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ORIGINAL ARTICLE

Prevalence of immune thrombocytopenia: analyses of administrative data

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Summary. *Background:* The prevalence of immune thrombocytopenic purpura (ITP) in the USA is unknown. The paucity of data makes clinical trial design and resource allocation challenging. *Objectives:* We aimed to quantify the prevalence of ITP in one state and to report on utilization of resources. *Methods:* The Maryland Health Care Commission supplied utilization data on all privately insured Maryland residents in 2002. We identified patients having two claims, separated by at least 30 days, for International Classification of Diseases, Ninth Revision, Clinical Modification code 287.3 (expected to be predominantly ITP). We excluded patients with concurrent diagnoses that made ITP unlikely. In sensitivity analyses, we varied the required visit interval between 14 and 180 days. We quantified ITP prevalence, resource utilization, and prevalence of concurrent autoimmune illnesses. *Results:* The age-adjusted prevalence of ITP was 9.5 per 100 000 persons (10.5 per 100 000 when requiring a minimum 14-day interval and 4.5 per 100 000 with a 180-day interval). There was a predominance of males in childhood and of females in the middle-adult years, with an overall prevalence rate ratio of 1.9 for females to males. Twenty per cent of these patients were hospitalized, but emergency department use was rare, as was splenectomy. A concurrent diagnosis of multiple sclerosis was 25 times more prevalent than anticipated. *Conclusions:* We conclude that the prevalence of ITP in one populous state in the USA is comparable with that which has been reported in Europe. The suggested co-occurrence of ITP and multiple sclerosis in children merits further investigation.

Keywords: immune thrombocytopenia, ITP, prevalence, primary thrombocytopenia.

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Introduction

There are exceedingly little data on the incidence and prevalence of immune thrombocytopenia purpura (ITP) in the USA; most incidence and prevalence data for this disease come from Europe. One population-based study retrospectively identified all incident cases of ITP diagnosed between 1979 and 1999 in the county of Funen in Denmark, a stable community with 370 000 people above the age of 15 years [1]. Using well-specified diagnostic criteria, the authors found an adult ITP incidence rate of 2.64 per 100 000 patients/year, with increasing incidence with age, a slightly higher incidence among women, and the absence of a gender difference among older patients. In a prospective study from the UK, data were collected from newly diagnosed adult patients with ITP between 1993 and 1999 in the Northern Health Region of England, which has a population of three million people. The authors reported an annual ITP incidence rate of 1.6 per 100 000 patients. There was no gender difference except in the 45–59-year-old group, where the incidence was higher in women [2]. A prospective, population-based registration of children with ITP conducted in Norway in 1996 and 1997 found an incidence of 5.3 per 100,000 children under 15 years old. The female:male ratio was 1.2:1 [3]. A population-based registry from 1998 to 2000 in five Nordic countries found a childhood incidence of 4.8 per 100 000 per year, with 25% of the children subsequently having chronic ITP [4].

Researchers in Sweden estimated the point prevalence for chronic ITP in children by surveying with a questionnaire the physicians in all pediatric departments in the country. Point prevalence of chronic ITP (defined as six months of illness) was 4.6 per 100 000 children, which can be considered consistent with the incidence estimates reported in the literature [5]. Little such data exist in the USA. Authors of a review of the epidemiology of autoimmune diseases in the USA, published in 1997, could not identify any population-based study of the incidence or prevalence of ITP in the preceding 10 years [6].

Given the structure of the US health system, it is difficult to quantify incident and prevalent ITP across the entire USA using administrative data, and there has been no population-based study. Therefore, we aimed to quantify the prevalent cases of ITP in one state with detailed description of resource

utilization, including hospital and ambulatory services, pharmacy utilization, and costs of care. Our goals were to estimate the prevalence of disease, and to quantify utilization of health care services by patients with ITP.

