REGULAR ARTICLE

blood advances

Misdiagnosis of primary immune thrombocytopenia and frequency of bleeding: lessons from the McMaster ITP Registry

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Key Points

- One in 7 patients suspected of having primary ITP was misdiagnosed at some point during their disease course; 56.1% had grade 2 bleeding.
- The McMaster ITP Registry is a useful tool to improve the diagnosis of ITP and identify unique subgroups of patients.

Nonspecific diagnostic criteria and uncertain estimates of severe bleeding events are fundamental gaps in knowledge of primary immune thrombocytopenia (ITP). To address these issues, we created the McMaster ITP Registry. In this report, we describe the methodology of the registry, the process for arriving at the diagnosis, and the frequency of bleeding. Consecutive patients with platelets $<150 \times 10^9$/L from a tertiary hematology clinic in Canada were eligible. Patients completed a panel of investigations and were managed per clinical need. Two hematologists initially determined the cause of the thrombocytopenia using standard criteria and reevaluated the diagnosis over time, which was adjudicated at regular team meetings. Bleeding was graded from 0 (none) to 2 (severe) prospectively using an ITP-specific tool. Data were validated by duplicate chart review and source verification. Between 2010 and 2016, 614 patients were enrolled. Median follow-up for patients with >1 visit was 1.7 years (interquartile range, 0.8-3.4). At registration, 295 patients were initially diagnosed with primary ITP; of those, 36 (12.2%) were reclassified as having a different diagnosis during follow-up. At registration, 319 patients were initially diagnosed with another thrombocytopenic condition; of those, 10 (3.1%) were ultimately reclassified as having primary ITP. Of 269 patients with a final diagnosis of primary ITP, 56.5% (95% confidence interval [CI], 50.4-62.5] experienced grade 2 bleeding at 1 or more anatomical site, and 2.2% (95% CI, 0.8-4.8) had intracranial hemorrhage. Nearly 1 in 7 patients with primary ITP were misdiagnosed. Grade 2 bleeding was common. Registry data can help improve the clinical and laboratory classification of patients with ITP.

Introduction

Primary immune thrombocytopenia (ITP) is an acquired autoimmune platelet disorder defined as a peripheral blood platelet count $<100 \times 10^9$/L with no known cause.[1,2] The incidence of ITP is estimated at 1.6 to 3.9 per 100 000 persons per year for adults.[3] The clinical presentation ranges from asymptomatic thrombocytopenia to nuisance bruising to life-threatening intracranial hemorrhage (ICH).[4-6] Currently, several fundamental gaps in knowledge limit the effective management of patients with ITP, including the lack of specific diagnostic criteria and uncertainty about the true frequency of severe, non-ICH bleeding events.[7]

In 2009, the international ITP working group established a standard definition for the diagnosis of primary ITP: platelet count $<100 \times 10^9$/L in the absence of an underlying cause.[1] This criterion lacks specificity

Submitted 25 July 2017; accepted 25 October 2017. DOI 10.1182/bloodadvances.2017010942.

The full-text version of this article contains a data supplement.

and can lead to misdiagnosis and inappropriate treatments.[8] Furthermore, clinical manifestations[9-11] and treatment responses are variable across patients, suggesting that ITP is a heterogeneous syndrome,[12] possibly representing a group of disorders, each with thrombocytopenia as the final common pathway. Thus, establishing the diagnosis is challenging; a description of the clinical diversity across patients could lead to better classification of patients and ultimately more individualized treatment strategies.

Bleeding is the most concerning outcome in ITP. Minor bleeding is troublesome but generally not associated with significant morbidity.[9,13] ICH, the most severe bleeding complication, is known to occur in approximately 1% to 1.5% of adults.[7] Precise estimates of the risk of severe, non-ICH bleeding based on prospective assessments are lacking; yet, this information is critical for patients and clinicians to make informed treatment decisions.

To address these gaps in knowledge, we created the McMaster ITP Registry. The goal was to describe clinical outcomes and laboratory features of patients with primary ITP. An integral part of the registry was to arrive at the diagnosis, a process that can involve reassessments over time. In this paper, we describe the design of the McMaster ITP Registry and the procedures for data validation. Using these data, we report the evolution of the diagnosis of primary ITP over time, and the frequency of grade 2 (severe) bleeding events.

