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Epidemiology, treatment patterns and cost analysis of Immune Thrombocytopenia (ITP) in Spain between 2014 and 2020: a population-based study

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Abstract:

Immune thrombocytopenia (ITP) is characterised by low platelet counts and often leads to bleeding, fatigue, and reduced health-related quality of life. This observational, retrospective, population-based study using BIG-PAC® database included Spanish paediatric and adult patients with primary ITP diagnosed in primary care and hospitals between 2014 and 2020 (median follow-up: 4 years). Epidemiology, baseline/clinical characteristics, treatment trends, healthcare resources and costs were analysed. The BIG-PAC® database contains records of 1,818,588 patients; 170 adults and 27 children with ITP were included in our analysis. Prevalence and annual incidence per 100,000 were estimated in 10.8 (2.8 in chronic [cITP] patients) and 1.5 (0.3 in cITP patients), respectively. Epistaxis was the most common bleeding event, followed by genitourinary and gastrointestinal bleeding; >50%/>75% of ITP/cITP patients reported fatigue. Chronic patients had lower platelet counts at baseline and required more transfusions. Corticosteroids, immunosuppressants and thrombopoietin receptor agonists were the most used agents in first-, second- and third-line treatment, respectively. Thirty-five patients, all of them in chronic phase, underwent splenectomy. Patients had on average 13.9, 6.6, and 1.2 visits/year to primary care, haematology/internal medicine, and emergency departments, respectively. More than one-fourth of adult patients took on average 16.3 days of sick leave annually. Mean annual total healthcare costs were €10,741 (ITP patients) and €19,809 (cITP patients).

This is the first study to provide an overall perspective on the situation of the Spanish ITP population in terms of epidemiology, treatment trends, healthcare resources and costs, highlighting unmet patient needs, and direct and indirect costs/resource use between 2014-2020.

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Epidemiology, treatment patterns and cost analysis of Immune Thrombocytopenia (ITP) in Spain between 2014 and 2020: a population-based study

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Abstract

Immune thrombocytopenia (ITP) is characterised by low platelet counts and often leads to bleeding, fatigue, and reduced health-related quality of life. This

observational, retrospective, population-based study using BIG-PAC[®] database included Spanish paediatric and adult patients with primary ITP diagnosed in primary care and hospitals between 2014 and 2020 (median follow-up: 4 years). Epidemiology, baseline/clinical characteristics, treatment trends, healthcare resources and costs were analysed. The BIG-PAC[®] database contains records of 1,818,588 patients; 170 adults and 27 children with ITP were included in our analysis. Prevalence and annual incidence per 100,000 were estimated in 10.8 (2.8 in chronic [cITP] patients) and 1.5 (0.3 in cITP patients), respectively. Epistaxis was the most common bleeding event, followed by genitourinary and gastrointestinal bleeding; >50%/>75% of ITP/cITP patients reported fatigue. Chronic patients had lower platelet counts at baseline and required more transfusions. Corticosteroids, immunosuppressants and thrombopoietin receptor agonists were the most used agents in first-, second- and third-line treatment, respectively. Thirty-five patients, all of them in chronic phase, underwent splenectomy. Patients had on average 13.9, 6.6, and 1.2 visits/year to primary care, haematology/internal medicine, and emergency departments, respectively. More than one-fourth of adult patients took on average 16.3 days of sick leave annually. Mean annual total healthcare costs were €10,741 (ITP patients) and €19,809 (cITP patients).

This is the first study to provide an overall perspective on the situation of the Spanish ITP population in terms of epidemiology, treatment trends, healthcare resources and costs, highlighting unmet patient needs, and direct and indirect costs/resource use between 2014-2020.

Keywords: primary immune thrombocytopenia, adult, paediatric

Summary table

What is known on this topic?	What does this paper add?
<ul style="list-style-type: none"> • Patients with ITP are prone to bleeding, fatigue, and poor health-related quality of life • In Europe, the prevalence and annual incidence of ITP is approximately 10-50 per 100,000 and 1 in 25,600 - 37,000 people, respectively • The disease behaves differently in children and adults 	<ul style="list-style-type: none"> • This is the first study of this kind to be carried out on the ITP population in Spain illustrating the situation of these patients in terms of different variables. • The analysis of the records of a total of 1,818,588 patients reveals the true incidence and prevalence of the disease in Spain, baseline and clinical characteristics, treatment trends, use of healthcare resources and management costs for paediatric and adult patients.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune haematological disorder caused by a decrease in the number of platelets ($< 100 \times 10^9 / L$) (1-3). This reduction is thought to result in part from autoantibodies that target platelets or megakaryocytes, which can then impair platelet production, or from T-cell dysregulation (4, 5). Thrombocytopenia may last <3 months (ITP of recent diagnosis), between 3 and 12 months (persistent) or >12 months (chronic), and may cause bleeding (1, 2, 6), fatigue (7) and reduced health-related quality of life (HRQoL) (1, 7, 8). ITP is

classified as primary or secondary (3), depending on the reduced platelet counts being caused by another disorder or not (2, 3). Children rarely have significant bleeding and their ITP usually resolves spontaneously, unlike adults whose ITP becomes chronic in 80% of cases (2, 4).

The annual incidence and the prevalence of primary ITP in adults have been estimated to be 3.3 per 100,000 and 9.5 per 100,000, respectively (9), but these figures may vary depending on the country analysed (2). The Orphanet database estimates a prevalence of ITP of 1-5 per 10,000 and an annual incidence of 1 in 25,600-37,000 in Europe (10).

Treatment focuses on preventing or treating bleeding by increasing patients' platelet counts ($>20 - 30 \times 10^9$), and on improving their HRQoL (11). Treatment should be individualised for each patient, taking into account the severity of the disease (11, 12). Therapy has evolved over the last decade, and immunosuppressive agents, maintenance treatment with corticosteroids, rituximab or splenectomy, which entail undesirable side effects and have in some cases reduced effectiveness, have given way to other drugs: the second-generation thrombopoietin receptor agonists (TPO-RAs) and, more recently, fostamatinib, while other molecules are still under development (6, 13, 14). The current standard of care (SOC) for newly diagnosed adult patients is corticosteroids (most likely prednisone or dexamethasone) or intravenous immunoglobulin (IVIG) if there is significant bleeding (15, 16). In general, TPO-RAs are the recommended therapy for subsequent lines of treatment over rituximab and splenectomy, always considering the patient's preferences (16). Most children (80-90%) recover from ITP in <12 months; for those who do not, the choice of treatment is challenging due to the potential side effects of different approaches at

such a young age, although the TPO-RAs romiplostim or eltrombopag are the proposed treatment of choice (17).

Characterisation of different variables including treatment of ITP has been studied in other countries (18-20), but no national data are available for Spain. Here, we describe the epidemiological characteristics of patients with ITP and chronic ITP (cITP) treated in Spanish primary care centres and hospitals between 2014 and 2020. With the aim to have an updated and global vision of various aspects related to ITP in Spain, we analysed the patients' baseline and clinical characteristics, their treatment and management, and the health resources and costs derived from their management in primary care and hospitals.

Material & Methods

Study design and population

This retrospective observational study was conducted using electronic medical records (EMR) of patients with ITP diagnosed between 1 January 2014 and 31 December 2020. ITP was defined according to the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes 287.31 and 287.39. EMRs were obtained from the BIG-PAC[®] administrative database (data source: secondary; owner: Atrys Health-RLD), which contains anonymised records of 1,818,588 patients from the Spanish National Health System (SNHS). These data belong to primary healthcare centres and referral hospitals from seven healthcare zones in seven different Spanish autonomous communities and are anonymised prior to inclusion in the BIG-PAC[®] database to avoid any type of individual identification of the patient or related healthcare information, such as hospitals or treating physicians. Each patient is assigned a unique code to avoid data duplication. The BIG-PAC[®] database is a unification of public clinical data from different

healthcare areas. The intermediary company running the software of the clinical centres also unifies fields in the patient's clinical history. Some fields may appear differently, depending on the templates of the Spanish Autonomous Communities (i.e. age may be found in different sections or under different titles of the clinical history in one Autonomous Community or another). Atrys Health does not have access to the primary data source. The BIG-PAC® database has been approved, validated, and registered by the European Medicines Agency and data processing is in accordance with the Spanish Personal Data Protection Act.