Methods

Data

We obtained data from the Medical Care Database of the Maryland Health Care Commission for services provided in 2002. This database contains information on health services provided by health care professionals and is collected annually from private insurance companies and health maintenance organizations that provide coverage to residents of the state of Maryland. Data on discharges from Maryland acute care hospitals are reported to the commission annually and were available for use. The database also contains data, collected by select prescription benefit management companies, regarding prescription drugs purchased from retail pharmacies and covered under private insurance plans. There is no information about inpatient pharmacy utilization.

We requested data for all inpatient and outpatient claims for patients having an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 287.3, primary thrombocytopenia, among the first ten diagnoses for any claim during 2002. This ICD-9-CM code is used for ITP and several other diagnoses (Table 1). The ICD-9-CM classification does not differentiate between idiopathic and immune thrombocytopenia. For brevity, we use the phrase ITP to refer to patients having this ICD-9-CM code. Patients with the human immunodeficiency virus (HIV) were excluded from all analyses. Similarly, children under the age of 1 year were excluded from the analysis as we thought that they were more likely to have a diagnosis of congenital or hereditary thrombocytopenia than ITP. We excluded patients who had a primary diagnosis in 2002 that indicated malignancies or secondary malignancies of the lymph nodes or Hodgkin's disease; myeloma or aplastic anemia; lymphoid, myeloid or monocytic leukemia; or other specified and unspecified leukemias. Although a data validation study demonstrated that sepsis syndrome accounted for a high proportion of admissions incorrectly coded with ICD-9-CM 287.3; [7] in the current data, only six patients had secondary or tertiary diagnoses of 287.3 with primary diagnoses of ICD-9-CM 785.59 (septic shock) or 785.50 (shock, unspecified). These few patients were not removed from the analyses. Drug-induced thrombocytopenia is expected to be coded with ICD-9-CM 287.4, so no exclusions were made based on medication usage. We required that a patient have at least two diagnoses of ITP, separated by at least 30 days, to improve the specificity of this code. We also conducted sensitivity analyses using the alternatives of two visits separated by 14 days and 180 days.

Table 1 Diagnoses coded as International Classification of Diseases, Ninth Revision, Clinical Modification code 287.3

Primary thrombocytopenia
Evans' syndrome
Megakaryocytic hypoplasia
Purpura, thrombocytopenic
Congenital
Hereditary
Idiopathic
Thrombocytopenia
Congenital
Hereditary
Primary
Tidal platelet dysgenesis

The pharmacy data included the date the prescription was filled, details about the drug, including its National Drug Code number, and the quantity of medication dispensed. We linked the National Drug Code number to the name of the medication using information from the database maintained by the Food and Drug Administration (FDA) [8].

Analyses

For our estimates of utilization we made several assumptions aimed at identifying unique visits for each patient. We assumed that if a patient had at least two observations with sequential service dates and a service place code indicating 'inpatient hospital', this represented a hospitalization. For outpatient services, we assumed that observations having the same start-of-service date and the same diagnosis code reflected the same visit, but sequential dates represented unique outpatient visits. To avoid duplication, patients who had a birthday that changed their age category were assigned to the lower of the two age categories.

Estimates of prevalence

We used the number of patients known to have private insurance in Maryland in 2002 as the denominator for our estimates of 1-year-period prevalence rates, as these are the only patients eligible to be in the numerator [9]. Period prevalence is defined as the number of patients with a diagnosis in the population during the specified time period. We calculated the age-adjusted prevalence rate using the 2000 Maryland Census data as the standard population [10].

The percentage of uninsured or publicly insured patients in Maryland does not affect our calculations of the age-specific prevalence rates, as there is no physiological reason to suspect that the rates differ for uninsured people [9]. Confidence intervals were calculated assuming a binomial distribution. Available data did not allow us to estimate the incidence of new cases of ITP during 2002. As a sensitivity analysis, we also estimated an age-adjusted prevalence while requiring that patients had two or more visits in 2002 with a code for ITP, separated by at least 14 days and by 180 days.