Methods

Patients

The McMaster ITP Registry is a prospective, longitudinal registry of consecutive adult patients 18 years or older who were referred to the tertiary hematology clinic at the McMaster University Medical Centre in Hamilton, Canada, for investigation of thrombocytopenia. The catchment area for the clinic was approximately 2 million people from south and central Ontario. Referrals were mainly from primary care physicians; some were from other hematologists. All patients with platelets $<150 \times 10^9$/L were eligible and no exclusions were applied other than temporary coenrollment in a separate clinical trial. Patients were treated per clinical need. All patients were followed prospectively every 6 months until discharge from clinic or death. Patients were discharged from the registry if the hematologist deemed their disease to be stable or mild, based on serial clinical evaluations and platelet count measurements. At registration, a medical chart review was done to obtain information on initial diagnosis, previous treatments, investigations, and platelet counts. All patients provided informed written consent. The McMaster ITP Registry was approved by the Hamilton Integrated Research Ethics Board.

Panel of investigations

A complete blood count, including the platelet count, was done at baseline and at each follow-up visit. Results of additional platelet counts obtained between visits were captured. The following investigations were done at baseline for all patients as part of the registry: blood film examination, liver enzymes, quantitative immunoglobulins, thyroid-stimulating hormone, serum protein electrophoresis, antinuclear antibody, direct antiglobulin test, anticardiolipin antibody, lupus anticoagulant, hepatitis B and C, HIV, and *Helicobacter pylori* serology. At baseline and 6 and 12 months, we collected serum, DNA, and platelet lysate samples, which were frozen for future testing.[14]

Diagnosis of the thrombocytopenia

Two experienced hematologists who worked together in the clinic (D.M.A. and J.G.K.) provided the diagnosis of the thrombocytopenia at the initial visit. The diagnosis was reevaluated at every follow-up by both physicians using all available clinical and laboratory information; when the diagnosis was uncertain, it was adjudicated by 1 of the hematologists (D.M.A.) and the study team during regular team meetings. Primary ITP was defined as isolated thrombocytopenia (platelet count $<100 \times 10^9$/L) with no other cause identified and no associated illness.[15] Secondary ITP was defined as ITP occurring in the context of infection (eg, HIV, hepatitis C, *H pylori*), autoimmune condition (eg, systemic lupus erythematosus, connective tissue diseases, antiphospholipid antibody syndrome, hemolytic anemia), pregnancy, common variable immune deficiency, or lymphoproliferative disorder. Other immune platelet disorders was used to classify patients with thrombotic microangiopathy or cyclical thrombocytopenia. Nonimmune thrombocytopenia was defined as physiologic thrombocytopenia occurring in the setting of splenomegaly, liver disease, familial thrombocytopenia, myelodysplastic syndrome, or malignancy. Isolated mild thrombocytopenia was defined as having platelet counts 100 to 150×10^9/L with no identifiable cause.[16] Unknown was used when the physician was unable to ascribe a specific cause based on all available information.

Clinical definitions

We defined time-based milestones in the registry as follows: initial presentation was the time of the first occurrence of the thrombocytopenia; registration was the time of enrollment. Disease stage was defined as previously described[1]: newly diagnosed (0 to 3 months from initial presentation); persistent (3 to 12 months from initial presentation), and chronic ITP (>12 months from initial presentation). The following disease states incorporated disease duration and severity: refractory ITP was used to describe patients who had received 5 or more treatment modalities, 1 of which was splenectomy, and who had a platelet count $<20 \times 10^9$/L on at least 2 occasions including at the last follow-up visit; remission (with the subcategories "remission on-therapy and "remission off-therapy") was defined as the achievement of a platelet count $>100 \times 10^9$/L for at least 3 months after having a platelet count $<100 \times 10^9$/L; relapse was defined as the occurrence of a platelet count $<100 \times 10^9$/L at the most recent follow-up visit after a period of remission.

