Title: Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France.

Running head: Epidemiology of incident immune thrombocytopenia.

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Incidence of ITP was 2.9/100000 person-years with age, seasonal and regional variations; in adults, 18% were secondary.

Severe (gastrointestinal or CNS) bleeding at ITP onset was rare (<1%); the risk increased with age.
Abstract

Epidemiology of immune thrombocytopenia (ITP) is not well known. The purpose of this study is to assess ITP incidence at a nationwide level (France) with recent data (mid-2009 to mid-2011, 129 248 543 person-years). Data source is French health insurance database. We selected cases with diagnosis codes in hospital stay and long-term disease attributions, thus restricting to ITPs necessitating healthcare. We studied incidence by age, gender, calendar month and regions, the proportion of secondary ITPs, of ITPs becoming persistent or chronic, and of severe bleeding at disease onset. We identified 3771 incident ITP patients. Incidence was 2.9/100 000 person-years with peaks among children and after 60 years. ITP was more frequent among males in these subgroups especially after 75 years (9/100 000 person-years). It was lower in overseas Caribbean French departments, suggesting a lower incidence among Afro-American people. There was a North-South gradient in mainland France and seasonal variations (peak in winter, nadir in summer). Persistence or chronicity occurred in 36% of children, compared with 67% of adults. Among adults, 18% of ITPs were secondary. Malignancy was the main cause (10.9%). Myelodysplastic syndromes were not rare (2.3%). Severe gastrointestinal or central nervous system bleedings at ITP onset were rare (<1%).

Keywords: immune thrombocytopenia; epidemiology
Introduction

Immune thrombocytopenia (ITP) is a rare condition.\(^1\) It is due to a B-cell (and in some patients to a CD8+T-cell) autoimmune reaction directed against circulating platelets and megakaryocytes, leading to life-threatening bleeding in some patients.\(^2\) Though this disease is being studied for more than a century,\(^3\) its epidemiology is not well known and several points need to be clarified:

i) ITP incidence has been estimated from 0.46 to 12.5/100 000 person-years in children and from 1.6 to 3.9/100 000 person-years in adults.\(^4\) The largest epidemiological study has been conducted in the United Kingdom into the Clinical Practice Research Datalink (CPRD) that covers about 3.4 million inhabitants: 1145 ITP cases were identified from 1990 to 2005 leading to an estimated overall incidence of 3.9/100 000 person-years with a peak in older patients.\(^5\) The estimated incidence of pediatric ITP was 4.2/100 000 person-years.\(^6\) Incidence was increased in females except in children and older patients.\(^5,6\) Other population-based studies were underpowered to confirm these particularities.\(^7\)

ii) Various viruses may be environmental factors triggering ITP onset, particularly in pediatric ITP.\(^8\) However, seasonal variations of ITP incidence have not yet been studied in adults.

iii) Incidence of ITP may be lower among black populations but this point is still debated.\(^9,10\) Apart ethnic particularities, geographical factors may affect the incidence of autoimmune diseases.\(^11\) The geographical variations of ITP incidence across a wide area has not yet been assessed.

iv) ITP is said “primary” when not associated to another disease. Secondary ITP might be due to malignancy, systemic autoimmune disease, chronic viral infection such as Human Immunodeficiency Virus (HIV) or Hepatitis Virus B or C (respectively, HBV and HCV), primary immune deficiency, or drugs. Expert opinion estimated that about 20% of ITP cases
are secondary, whereas only 8.7% of the patients had a comorbid condition associated to ITP in the CPRD study. This assessment deserves to be repeated, due to changes in the epidemiology of diseases associated to ITP, such as myelodysplastic syndromes or HIV infection.

v) Prevalence of severe bleeding at diagnosis is not well known. In a multinational ITP registry, gastrointestinal bleeding has been observed in 2.9% of children and 1.2% of adults, and central nervous system (CNS) bleeding in 0.6% and 1.8%, respectively. However, this registry stemmed from reference centers and few adult patients (n=340) were included. Bleeding risk might increase with age, but faithful assessment of such rare events needs larger cohorts.

vi) Based on ancient case-series, the proportion of primary ITP leading to persistency (lasting more than three months) or chronicity (lasting more than twelve months) has been estimated at 20% in children and 70% in adult patients. This information has not been yet confirmed in any population-based study.