Comorbid autoimmune illnesses

We tabulated the number of unique patients having diagnoses of systemic lupus erythematosus (SLE; ICD-9-CM 710.0), Graves' disease (242.0) or Hashimoto's thyroiditis (245.2), rheumatoid arthritis (714.0), multiple sclerosis (340), and autoimmune hemolytic anemia (283.0). We adjusted the prevalences for the age and sex distribution of our sample population, and report the sex-specific age-adjusted rates, and the combined age-adjusted rates. We compared the prevalence of these diseases among patients with ITP with estimates of the prevalences of these diseases in the USA, recognizing that the reported prevalences depend heavily on the population and the methods of case-ascertainment. Our source of these estimates was primarily a systematic review by Jacobson *et al.*, with additional review of the literature [6].

Results

Prevalent thrombocytopenia

In 2002, 97 583 claims were submitted to private insurers in Maryland for patients with ITP among their first 10 diagnoses. These claims are for 1322 unique patients with ITP. In our effort to identify those patients with primary ITP rather than thrombocytopenia secondary to another cause, we excluded 13 patients who had a diagnosis of HIV, and 34 children who were younger than 1 year of age. An additional 106 patients were eliminated from the analyses as they were deemed unlikely to have ITP on the basis of having other primary diagnoses that should preclude a diagnosis of ITP. After these exclusions, we had 1169 patients with ITP for analysis. The requirement that there be two diagnoses separated by at least 30 days further reduced the sample size to 454 (Fig. 1). Based on these data, we estimated the age-adjusted prevalence rate to be 9.5 per 100 000 persons and the prevalence rate ratio for females to males as 1.9:1 (Table 2). The estimated prevalence rates were highest in childhood and late adulthood (Table 3). When we required two or more visits for ITP separated by a minimum of only 14 days, the estimated age-adjusted prevalence was 10.5 per 100 000 persons. When we required two visits separated by at least 180 days, the age-adjusted prevalence was 4.5 per 100 000 persons.

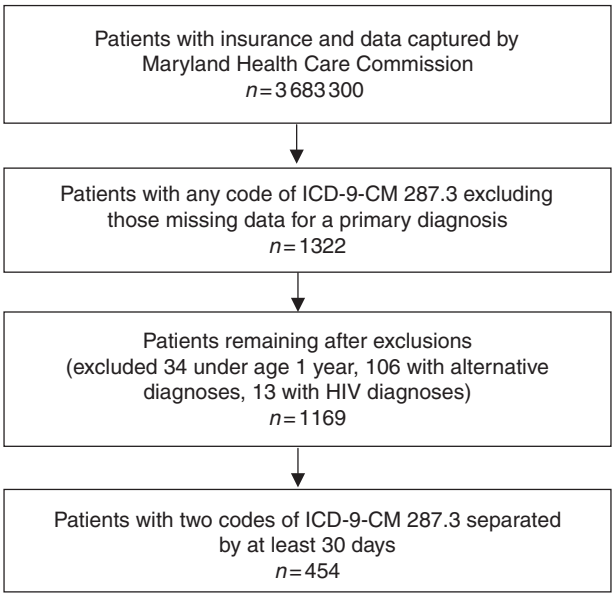

Fig. 1. Patients included in cohort. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification code.

Sixty-two percent of the 454 patients in our sample were female. The median age of these patients was 49 years with an interquartile range of 31–64 years. The frequency distribution of these patients by age is shown in Fig. 2. The females were younger than the males (median age 46 vs. 51 years, $P < 0.006$). In this data set there is a paucity of older adults because claims to Medicare are not included. The plot of the cumulative frequency distribution by age, stratified by sex, shows a predominance of male patients among the children, and then a higher frequency of female patients in the middle-adult years (Fig. 3).

Utilization of services

Seventy-one patients (16%) were hospitalized with ITP during 2002. In total, there were 71 unique patients with 153 hospitalizations in 2002. These hospitalized patients had a median age of 49 years, with an interquartile range from 31 to 68 years. Only 6% of the hospitalized patients were under 14 years old. Sixty-five per cent of the hospitalized patients

Table 2 Prevalence of International Classification of Diseases, Ninth Revision, Clinical Modification code 287.3 among privately insured people under the age of 65 years in 2002 in Maryland

	Prevalence per 100 000	95% confidence intervals
Crude prevalence (both sexes)	9.6	8.6–11
Crude prevalence for males	6.1	5.0–7.3
Crude prevalence for females	11.3	10–13
Age-adjusted prevalence (both sexes)*	9.5	8.5–10

*Adjusted to Maryland population distribution (2000 Census).