Patients were divided into paediatric (< 18 years old) and adult (\geq 18 years old) groups for analysis and were followed until death or the end of the study. The index date was the date of the ITP diagnosis. From their diagnosis, patients were followed and classified in patients of recent diagnosis (the last ITP registry would take place within 3 months from diagnosis), persistent (the last ITP registry would take place from 3 to 12 months from diagnosis) and chronic (the last ITP registry would take place >12 months from diagnosis). A subanalysis of the cITP population was performed for some of the variables. Inclusion and exclusion criteria are shown in Table S1.

Study variables

Baseline characteristics

Sociodemographic characteristics of paediatric and adult patients (age and sex) were recorded at the index date, while comorbidities (hypertension, diabetes, alcohol consumption, cardiovascular disease, gastrointestinal disease, infectious complications, bone disease, fractures, thyroid disease, and malignant neoplasms) were recorded in the 6 months prior to the index date. The Charlson comorbidity index (CCI) was calculated to reflect general comorbidity and to approximate the

general status of patients. Data on the total ITP population and cITP patients were analysed.

Clinical characteristics

Signs and symptoms of ITP such as bleeding episodes (intracranial, gastrointestinal, genitourinary, nasal bleeding [epistaxis], and bleeding at other sites [specified in Table S2]), major bleeding (at any location) requiring hospital admission, fatigue/asthenia, transfusions, or all-cause mortality (if information was available) were estimated during the follow-up period. Major bleeding was defined as any bleeding that could lead to hospitalisation. ICD-9-CM codes are shown in Table S2. Platelet count was measured at baseline and at the end of follow-up. All data were estimated separately for the paediatric and adult populations.

Epidemiological data

Prevalence and incidence were calculated independently of other outcomes. They were estimated using data from the 31st of December, 2021. Prevalence was calculated as the total number of active cases with a diagnosis of ITP in the population analysed in that year, and incidence was calculated as the number of new cases diagnosed per 100,000 patients/year among the patients being actively managed in 2021, without standardisation for patient age/sex (the BIG-PAC® database is similar to the Spanish population pyramid) (21). Data were available for total ITP and cITP patients.

Treatment trends

Treatments received by paediatric and adult patients were analysed at the time of first diagnosis of ITP (12 months prior to the index date) and during the follow-up period of the study using drug dispensing records. The drugs of interest were IVIG, danazol, cyclophosphamide, rituximab, mycophenolate, cyclosporine, azathioprine,

spleen tyrosine kinase inhibitors (fostamatinib), TPO-RAs (romiplostim and eltrombopag) and corticosteroids (dexamethasone, methylprednisolone, prednisolone, prednisone).

They were prescribed according to medical practice; their Anatomical Therapeutic Chemical Classification System codes are given in Table S3. Splenectomies were analysed during follow-up, but also two years before index date to understand changes in treatment patterns (codes in Table S3).

Healthcare resources and costs

Resource use included those for general practice related to ITP (primary care visits, emergency department visits, hospital admission rate and length of stay), specialised care visits (haematology and internal medicine), diagnostic tests (laboratory tests [any conventional lab analysis request], conventional radiology, computed tomography [CT], nuclear magnetic resonance [NMR], other tests [lumbar puncture, bone marrow examination and scintigraphy]), and work disability. Direct healthcare costs were estimated by the frequency with which resources were used during follow-up and their unit cost (based on hospital accounts, Table S4). In the case of medical prescriptions, the retail price/package at the time of prescription was obtained from Bot Plus, a database of the General Council of Colleges of Official Pharmacists of Spain (22). The cost of lost productivity (indirect healthcare costs) was estimated on the basis of the number of days and percentage of patients on sick leave due to temporary or permanent disability in people aged <65 years old and the mean salary of the Spanish population, according to the National Institute of Statistics (23).

Statistical methods

Descriptive univariate statistical analyses were performed for the variables of interest in each study group. Qualitative variables were described using absolute and relative frequencies (N, %), and quantitative variables with means and standard deviations (SD) (symmetric distributions) or medians and interquartile ranges (IQR, P25-P75; Q1-Q3) (asymmetric distributions). Confidence intervals (CI) of 95% were calculated for the estimation of population parameters.

SPSSWIN version 27 was used for statistical analysis; values $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics

In 2021, the BIG-PAC® database contained information on 1,818,588 patients from public primary care centres and hospitals in Spain. Due to the nature of our analysis, we divided this population into two groups according to their age: paediatric population (<18 years old) and adult population (≥ 18 years old). This reduced the two groups to 360,587 and 1,458,001 patients, respectively. From 2014 to 2020, 288,258 children and 1,254,879 adults sought medical care. Two patients initially diagnosed with ITP were excluded due to data inconsistency or inclusion/exclusion criteria (Table S1). A final diagnosis of ITP was established in 27 children and 170 adults. Of these, 6 and 44 were diagnosed with cITP, respectively. A summary of attrition is shown in Figure 1.

The mean age of the children with cITP was 9.9 years while that of the adults was 69.2 years. Most patients in the cITP subgroups were female (83.3% of children and 59.1% of adults). In both groups, patients with cITP were older than their counterparts in the overall ITP population (mean age was 9.9 [SD 3.4] vs 6.7 [SD

3.5] years old in children and 69.2 [SD 15.4] vs 58.5 [SD 18.4] years old in adults). In general, patients with cITP had more comorbidities than the overall ITP group (mean 3.8 [SD 1.9] vs 2.5 [SD 1.8]). The most common comorbidities in ITP patients were arterial hypertension (25.9%), infectious diseases (12.7%), diabetes (12.2%) and cardiovascular diseases (11.2%). The distribution of these comorbidities in patients with cITP was 46.0%, 14.0%, 26.0% and 12.0%, respectively. In addition, comorbidities such as previous bleeding (14.0%), anaemia (12.0%), neoplasm (12.0%) or gastrointestinal disease (12.0%) were also common in cITP patients. The mean CCI was 0.9 [SD 1.3] in the ITP group, and 2.4 [SD 1.6] in the cITP group; most adult patients in the cITP group had a CCI score of +2 (88.6%). Children with cITP had a CCI of 0. Baseline characteristics are outlined in Table 1.

Clinical characteristics

Clinical characteristics are shown in Table 2. Mean and median follow-up in the overall ITP population were very similar between paediatric and adult patients. Patients were followed for a mean/median of four years; 47.7% were newly diagnosed. The most common bleeding event in both children and adults was epistaxis (61.9%), followed by genitourinary bleeding (15.2%), and gastrointestinal bleeding (7.6%). Bleeding at other sites represented the 21.8% of cases. Intracranial bleeding was reported in only one adult patient (Table 2). Major bleeding requiring hospital admission was 8.1%.

In patients with cITP, median follow-up was 3.6 (1.6 – 5) years; children had longer follow-up than adults, although this was not statistically significant. The most common bleeding events in this population were epistaxis, (which was less frequent in children (33.3%) than adults (84.1%)), and gastrointestinal bleeding (20.0%). Genitourinary (18.2%) and intracranial (2.3%) bleeding were reported only in the

adult population, as well as bleeding at other sites (22.7%). Major bleeding requiring hospitalisation was present in 16.0% of the population (Table 2).

Regarding other variables, more than half of the patients in the ITP group and >75% of the cITP patients suffered from fatigue/asthenia. Transfusions were twice as frequent in cITP patients as in the overall ITP population, and mortality was also increased in the cITP population (Table 2).

In addition, mean and median platelet counts at baseline were lower in cITP patients than in the overall ITP population and lower in children than in adults. At the end of follow-up, total ITP patients still had higher mean platelet count than cITP patients (126 vs 122.4 x 10⁹ / L) (Table 2).

