Predictors for splenectomy among patients with primary chronic immune thrombocytopenia: a population-based cohort study from Denmark

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Abstract

We conducted a nationwide cohort study of adult Danish patients with primary chronic immune thrombocytopenia (cITP) to examine selected patient and clinical characteristics as predictors for splenectomy. We analyzed data from the Danish National Patient Registry (DNPR) and patient medical records from 1996 through 2007. Using Cox regression analyses, we calculated incidence rate ratios (IRR) and associated 95% confidence intervals (CI) for splenectomy. We included 371 adult cITP patients. Of these 87 patients (23%) received a splenectomy during a median of 3.6 years of follow-up. The majority (84%) of cITP patients who underwent splenectomy received their splenectomy within the first year after cITP diagnosis. Predictors for splenectomy included age ≤75 years (adjusted one-year IRR = 6.79 (95% CI: 2.10-21.90),) at least one platelet count ≤30 x 10^9/L (i.e., high disease activity) (adjusted one-year IRR=2.67 (95% CI: 1.37-5.22)) during follow-up, and year of cITP diagnosis in early period (1996–2001) (adjusted one year IRR=2.37 (95% CI: 1.46-3.85)). Presence of chronic comorbidity was associated with lower rates of splenectomy (adjusted one year IRR=0.58 (95% CI: 0.33-1.05)). Our findings suggest that high disease activity and absence of chronic comorbidity may be associated with higher rates of splenectomy, and that contraindications for splenectomy (*i.e.*, patients' perceived frailty) cause the physicians to use the procedure cautiously.

Key words: Chronic immune thrombocytopenia, splenectomy, cohort study, risk

Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by increased platelet destruction and inadequate platelet production [1]. It is presumed that the presence of anti-platelet auto-antibodies results in decreased platelet counts because of the clearance of platelets, typically by the reticuloendothelial system of the bone marrow, spleen, and/or liver [1].

A review including cITP case series has shown a response rate of 66% following splenectomy with follow-up for 1 to 153 months [2]. Some ITP patients who are unresponsive to medical treatment, however, never undergo a splenectomy, perhaps because patients and physicians are reluctant to have a healthy organ removed, and they fear surgical complications like severe bleeding in the setting of low platelet count [3, 4]. It is likely that the age or frailty of a patient plays an important role in whether a splenectomy is recommended; thus, patients who ultimately undergo a splenectomy probably represent a selected group. Comparison of disease remission rates following splenectomy and medical treatments for cITP outside randomized controlled trials may thus be confounded by patient-related characteristics (*i.e.*, confounding by indication).

We conducted a nationwide cohort study of adult (aged ≥18 years) primary cITP patients in Denmark to examine selected patient and clinical characteristics as predictors for the rate of splenectomy.

Materials and Methods

We conducted this nationwide, population-based cohort study in Denmark, with a population of approximately 5.3 million inhabitants. Residents are provided free tax-supported healthcare by the National Health Service. All patients with primary ITP are treated at public hospitals operating under the auspices of the National Health Service. Since 1968, the Danish Civil Registration System has kept electronic records, updated daily, on date of birth, gender, address, date of emigration, and vital status for all residents. All Danish residents are assigned a unique 10-digit civil registry number, which encodes date of birth and gender [5], enabling us to link national data on hospital diagnoses.

Study cohort

The DNPR, established in 1977, includes more than 99.4% of all admissions to nonpsychiatric hospitals in Denmark [6]. Outpatient visits at hospitals have been included since 1995. Information includes date of admission and discharge, surgical procedure(s) performed, and up to 20 discharge diagnoses. Since 1994, diagnoses have been coded according to the tenth revision of the International Classification of Diseases (ICD-10) [6]. The ICD-10 code for primary ITP is D69.3. We identified all adult patients with a diagnosis of primary ITP from admission and outpatient specialised clinic visits from January 1, 1996, to July 31, 2007.