Table 3 Age-stratified prevalence of International Classification of Diseases, Ninth Revision, Clinical Modification code 287.3 among privately insured people under the age of 65 years in 2002 in Maryland

Age range (years)	Prevalence per 100 000 (95% confidence interval)
1–5	9.3 (5.8–14)
6–11	7.3 (4.9–10)
11–14	4.1 (2.1–7.1)
15–18	5.6 (3.2–9.3)
19–24	4.1 (2.0–7.3)
25–34	9.3 (6.8–12)
35–54	11 (9.1–13)
55–64	16 (13–20)

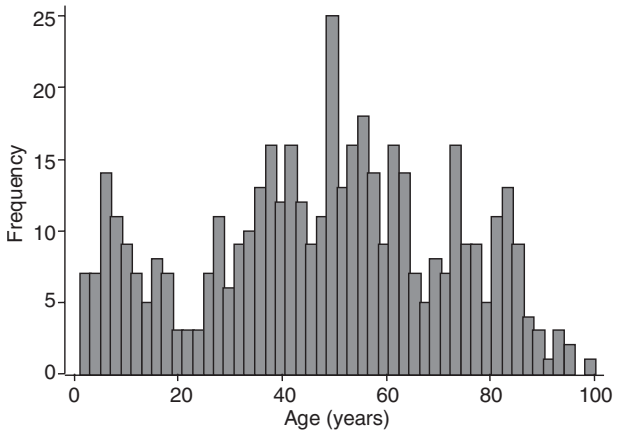

Fig. 2. Frequency of International Classification of Diseases, Ninth Revision, Clinical Modification code 287.3 in 2002 in Maryland by age. Total number of patients is 454.

were female, a comparable percentage to the whole population of patients.

Twenty-one per cent of all patients with ITP used a hospital for outpatient care, including diagnostic, therapeutic and rehabilitation services. There were 243 visits by 95 patients for outpatient hospital care. The majority of these visits listed ITP as the primary diagnosis, and most visits were for laboratory services.

Three hundred and forty-three patients had 1,113 office visits for ITP in 2002. Office visits are ambulatory care visits to sites other than a hospital, nursing facility, or community health clinic. For the vast majority of these visits, ITP was coded as the primary diagnosis (1 000 visits involving 304 patients). For these 304 patients, the mean number of office visits in the year was 3.3 (standard deviation of 3), with a median of two visits per person. Sixty-five patients had 133 office visits where the secondary or tertiary diagnosis code was ITP, without their ever having had a primary diagnosis code for ITP during that year. For those patients, the most frequent primary diagnoses were agranulocytosis and diabetes mellitus. The number of office visits per person differed across decades of age of the patient ($P < 0.0001$, analysis of variance). The greatest absolute number of office visits was for people in the middle decades of life.

Only nine emergency department (ED) visits for seven unique patients have claims in these data. All but two of the ED visits were for children.

Procedures administered to patients with ITP

Eight patients were coded as having splenectomy [Current Procedural Terminology (CPT) codes 38100 or 38120] in 2002. One was an open procedure and seven were laparoscopic. None of these was done in children; the age of the patients ranged from 18 to 62 years. No patient was coded as having received a transfusion of blood products during the year. Intravenous infusions, most of which were delivered as outpatients, for therapy or diagnosis were coded 225 times for 28 patients. Chemotherapy infusion or injection was coded 51 times for 10 patients.

Practitioners

Hematologists and oncologists comprised 48% of the specialists claiming for inpatient services. Internists made up another 16% while pediatricians were the listed specialists for less than 1% of inpatient claims. For the 1 119 office visits for which a practitioner specialty is listed, 65% were to hematologists or oncologists, an additional 15% to internists, and 4% to pediatricians.

