infusions,  $n = 5$ ), hydroxychloroquine ( $n = 3$ ) and splenectomy ( $n = 1$ ).

## 4 | DISCUSSION

This first prospective study aimed at completeness of adult ITP case recording in a given area confirmed the variations of incidence by gender and age groups. In particular, it confirms the higher incidence of

ITP in older men, as suggested by previous population-based studies.<sup>10,11</sup> Of note, incidence values of this study are very closed to those of the nationwide French population-based study by our group.<sup>11</sup> The frequency of secondary ITP (20.3%) is superimposable to what was hypothesized by expert opinion.<sup>1</sup> Interestingly, 4 patients had myelodysplastic syndrome revealed by ITP. This confirms that myelodysplastic syndrome is an emerging cause of ITP.<sup>11,25</sup> The rarity of serious bleeding at ITP onset is fully in accordance with previous studies, with central nervous system bleeding in  $<1\%$  of patients and gastrointestinal bleeding in about 2-4%.<sup>12,20,26</sup> The frequency of cutaneous bleeding is in accordance with data from the UK-ITP registry. However, mucosal bleeding were less frequent in our study.<sup>26</sup> Hematuria was noticed in 3.5% of our patients. Hematuria has been identified as a marker of disease severity in childhood ITP.<sup>27</sup> Further studies are needed in adults.

Interestingly, 21.4% of the patients had a concurrent or history of autoimmune disease. The huge variety of these associated diseases indicates a general susceptibility to autoimmune diseases but prevent from any hypothesis regarding gene candidates.

One fifth of the patients (20.3%) experienced an infection within the six weeks before ITP onset, mainly respiratory tract viral infections. The role of virus in ITP pathophysiology is suspected for long, in

TABLE 1 Factors associated with chronicity (*n* = 97 patients with chronicity status available)

Variables	Univariate analyses		Multivariate analyses	
	OR [95% CI]	<i>P</i>	OR [95% CI]	<i>P</i>
Age ≥65 years	1.19 [0.53–2.67]	.67	–	–
Male gender	1.63 [0.72–3.67]	.24	–	–
Charlson's score ≥1	1.95 [0.85–4.46]	.11	–	–
Secondary ITP	4.63 [1.24–17.27]	.022	2.63 [0.65–10.68]	.17
History of autoimmune disease	0.76 [0.31–1.85]	.54	–	–
Antinuclear antibody positive <sup>a</sup>	3.12 [1.22–8.00]	.017	2.89 [1.08–7.74]	.035
Infection prior to ITP, overall	1.12 [0.41–3.06]	.82	–	–
Viral infection symptoms before ITP	0.55 [0.14–2.20]	.40	–	–
Bleeding				
Bleeding as first symptom	0.49 [0.22–1.12]	.09	0.54 [0.21–1.35]	.18
Mucosal bleeding	0.66 [0.26–1.67]	.39	–	–
Khellaf's score without the age >8	0.71 [0.19–2.62]	.60	–	–
Platelet count				
<10 × 10 <sup>9</sup> /L	0.71 [0.31–1.62]	.41	–	–
≤20 × 10 <sup>9</sup> /L	0.75 [0.33–1.68]	.48	–	–
≤30 × 10 <sup>9</sup> /L	0.78 [0.35–1.76]	.55	–	–
≤50 × 10 <sup>9</sup> /L	0.64 [0.27–1.51]	.31	–	–
Initial dose of corticosteroids >1 mg/kg/jour <sup>b</sup>	0.84 [0.27–2.58]	.76		

<sup>a</sup>Tested in 85 patients.

<sup>b</sup>Corticosteroids were initiated in 62 of these 97 patients.

particular as concerns viruses infecting the respiratory tract.<sup>1,28</sup> Winter peaks of ITP incidence in adults<sup>11,29</sup> and trend to a protective effect of influenza vaccine against ITP occurrence<sup>30</sup> sustain this hypothesis.

This study is consistent with both historical and new data regarding the frequency of persistent and chronic disease.<sup>11,13–16</sup> Interestingly, this study demonstrates that 16.2% of persistent ITP patients may be with normal platelet count without treatment at twelve months, including 4.0% spontaneously. This sustains the current classification differentiating persistent from chronic ITP.<sup>2</sup> Of note, we choose the threshold of <150 × 10<sup>9</sup>/L for ITP definition in this real-life practice study to fit the 2009 French guidelines, not revised yet at the time of the inclusion of these patients.<sup>5</sup> Eight primary ITP patients had a platelet count between 100 and 150 × 10<sup>9</sup>/L at ITP diagnosis, and one patient only experienced platelet count <100 000 × 10<sup>9</sup>/L during follow-up. Consequently, the results presented here slightly overestimate the frequency of patients with normal platelet count without treatment at both 3 and 12 months when considering the standardized definition of ITP using the threshold of <100 × 10<sup>9</sup>/L for platelet count.<sup>2</sup> However, this does not affect the estimation of frequency of patients with persistent ITP who achieved normal platelet count without treatment at 12 months.