Prevalence and incidence of ITP in Spain

The prevalence of ITP in the general population was 10.8 (95% CI: 9.7 - 11.9) per 100,000 population. Children had a lower prevalence rate (7.5 [95% CI: 6.4 - 8.6]) compared to adults (11.7 [95% CI: 10.6 - 12.8]) ($p<0.001$). This trend was also observed for cITP. The prevalence rate was 2.7 (95% CI: 2.5 - 2.9), 1.7 (95% CI: 1.5 - 1.9) and 3.0 (95% CI: 2.8 - 3.2) for the whole ITP cohort, children, and adult patients, respectively (Table 3).

However, the annual incidence rate of ITP in adults (1.4 per 100,000 population [95% CI: 1.2 - 1.6]) was lower than in children (2.2 [95% CI: 2.0 - 2.4]) ($p<0.001$). The general incidence rate was 1.5 (95% CI: 1.4 - 1.7). Annual incidence for cITP patients was 0.3 per 100,000 people, and it was higher in children (0.5 per 100,000 people). Incidence and prevalence data are presented in Table 3.

Treatment trends

Overall, the majority of diagnosed patients received treatment (98.0%) (Table 4). Corticosteroids alone (69%) or associated to IVIG (13.7%) were widely used in the first-line setting (84.4% of treated patients) and were administered for a median of 3 cycles ($P_{25} - P_{75}$, 2 - 3). IVIG was used in 28.9% of patients in the first-line setting. Immunosuppressants were the most commonly used drugs in the second-line. There was a similar use of rituximab and eltrombopag, and romiplostim was prescribed less frequently than the other TPO-RA. Fostamatinib was used in 4.5% of adult patients. Only three children required third-line treatment, and each used a different drug (romiplostim, immunosuppressants, or corticosteroids + immunomodulators), and only one had to restart the cycle with the combination of corticosteroids and IVIG. Adult patients who received third-line treatment were most likely to receive TPO-RA (32.4%), followed by immunosuppressants (29.4%) and corticosteroids + immunomodulatory drugs (20.6%). Those who required additional treatment were given corticosteroids (17.6%) or corticosteroids + IVIG (11.8%).

Between 2012 and 2019, five and thirty splenectomies/splenic embolisations were performed in children and adults, respectively, all in cITP patients (Table 4).

Healthcare resources and management costs associated with ITP

The use of healthcare resources, which includes activities related to medical practice and complementary tests, and work disability are described in Table 5. Visits to primary care, specialised care and emergency departments resulted in an average of 13.9, 6.6 and 1.2 episodes per year in the total ITP population; 15, 9.7 and 1.4 times, respectively, in cITP patients. Regarding hospitalisation, 48.2% of ITP patients and 86% of cITP patients were hospitalised at least once a year during follow-up, with a mean (SD) of 0.8 (0.9) admissions per ITP patient and 1.5 (0.9) per cITP patient per year, and a mean (SD) of 4.9 (5.8) and 10.7 (5.1) days of stay, respectively.

Significant differences were found between children and adults with ITP in day hospital visits, laboratory tests and other tests. Children with ITP spent more time in the hospital than adults (mean [SD], 1.6 [1.0] vs 1.1 [0.8] days), while adults with ITP had more laboratory tests (mean [SD], 7.8 [3] vs 11.7 [3.5]) and other tests (mean [SD], 1.2 [0.8] vs 3.4 [1]). These differences were more pronounced in the cITP population, where children spent a mean (SD) of 12.5 (0.5) days in hospital compared to 1.3 (0.75) days for adults. In addition, children with cITP underwent a mean (SD) of 11.7 (2.1) laboratory tests and adults, 15.4 (2.1) per year. Finally, other tests were performed more often in adults than in children with cITP (mean [SD], 1.5 [0.8] vs. 3.7 [0.8]). Regarding work incapacity, 26.6% of adult patients with ITP required sick leave and spent an average of 16.3 (37.8) days of sick leave annually. The distribution of patient costs is shown in Table 6. Mean (SD) annual total cost for ITP patients was €10,741 (11,285). This cost was almost doubled for patients with cITP (€19,809 [14,656]). For patients with cITP, the mean annual cost of specialised care (€891 [€311]) was twice the cost of primary care (€357 [€175]). Medication costs were the most expensive item (€11,597 [€13,885]), followed by hospitalisation (€5,165 [€2,467]).

Discussion

To the best of our knowledge, this is the first study to focus on the epidemiology, characteristics, treatment choices, healthcare resources and costs of the primary ITP population in children and adults in Spain. The information gathered here captures the reality of patients living with ITP and cITP between 2014 and 2020. Data show that patients with ITP have a unique set of characteristics, in terms of comorbidities, and use of healthcare resources, with all the strengths and limitations of the methodology used.

Patients living with ITP experience a range of symptoms, such as the risk of bleeding or fatigue, which negatively affect their HRQoL (1, 2, 6, 7, 17, 24). In our study, epistaxis was the most common type of bleeding, followed by genitourinary and gastrointestinal bleeding. Major bleeding requiring hospital admission, was only 8.1% of cases in the ITP population (16.0% in cITP patients), despite many patients had risk factors for haemorrhages.

Epidemiological data in our analysis showed that the prevalence of ITP in Spain was 10.8 (95% CI: 9.7 - 11.9) per 100,000 inhabitants in 2021, and that of cITP, 2.7 (95% CI: 2.5 - 2.9), similar to results obtained in other locations (12, 25). In addition, adults had a higher prevalence of ITP and cITP than children, which has been previously reported in the literature (12, 26, 27). The incidence was higher in children, similar to previous findings (25).

Regarding treatments, previous data from the Spanish ITP population was reported by Palau *et al.*, who performed an observational study using information from the Haematology Services Registry between 2009 and 2011 (28). In their study, 81.1% of diagnosed patients received treatment, in contrast to our study where 98.0% of diagnosed patients were treated. These frequencies are in contrast to other international studies reporting 50% and 75% of patients treated (29, 30). However, study populations were different in all cases, a situation that should be considered to properly analyse these data. For example, the selection periods differed in all studies compared to our study (we used data from 2014 to 2020): Palau *et al.* reported data from 2009 to 2011,(28) Weide *et al.* from 1995 to 2014,(29) and Depre *et al.*, from 1996 to 2016.(30) In addition, our study was at a national level (BIG-PAC® has demonstrated representativeness at a national level)(21, 31), while Palau *et al.* study was regional,(28) Weide *et al.* patients were in a community-based oncology group

practice in Germany and only outpatients treated by haematologists would be considered,(29) and Depre et al. patients were from a single institution.(30)

In accordance with recommendations in guidelines, in our study corticosteroids were the most commonly used first-line treatment (in 82.7% of cases in our study; 73.4% in the study by Palau *et al.*) (28), and patients were re-exposed to corticosteroids for a median of 3 cycles (in Palau *et al.*, 59.5% of patients received corticosteroids for more than 6 weeks). Prolonged use of this type of therapy is known to have important side effects (hyperglycaemia, hypertension, mood and sleep changes, Cushing's syndrome, osteoporosis, etc.) (32), increasing disease burden, and contributing to decreasing patients' HR-QoL (14, 33). It has also been shown to adversely affect growth and development in children (32). Nevertheless, a recent review suggested that corticosteroids remain the main drug administered in current practice for ITP (33). Romiplostim and eltrombopag were approved by the European Medicines Agency (EMA) in 2009 (34) and 2010 (35), respectively; TPO-RAs have been available as second-line treatment in Spain since 2010-2011, initially as therapies to be considered when splenectomy was contraindicated, or patients were not willing to undergo the surgical procedure (36). Currently, according to the American Society of Hematology (37) and the International Consensus Report (11), these agents constitute a recommended second-line therapy immediately after corticosteroid failure. It is therefore striking to see that immunosuppressants and immunomodulatory drugs (danazol, cyclophosphamide, mycophenolate, and azathioprine) were the most commonly used second-line drugs in our study. In addition, it should be noted that, contrary to recommendation in guidelines, 70.5% of the patients in this study were treated with 3 or more cycles of corticosteroids (with or without IVIG) before initiating second-line therapy. This is a substantial gap from

current guidelines (11, 37), which recommend a rapid switch to second-line therapy after a first course of steroids. Similarly, a study conducted in Spain that included patients diagnosed with ITP between 2011 and 2012 showed that more than one-third of patients who were re-treated due to failure or loss of response to prior steroid therapy were re-exposed to corticosteroids for two additional cycles (38). Similar to current findings, the previous study also showed that TPO-RA were used immediately after failure of first-line therapy in only 25% of patients (38)