Bleeding assessments

Bleeding assessments were done at baseline and at each follow-up visit by a dedicated research assistant using a validated ITP bleeding scale.[17] Using this scale, bleeds were described by anatomical site; severity was graded from 0 (none) to 2 (severe) based on defined criteria. Bleeding assessments at baseline captured the worst bleed ever and bleeding assessments at follow-up visits captured the worst bleed since last assessment.

Database creation and data validation

Data were stored within a custom software application designed with appropriate, normalized data models in PostgreSQL, an open-source object-relational database system (www.postgresql.org). Patient information was de-identified and entered using a Web-based data collection platform on a weekly basis. All data were entered by authorized users over secure communication channels and housed within a secure data network. All data entries were

logged and reviewed regularly by registry staff. To validate the accuracy of data collection, a sample of patients' medical charts was selected at random and reviewed independently by 2 assessors. We held monthly face-to-face meetings with the study team to establish and refine clinical definitions and terms (eg, refractory, relapse, remission); review and classify unclear diagnoses with the treating physician; identify and correct data entry errors; and ensure consistency of data abstraction and reporting. Data integrity was optimized via 3 mitigation strategies: (1) use of predefined response values to ensure consistency of fields requiring precise values; (2) regular automatic audits on constrained data fields to identify data entry errors; and (3) regular data query reports to review completeness and accuracy of the data.

Statistical analysis

Continuous variables were reported as median (interquartile range [IQR]); categorical variables were reported as frequency and/or proportions with 95% confidence intervals (CIs). We used Cohen κ coefficient with 95% CI to calculate agreement on a sample of variables from duplicate chart review.

Results

Diagnosis of primary ITP

From 4 January 2010 to 11 January 2016, 687 consecutive patients with thrombocytopenia were invited to participate; 73 (10.6%) declined. For patients with >1 visit, median follow-up from enrollment in the registry until the end of follow up was 1.7 years (IQR, 0.8-3.4). Median follow-up from initial presentation was 6.5 years (IQR, 2.7-14.7). At last follow-up, there were 269 patients with primary ITP, 93 patients with secondary ITP, 149 patients with nonimmune thrombocytopenia, 67 patients with mild thrombocytopenia only, and 23 patients with other immune platelet disorders (Table 1). Thirteen patients were classified as unknown: these patients met the definition of primary ITP (platelets $<100 \times 10^9$/L with no associated cause), yet the treating physicians were unable to determine the diagnosis because other causes of the thrombocytopenia were possible. Reasons included persistent nonsevere thrombocytopenia (platelet counts ranging between 40 and 97×10^9/L) never requiring therapy (n = 10) and transient thrombocytopenia (n = 3), including 1 patient who did not respond to prednisone (see supplemental Table 1).

Of the 269 patients with primary ITP, 168 (62.5%) were female, the median age at initial presentation was 50 years (IQR, 33-64), and the median lowest platelet count was 15×10^9/L (IQR, 4-48 $\times$ 10^9/L) (Table 2). A total of 152 (56.5%) patients had a platelet count $<20 \times 10^9$/L at any time. Since initial presentation, patients with primary ITP had received a median of 3 treatment modalities (IQR, 1-4). At last follow-up, 8 (3.0%) patients were considered refractory. Median follow-up for patients with primary ITP was 7.0 years (IQR, 2.9-14.8) from initial presentation and 1.5 years (IQR, 0.5-3.3) from the time of registration. Agreement on duplicate data abstraction was excellent for the diagnosis (κ = 0.89; 95% CI, 0.78-1.00); lowest recorded platelet count (κ = 0.81; 95% CI, 0.70-0.92), and ITP disease stage (κ = 0.80; 95% CI, 0.67-0.94).