Across all types of visits (e.g. hospitalizations, office visits, emergency visits), 304 of 454 patients had visits to a hematologist or oncologist and 164 of these also saw an internist during that year. Of the 243 patients who saw an internist, 164 also saw a hematologist or oncologist that year, and 79 (32%) did not.

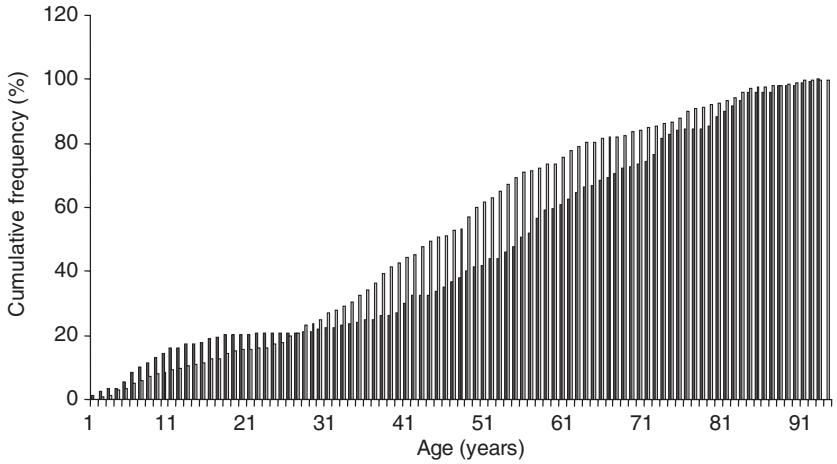

Fig. 3. Cumulative distribution of ages by sex of patients with International Classification of Diseases, Ninth Revision, Clinical Modification code 287.3 in 2002 in Maryland. Black bars represent males; white bars represent females.

Table 4 Autoimmune illnesses among insured patients with an International Classification of Diseases, Ninth Revision, Clinical Modification code 287.3 in 2002 in Maryland

Diagnosis	Number	Percent female	Mean age (median), years	Crude prevalence per 100 patients with ITP	Age-adjusted prevalence per 100 patients with ITP*	Expected population prevalence per 100	References
Systemic lupus erythematosus	14	72	48 (49)	2.4 (males) 3.5 (females) Combined: 3.1	1.6 (males) 3.7 (females) Combined: 3.3	0.024	[6,24]
Rheumatoid arthritis	5	60	60 (60)	1.2 (males) 1.1 (females) Combined: 1.1	0.68 (males) 0.79 (females) Combined: 0.84	0.86	[6,25,26]
Autoimmune hemolytic anemia	4	50	50 (53)	1.2 (males) 0.71 (females) Combined: 0.89	0.71 (males) 0.54 (females) Combined: 0.78	No reliable estimates	
Graves' disease or Hashimoto's thyroiditis	3	100	23 (25)	0 (males) 1.1 (females) Combined: 1.1	0 (males) 1.5 (females) Combined: 1.9	1.2 (Graves') 0.79 (thyroiditis)	[6]
Multiple sclerosis	4	50	8 (7)	1.2 (males) 0.7 (female) Combined: 0.89	1.2 (males) 1.4 (females) Combined: 1.4	0.058 to 0.077	[6,27]

*Adjusted to Maryland population distribution (2000 census). ITP, immune thrombocytopenia purpura.

Pharmacy utilization

Pharmacy data were available for 124 patients meeting our inclusion criteria. The patients for whom there were no pharmacy data were significantly younger than the whole set of 454 patients ($P < 0.0001$), but the proportion of males and females was similar. Twenty-seven per cent of the patients with available data had filled a prescription for a corticosteroid during the year. An additional seven patients (6%) filled a prescription for methotrexate, mycophenolate mofetil, cyclosporine or plaquenil.

Diagnoses of other autoimmune illnesses

We looked specifically for diagnoses of SLE, rheumatoid arthritis, autoimmune thyroid disease (Graves' disease or Hashimoto's thyroiditis), multiple sclerosis, and autoimmune hemolytic anemia. Results are presented in Table 4.