Immunosuppressants and immunomodulatory drugs were previously used as alternatives due to their lower cost and greater availability, but according to their data on their efficacy and safety, they are currently only recommended in patients who cannot tolerate or do not respond to other evidenced-based second-line therapies (39). The fact that this study includes patients who are followed up in non-specialist clinics and in primary care may be the reason for these data. Thus, it is possible that the out-of-hospital setting and also the management by physicians who are not necessarily experts in this disease explains an overuse of immunosuppressants and immunomodulators with respect to current recommendations.

Four patients received fostamatinib as second-line treatment; this drug was recently approved by the EMA in late 2019 (14), and in Spain in June 2020. It is likely that, together with the available treatments, fostamatinib and other recent-approved drugs such as avatrombopag will change the treatment landscape and improve patient's health and HRQoL in the near future.

In 2011, splenectomy was considered the standard second-line treatment for ITP (36). Since the availability of the TPO-RA has substantially changed this practice, we decided to analyse the number of splenectomies performed before and after 2016 to confirm an apparent change in patient management. Indeed, this change is reflected

in the number of splenectomies performed before and after 2016 (5 vs 0 in children and 26 vs 4 in adult patients). In terms of patient differences, all splenectomies were performed in cITP patients, according to guidelines (11).

ITP patients' symptoms and HRQoL have sometimes a worse outcome than those in patients with other chronic diseases (40). We cannot directly compare the distribution of costs with other diseases because of the different time period, but it is worth noting that our results indicate that the annualised mean (SD) cost of hospitalisation episodes in the total population of patients with ITP was €2,365 (€2,792) and in cITP was €5,165 (€2,467). Previous data indicate that hospitalization due to cardiovascular disease had a cost of €2146 (€4947) in 2019 and decreased over time (41), and hospital admissions for patients with type 2 diabetes mellitus (2DM) initiating treatment with glucagon-like peptide-1 receptor agonists also had lower costs (mean [SD] 588.3 [1642.6], data calculated in 2020 based on 2017 unit prices) than cITP patients and the total ITP population. In this last case, comparison of our data and data gathered by Norrbacka *et al.* indicated that primary care and specialist visits, laboratory tests, computed tomography, nuclear magnetic resonance, and medication costs were higher for ITP and cITP patients than for those with 2DM. In fact, 2- fold and 3-fold increases are observed in specialist visit, laboratory tests, nuclear magnetic resonance, and medication with regards to 2DM vs ITP, while 3-, 4-, 5- and 6-fold increases were evident in the same categories when compared to cITP costs. (42) (Table 6).

This retrospective study has the inherent limitations intrinsic to these types of studies: some variables may be missing or there may be selection bias. In addition, as the BIG-PAC® database is an administrative database with information from seven different health care sectors, limitations inherent to its nature may be present

(the data source may be incomplete, and disease categorisation, patient classification or cost range may be subject to bias). For example, if the primary ITP diagnosis were incorrect, and the specialists did not remove it from the medical history after confirming a wrong diagnosis, this patient would be considered to have an ITP diagnosis, which would overestimate our population. Lastly, it is worth noting that, although hospitalisations were associated with ITP, they could be caused by reasons other than bleeding, but still attributable to ITP according to the specialist. Future studies including the cause of admission could help to identify the impact of treatments, e.g. negative outcomes produced by possible infections caused by the treatment, or, on the contrary, early treatment improving patients' HRQoL.

Conclusion

This is the first study to analyse aspects of the epidemiology, treatment landscape, healthcare resources use and management costs of ITP in Spain. Paediatric and adult patients with ITP suffer a significant burden, which is accentuated by the chronification of the disease. In addition, the choice of treatment, which highlights an overuse of corticosteroids coupled with an underuse of two-line treatments such as TPO-RA, increased medical visits, and sick leave, among others, contribute to the increase in direct and indirect costs, which seem to be higher than in other chronic pathologies. Therefore, information on the above variables could be of interest to health authorities and health policy makers.

CONFLICTS OF INTEREST

TJGL has received research grants from Amgen, Novartis, Sobi and Grifols and speaker honoraria from Amgen, Novartis, Sobi, Grifols, Momenta, Alpine and Argenx; GA was an employee of SOBI at the time of the study realization; she is currently an

employee of CSL Vifor; EB, MESS, and JLL are employees of SOBI; ERG and IH are employees of Atrys Health; and MLL received consultancy fees from Amgen, Novartis, Grifols, Argenx, Sobi, and UCB.

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BIBLIOGRAPHY

1. Al-Samkari H, Cronin A, Arnold DM, Rodeghiero F, Grace RF. Extensive variability in platelet, bleeding, and QOL outcome measures in adult and pediatric ITP: Communication from the ISTH SSC subcommittee on platelet immunology. *Journal of Thrombosis and Haemostasis*. 2021;19(9):2348-54 %U <https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.15366>.
2. Kistangari G, McCrae KR. Immune thrombocytopenia. *Hematology/Oncology Clinics of North America*. 2013;27(3):495-520.
3. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, 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):2386-93.
4. Kohli R, Chaturvedi S. Epidemiology and Clinical Manifestations of Immune Thrombocytopenia. *Hamostaseologie*. 2019;39(3):238-49.
5. Mingot-Castellano ME, Román MTÁ, Fernández Fuertes LF, González-López TJ, Guinea de Castro JM, Jarque I, et al. Management of Adult Patients with Primary Immune Thrombocytopenia (ITP) in Clinical Practice: A Consensus Approach of the Spanish ITP Expert Group. *Advances in Hematology*. 2019;2019:4621416.
6. Provan D, Semple JW. Recent advances in the mechanisms and treatment of immune thrombocytopenia. *EBioMedicine*. 2022;76:103820.
7. Efficace F, Mandelli F, Fazi P, Santoro C, Gaidano G, Cottone F, et al. Health-related quality of life and burden of fatigue in patients with primary immune thrombocytopenia by phase of disease. *American Journal of Hematology*. 2016;91(10):995-1001.
8. Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, et al. Immune thrombocytopenia (ITP) World Impact Survey (I-WISH): Impact of ITP on health-related quality of life. *American Journal of Hematology*. 2021;96(2):199-207.
9. Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. *Blood*. 2017;129(21):2829-35.
10. Orphanet: Portal de información de enfermedades raras y medicamentos huérfanos. Immune thrombocytopenia 2020 [Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?data_id=784&lng=en.
11. Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Advances*. 2019;3(22):3780-817 %U <https://doi.org/10.1182/bloodadvances.2019000812>.