The objectives of the present work was to assess at a nationwide scale the overall incidence of ITP requiring healthcare, the incidence by age, gender, seasons and across regions, the proportion of secondary ITP and of ITP leading to persistency, and the frequency of severe bleeding at presentation. Indeed, ITP requiring healthcare represent the population of interest on a public health point of view.

Methods

Data source

Data source is the Système National d'Information Inter-Regimes de l'Assurance Maladie (SNIIR-AM), the unique database of the French National Health Insurance System. This has been widely used to conduct large epidemiological studies. Further information regarding
its organization is provided in Appendix. The SNIIR-AM collects prospectively data on demographic and health expenditures reimbursements of the entire French population (65,586 million inhabitants in January 2013). It includes data on hospital stays, outpatient drug reimbursements, procedures, examinations and sick-leaves. The medical indication for outpatients’ reimbursements is not available, except for patients with a costly long-term disabling disease (LTD), who are fully reimbursed for most of their disease-related expenditures. LTDs and hospital diagnosis codes are encoded with the International Classification of Diseases, version 10 (ICD-10). Demographic data include age, gender, town of residence, date of death, and insurance system. These data are individualized, anonymous, exhaustive, and linkable for a given patient.

SNIIR-AM data extractions cannot excess three years prior to the date of extraction. Identification of ITP patients from the SNIIR-AM has received ethical approval as part of the French Adult primary Immune Thrombocytopenia: a pharmacoepidemiological study (FAITH), an ongoing cohort of all primary ITP adult patients persistently treated in France from 2009 to 2022. FAITH is registered in the European Post-Authorisation Safety studies registry of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (n°ENCePP/SDPP/4574). FAITH methodology has been awarded by the ENCePP study seal approval. All ethical authorizations have been obtained (Institut des Données de Santé approval, n°40, March 2012; Commission Nationale de l’Informatique et des Libertés authorization, n°DE-2012-076, July 2012).

Selection process of incident ITP patients requiring healthcare

Incident ITP patients were identified among patients with hospitalization and/or LTD attribution for ITP. The selection process followed several steps. First, 2009 to 2011 data from patients with a LTD encoded as ITP (ICD-10 code D69.3) and/or at least one hospital
stay with a main or related diagnosis encoded as D69.3 during this period were extracted from the SNIIR-AM.

Second, we dropped out the cases that may have been miscoded. That is, patients having i) a LTD or hospital diagnosis code starting by D69 but different from D69.3 (ITP), D69.6 (“thrombocytopenia, unspecified”) and D69.9 (“hemorrhagic condition, unspecified”), from study start (January 1\textsuperscript{st} 2009) to six months after the occurrence of first ITP code.

Third, we defined the date of diagnosis. For that purpose, we searched for out-hospital dispensing of ITP drugs (systemic steroids, dapsone, danazol, thrombopoietin receptor agonists, azathioprine, ciclosporin, mycophenolate)\textsuperscript{27,28} before the first LTD or hospital stay with ITP code. Date of diagnosis was then defined as: i) the date of first ITP drug dispensing if a patient had a persistent dispensing of ITP drugs before the first LTD or hospital stay with ITP code, or ii) the first LTD or hospital stay with ITP code otherwise. Persistent dispensing was defined as at least three consecutive dispensing within a six-month period.

Lastly, we restricted the cohort to incident patients, excluding those with a date of diagnosis before July 1\textsuperscript{st} 2009. Indeed, we could not assess whether a patient with a date of diagnosis during the first semester of 2009 was prevalent or incident, because we could not access to data prior to January 1\textsuperscript{st} 2009. We also excluded the patients with a date of diagnosis after June 30\textsuperscript{th} 2011 because we could not ascertain the absence of erroneous D69 code during the semester following diagnosis. Therefore, the incident ITP cases included in this study occurred between July 1\textsuperscript{st} 2009 and June 30\textsuperscript{th} 2011, and the follow-up was \(\geq 6\) months for all cases.