At initial assessment by our team, 295 patients were diagnosed as having primary ITP. During follow-up, 36 of those patients (12.2%) were reclassified as having nonimmune thrombocytopenia (from myelodysplastic syndrome [n = 7]; familial thrombocytopenia [n = 4]; splenomegaly/hypersplenism [n = 3]; liver disease [n = 3]; pseudothrombocytopenia [n = 2]; Bernard-Soulier syndrome [n = 1]; or thrombocytopenia associated with malignancy [n = 1]), secondary ITP (from drug-induced ITP [n = 2]); *H pylori* infection, which was confirmed after the infection was treated, eradication was confirmed, and platelet count response was observed (n = 2); antiphospholipid antibody syndrome (n = 1); rheumatoid arthritis (n = 1); systemic lupus erythematosus (n = 1); common variable immune deficiency (n = 1); mixed connective tissue disease (n = 1); Evan's syndrome (n = 1); general infection (n = 1); and autoimmune optic neuritis with associated thrombocytopenia (n = 1), mild thrombocytopenia only (n = 1), cyclical thrombocytopenia (n = 1), or unknown (n = 1). Of the 7 patients who were ultimately reclassified as having myelodysplastic syndrome (n = 7), 6 had abnormalities in other blood cells including leukopenia or macrocytosis, and 6 patients eventually had a bone marrow examination that showed single or multilineage dysplasia and a normal karyotype.

Table 1. Patients enrolled in the McMaster ITP Registry (2010-2016)

Diagnosis (at last follow-up)	No. of patients
ITP	362
Primary ITP	269
Secondary ITP	93
Evan's syndrome	14
Systemic lupus erythematosus	13
Drug-induced ITP	9
Antiphospholipid antibody syndrome	6
Helicobacter pylori	7
Hepatitis C	6
ITP in pregnancy	8
Common variable immune deficiency	4
HIV	3
ITP following nonspecific viral illness or infection	4
Chronic lymphocytic leukemia	2
Lymphoproliferative disease	2
Other associated autoimmune conditions	15
Nonimmune thrombocytopenia	149
Familial thrombocytopenia (suspected or confirmed)	35
Splenomegaly	27
Incidental thrombocytopenia of pregnancy	20
Myelodysplastic syndrome	20
Liver disease	16
Pseudothrombocytopenia	13
Alcohol-related thrombocytopenia	6
Pancytopenia	2
Thrombocytopenia associated with malignancy	1
Other	9
Isolated mild thrombocytopenia (100-150 $\times$ 10^9/L)	67
Other immune platelet disorders	23
Thrombotic microangiopathy	19
Cyclic thrombocytopenia	4
Unknown	13
Total	614

Table 2. Patients with a final diagnosis of primary ITP

	Primary ITP (n = 269)
Age at initial presentation, median (IQR), y	50 (33-64)
Female, n (%)	168 (62.5)
Follow-up from initial diagnosis, >1 visit, median (IQR), y	7.0 (2.9-14.8)
Nadir platelet count, median (IQR)	15 (4-48)
Number of ITP treatments received (IQR)	3 (1-4)
Splenectomy, n (%)	83 (30.9)
ITP disease stage at the time of registration,* n (%)	
Newly diagnosed (within first 3 mo)	28 (10.4)
Persistent (3 to 12 mo)	23 (8.6)
Chronic (>12 mo)	122 (45.4)
Relapsed	5 (1.9)
Refractory	24 (8.9)
Remission off therapy	52 (19.3)
Patients with a diagnosis other than ITP at registration	10 (3.7)
Unknown	5 (1.9)
Patients with refractory ITP at last follow-up, n (%)	8 (3.0)
Worst bleed ever, n (%)	
None	40 (14.9)
Grade 1 only	77 (28.6)
Grade 2	152 (56.5)

*The ITP stages at registration were based on physician assessment because patient recall of dates of initial presentation was often unreliable. Disease stages were mutually exclusive.

Of the 319 patients who were felt to have another thrombocytopenic condition at initial assessment by our team, 10 (3.1%) were later reclassified as having primary ITP during follow-up. These patients were initially labeled as having mild thrombocytopenia (n = 3), nonimmune thrombocytopenia (n = 3), secondary ITP (n = 2), or unknown (n = 2). Thus, of patients who were classified as having primary ITP either at registration or during follow-up (n = 305), 46 (15.1%) were ultimately reclassified at some point during their disease course. Misdiagnosed patients were more often male, had milder thrombocytopenia, and fewer grade 2 bleeds (Table 3). Reclassifications occurred as additional investigations were performed over time.