12. Segal JB, Powe NR. Prevalence of immune thrombocytopenia: analyses of administrative data. *Journal of thrombosis and haemostasis: JTH*. 2006;4(11):2377-83.
13. Jiang D, Al-Samkari H, Panch SR. Changing Paradigms in ITP Management: Newer Tools for an Old Disease. *Transfusion Medicine Reviews*. 2022;36(4):188-94.
14. González-López TJ, Provan D. Proposal for a New Protocol for the Management of Immune Thrombocytopenia (ITP). *Advances in Therapy*. 2022;39(6):2287-91.
15. Recomendaciones del Grupo de Trabajo de la SyG. Directrices de diagnóstico, tratamiento y seguimiento de la PTI %U https://www.hematoportal.es/sites/default/files/2021-04/directricesdediagnosticotrata mientoyseguimientodelapti.pdf_3.pdf. 2021.
16. Song F, Al-Samkari H. Management of Adult Patients with Immune Thrombocytopenia (ITP): A Review on Current Guidance and Experience from Clinical Practice. *Journal of Blood Medicine*. 2021;12:653 %U <https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8323851/>.
17. Cooper N, Cines DB. The child with immune thrombocytopenia: to treat or not to treat, is that still the question? *Haematologica*. 2019;104(11):2132-4 %U <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6821618/>.
18. Pogna EA, Middleton S, Nazir J, Ralph L, Wilson K, Jurczak W. Characterization and treatment of immune thrombocytopenia in Europe: a qualitative observational study. *Hematology (Amsterdam, Netherlands)*. 2021;26(1):860-9.
19. Shaw J, Kilpatrick K, Eisen M, Tarantino M. The incidence and clinical burden of immune thrombocytopenia in pediatric patients in the United States. *Platelets*. 2020;31(3):307-14.
20. Weycker D, Hanau A, Hatfield M, Wu H, Sharma A, Bensink ME, et al. Primary immune thrombocytopenia in US clinical practice: incidence and healthcare burden in first 12 months following diagnosis. *Journal of Medical Economics*. 2020;23(2):184-92.
21. Sicras-Mainar A, Enriquez JL, Hernández I, Sicras-Navarro A, Aymerich T, Leon M. PMU146 validation and representativeness of the spanish big-pac database: integrated computerized medical records for research into epidemiology, medicines and health resource use (real word evidence). *Value in Health*; 2019.
22. Consejo General de Colegios Oficiales de Farmacéuticos. BOT Plus 2. Base de Datos de Medicamentos [Available from: <https://botplusweb.portalfarma.com/>].
23. Instituto Nacional de Estadística. Ganancia media laboral por edad y sexo [Available from: [https://www.ine.es/dynt3/inebase/index.htm? padre=4563&capsel=4563](https://www.ine.es/dynt3/inebase/index.htm?padre=4563&capsel=4563)].
24. Grace RF, Neunert C. Second-line therapies in immune thrombocytopenia. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):698-706.
25. Terrell DR, Beebe LA, Neas BR, Vesely SK, Segal JB, George JN. Prevalence of primary immune thrombocytopenia in Oklahoma. *Am J Hematol*. 2012;87(9):848-52.
26. Bennett CM, Neunert C, Grace RF, Buchanan G, Imbach P, Vesely SK, Kuhne T. 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).
27. Neunert CE, Buchanan GR, Imbach P, Bolton-Maggs PH, Bennett CM, Neufeld E, 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):4457-62.

28. Palau J, Sancho E, Herrera M, Sánchez S, Mingot ME, Upegui RI, et al. Characteristics and management of primary and other immune thrombocytopenias: Spanish registry study. *Hematology (Amsterdam, Netherlands)*. 2017;22(8):484-92.

29. Weide R, Feiten S, Friesenhahn V, Heymanns J, Kleboth K, Thomalla J, et al. Outpatient Management of Patients with Immune Thrombocytopenia (ITP) by Hematologists 1995-2014. *Oncol Res Treat*. 2016;39(1-2):41-4.

30. Depré F, Aboud N, Mayer B, Salama A. Efficacy and tolerability of old and new drugs used in the treatment of immune thrombocytopenia: Results from a long-term observation in clinical practice. *PLoS One*. 2018;13(6):e0198184.

31. Sicras-Mainar A, Sicras Navarro A, Enríquez JL, Hernández I, Aymerich T, León M, et al. Validation and representativeness of the Spanish BIG-PAC Database: integrated computerized medical records for research into epidemiology, medicines and health resource use (Real World Evidence). *ISPOR Europe Copenhagen2019*.

32. Monteagudo E, Astigarraga I, Cervera Á, Dasí MA, Sastre A, Berrueco R, Dapena JL. Protocolo de estudio y tratamiento de la trombocitopenia inmune primaria: PTI-2018. *Anales de Pediatría*. 2019;91(2):127.e1-e10 %U <https://linkinghub.elsevier.com/retrieve/pii/S1695403319301821>.

33. Cuker A, Liebman HA. Corticosteroid overuse in adults with immune thrombocytopenia: Cause for concern. *Res Pract Thromb Haemost*. 2021;5(6):e12592.

34. European Medicines Agency. Summary of the European public assessment report (EPAR) for Nplate 2022 [Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/nplate>].

35. European Medicines Agency. Summary of the European public assessment report (EPAR) for revolade 2023 [Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/revolade>].

36. Sociedad Española de Hematología y H. Directrices de diagnóstico, tratamiento y seguimiento de la PTI: documento de consenso. Madrid: Prodrug Multimedia %@ 978-84-95972-63-7; 2011.

37. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-66.

38. Lozano ML, Revilla N, Gonzalez-Lopez TJ, Novelli S, González-Porrás JR, Sánchez-Gonzalez B, et al. Real-life management of primary immune thrombocytopenia (ITP) in adult patients and adherence to practice guidelines. *Annals of Hematology*. 2016;95(7):1089-98.

39. Cuker A. Transitioning patients with immune thrombocytopenia to second-line therapy: Challenges and best practices. *American Journal of Hematology*. 2018;93(6):816-23 %U <https://onlinelibrary.wiley.com/doi/10.1002/ajh.25092>.

40. McMillan R, Bussel JB, George JN, Lalla D, Nichol JL. Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. *American Journal of Hematology*. 2008;83(2):150-4.

41. Escobar C, Varela L, Palacios B, Capel M, Sicras A, Sicras A, et al. Costs and healthcare utilisation of patients with heart failure in Spain. *BMC Health Serv Res*. 2020;20(1):964.

42. Norrbacka K, Sicras-Mainar A, Lebec J, Artime E, Diaz S, Tofe-Povedano S, et al. Glucagon-Like Peptide 1 Receptor Agonists in Type 2 Diabetes Mellitus: Data from a Real-World Study in Spain. *Diabetes Ther*. 2021;12(5):1535-51.

Figure 1. Study overview



Supplementary material

Table S1. Inclusion and exclusion criteria	
INCLUSION CRITERIA	EXCLUSION CRITERIA
a) Patients with a diagnosis of ITP b) Patients included in the database for ≥ 12 months, prior to study entry, c) Enrolled in the program for obtaining prescriptions (with recorded daily dose, time interval and duration of each treatment administered; ≥ 2 prescriptions during the follow-up period), d) Regular monitoring of patients (≥ 2 health records in the computer system)	a) Subjects transferred to other centres, displaced or out-of-area, b) Residents of nursing homes, c) Patients with secondary immune thrombocytopenia or any other cause of thrombocytopenia other than primary ITP.

Table S2. ICD-9-CM codes of sign and symptoms of ITP	
	ICD-9-CM Codes
Bleeding episodes	
Intracranial bleeding	430, 431, 432.x, 852.x, 853.x
Gastrointestinal bleeding	456.0, 456.20, 459.0x, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
Genitourinary bleeding	593.81, 596.7x, 596.89, 599.7x, 602.1x, 620.1, 621.4, 622.8, 626.2, 626.5, 626.7, 626.8, 626.9
Nasal bleeding (epistaxis)	784.7
Other events	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 719.1x, 782.7, 784.8, 786.3x, 958.2, 997.02, 998.11, 99.04
Fatigue/asthenia	780.79

Transfusions	99.0
ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification	

Table S3. Anatomical Therapeutic Chemical Classification System (ATC) codes for the treatment drugs and ICD-9-CM codes for splenectomies (1)

DRUG	CODE
azathioprine	L04AX01
cyclophosphamide	L01AA01
cyclosporin	L04AD01
danazol	G03XA01
dexamethasone	H02AB02
eltrombopag	B02BX05
fostamatinib	B02BX09
intravenous immunoglobulin therapy	J06BA
methylprednisolone	H02AB04
mycophenolate	L04AA06
prednisolone	H02AB06
prednisone	H02AB07
rituximab	L01XC02
romiplostim	B02BX04
partial and total splenectomies	41.43 and 41.5

1. World Health Organization. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD) [Available from: <https://www.who.int/standards/classifications/other-classifications/the-anatomical-therapeutic-chemical-classification-system-with-defined-daily-doses>].