Antinuclear antibody positivity was associated with chronic evolution of ITP in the whole cohort as well as in the subgroup of primary ITP patients. This factor has been demonstrated as a predictor of chronicity in childhood ITP.<sup>31</sup> However, this finding is still debated in adults.<sup>16,32–34</sup> Of note, we used the threshold of ≥1/160 to define

antinuclear antibody positivity because it is the best cut-off value to discriminate between healthy subjects and patients with autoimmune disorders.<sup>35–38</sup> In contrast, the previously quoted studies used the threshold of ≥1/40 or ≥1/80, that may be not clinically relevant, and showing no association with any ITP feature.<sup>16,32</sup> We found a trend in univariate analysis for the absence of mucosal bleeding, and more generally for bleeding symptoms at ITP onset, as predictor of chronicity. This has been demonstrated in children<sup>31</sup> and suggested in adults.<sup>16</sup> Similarly, we found also a trend for a decreased risk of chronicity in patients who experienced viral infection prior to ITP onset. We may have lacked of power to demonstrate this association. This has been demonstrated in children.<sup>31</sup> Recently, we showed in a French ecological retrospective study that ITP incidence was correlated to viral outbreaks in adult patients with normal platelet count without treatment at 3 months, while ITP becoming persistent or chronic did not demonstrate any seasonal variation of incidence.<sup>29</sup> In contrast, we did not find in this study any relationship between platelet count and chronic evolution, perhaps due to the distribution of the variable with no linear association with the outcome.<sup>16</sup> The identification of predictors of chronicity in adults remain a major concern.

In this study, the rate of patients treated during the week following the diagnosis (60.2%) was lower than in the recent study by Grimaldi-Bensouda et al. (87.4%).<sup>16</sup> This may be explained by the fact that in the latter study, patients stemmed for referral centers (they were more serious: 83.9% of the patients had bleeding symptoms) and because insidious-onset ITPs were excluded.<sup>16</sup> The fact that 31.3% of the

treated patients were empirically exposed to IV corticosteroids at standard dose (1 mg/kg/d) in most of the cases is intriguing and has not been reported to the best of our knowledge. Interestingly, 4.4% of the treated patients necessitated rescue therapy in the first week following the diagnosis, using romiplostim ( $n = 2$ ) and rituximab ( $n = 1$ ). Another interesting point is that French recommendations regarding the use of IVIg in case of Khellaf's bleeding score  $>8$  were adequately used in practice. Of note, this practical score is not consensual but had been precisely developed to help the physician in the management of bleeding ITP, indicating when IVIg should be added to corticosteroids.<sup>6</sup>

The use of non-corticosteroids treatments before the chronic phase was frequent (47.1% of treated patients). TPO-RAs and rituximab were mostly used, has previously shown by a nationwide population-based study conducted in France between 2009 and 2011.<sup>7</sup>

This study has some limitations: it was conducted in a region in South of France. Consequently, the results cannot be extended to other regions or countries, particularly regarding treatment exposure. The completeness of the registry cannot be exactly assessed. By crossing with insurance health database and medical chart review, the sensitivity of CARMEN registry in capturing all newly diagnosed ITP adults necessitating health care during the study period was 82.9%, 95% CI: 74.8%–88.8%.<sup>39</sup> Moreover, the participating centers reflect the whole health care institutions implicated in ITP care in the region, including public and private, primary, secondary and tertiary hospitals. Only 7 patients (5.8%) were excluded due to opposition to participate, and 1 patient was lost of follow-up at 3 months and 5 at 12 months. Tests such as antinuclear antibodies were not performed in all patients (86.8%), restricting the analyses to tested patients. In contrast, we had no missing value for other clinical and laboratory variables described here, and prospective recording prevents from recalling bias. Lastly, we have probably lacked of statistical power to assess the weight of some variables such as viral infection as predictor of chronicity. Consequently, the estimates of regression models must be taken with caution.

In conclusion, this study confirms the epidemiology of newly diagnosed ITP in adults regarding its incidence and that severe bleeding is rare at ITP onset. New findings are that associated autoimmune diseases and recent infections prior to ITP onset were frequent. This study also confirms the rates of persistent and chronic ITP, and that 16.2% of persistent ITP adults may be with normal platelet count without treatment at 12 months, sustaining the current classification of ITP. Similarly to children, this study suggests that antinuclear antibodies were predictors of chronicity using the threshold of  $\geq 1/160$ . Regarding first-line treatment exposure, intravenous corticosteroids and IVIg were frequently used, particularly in case of severe ITP. TPO-RAs were the most frequent prescribed drugs during the year after the diagnosis in case of persistency.

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## CONFLICT OF INTERESTS

GM received research grants from CSL Behring and Novartis for the CARMEN registry in 2016 and 2017. These sponsors have no role in data collection and have not the property of data; they have no role in the conception, the methodology, the analyses, the interpretation of the studies conducted in the registry; manuscripts of research studies conducted in the CARMEN registry are not submitted to the sponsors before publication. BG received a grant from Roche and personal fees from Amgen, LFB, Novartis, GSK. DA received personal fees from Amgen, Novartis, GSK. All other authors declare having no conflict of interest.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

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