LONG-TERM RISK OF PROGRESSION TO IMMUNE THROMBOCYTOPENIA OR HEMATOLOGIC NEOPLASIA IN PATIENTS WITH MILD THROMBOCYTOPENIA

SUPPLEMENTARY APPENDIX

SUPPLEMENTAL METHODS

Patient Selection

Individuals with platelet count 100-149 × 10^9/L measured at least 3 times between January 1, 1995 and December 31, 2004 at Massachusetts General Hospital were identified using the Mass General Brigham Research Patient Data Registry, a comprehensive database containing comprehensive and detailed patient-level chart data for over 7 million persons. Queries were designed to exclude patients with known causes of thrombocytopenia (such as myelodysplastic syndrome or immunosuppressant medications). Cases that passed through the below criteria who had a hematologist evaluation of persistent isolated mild thrombocytopenia were selected and patient charts were reviewed manually in detail by a hematologist (**Supplemental Figure 1**). Other blood count abnormalities were exclusionary except those diagnosed as transient (e.g., nutritional anemia) and which resolved promptly with treatment.

Research Patient Data Registry Query Parameters:

1) Independent Encounter Exclusions before January 1995: ICD-9/ICD-10 codes for systemic lupus erythematosus OR human immunodeficiency virus OR myeloproliferative neoplasms OR myelodysplastic syndromes OR aplastic anemia OR organ transplant OR antineoplastic medications OR immunosuppressant medications OR machine-learned query terms for oncology phenotypes (to exclude patients with known cancer diagnoses).

2) Same Encounter Exclusions January 1995-December 2004: Laboratory test values of hemoglobin <10 mg/dL OR white blood cell count <4 × 10^9/L OR C-reactive protein >48 mg/L OR erythrocyte sedimentation rate >100 mm/hr.

3) Age <18 years OR age>65 years before January 1995.

4) Same Encounter Exclusions January 1995-December 2004: admission to emergency observation unit OR postoperative surgical care OR same day major surgery OR intensive care unit OR receipt of blood product.