Table S4. Table of costs (unit cost [€])^a

Medical visits
Primary care medical visit

23.19

Specialized care medical visit ^b	92.00
Emergency medical visit	117.53
Hospitalization (one day)	480.90
Day hospital visit	185.00

Complementary tests

Laboratory tests	22.30
Conventional radiology	18.50
Computed tomography	96.00
Magnetic nuclear resonance	177.00
Other tests	37.50

Pharmaceutical prescription

Retail price

Work disability - Indirect costs

Cost per day not worked ^c	101.20
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^aIt includes costs related to ITP; ^bOnly in Haematology and Internal medicine departments; ^cNational Institute on Statistics (INE). Average employment earnings by age and sex. Sources: Sicras-Mainar et al., 2015(2) and INE(3)

2. Sicras-Mainar A, Enriquez JL, Hernández I, Sicras-Navarro A, Aymerich T, Leon M. PMU146 validation and representativeness of the spanish big-pac database: integrated computerized medical records for research into epidemiology, medicines and health resource use (real word evidence). *Value in Health*; 2019.

3. Estadística INE. Ganancia media laboral por edad y sexo [Available from: <https://www.ine.es/dynt3/inebase/index.htm?padre=4563&capsel=4563>].

Table 1. Baseline characteristics (demographics and comorbidity) of the population of the study

Study groups	TOTAL ITP POPULATION				CHRONIC ITP POPULATION			
	Paediatric (<18 years)	Adults (≥18 years)	Total	<i>p</i>	Paediatric (<18 years)	Adults (≥18 years)	Total	<i>p</i>
Number of patients	27 (13.7%)	170 (86.3%)	197 (100%)		6 (12.0%)	44 (88.0%)	50 (100%)	
Sociodemographic characteristics								
Average age (<i>SD</i>), years	6.7 (3.5)	58.5 (18.4)	51.4 (24.8)	<0.001	9.9 (3.4)	69.2 (15.4)	62.1 (24.3)	<0.001
Age ranges								
1 - 6 years	17 (63.0)	0	17 (8.6)		1 (16.7)	0	1 (2.0)	
7 - 17 years	10 (37.0)	0	10 (5.1)		5 (83.3)	0	5 (10.0)	
18 - 44 years	0	42 (24.7)	42 (21.3)	<0.001	0	4 (9.1)	4 (8.0)	<0.001
45 - 64 years	0	61 (35.9)	61 (31.0)		0	13 (29.5)	13 (26.0)	
≥ 65 years	0	67 (39.4)	67 (34.0)		0	27 (61.4)	27 (54.0)	
Gender (females), <i>N</i> (%)	15 (55.6)	94 (55.3)	109 (55.3)	0.980	5 (83.3)	26 (59.1)	31 (62.0)	0.484
Associated comorbidities, <i>N</i> (%)								
Arterial hypertension	1 (3.7)	50 (29.4)	51 (25.9)	0.005	1 (16.7)	22 (50.0)	23 (46)	0.199
Diabetes	1 (3.7)	23 (13.5)	24 (12.2)	0.147	0 (0)	13 (29.5)	13 (26)	0.319
Alcoholism	0 (0.0)	6 (3.5)	6 (3.0)	0.321	0 (0)	4 (9.1)	4 (8)	0.999
Cardiovascular diseases ^a	1 (3.7)	21 (12.4)	22 (11.2)	0.185	0 (0)	6 (13.6)	6 (12)	0.999
Gastrointestinal diseases	2 (7.4)	14 (8.2)	16 (8.1)	0.884	1 (16.7)	5 (11.4)	6 (12)	0.556
Infectious diseases	10 (37.0)	15 (8.8)	25 (12.7)	<0.001	1 (16.7)	6 (13.6)	7 (14)	0.999
Bone diseases	1 (3.7)	12 (7.1)	13 (6.6)	0.514	0 (0)	3 (6.8)	3 (6)	0.999
Fractures	1 (3.7)	7 (4.1)	8 (4.1)	0.919	0 (0)	5 (11.4)	5 (10)	0.999
Thyroid disease	1 (3.7)	10 (5.9)	11 (5.6)	0.647	0 (0)	4 (9.1)	4 (8)	0.999
Neoplasms (malignant tumours)	1 (3.7)	9 (5.3)	10 (5.1)	0.727	1 (16.7)	5 (11.4)	6 (12)	0.556
Previous bleeding	2 (7.4)	12 (7.1)	14 (7.1)	0.948	0 (0)	7 (15.9)	7 (14)	0.576
Anaemia	1 (3.7)	9 (5.3)	10 (5.1)	0.727	0 (0)	6 (13.6)	6 (12)	0.999
General comorbidity								
Chronic diseases, mean (<i>SD</i>)	0.9 (0.9)	2.8 (1.7)	2.5 (1.8)	<0.001	1 (1.5)	4.2 (1.6)	3.8 (1.9)	<0.001
Charlson index, mean (<i>SD</i>)	0.2 (0.4)	1.0 (1.3)	0.9 (1.3)	0.002	0 (0)	2.7 (1.4)	2.4 (1.6)	<0.001
Charlson index, <i>N</i> (%)								

0	22 (81.5)	80 (47.1)	102 (51.8)		6 (100)	0 (0)	6 (12)	
1	5 (18.5)	46 (27.1)	51 (25.9)	0.010	0 (0)	5 (11.4)	5 (10)	<0.001
2+	0 (0.0)	44 (25.9)	44 (22.3)		0 (0)	39 (88.6)	39 (78)	

^aIncluded: Ischemic cardiopathy, stroke and heart failure; Values expressed in *N* (percentage) or mean (*SD*: standard deviation); *p*: statistical significance. ITP, Immune Thrombocytopenia

Table 2. Clinical variables associated with Immune Thrombocytopenic

Study groups	TOTAL ITP POPULATION				CHRONIC ITP POPULATION			
	Paediatric (<18 years)	Adults (≥18 years)	Total	<i>p</i>	Paediatric (<18 years)	Adults (≥18 years)	Total	<i>p</i>
Number of patients	27 (13.7%)	170 (86.3%)	197 (100%)		6 (12%)	44 (88%)	50 (100%)	
Follow-up period, years								
Mean (<i>SD</i>)	4.1 (1.2)	4.1 (1.8)	4.1 (1.7)	0.587	4.4 (1.9)	3.3 (1.9)	3.4 (1.9)	0.210
Median (P25; P75)	4 (4 - 5)	4 (3 - 6)	4 (3 - 6)		4.4 (4.2 - 5.4)	3.4 (1.5 - 4.8)	3.6 (1.6 - 5)	
Follow-up period, patients (ITP), <i>N</i> (%)								
ITP of recent diagnosis ^a	14 (51.9)	80 (47.1)	94 (47.7)					
Persistent ITP ^b	7 (25.9)	46 (27.1)	53 (26.9)	0.884				
Chronic ITP ^c	6 (22.2)	44 (25.9)	50 (25.4)					
Bleeding events, <i>N</i> (%)								
Intracranial bleeding	0 (0.0)	1 (0.6)	1 (0.5)	0.689	0 (0)	1 (2.3)	1 (2)	0.999
Gastrointestinal bleeding	1 (3.7)	14 (8.2)	15 (7.6)	0.410	1 (16.7)	9 (20.5)	10 (20)	0.999
Genitourinary bleeding	3 (11.1)	27 (15.9)	30 (15.2)	0.522	0 (0)	8 (18.2)	8 (16)	0.572
Other events	9 (33.3)	34 (20.0)	43 (21.8)	0.119	0 (0)	10 (22.7)	10 (20)	0.327
Nasal bleeding (epistaxis)	15 (55.6)	107 (62.9)	122 (61.9)	0.463	2 (33.3)	37 (84.1)	39 (78)	0.017
Major bleeding with hospital admission	2 (7.4)	14 (8.2)	16 (8.1)	0.884	1 (16.7)	7 (15.9)	8 (16)	0.999
Other variables, <i>N</i> (%)								
Fatigue / asthenia	13 (48.1)	96 (56.5)	109 (55.3)	0.419	4 (66.7)	34 (77.3)	38 (76)	0.621
Transfusions	2 (7.4)	15 (8.8)	17 (8.6)	0.808	1 (16.7)	8 (18.2)	9 (18)	0.999
Death (all causes)	0 (0)	2 (1.2)	2 (1.0)	0.571	0 (0)	1 (2.3)	1 (2)	0.999
Clinical parameters								