As expected, the prevalence of SLE was high in this population of patients with ITP. Immune thrombocytopenia is common among patients with SLE; these patients would not be considered to have idiopathic thrombocytopenic purpura, although immune thrombocytopenic purpura is an accurate diagnosis. There are no reliable estimates of the prevalence of autoimmune hemolytic anemias in the population; the prevalence in our sample of patients with ITP is close to 1%. The prevalences of rheumatoid arthritis and autoimmune thyroid disease are closely comparable with those that have been reported in the literature. In contrast, the prevalence of multiple sclerosis was high in this sample, approximately 25 times the prevalence that would be expected in the general population. All four of these patients were children and pharmacy data were available for them. None had claims for medications that are expected to cause thrombocytopenia, including interferon-β (IFN-β), although three patients filled prescriptions for amoxicillin or amoxicillin/clavulanate, which can occasionally cause thrombocytopenia [11–13]. We acknowledge that the incompleteness of the pharmacy data reduces our certainty that no patient received IFN-β.

Discussion

We have used administrative data to estimate the burden of ITP in one state, which has a mix of urban, suburban, and rural health care providers, and a population that is ethnically and socioeconomically diverse. We found the prevalence of ITP in Maryland to be approximately 9.5 per 100 000 residents. The ICD-9-CM code cannot differentiate idiopathic (non-immune mediated) from immune thrombocytopenia, so this may be an overestimate of the number of patients with ITP. However, if one assumes that this rate reasonably represents the prevalence of ITP, the incidence rate of ITP in the USA may be comparable to that reported in northern Europe. European studies report incidence rates in adults between 1 and 3 per 100 000 patients [1,2]. Illnesses such as ITP, which affect patients for a long time, have prevalence rates that are substantially higher than their incidence rates because, by definition, the prevalence rate equals the incidence rate multiplied by the duration of disease. European studies report, in children, fairly similar incidence and prevalence rates (between four and five cases per 100 000 children per year) reflecting the often short duration of childhood ITP [3–5]. Our data on prevalence in children is comparable to this (7.2 per 100 000 per year for children 1–14 years old).

To substantiate the generalizability of our findings, we compared the state of Maryland with the rest of the USA. The population of Maryland has an age distribution very comparable to the rest of the USA. The percentage of black residents is higher in Maryland than nationally (27.9% vs. 12.3%), while the percentage of Hispanic residents is lower (4.3% vs. 12.5%).

Median household income is higher than the national median ($53,000 vs. $42,000) and the percentage of people below the poverty line is lower [14]. Terrell and colleagues reviewed six studies that reported data on ITP and race, and concluded that the prevalence of ITP among black Americans may be lower than among white Americans [15]. If this is so, then the prevalence of ITP in other states may be higher than that reported for Maryland. In this data set, we did not have information on patient race or income. We found the prevalence of disease to be higher in adult women than in men, and the converse true in children. The study from Sweden also found more males among the youngest affected and more females among the older children [5].

The high prevalence of codes for multiple sclerosis among these young patients with ITP is intriguing and resulted from a hypothesis-driven analysis. Certainly, we cannot entirely exclude that these were patients with primary diagnoses of multiple sclerosis who had been incorrectly coded as having ITP when in fact they had a drug-induced thrombocytopenia, although drug-induced thrombocytopenia should be coded as ICD-9-CM code 287.4 (rather than 287.3). Given the incompleteness of the pharmacy data, we cannot definitively identify the medications administered to these patients with multiple sclerosis. The disease-modifying FDA-approved treatments for multiple sclerosis in 2002 were IFN-β-1a and IFN-β-1b, glatiramer and mitoxantrone. None of these medications is expected to cause thrombocytopenia [16]. Case reports have described pancytopenia associated with methotrexate infusion. In the literature, we identified two reports describing ITP and multiple sclerosis (one French and one Italian) [17,18]. It is easy to hypothesize that a common exposure, such as a virus or an environmental toxin in a genetically susceptible host, could elicit autoimmune processes directed at more than one self-antigen. We suggest that this association deserves further study, such as in a cohort of patients with multiple sclerosis, with particular attention to childhood onset of multiple sclerosis.