Initially, we identified 2908 patients registered in the DNPR who were aged ≥18 years and had a relevant ICD-10 code. Of these, 513 (17.6%) had at least two ITP diagnosis over the course of >6 months, with no clinically apparent associated conditions or other causes of thrombocytopenia and were thus categorized as having primary cITP. We were able to obtain medical records for 439 (85.6%) of these patients. Through medical record review we found that 410 patients (93.4%) had thrombocytopenia, defined as a platelet count below 150 x 10^9/L without an obvious cause, and

received medications and/or medical treatment/procedures to resolve the cITP. These patients were considered to have a valid diagnosis of cITP. Of the 410 patients, 37 patients (9.0%) who had had a splenectomy prior to their cITP diagnosis and 2 patients (0.5%) who had emigrated before their diagnosis of cITP were excluded. Thus, 371 adult cITP patients were included in this study cohort.

Patient and clinical characteristics

Information on the individual patient's lowest platelet count during follow-up and the last hospital **contact** date for cITP were abstracted from the medical records. As a measure of disease activity we classified lowest platelet count during follow-up as either $<30 \times 10^9$/L or $\geq 30 \times 10^9$/L because patients with a lowest platelet count below 30×10^9/L are indicated for splenectomy, according to current guidelines [8].

Five patients had missing information about platelet counts, and were categorized as having a lowest platelet count $\geq 30 \times 10^9$/L.

Using the DNPR, we identified patients who underwent splenectomy based on the Nordic Classification of Surgical Procedures codes 48900, 48901, 48910, and KJMA00-KJMA96. As a measure of level of comorbidity we retrieved all hospital diagnoses for these patients recorded between 1977 and the date of cITP diagnosis. We categorized comorbidity according to the Charlson comorbidity index. This is a validated index originally developed to predict one-year patient mortality [7], mainly used for control of confounding with a specific exposure. Two comorbidity levels were defined: 0, corresponding to no recorded underlying disease; and 1+, corresponding to one or more of the 19 diseases included in the Charlson Index being recorded in DNPR. Additionally, we categorised the patients according to 5 distinct comorbid categories: (1) cardiopulmonary disease, which included acute myocardial infarction, congestive heart disease, peripheral vascular disease and cerebrovascular disease, emphysema and chronic obstructive

pulmonary disease; (2) connective tissue disease which included diffuse connective tissue disease, rheumatoid arthritis and other inflammatory polyarthropathies, and polymyalgia rheumatica; (3) moderate to severe renal disease which included glomerulonephritis, nephropathies, and end-stage renal disease; (4) hepatic disorder which included hepatitis acuta, cirrhosis hepatitis, cholelithiasis and cholangitis; and (5) diabetes (insulin- and noninsulin–dependent) (See Appendix for the relevant ICD-8 and ICD-10 codes).

Statistical analyses

We constructed Kaplan-Meier curves for time until splenectomy among all study subjects, and calculated the cumulative incidence of splenectomy, and splenectomy rates per 1000 patient-years. We stratified these analyses by age at cITP diagnosis (≤75 years and >75 years, as this age limit may determine whether the patient are offered a splenektomy or not), gender, lowest platelet counts (<30 x 10^9/L and ≥30 x 10^9/L) during follow-up, period of cITP diagnosis (1996–2001 and 2002–2007), and history of comorbidity (by the two co-morbidity levels the aforementioned disease groupings) at cITP diagnosis. Patients were censored at date of death, date of emigration, or last day of follow-up (September 24, 2009), whichever came first.

We estimated the incidence rate ratio (IRR) of splenectomy and the associated 95% confidence intervals (CIs) from the hazard rate ratio on the basis of a Cox regression analysis to compare splenectomy rates stratified by age at cITP diagnosis, gender, lowest platelet count, diagnostic period, and comorbidity recorded before date of cITP diagnosis. The estimates were mutually adjusted for these factors. In addition, we estimated the IRR of splenectomy by specific history of categorised comorbidities, including cardio-pulmonary disease (yes/no), connective tissue

disease (yes/no), moderate to severe renal disease (yes/no), hepatic disorder (yes/no, and diabetes (yes/no).

The assumption of proportional hazards was assessed graphically and found appropriate in all Cox models. This study was approved by the Danish Data Protection Agency (Record no. 2007-41-1101). The statistical software package SAS, version 9.2 (SAS Institute Inc., Cary, NC), was used for all statistical analyses.