<i>Platelet count. initial (baseline), × 10⁹/L</i>								
Mean (SD)	12.5 (8.5)	13.9 (7.8)	13.7 (7.8)	0.658	10.5 (9)	12.4 (7)	12.2 (7)	0.386
Median (P25; P75)	11 (5 - 18)	13 (8 - 18)	12 (8 - 18)		8 (4.5 - 12)	10 (7 - 18)	10 (7 - 18)	
<i>Platelet count, end of follow-up, × 10⁹/L</i>								
Mean (SD)	127.8 (23.6)	125.7 (19.6)	126 (20.2)	0.692	123 (32)	122.3 (21)	122.4 (22)	0.581
Median (P25; P75)	121 (110 - 145)	122 (112 - 135)	122 (112 - 137)		106 (103.25 - 136)	116 (105 - 135)	115 (104.2 - 135)	
^a 3 months from diagnosis; ^b between 3 - 12 months from diagnosis; ^c > 12 months from diagnosis; Values expressed in <i>N</i> (percentage) or mean (SD: standard deviation); <i>p</i> : statistical significance; P: percentile. ITP, Immune Thrombocytopenia								

Table 3. Incidence and prevalence of immune thrombocytopenia		
TOTAL		
Population on the 31 st of December 2021	1,818,588	
Patients with a diagnosis of ITP	197	
New diagnoses of ITP	28	
ITP	197	
Prevalence rate (100 000 inhabitants)	10.8	(95% CI: 9.7 – 11.9)
Incidence rate (100 000 inhabitants)	1.5	(95% CI: 1.4 – 1.7)
cITP	50	
Prevalence rate (100 000 inhabitants)	2.7	(95% CI: 2.5 – 2.9)
Incidence rate (100 000 inhabitants)	0.3	(95% CI: 0.2 – 0.4)
PAEDIATRIC (<18 years)		
Population on the 31 st of December 2021	360,587	
Patients with a diagnosis of ITP	27	
New diagnoses of ITP	8	
ITP	27	

Prevalence rate (100 000 inhabitants)	7.5	(95% CI: 6.4 – 8.6)
Incidence rate (100 000 inhabitants)	2.2	(95% CI: 2.0 – 2.4)
cITP	6	
Prevalence rate (100 000 inhabitants)	1.7	(95% CI: 1.5 – 1.9)
Incidence rate (100 000 inhabitants)	0.5	(95% CI: 0.3 – 0.7)
ADULTS (≥ 18 years)		
Population on the 31 st of December 2021	1,458,001	
Patients with a diagnosis of ITP	170	
New diagnoses of ITP	20	
ITP	170	
Prevalence rate (100,000 inhabitants)	11.7	(95% CI: 10.6 – 12.8)
Incidence rate (100,000 inhabitants)	1.4	(95% CI: 1.2 – 1.6)
cITP	44	
Prevalence rate (100,000 inhabitants)	3.0	(95% CI: 2.8 – 3.2)
Incidence rate (100 000 inhabitants)	0.3	(95% CI: 0.2 – 0.4)
CI, confidence intervals, cITP, Chronic Immune Thrombocytopenia; ITP, Immune Thrombocytopenia.		

Study groups	Total ITP patients			<i>p</i>
	Paediatric (<18 years)	Adults (≥18 years)	Total	
Number of patients	27 (13.7%)	170 (86.3%)	197 (100%)	
Therapeutic procedures				
Splenectomy, N (%)				
Before index date [†]	5 (18.5)	26 (15.3)	31 (15.7)	

<i>After index date[†]</i>	0 (0)	4 (2.4)	4 (2)	
<i>During active period - pre&post index date^a</i>	5 (18.5)	30 (17.6)	35 (17.8)	0.912
2012	2 (7.4)	11 (6.5)	13 (6.6)	
2013	1 (3.7)	10 (5.9)	11 (5.6)	
2014	1 (3.7)	4 (2.4)	5 (2.5)	
2015	0 (0)	1 (0.6)	1 (0.5)	
2016	1 (3.7)	0 (0)	1 (0.5)	
2017	0 (0)	1 (0.6)	1 (0.5)	
2018	0 (0)	1 (0.6)	1 (0.5)	
2019	0 (0)	2 (1.2)	2 (1.0)	
Treatments				
Patients in treatment, N (%)				
No treatment	2 (7.4)	2 (1.2)	4 (2)	
With treatment	25 (92.6)	168 (98.8)	193 (98)	
First line of treatment, N (%)	25	168	193	
Corticosteroids	15 (55.6)	121 (71.2)	136 (69)	
Immunoglobulin G (IVIG)	6 (22.2)	24 (14.1)	30 (15.2)	0.097
Corticosteroids + IVIG	4 (14.8)	23 (13.5)	27 (13.7)	
<i>Not requiring further cycle treatment, N (%)</i>	6	30	36	
Requiring 2nd cycle treatment, N (%)	19	138	157	
Corticosteroids	10 (52.6)	76 (55.1)	86 (54.8)	
IVIG	0 (0)	0 (0)	0 (0)	
Corticosteroids + IVIG	9 (47.4)	62 (44.9)	71 (45.2)	
<i>Not requiring further cycle treatment, N (%)</i>	1	20	21	0.424
Requiring 3rd cycle treatment, N (%)	18	118	136	
Corticosteroids	9 (50)	64 (54.2)	73 (53.7)	
IVIG	0 (0)	0 (0)	0 (0)	
Corticosteroids + IVIG	9 (50)	54 (45.8)	63 (46.3)	0.909
<i>Not requiring further cycle treatment, N (%)</i>	15	117	132	
^L <i>And not requiring 2nd line treatment, N (%)</i>	5	28	33	
Requiring 4th cycle treatment, N (%)	3	1	4	0.008
Corticosteroids	0 (0)	0 (0)	0 (0)	