\textbf{Definitions}

\textit{Adult patients} are aged of 18 years or more at the date of diagnosis. \textit{Secondary ITP patients} were defined as patients having a new LTD code and/or hospital stay diagnosis code for a
disease associated to ITP from the year before to the semester after the date of diagnosis (ICD-10 codes are detailed in Table 1). Evans syndrome was defined similarly, using the ICD-10 code D59.1 (“autoimmune hemolytic disease”). Persistent or chronic ITP was defined as an ITP LTD attribution, or two hospital stays with ITP code at least three months apart, or a continuous exposure to ITP drugs (including polyvalent intravenous immunoglobulins) during more than three consecutive months, or exposure to rituximab or splenectomy. Because some patients entering in remission during the persistent phase of the disease may have relapsed during the chronic phase after end of follow up, it was not possible to distinguish accurately patients in complete remission at the end of the persistency phase from those who entered the chronic phase of the disease. However, that concerns a very low proportion of patients in practice.29

To assess severe bleedings at diagnosis, we assumed that all the patients with such severe bleeding were hospitalized. We searched the ICD-10 codes corresponding to gastrointestinal and CNS bleeding at first hospital stay for ITP, when its date corresponded to the date of diagnosis.

Statistical analyses

For incidence calculations, we used as denominator French population data edited by the Institut National de la Statistique et des Etudes Economiques (INSEE).30 As there is no detailed data regarding ethnicity in France,31–33 we compared incidence of ITP in mainland France to incidence in overseas French departments (Reunion island and French departments of America: Guadeloupe, Martinique and French Guyana) where black and mixed-race population prevalence is high.34–37 Afro-American population is main ethnic group in Caribbean (Guadeloupe, Martinique) departments.35 We calculated overall incidence and its 95% confidence intervals as well as incidence by age, gender, calendar months and across the
22 mainland administrative regions. To detect variations of incidence across regions, we
directly standardized incidence rates on age (by 10 years intervals) and gender characteristics
of the entire French population, and used the Local Indicators of Spatial Associations (LISA)
method. We searched for a relation between age groups and severe bleeding using a linear
regression model (α=5%).

Results

Patients’ selection

Out of 7890 patients with a LTD or hospital stay diagnosis code D69.3 from January 1st 2009
to December 31st 2011, we identified 3771 incident ITP cases requiring healthcare during a
two-year period (Figure 1), 2885 (76.5%) being adults.

Incidence

Overall ITP incidence was 2.92/100 000 person-years (95%CI: 2.83-3.01). It was higher in
females (3.03/100 000 person-years, 95%CI: 2.90-3.16) than in males (2.77/100 000 person-
years, 95%CI: 2.64-2.90). Incidence was 2.83/100 000 person-years under 18 years of age
(95%CI: 2.63-3.00) and 2.94/100 000 person-years in adults (95%CI: 2.84-3.05). A peak was
observed in children aged 1-5 years, with a highest incidence in younger boys. A second peak
was observed in adults over 60 years, reaching 9/100 000 person-years (95%CI: 8.21-9.95) in
men over 75 years (Figure 2).

Incidence varied cyclically in the year with a peak in January and a nadir in summer
both in adults and children (Figure 3). This finding was observed in all age groups except in
the 0-1 years (peak was in spring, Figure S1) and across regions (data not shown).

Incidence was higher in mainland France (2.93/100 000 person-years, 95%CI: 2.84-
3.02) than in overseas French departments (1.45/100 000 person-years, 95%CI: 1.11-1.89). It
was 1.14/100 000 person-years (95%IC[0.72-1.79]) in Caribbean departments. Mean age at ITP onset was lower in overseas departments in comparison with mainland France (median: respectively, 28 and 48 years, p=0.005), while female gender (respectively, 58.8% and 53.6%, p=0.5) and frequency of severe bleeding at diagnosis (1.44% and 1.35%, p=1) were similar.

Age and gender-standardized incidence is mapped in Figure 4. There was no correlation with population density (data not shown). LISA analyses detected high incidence areas in West-Northern France (centered by Basse-Normandie and Pays de Loire regions) and low incidence areas in Southern France (centered by Midi-Pyrénées region) (p<0.05).