Results

Table 1 shows characteristics for the 371 adult cITP patients included in this study. At cITP diagnosis date 283 (76%) were 75 years or younger. The median age at cITP diagnosis was 56 years (range; 18-100 years). Most were women (n=231; 62%), and 273 (74%) had at least one platelet count below 30 x 10^9/L during follow-up. Five patients (1%) had missing platelet count information and were included in the group of patients with platelet counts above 30 x 10^9/L in the analyses. A total of 154 patients (42%) were diagnosed in the period 1996-2001, and 223 patients (60%) had no hospital-recorded co-morbidities on the date of cITP diagnosis.

A total of 87 (23%) cITP patients received a splenectomy procedure during a median follow-up of 3.6 years (range; 0-13.0 years), corresponding to an overall splenectomy rate of 57 per 1000 person-years. The majority splenectomy (n=73; 84%) occurred within the first year after cITP diagnosis yielding a splenectomy rate within the first year of 254 per 1000 person years. Of those, who received a splenectomy within the first year after cITP diagnosis, 58 (79%) had no hospital-recorded co-morbidities and 63% were diagnosed in earlier years (1996-2001) (Table 1).

The splenectomy rate within the first year after ITP diagnosis was 325 (95% CI: 257-411) per 1000 patient-years in patients ≤75 years compared with 41 (95% CI: 13-128) per 1000 person-years in patients >75 years (Table 2) which corresponded to an adjusted one-year IRR of 6.79 (95% CI: 2.10-21.90). The splenectomy rate after the first year of ITP diagnosis decreased to 12 (95% CI: 7-21) per 1000 person years and 9 (95% CI: 2-35) per 1000 person years, respectively. The rate of splenectomy within the first year after cITP diagnosis were also higher for those with at least one recorded platelet count < 30 x 10^9/L (adjusted one-year IRR=2.67 (95% CI: 1.37-5.22)) compared to those with lowest recorded platelet counts ≥ 30 x 10^9/L. Furthermore, the rate of splenectomy was higher for those diagnosed in 1996-2001 (adjusted one year IRR=2.37 (95% CI: 1.46-3.85)) compared to those diagnosed in 2002-2007 (Table2).

Patients with cITP who had at least one comorbid disease at diagnosis were less likely to undergo splenectomy within the first year after ITP diagnosis: splenectomy rates for the first year after ITP diagnosis was127 (95% CI: 77-211) per 1000 person years in those with at least one comorbid disease compared with 341 (95% CI: 264-441) per 1000 person years in those without comorbidity. In contrast, after the first year of ITP diagnosis the splenectomy rate among patients with at least one comorbidity was higher than the rate in those without comorbidity (19 (95% CI: 9-40) vs. 8 (95% CI: 4-17) per 1000 person years, yielding an adjusted IRR of 1.81 (95% CI: 0.59-5.49). (Table 2). We also found lower splenectomy rates within the first year of cITP for patients with each of the five distinct groups of comorbid diseases compared with cITP patients without these comobidities (Table 2).

Discussion

In this nationwide cohort of adults diagnosed with primary cITP during a 13-year period in Denmark, we found that younger age, high disease activity (measured as at least one platelet count below30x10^9/L), and an absence of chronic comorbidities were associated with higher rates of splenectomy within the first year after cITP diagnosis.

Although splenectomy is currently regarded as the definitive treatment for cITP [3], only 23% of the cITP patients in our study underwent this procedure. Further, the splenectomy rate decreased in the later time period (2002–2007). A change in attitude towards splenectomy, or recent introduction of new drugs for the treatment of ITP may explain the lower rates of splenectomy we observed for patients diagnosed with cITP after 2001 [9]. Our observation of lower rates of splenectomy among older patients and patients with a history of comorbidity could be explained by the fact that physicians may be more reluctant to recommend a splenectomy for frail patients because of general concerns regarding surgery and other specific patient safety risks. A splenectomy may lead to severe postoperative complications, including venous thromboembolism, serious infections, or bleeding [10], and even mortality, all of which are of even greater concern for elderly and frail patients [11, 12]. Moreover, older ITP patients may be less likely to respond to splenectomy [8, 13, 14]. Our finding that rate of splenectomy was higher among patients with higher disease activity are consistent with the guidelines for cITP treatment. Both the American Society of Hematology [8] and the British Committee for Standards in Haematology recommend splenectomy for patients with persistent platelet counts <30 x 10^9/L once an adequate trial of medical therapy has been completed.