Grade 2 bleeding occurred in 152 (56.5%) primary ITP patients (Figure 1). Of those, 127 (83.6%) had nonskin grade 2 bleeding, 25 (16.4%) had skin bleeding only, and 95 (62.5%) had grade 2 bleeding at more than 1 site. Most grade 2 bleeds were localized to the skin or mouth (n = 115; 42.8%); others were gastrointestinal (n = 19; 7.1%) or genitourinary bleeds (n = 11; 4.1%). Six patients (2.2%) experienced ICH after a median follow-up of 12.4 years (IQR, 11.3-32.1) from initial diagnosis. One patient died as a result of ICH; the others recovered with no neurological sequelae. Six patients with primary ITP died (2.2%) after a median follow-up of 15.4 years (IQR, 9.5-38.4) from initial diagnosis: 1 death was due to bleeding, the others were attributed to malignancy (including lymphoma, which developed decades after ITP, melanoma, and metastatic lung cancer); thrombotic stroke; and congestive heart failure.

Discussion

ITP is a heterogeneous clinical syndrome. A clear understanding of the clinical and biological features of ITP is needed to improve the accuracy of the diagnosis, identify subgroups of patients, and ultimately tailor treatment to individual patients. Results from this registry study support the notion that establishing the diagnosis of primary ITP can be difficult, even by highly habituated clinicians. Our results also suggest that the frequency of grade 2 bleeding is higher than previously reported when measured systematically using an ITP-specific bleeding tool. This information adds to the data on severe bleeding estimates in this population, which is critical for patients and providers.

The criterion for the diagnosis of primary ITP, a platelet count $<100 \times 10^9$/L in the absence of an identifiable cause, is nonspecific. The process used in this registry study to arrive at the diagnosis of ITP mirrors clinical practice. Results of investigations accumulated over time to help clinicians rule in or rule out a secondary cause of ITP or

Table 3. Characteristics of patients misdiagnosed as having primary ITP compared with patients who were properly diagnosed

	All misdiagnosed patients (n = 46)	Patients correctly diagnosed as primary ITP (n = 259)
Age, median (IQR), y	59.5 (38.8-73.5)	50 (32.5-64)
Female, n (%)	25 (54.3)	163 (62.9)
Lowest platelet count ever, median (IQR)	43 (15-62.5)	14 (3.5-45.5)
Patients with platelet nadir $<20 \times 10^9$/L, n (%)	13 (28.3)	146 (56.4)
No bleeding, n (%)	9 (19.6)	39 (15.1)
Minor bleeding only, n (%)	21 (45.7)	73 (28.2)
Any grade 2 bleed, n (%)	16 (34.8)	147 (56.8)
Any nonskin grade 2 bleed, n (%)	4 (8.7)	123 (47.5)
ICH, n (%)	1 (2.2)	6 (2.3)
Number of ITP treatments until last follow-up, median (IQR)	1 (0-2)	3 (1-5)
Untreated patients, n (%)	15 (32.6)	53 (20.5)