Secondary ITP

Eighteen percent of adult incident ITP patients requiring healthcare had secondary ITP (Table 1). Cancers (mainly hematological) were most frequent. Malignant lymphoid disorders (lymphoma and B-cell chronic leukemia) were observed in 5.9% of incident adult ITPs. Other causes were connective tissue diseases (2.5%, mainly systemic lupus erythematosus), myelodysplastic syndromes (2.3%), immune deficiencies (excluding HIV infection, 1.7%), HIV infection (0.9%), sarcoidosis (0.6%), antiphospholipid syndrome (0.3%) and HCV infection (0.2%). Adult secondary ITP patients were older than primary ITP patients (mean ± standard deviation, 61.5 ± 18.8 versus 56.2 ± 22.0 years, p<0.0001) and were predominantly males (48.4% versus 42.5%, p=0.01), but they had a similar rate of severe bleeding at ITP onset (1.54% versus 1.61%, p=0.9).

ITP was secondary in 2.4% of children cases. Causes were mainly primary immune deficiency, systemic lupus erythematosus, blood cancers and HIV infection. Among children, secondary ITP patients were also older (median ± interquartile range, 7 ± 11 versus 5 ± 10) and were more frequently females (56.5% versus 36.8%).

The frequency of secondary ITP increased with age (Figure 5).
Forty-seven adult patients (1.63%) and 9 children (1.1%) had Evans’ syndrome.

**Persistent or chronic primary ITP patients**

With a mean follow-up of 17.6 ± 6.8 months (range 6-30 months), 1556 (66.7%) of incident primary adult ITPs became persistent or chronic. Fifty-two percent of adult patients had a marker of the disease (ITP hospital diagnosis or LTD, or exposure to any ITP treatment) during the period M12-M18 after the diagnosis, and 47.8% in the M18-M24 period. Among children, 276 (35.7%) incident primary ITP cases were persistent or chronic with a mean follow-up of 17.9 ± 6.7 months (range 6-30 months).

**Major bleeding symptoms at diagnosis**

Diagnosis date corresponded to a hospital stay for 2899 (76.9%) incident patients. Gastrointestinal bleeding at diagnosis was found in 1.45% of hospitalized patients at diagnosis and CNS bleeding in 0.48%. Therefore, 1.11% of all patients presented with gastrointestinal bleeding and 0.37% with CNS bleeding. There was a linear increasing relation between age and gastrointestinal bleeding among adults, and between age and CNS bleeding in the whole population (Figure 6). Adults with severe bleeding at ITP onset were older (median age: 73 versus 60 years, p=0.01). There was no statistically significant difference as regards gender (males, 52.2% versus 43.4%, p=0.2) and exposure to anti-platelet or anticoagulant drugs (10.9% versus 10.6%, p=1). Among children, severe bleeding rates decreased with age: 1.3% in pre-pubertal patients and 0.6% over 12 years. Bleeding at diagnosis resulted in 5 deaths, 1 due to CNS bleeding at 73 years of age and 4 due to gastrointestinal bleeding (age: 82 to 85 years).
Discussion

This study estimated the incidence of ITP necessitating healthcare at a nationwide scale with recent data (2009-2011). Including 3771 incident patients in two years, it confirmed the age and gender characteristics of the CPRD study that included 1145 patients over 16 years and it allowed calculation of incidence rates according to calendar months and regions. The completeness of the database allowed assessment of rare events such as rare disease associations and severe bleeding risk at ITP onset.

We found an overall incidence of 2.9/100 000 person-years (95%CI[2.8-3.0]) which is within the range of previous studies. It is lower than in the CPRD study (3.9/100 000 person-years, 95%CI[3.7-4.1]). The CPRD is supplied by general practitioners and so every diagnosis of ITP is recorded even if it is mild and not requiring treatments. Our study identified only incident ITP patients requiring healthcare for ITP, i.e. those generating health expenditures. Therefore, our method underestimated the overall ITP incidence. Incidence of pediatric ITP is more debated, ranging from 0.46 to 12.5/100 000 person-years in previous studies. Once again, our estimate in children was lower than in the CPRD study, probably due to the same material discrepancy.