	(<18 years)		(≥ 18 years)		(<18 years)		(≥ 18 years)	
Number of patients (<i>n</i> , %)	27 (13.7%)	170 (86.3%)	197 (100%)		6 (12%)	44 (88%)	50 (100%)	
Medical practice ^a								
Primary care visits (mean, <i>SD</i>)	12 (8.1)	14.2 (7.9)	13.9 (7.9)	0.183	15 (8)	15 (4)	15 (8)	0.500
Specialised visits ^b (mean, <i>SD</i>)	6.2 (3.1)	6.6 (3.5)	6.6 (3.5)	0.569	11.2 (1.2)	9.5 (3.5)	9.7 (3.4)	0.120
Emergency rooms visits (mean, <i>SD</i>)	0.9 (1.0)	1.2 (1)	1.2 (1)	0.136	1.33 (1.03)	1.45 (0.73)	1.4 (0.8)	0.999
Day hospital sessions (mean, <i>SD</i>)	1.6 (1.0)	1.1 (0.8)	1.2 (0.9)	0.006	12.5 (0.5)	1.3 (0.75)	1.5 (0.8)	0.001
Hospitalized patients, (<i>n</i> , %)	13 (48.2)	82 (48.2)	95 (48.2)	0.993	5 (83.3)	38 (86.4)	43 (86)	0.999
Average/patient. hospital admissions (mean, <i>SD</i>)	0.7 (0.9)	0.8 (0.9)	0.8 (0.9)	0.552	1.2 (1)	1.6 (1)	1.5 (0.9)	0.300
Average/patient of days in hospital (mean, <i>SD</i>)	4.3 (5.6)	5 (5.8)	4.9 (5.8)	0.574	11 (6.5)	10.7 (5)	10.7 (5.1)	0.800
Complementary tests ^a								
Laboratory tests ^c (mean, <i>SD</i>)	7.8 (3)	11.7 (3.5)	11.2 (3.7)	<0.001	11.7 (2.1)	15.4 (2.1)	15 (2.4)	0.002
Conventional radiology (mean, <i>SD</i>)	0.6 (0.5)	0.7 (0.7)	0.7 (0.7)	0.509	1 (0)	1 (0)	1 (0)	0.999
Computed tomography (mean, <i>SD</i>)	0.8 (0.4)	0.9 (0.4)	0.9 (0.4)	0.063	0.8 (0.4)	0.9 (0.5)	0.9 (0.4)	0.500
Magnetic nuclear resonance (mean, <i>SD</i>)	1.9 (1)	1.9 (0.9)	1.9 (0.9)	0.995	3.5 (0.5)	3.1 (0.3)	3.1 (0.3)	0.008
Other tests ^d	1.2 (0.8)	3.4 (1)	3.1 (1.2)	<0.001	1.5 (0.8)	3.7 (0.8)	3.4 (1.1)	<0.001

(mean, SD)								
Work disability ^a								
Patients in sick leave (n, %)	0	45 (26.6)	45 (22.9)	0.002	0	3 (6.8)	3 (6)	0.999
Average/patient sick leave, days (mean, SD)	0	16.3 (37.8)	14.1 (35.5)	0.026	0	2.6 (9.6)	2.3 (9.1)	0.999

^aIt includes costs related to ITP; ^bOnly in Haematology and Internal medicine departments; ^cany conventional lab analysis request; ^dlumbar puncture, bone marrow examination and scintigraphy; Values expressed in percentage (%) or mean (SD: standard deviation); p: statistical significance; ITP, Immune Thrombocytopenia

Table 6. Costs distribution (average patient/year; annualized; EUR)

Study groups	TOTAL ITP POPULATION				CHRONIC ITP POPULATION			
	Paediatric (<18 years)	Adults (≥18 years)	Total	p	Paediatric (<18 years)	Adults (≥18 years)	Total	p
Number of patients	27 (13.7%)	170 (86.3%)	197 (100%)		6 (12%)	44 (88%)	50 (100%)	
<i>Medical practice</i>								
Primary care medical visit	278 (188)	329 (182)	322 (183)	0.183	344 (87)	359 (185)	357 (175)	0.500
Specialised care medical visit	572 (287)	610 (326)	605 (321)	0.569	1,027 (108)	872 (326)	891 (311)	0.120
Emergency medical visit	109 (113)	146 (120)	141 (120)	0.136	157 (121)	171 (86)	169 (89)	0.999
Day hospital sessions	295 (194)	202 (154)	215 (162)	0.006	462 (101)	248 (138)	274 (151)	0.001
Hospitalisation	2084 (2704)	2410 (2811)	2365 (2792)	0.574	5290 (3131)	5148 (2407)	5165 (2467)	0.800
<i>Complementary tests</i>								
Laboratory tests	173 (68)	261 (79)	249 (83)	<0.001	260 (48)	343 (47)	333 (54)	0.002
Conventional radiology	11 (9)	13 (13)	12 (13)	0.509	18.5 (0)	18.5 (0)	18.5 (0)	0.999
Computed tomography	75 (41)	89 (37)	87 (38)	0.063	80 (39)	94 (44)	92 (43)	0.500
Nuclear magnetic resonance	328 (182)	328 (158)	328 (161)	0.995	620 (97)	547 (51)	556 (62)	0.008
Other tests	44 (29)	127 (38)	116 (46)	<0.001	56 (31)	138 (31)	128 (41)	<0.001
Medication cost	4246 (7182)	4977 (9662)	4876 (9349)	0.707	12,378 (8741)	11,490 (14,516)	11,597 (13,885)	0.400
Total Healthcare cost	8215 (9557)	9492 (11,190)	9317 (10,967)	0.575	20,693 (10,830)	19,428 (14,805)	19,580 (14,300)	0.700
Indirect costs (sick leave)	0	1650 (3823)	1423 (3595)	0.026	0 (0)	260 (974)	229 (917)	0.500

days)							
	8215	11,142	10,741	0.211	20,693	19,688	19,809
Total cost	(9557)	(11,509)	(11,285)		(10,830)	(14,656)	(14,162)
Values expressed as mean (SD, standard deviation) per patient/year; Average / patient / year in EUR; p: statistical significance; ITP, Immune Thrombocytopenia							



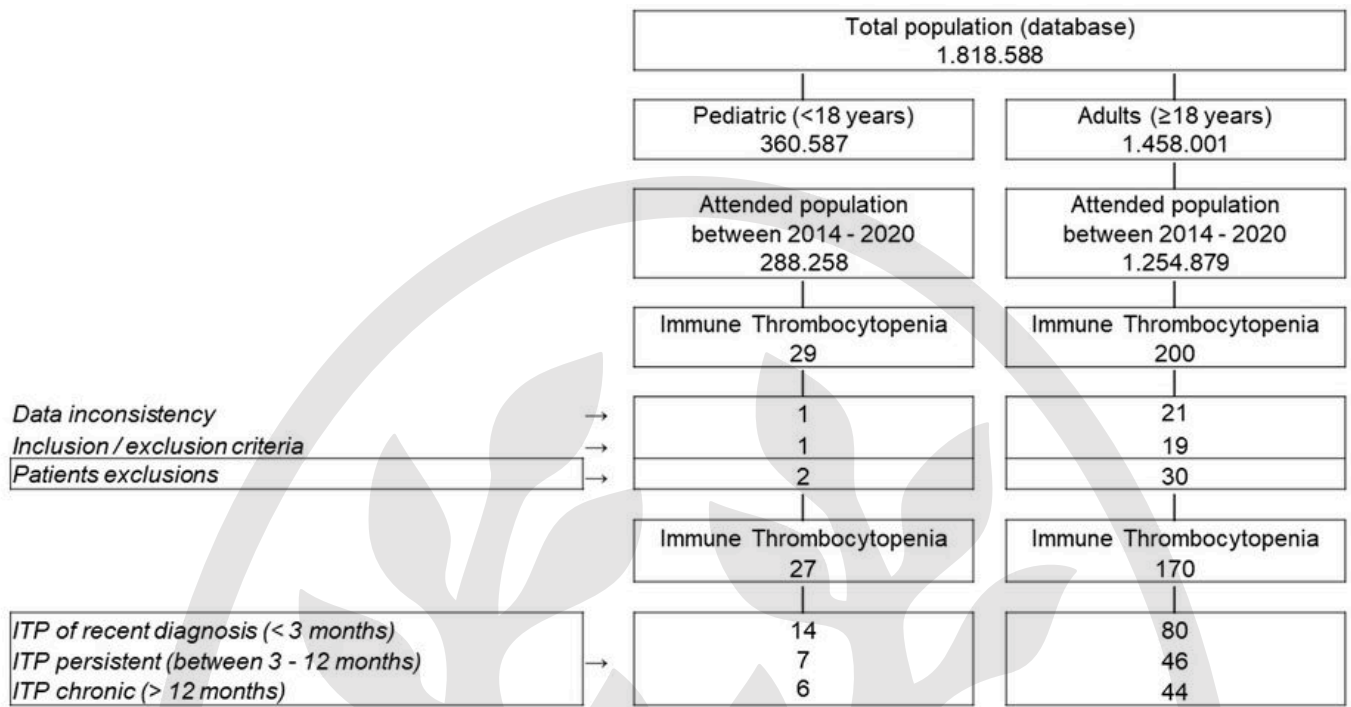


Figure 1. Study overview