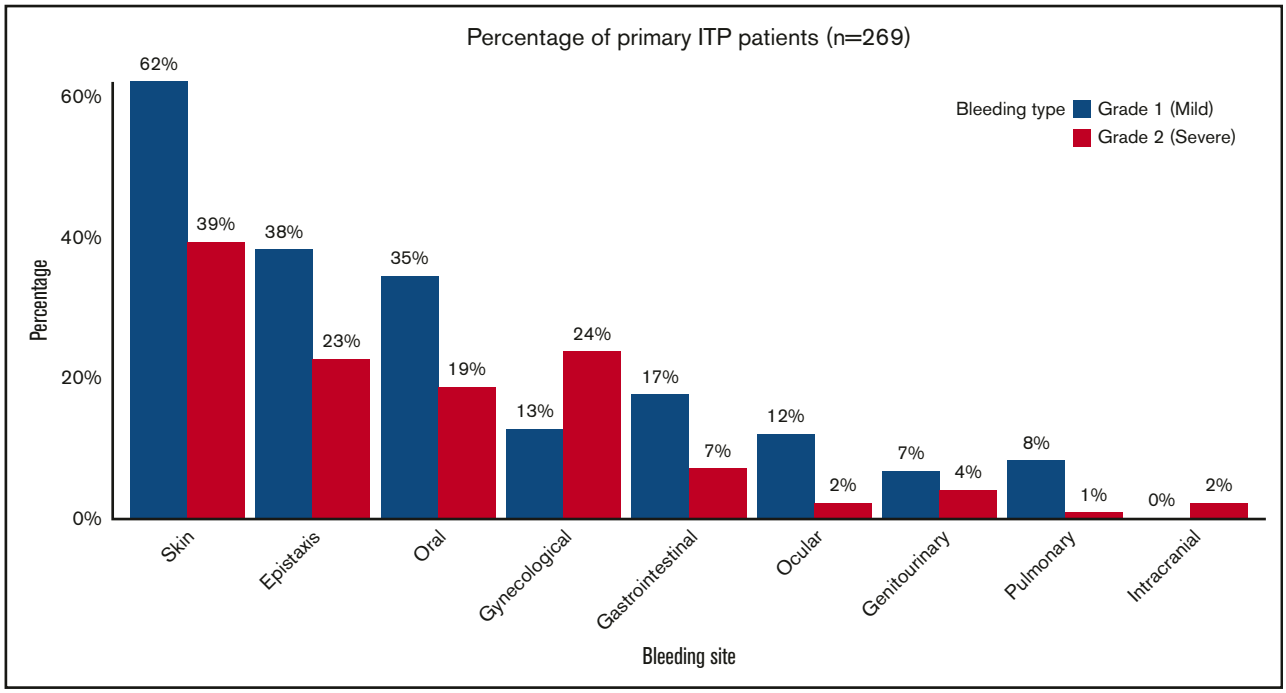

Figure 1. Worst bleed ever by anatomical site among patients with primary ITP. Of 269 patients, 152 (56.5%) experienced 1 or more grade 2 bleed; 25 (16.4%) had skin bleeding only.

an underlying condition responsible for the thrombocytopenia. Yet, even in a tertiary clinic dedicated to ITP in which 2 physicians cooperated in the evaluation of patients, 1 in 7 patients was misdiagnosed as having, or not having, ITP at some point during the disease course. Thus, for most patients with primary ITP, current clinical criteria are useful; however, for a subset of patients, the diagnosis can only be made after following patients over time as the disease evolves and additional investigations are done to exclude other causes. Even then, the diagnosis can still be elusive.

We included patients whose diagnosis changed from primary to secondary ITP (or vice versa) in our definition of "misdiagnosis" because our referral clinic included many patients who already had initial investigations done by their primary physicians. One potential explanation for the proportion of misdiagnoses in this study was referral bias because diagnostically challenging patients may be overrepresented in our referral clinic. We recently proposed additional diagnostic criteria for ITP, which include very severe thrombocytopenia (platelet count $<20 \times 10^9$/L) and platelet count response after intravenous immune globulin or corticosteroids[18]; however, these criteria cannot be applied prospectively and they do not exclude secondary forms of ITP. In addition, our study identified a group of patients (n = 13) who met standard criteria, yet could not be classified as primary ITP because of the mildness or transient nature of the thrombocytopenia and that they never required treatment. These features may help refine classification systems in the future. The identification of novel biomarkers to classify ITP patients and identify disease subgroups is a research priority.

We found that 56% of patients with primary ITP experienced severe bleeding at some point during their disease course. This estimate is higher than what has been previously reported: in a recent systematic review, the frequency of severe bleeding was approximately 10% for adults.[7] Reasons for our higher estimate include: (1) possible referral bias from our tertiary clinic; (2) cumulative risk reported over a long follow-up period; (3) the consistent use of a bleeding tool that was fairly liberal in its definition of grade 2 bleeding[7]; and (4) overrepresentation of skin or mouth grade 2 bleeds. Skin bleeds, although troublesome, do not have the same clinical implications as bleeds at other sites; however, health-related quality of life and other metrics are needed to determine their clinical impact.