The increased incidence among patients aged ≥60 years was first suggested by Frederiksen et al. Schoonen et al. refined these results in 2009, demonstrating the bimodal incidence with increased incidence among children and older patients. Our findings are fully in accordance with these data. The peak of incidence in the patients aged 1-5 years has been previously suggested by the CPRD study and an international registry. We confirmed this finding calculating incidences in the general population. We also confirm the overall female predominance and male predominance in pediatric and older patients. In our study, the frequency of incident ITPs becoming persistent or chronic is also very close to experience-and smaller series-based findings for both adults and children. As previously said, we
could not accurately measure the frequency of complete remission during the persistency phase, before the chronic phase: in clinical practice, exposure to rituximab or splenectomy can occur early in the course of the disease when patients have a poor response to corticosteroids and/or polyvalent immunoglobulins. Both treatments have long-lasting effects and lead to prolonged remissions allowing drug withdrawal in many cases, but relapses are not rare after some months or years. One can speculate that some patients would have cured spontaneously if not treated by rituximab or splenectomy. Moreover, patients entering in remission during the persistent phase of the disease may have relapsed during the chronic phase after end of follow up, and so we could not identify accurately persistent from chronic ITP patients. Our study identified an increased ITP incidence in winter. Only one pediatric multinational registry assessed the role of seasonality in ITP and found an increased incidence in summer. Further studies are necessary to clarify this discrepancy. Our results add indirect argument to the role of virus in ITP genesis. In children, two-thirds of the patients experience flu-like fever during the weeks preceding ITP onset. The role of influenza virus is suspected for long. It could play a direct role in ITP pathogenesis by promoting antiplatelet-antibodies production and/or decreasing platelet production. Infection may also prompt the prescription of blood cell count leading to a “fortuitous” discovering of thrombocytopenia. The pathogenic role of influenza vaccine is also debated, particularly in older patients. Further studies are ongoing in our cohort to study the impact of influenza vaccination on the occurrence of ITP.

For the first time, we also describe a gradient of incidence in mainland France, independent from age, gender and population density. This suggests the role of unknown environmental factors in ITP pathogenesis. This should be confirmed by other studies across Europe using the same methodology. The lower incidence in overseas French departments (particularly Caribbean departments) compared with mainland France is a rough comparison.
among a dominant Afro-American and mixed-race population and area with a dominant white population. It is unclear whether it is related to a different genetic background, to protective environmental factors or to differences in the healthcare organization. In 2005, Terrell et al. reviewed seven studies and concluded to such racial disparities. In 2006, a retrospective age-adjusted prevalence study carried out in US nationwide Veteran Affairs hospitals did not found any difference between whites and African Americans.

Secondary ITP accounted for 18% of adult cases. This is very close to the experience-based 20% estimate by Cines et al. Nevertheless, malignancies (except B-cell chronic lymphocytic leukemia, 2%) were excluded from this latter assessment, while they are associated with 10.9% of ITPs in our cohort. Frequency of HIV infection (1%) and Evans syndrome (2%) are consistent. In the CPRD study, 8.7% of ITP patients had secondary ITP, but diagnosis search was not as extensive as in our study, authors focusing their search mainly in the semester before and the semester after ITP diagnosis. Both hematological and solid cancers were more frequent in our cohort (respectively, 6.80% versus 3.4% and 4.1% versus 0.7%). We do not explain these discrepancies. In contrast, frequency of association with systemic lupus erythematosus was found very close to our findings (1.3%), as well as HCV infection (0.2%) and antiphospholipid syndrome (0.4%). Interestingly, we found an unexpected association with myelodysplastic syndromes (2.32% of ITP cases) as well as an association with neglected diseases in the context of ITP such as sarcoidosis (0.6%). However, ITP may have been misdiagnosed in some myelodysplastic syndrome patients as this disease can be confused with ITP at an early stage.

We found a very low risk of severe bleeding at diagnosis. As expected, it is lower in this population-based study than in the multinational registry including patients from reference centers, who may have a more severe disease. A higher risk of gastrointestinal bleeding was observed in children as previously suggested. We found a linear increase in
the incidence of gastro-intestinal bleeding among adults and of CNS bleeding in the whole cohort. The role of exposure to anticoagulant or anti-aggregant in these events needs further investigation.\textsuperscript{14}