We were limited in this study by the data available to us. Whereas a large national data set, such as the Nationwide Inpatient Sample [19], is ideal for investigation of diseases requiring hospital-based care, there is no comparable national data set of this size for examining the prevalence of a disease that is treated mostly in the outpatient setting. The national surveys conducted by the National Center for Health Statistics that do include outpatient data, such as the National Ambulatory Medical Care Survey [20] and the National Hospital Ambulatory Medical Care Survey [21], contain too few observations to detect a substantial number of patients with ITP, given its low prevalence. Given few alternatives, we turned to a data set consisting of data from insurers and large health care providers, which supplied a good source of data on prevalence, although the data excluded uninsured patients and patients with public sources of insurance (e.g. Medicaid, Medicare, VA-service recipients). The data set we have used has limitations, most notably incomplete pharmacy data and an absence of procedure codes for most inpatient procedures.

Similarly, our analyses have several limitations. We cannot be certain of the specificity of the use of the code 287.3 for identifying patients with ITP. In the October 1, 2005 addendum to the ICD-9-CM, ITP (immune thrombocytopenia and idiopathic thrombocytopenia) is assigned its own code (287.31). If health care providers use the code conscientiously, this should simplify future research using administrative data although it still will not allow differentiation between idiopathic and immune causes of thrombocytopenia, although clinically this is not always clear. A prior validation study suggested that the use of code 287.3 to identify patients with ITP is reasonably reliable for identifying inpatients with ITP, with a sensitivity of 100% and a specificity of 89%, although it is less valid for outpatients, with a sensitivity of 84% and a specificity of 66% [7]. This, however, is an extremely conservative estimate of specificity because the patients were included in the analysis because they had platelet disorder diagnoses. The authors noted that the specificity would be much higher in an unselected population of patients and may approach 90%. We expect that we improved upon the specificity in these analyses by our process of excluding patients who had ever had an ICD-9-CM code suggesting an alternative diagnosis, such as leukemia. This being said, we suspect that included in this data set there may be patients with alternative diagnoses that were not excluded using our chosen ICD-9-CM codes for exclusion. Similarly, we cannot know how often 287.3 should have been coded for a patient having ITP and was not. The accuracy of these data from the Maryland Health Care Commission has been established by other investigators who were primarily interested in CPT codes for inpatient procedures, which may be more often correctly coded than ICD-9-CM codes [22,23].

We further improved the specificity of the code by requiring two visits with this code separated by at least 30 days. This should have reduced inclusion of patients with drug-induced thrombocytopenia (incorrectly) coded with 287.3 as this condition should not persist for more than 30 days after first noted. It should have also reduced inclusion of patients with entirely errant codes of 287.3. In our sensitivity analysis, we calculated prevalence using less stringent criteria by requiring two visits separated by only 14 days. As expected, the prevalence estimates increase, although not dramatically. We also estimated in our sensitivity analyses the prevalence if we required two visits separated by 6 months, which would be appropriate criteria for a diagnosis of chronic ITP. The prevalence decreased to 4.5 per 100 000. However, because we only have one calendar year of data, this is certainly a low estimate as we do not have the data on visits at a gap of 6 months that occurred in another calendar year.

There are other important limitations to this dataset. We only had records of therapies if the patient filled a prescription in an outpatient pharmacy, or if there was a procedure code for therapies received as an inpatient. This information would have helped with confirming the validity of the ICD-9-CM code. Additionally, the pharmacy data are incomplete, hence our description of pharmacy utilization should be considered only exploratory.

In conclusion, if our assumptions are correct and this diagnosis code with the exclusions we made correctly identifies patients with ITP, then diagnosed ITP has a prevalence that is probably comparable to the prevalence in Europe. The actual number of people with ITP may be considerably higher, as cases occurring without bleeding are unlikely to come to the attention of health care providers unless noted on a routine laboratory examination. The data we report should prove useful in planning future clinical studies of ITP, and for directing resources. Studies using alternative data sources to confirm our findings, to investigate incidence rates, and to investigate racial differences would be important contributions to medical knowledge.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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