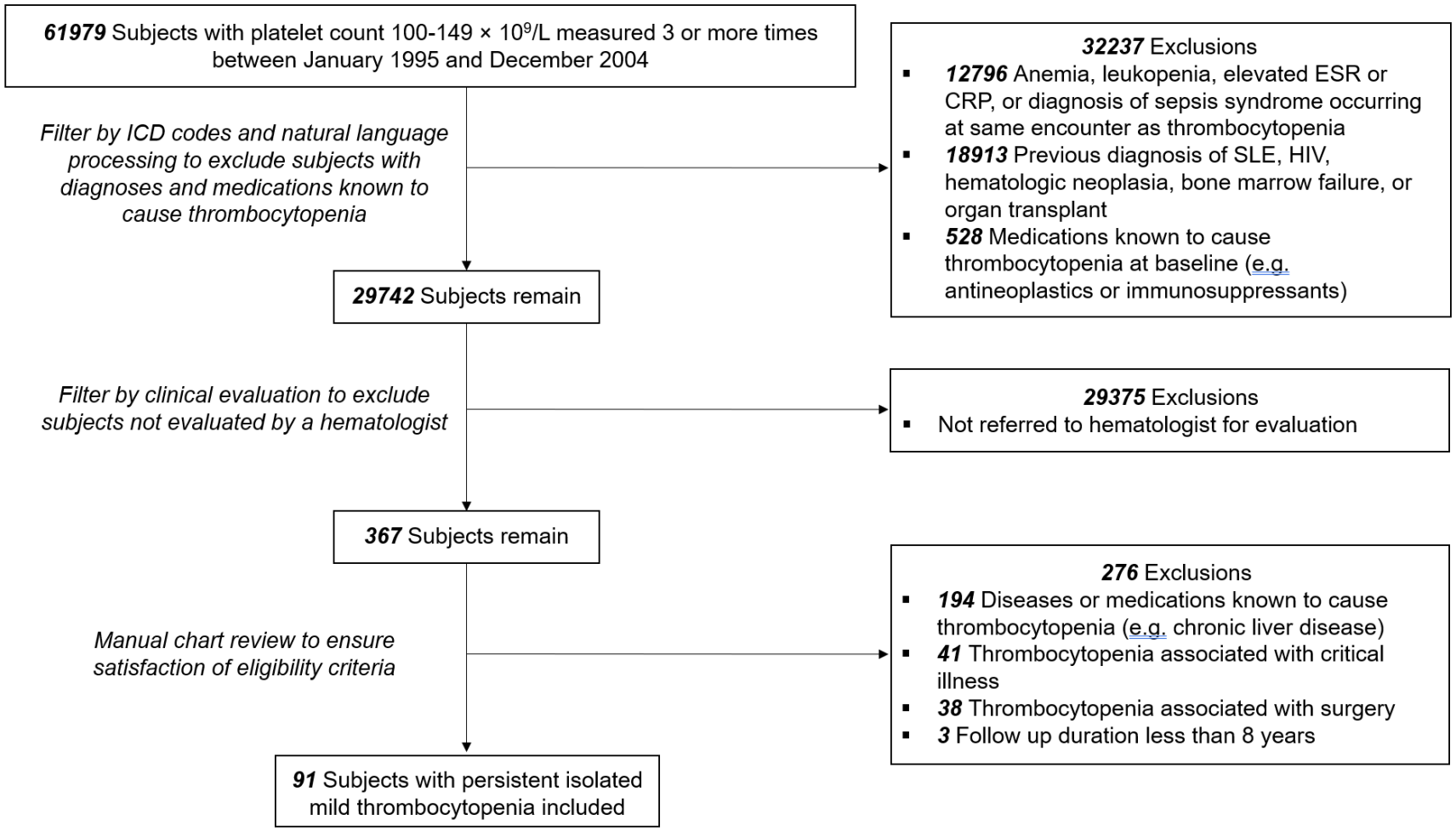
Matching

Subjects in the persistent isolated mild thrombocytopenia group were matched with healthy subjects in a 1:4 ratio. Subjects were matched according to age, sex, race, and synchronized at time zero to avoid immortal time bias. Time zero for patients in the thrombocytopenia group was the date of initial hematology evaluation. Synchronization of time zero for the thrombocytopenia and healthy subject groups meant that in addition to matching for age, sex, and race, to be matched with a subject in the persistent isolated mild thrombocytopenia group, a healthy subject had to also have a normal platelet count checked at that time in their chart history. For example, when matching for a 55-year-old Caucasian male in the thrombocytopenia group evaluated in 1999 by hematology (which would be time zero for this subject), a healthy subject who was a 55-year-old Caucasian male in 1999 with no platelet count checked until 2009 would not be matched with this

subject as time zero would not have been synchronized. A 55-year-old Caucasian male with a platelet count checked and found to be normal in 1999 (also at age 55*)* would be a suitable match.

SUPPLEMENTAL FIGURE

Supplemental Figure 1. Flow chart illustrating generation of at-risk subjects (those with persistent isolated mild thrombocytopenia).



SUPPLEMENTAL TABLES

Supplemental Table 1. Subhazard ratio (SHR) by unadjusted and age adjusted competing risks models of developing (A) any hematologic disease, (B) immune thrombocytopenia, and (C) hematologic neoplasia. Risk for development of ITP was not evaluable due to no incidences of ITP in the healthy subject group.

Hematologic Event	Competing Risks Model, Unadjusted SHR	Competing Risks Model, Age Adjusted SHR
Any hematologic disease	18.62 (95% CI, 8.18-42.35, *P*<0.001)	18.99 (95% CI, 8.39-42.96, *P*<0.001)
Immune thrombocytopenia	70.91 (95% CI, 9.40-535.20, *P*<0.001)	71.09 (95% CI, 9.38-538.70, *P*<0.001)
Hematologic neoplasia	9.26 (95% CI, 3.52-24.31, *P*<0.001)	10.33 (95% CI, 3.81-27.99, *P*<0.001)

Supplemental Table 2. Rates of development of ITP and hematologic neoplasia in persistent isolated mild thrombocytopenia group by presence of previously documented normal platelet counts (N=42) or lack of previously documented normal platelet counts (N=49).

Hematologic Event	Previously Documented Normal Platelet Count (N=42)	No Previously Documented Normal Platelet Count (N=49)	*P* value*
Immune thrombocytopenia	6	11	0.421
Hematologic neoplasia	6	7	1.000

*By Fisher's Exact test.

Supplemental Table 3. Systemic autoimmune diseases developed by the healthy subject group and persistent isolated mild thrombocytopenia groups over the course of follow-up. No subject in either group had a systemic autoimmune disease at baseline.

Autoimmune Disease	Healthy Subject Group (N=364)	Persistent Isolated Mild Thrombocytopenia Group (N=91)
None	353 (97%)	79 (87%)
Multiple sclerosis	1 (0.3%)	0 (0%)
Systemic lupus erythematosus	1 (0.3%)	3 (3%)
Antiphospholipid antibody syndrome	1 (0.3%)	6 (7%)
Hashimoto thyroiditis	8 (2.2%)	3 (3%)

Supplemental Table 4. Clinically-significant bleeding events in individuals with persistent isolated mild thrombocytopenia, in comparison to the healthy subject group, classified by bleeding location and severity.

Bleeding	Number of Subjects in Persistent Isolated Mild Thrombocytopenia Group	Number of Subjects in Healthy Group
A. Location		
Skin	14 (16%)	1 (0.3%)
Mucosa	5 (5%)	0 (0%)
Organ/Internal Mucosa	5 (5%)	5 (1.4%)
None	67 (74%)	358 (98%)
B. Severity*		
Major	4 (4%)	0 (0%)
Clinically Relevant Non-Major	11 (10%)	2 (0.5%)
Minor	9 (12%)	4 (1.1%)
None	67 (74%)	358 (98%)

*Classified according to International Society for Thrombosis and Haemostasis (ISTH) definitions