The limitations of this study are inherent to all studies in administrative databases. We cannot rule out some misclassifications. However, we think that misclassification should not have concerned a significant proportion of patients. Indeed, i) we dropped out the patients with probable erroneous codes (second step of patients’ selection process); ii) 69.0\% of incident patients received outpatient ITP drugs after the date of diagnosis, which is in accordance with previous data;\textsuperscript{5} iii) ICD diagnosis codes to identify ITP patients have been previously assessed in other administrative databases with a good predictive positive value.\textsuperscript{50,51}

As quoted above, ITP incidence assessment among ethnic groups is quite rough due to the lack of data in France.\textsuperscript{31,32} Because examination results are not recorded in the SNIIR-AM, we could not assess the role of some cause of secondary ITP such as \textit{Helicobacter pylori} infection and we could not check for cancer diagnosis accuracy through histological findings. We did not assess exposure to drugs known as ITP-inducers, because of the impossibility to assess causality. However, drug-induced thrombocytopenia is a rare cause of ITP.\textsuperscript{8} Moreover, drug-induced thrombocytopenia generally does not become persistent or chronic.\textsuperscript{52} Therefore, we might have slightly underestimated the incidence of acute, but not that of chronic or persistent ITP. Bleeding symptoms might have been omitted in hospital stays coding for some patients. That’s why we restricted the study to severe bleedings necessitating active and costly treatments, which may be therefore mentioned uppermost. Lastly, as previously underscored, our study population was patients necessitating health care. These results cannot be generalized to the overall ITP population including untreated and never hospitalized patients, who are generally asymptomatic and/or have mild thrombocytopenia. Similarly, as compared
with the entire ITP population, the percentage of cases leading to persistency or chronicity, and the frequency of severe bleeding at disease onset might be overestimated.

In conclusion, ITP requiring healthcare is a rare disease with an overall incidence about 3/100 000 person-years in France, increasing up to 9/100 000 person-years in males aged over 75 years and peaking in winter. Geographical variations and North-South increasing gradient were seen in France. Diagnosis of malignancy before or within six months after ITP diagnosis is frequent (11%). Confusion or association with myelodysplastic syndromes underlines the need of bone marrow aspiration at diagnosis in older patients.

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Authorship Contributions:

GM, MLM and LS designed the study and wrote the paper; GM and AP carried out the data management and statistical analyses; JLM and BG critically reviewed the manuscript. All the authors reviewed the manuscript and gave final approval.

Conflict of interest

None. This study is fully academic (INSERM, University of Toulouse).

References


during a context of pandemic influenza A(H1N1) in 2009. *Vaccine.*


Table 1. Causes of secondary ITP in adults

<table>
<thead>
<tr>
<th>Cause *</th>
<th>ICD10 codes</th>
<th>n</th>
<th>% of secondary ITP (n=518)</th>
<th>% of ITP (n=2882)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ neoplasms</td>
<td>D00-D09</td>
<td>1</td>
<td>0.19%</td>
<td>0.03%</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>C00-C97</td>
<td>314</td>
<td>60.62%</td>
<td>10.89%</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>C77, C81-C96</td>
<td>196</td>
<td>37.84%</td>
<td>6.80%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>C77, C81-C86</td>
<td>91</td>
<td>17.57%</td>
<td>3.16%</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>C81</td>
<td>16</td>
<td>3.09%</td>
<td>0.55%</td>
</tr>
<tr>
<td>B-cell chronic lymphocytic leukaemia</td>
<td>C91.1</td>
<td>49</td>
<td>9.46%</td>
<td>1.70%</td>
</tr>
<tr>
<td>Multiple myeloma and malignant plasma cell neoplasms</td>
<td>C90</td>
<td>16</td>
<td>3.09%</td>
<td>0.55%</td>
</tr>
<tr>
<td>Waldenström macroglobulinaemia</td>
<td>C88.0</td>
<td>13</td>
<td>2.51%</td>
<td>0.45%</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
<td>D46</td>
<td>67</td>
<td>12.93%</td>
<td>2.32%</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>D68.6</td>
<td>8</td>
<td>1.54%</td>
<td>0.28%</td>
</tr>
<tr>
<td>Viral hepatitis C or B</td>
<td>B16, B18.0-B18.2</td>
<td>9</td>
<td>1.74%</td>
<td>0.31%</td>
</tr>
<tr>
<td>Viral hepatitis C</td>
<td>B18.2</td>
<td>5</td>
<td>0.96%</td>
<td>0.17%</td>
</tr>
<tr>
<td>Viral hepatitis B</td>
<td>B16, B18.0-B18.1</td>
<td>4</td>
<td>0.77%</td>
<td>0.14%</td>
</tr>
<tr>
<td>Human immunodeficiency virus disease</td>
<td>B20-B24</td>
<td>27</td>
<td>5.21%</td>
<td>0.94%</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>M32-M35.1</td>
<td>71</td>
<td>13.71%</td>
<td>2.46%</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>M32</td>
<td>49</td>
<td>9.45%</td>
<td>1.70%</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>M34</td>
<td>3</td>
<td>0.58%</td>
<td>0.10%</td>
</tr>
<tr>
<td>Dermatopolymyositis</td>
<td>M33</td>
<td>2</td>
<td>0.39%</td>
<td>0.07%</td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td>M35.0</td>
<td>16</td>
<td>3.09%</td>
<td>0.55%</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>M35.1</td>
<td>3</td>
<td>0.58%</td>
<td>0.10%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>M05, M06.0, M06.2-M06.3, M06.8-M06.9</td>
<td>11</td>
<td>2.12%</td>
<td>0.38%</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>D86</td>
<td>18</td>
<td>3.47%</td>
<td>0.62%</td>
</tr>
<tr>
<td>Immunodeficiency†</td>
<td>D80-D84</td>
<td>49</td>
<td>9.46%</td>
<td>1.70%</td>
</tr>
</tbody>
</table>