Registries are powerful scientific tools for the collection of data from a large number of patients, especially for uncommon disorders.[19] Understanding the epidemiology of ITP requires large observational cohort studies or prospective registries with prolonged follow-up. Other ITP registries have yielded important information. Children and adults with newly diagnosed ITP were evaluated in the Intercontinental Cooperative Immune Thrombocytopenia Study, which highlighted similarities in presenting platelet counts and bleeding and provided a description of patients' comorbidities, diagnostic procedures, and therapies.[5] The UK ITP Registry found that fibrosis in bone marrow biopsies was not increased in patients receiving thrombopoietin receptor agonist medications, which helped to support the safety of this treatment.[20] We established the McMaster ITP Registry to study the clinical, laboratory, and mechanistic features of ITP prospectively over a prolonged follow-up period.

Strengths of the McMaster ITP Registry include ongoing data validation procedures, clinical assessments done by 2 physicians to establish and reevaluate the diagnosis over time, and prospective data collection with bleeding assessments for consecutive patients.

We included all patients with any degree of thrombocytopenia to avoid missing patients with ITP, even those whose diagnosis was uncertain at the time of registration. Patients in the registry with nonimmune thrombocytopenia can serve as controls for clinical analyses and future basic experiments.[21] This registry was designed specifically to study ITP; thus, it avoids the shortcomings related to disease classification often encountered with hospital or administrative databases.[22,23] The registry is unique in that it focuses on capturing detailed, accurate data from a well-described group of patients linked to a biorepository of patient samples, which can be used in future studies to address basic translational questions.

Limitations of this study were referral bias, because patients from a tertiary referral platelet disorders clinic were more likely to have severe disease; and the single-center design, which limited the generalizability of the results. Information on initial presentation of disease, which often preceded the patient's registration visit, relied on information from medical charts or, when unavailable, from patient self-reporting. Similarly, recall bias could have resulted in underreporting of minor (and less likely major) bleeding because the bleeding assessment tool relied on patient-reported bleeding events since the last encounter.[17]

This study demonstrated that misdiagnosis of patients with primary ITP was common, affecting 1 in 7 patients who were labeled as primary ITP: 12% of patients who were initially thought to have primary ITP turned out not to have it; and 3% of patients who were felt not to have primary ITP initially turned out to have it. Misdiagnosis has important implications on exposing patients to harms of unnecessary treatments,[24] case mix in clinical trials,[18] and sample selection for basic studies of pathophysiology.[21] The frequency of grade 2 bleeding, as defined by an ITP-specific bleeding scale applied uniformly, was 56%. The McMaster ITP Registry is a useful tool to help classify patients according to their clinical characteristics and provides denominator data from all thrombocytopenic patients. This information can lead to improvements in the diagnosis and classification of patients, which will help establish individualized, rather than empiric treatment strategies, and minimize severe bleeding complications.

Acknowledgments

The authors thank all participants and their families for their support in this study; Ron Movilla, Zakia Islam, Kate Moore, Robert Clayden, Sumayra Chowdhury, and Reda Siddiqui for assistance with data entry and data validation; and Korinne Hamilton, Julie Carruthers, and Naushin Sholapur for assisting in consenting patients and data collection.

This study was funded by the Canadian Institute for Health Research (CIHR Operating Grant #89897). A sub-study summarizing the first 3 years of data was funded by Amgen Canada. Program funding was provided by Canadian Blood Services, the federal government of Canada (Health Canada), and provincial and territorial ministries of health.

Authorship

Contribution: D.M.A. designed and established the study, interpreted data, supervised the research, and wrote the manuscript; I.N. supervised the sample collection and the laboratory testing, analyzed the data, and wrote the manuscript or edited the final version; R.C. consented patients, collected data, wrote the manuscript, and edited the final version; A.M.J. coordinated the day-to-day tasks of the registry, consented patients, collected data, assisted with the development of the Web-based data collection platform, and edited the manuscript; B.A. developed the Web-based data collection platform, developed the automated data analysis features, and edited the manuscript; N.L. provided statistical support, interpreted the data, and edited the manuscript; J.G.K. helped conceive the study, assessed patients, and edited the manuscript; and all authors reviewed and approved the final version of the manuscript.

Conflict-of-interest disclosure: D.M.A. has been a consultant for Amgen, Novartis, BMS, Rigel, and UCB on new and established ITP medications and received research funding for ITP studies from Amgen and Novartis. The remaining authors declare no competing financial interests.

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