*Causes of secondary ITP were searched from the year before and up to six months after ITP date of diagnosis.
†Other than HIV infection. Sensitivity analysis excluding the codes possibly corresponding to secondary immunodeficiency: n=25

Figure legends

Figure 1. Flowchart illustrating patients’ selection. Abbreviations: ICD-10: International Classification of Diseases, version10; ITP, immune thrombocytopenia. LTD, long-term
disease. The date of diagnosis was refined for 478 patients who had \( \geq 3 \) ITP drug dispensing during a 6-month period before the first D69.3 code.

**Figure 2.** Incidence of immune thrombocytopenia in France during the period mid-2009 to mid-2011 by age and gender (female: white bars; males: black bars). Stars indicate statistically significant differences among males and females (\( \alpha=5\% \)).

**Figure 3.** Variation of incidence of immune thrombocytopenia in France during the period mid-2009 to mid-2011 by calendar month in children aged <15 years (A) and in adults aged \( \geq 20 \) years (B).

**Figure 4.** Age and gender-standardized incidence of ITP across administrative regions in mainland France. Direct standardization was made on age (by 10 years intervals) and gender in the general population in France.

**Figure 5.** Percentages of secondary ITPs by age.

**Figure 6.** Percentages of incident ITP patients with gastrointestinal (white bars) and central nervous system (black bars) bleeding by age. Linear testing for an increasing relation between age and severe bleeding at diagnosis was significant for gastrointestinal bleeding among adults (\( p=0.003 \)) and for CNS bleeding in the whole population (\( p=0.02 \)).
7890 patients with a LTD or hospital stay diagnosis encoded D69.3 (ICD-10) from 1st January 2009 to 31st December 2011

6516 ITP patients from 1st January 2009 to 31st December 2011

4468 incident ITP patients from 1st July 2009 to 31st December 2011

3771 incident ITP patients from 1st July 2009 to 30th June 2011

1374 ITP patients with at least one D69.0, D69.1, D69.2, D69.4, D69.5, D69.7 or D69.8 LTD or hospital stay diagnosis code from study start (1st January 2009) to six months after the first D69.3 code

2048 prevalent ITP patients (date of diagnosis before 1st July 2009)

697 incident ITP patients from 1st July 2011 to 31st December 2011
Figure 5

The bar graph shows the percentage distribution of age categories. The age categories and their corresponding percentages are as follows:

- 0-1: 1.23%
- 2-12: 2.11%
- 12-17: 4.24%
- 18-29: 10.07%
- 30-49: 20.95%
- 50-69: 21.15%
- ≥70: 21.15%

The x-axis represents age in years, and the y-axis represents the percentage.
Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France

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