Several strengths indicate the validity of our results. Our study was conducted in a uniformly organized Danish healthcare system which allows for a truly population-based design, avoiding selection bias due to loss of follow-up. Data on cITP diagnosis and platelet count were

obtained from medical records, limiting the potential for information bias, such as misclassification of diagnosis and laboratory values. The rate of splenectomy was accessed through the DNPR, which is known to be a reliable source of procedure codes [15]. A limitation to our study is the use of routine hospital data to identify patients with primary ITP, as some coding errors may have occurred. To be included in the study population, the patients should have two or more hospital diagnoses of ITP over a period >6 months. In a previous study this algorithm was found to have a positive predictive value of 92% [16], but since the completeness of an ITP diagnosis in the DNPR is probably not perfect, we may have missed some cITP patients. It is possible that we could have missed those cITP patients who were only hospitalized for cITP once, and then referred to their general practitioners for future control. However, we would expect this to happen only for patients with a relatively high platelet count and a self-limiting form of ITP. Recently, new consensusx criteria and definitions for primary ITP have been introduced [17]. These definitions established a platelet count less than 100 x 10^9/L was as the threshold for diagnosis instead of the more commonly used level of 150 x 10^9/L. In our study we used the 150 x 10^9/L level because this definition was used by the clinicians who treated the included patients and our medical record review secured that we did only include patients who were clinically regarded as having ITP.

The consensus criteria [17] also introduced a new category, of ITP patients called “persistent ITP” to define the period lasting between 3 and 12 months and the term chronic ITP was changed from lasting more than 6 months to lasting more than 12 months. Since we followed the old definitions we may therefore have included patients who by current guidelines have persistent ITP as chronic ITP patients. Actually, among splenectomised, 66 (76%) received the splenectomy procedure less than 12 months after the initial ITP diagnosis date i.e. when they would be categorised as having persistent ITP.. We did, however, stick to the former diagnostic criteria (i.e., cITP patients defined

as primary ITP patients with a disease course lasting >6 months) [8], as the data were collected before the introduction of the new diagnostic criteria.

In conclusion, selection mechanisms seem to influence splenectomy among cITP patients in Denmark. This study suggests that younger age and high disease activity predicts splenectomy and contraindications, such as high age and presence of comorbidity, are associated with a more cautiously use of this procedure.

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References

1. Beardsley DS (2006) **ITP in the 21st century**. *Hematology Am Soc Hematol Educ Program:*.402-407.
2. Kojouri K, Vesely SK, Terrell DR, George JN (2004) **Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications**. *Blood* **104**(9):2623-2634.
3. Rodeghiero F, Ruggeri M (2008) **Is splenectomy still the gold standard for the treatment of chronic ITP?** *Am J Hematol* **83**(2):91.
4. Dolan JP, Sheppard BC, DeLoughery TG (2008) **Splenectomy for immune thrombocytopenic purpura: surgery for the 21st century**. *Am J Hematol* **83**(2):93-96.
5. Frank L (2000) **Epidemiology. When an entire country is a cohort**. *Science* **287**(5462):2398-2399.
6. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH (1999) **The Danish National Hospital Register. A valuable source of data for modern health sciences**. *Dan Med Bull* **46**(3):263-268.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation**. *J Chronic Dis* **40**(5):373-383.
8. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG *et al* (1996) **Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology**. *Blood* **88**(1):3-40.
9. Boye J, Elter T, Engert A (2003) **An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab**. *Ann Oncol* **14**(4):520-535.
10. Thomsen RW, Schoonen M, Farkas DK, Riis A, Jacobsen J, Fryzek JP, Sørensen HT (2009) **Risk for Hospital Contact with infection in patients with splenectomy. A population-based cohort study**. *Annals of Internal Medicine* **151**(8):546-555.
11. Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A (2001) **Morbidity and mortality in adults with idiopathic thrombocytopenic purpura**. *Blood* **97**(9):2549-2554.
12. Mazzucconi MG, Arista MC, Peraino M, Chistolini A, Felici C, Francavilla V, Macale E, Conti L, Gandolfo GM (1999) **Long-term follow-up of autoimmune thrombocytopenic purpura (ATP) patients submitted to splenectomy**. *Eur J Haematol*, **62**(4):219-222.
13. Cooper N, Evangelista ML, Amadori S, Stasi R (2007) **Should rituximab be used before or after splenectomy in patients with immune thrombocytopenic purpura?** *Curr Opin Hematol* **14**(6):642-646.
14. Akwari OE, Itani KM, Coleman RE, Rosse WF (1987) **Splenectomy for primary and recurrent immune thrombocytopenic purpura (ITP). Current criteria for patient selection and results**. *Ann Surg* **206**(4):529-541.
15. Andersen TF, Madsen M, Loft A (1987) **[Validity of surgical information from the Danish National Patient Registry with special attention to the analysis of regional variations in hysterectomy rates]**. *Ugeskr Laeger* **149**(36):2420-2422.
16. Klith Heden KE, Jensen AO, Farkas DK, Nørgaard M (2009) **Validity of a procedure to identify patients with chronic idiopathic thrombocytopenic purpura in the Danish National Registry of Patients**. *Clinical Epidemiology* **1**:7-10.

17. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N *et al* (2009) **Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group**. *Blood* **113**(11):2386-2393.

Table 1 Characteristics of patients with chronic immune thrombocytopenia (cITP) in Denmark, 1996-2007

	Total cITP cohort		Splenectomised cITP patients		
			Total	Within first year after cITP diagnosis	After the first year after cITP diagnosis
	N	%	N (%)	N (%)	N (%)
Total	371	100	87 (100)	73 (100)	14 (100)
Age at cITP diagnosis					
≤75 years	283	76	82 (94)	70 (96)	12 (86)
> 75 years	88	24	5 (6)	3 (4)	2 (14)
Gender					
Women	231	62	57 (66)	47 (64)	10(71)
Men	140	38	30 (34)	26 (36)	4 (29)
Platelet group					
< $30x10^9$/L	273	74	77 (89)	63 (86)	14 (100)
≥ $30x10^9$/L	98	26	10 (11)	10 (14)	0
Year of cITP diagnosis					
1996-2001	153	41	50 (57)	46 (63)	4 (29)
2002-2007	218	59	37 (43)	27 (37)	10 (71)
Charlson comorbidity score					
0	223	60	65 (75)	58 (79)	7 (50)
1+	148	40	22 (25)	15 (21)	7 (50)

Table 2 Incidence rate (IR) per 1000 person-years and incidence rate ratio (IRR) of a splenectomy procedure among patients with chronic immune thrombocytopenia (cITP) in Denmark, 1996-2007

	First year after cITP diagnosis		More than one year after cITP diagnosis	
	IR (95% CI)	**Adjusted* IRR (95% CI)**	**IR (95% CI)**	**Adjusted* IRR (95% CI)**
Age				
≤75 years	325 (257 – 411)	1.00	12 (7 – 21)	1.00
> 75 years	41 (13 – 128)	6.79 (2.10-21.90)	9 (2- 35)	2.00 (0.42-9.48)
Lowest platelet count				
< 30x10E9/L	312 (244 – 399)	2.67 (1.37-5.22)	17 (10 – 28)	-
≥ 30x10E9/L	116 (63- 216)	1.00	0	-
Gender				
Women	261 (196 – 347)	1.00	12 (7 – 23)	1.00
Men	242 (165- 355)	1.18 (0.73-1.92)	10 (4 – 26)	0.71 (0.22-2.29)
Year of ITP diagnosis				
1996-2001	422 (316 – 564)	2.37 (1.46-3.85)	6 (2 – 15)	0.44 (0.12-1.65)
2002-2007	151 (104 – 220)	1.00	18 (10 – 34)	1.00
Charlson comorbidity				
Index score 0	341 (264 – 441)	1.00	8 (4 – 17)	1.00
Index score 1+	127 (77 – 211)	0.58 (0.33-1.05)	19 (9 – 40)	1.81 (0.59-5.49)
	IR (95% CI)	**Adjusted$ IRR (95% CI)**	**IR (95% CI)**	**Adjusted$ IRR (95% CI)**
No cardio-pulmonary disease	301 (238 – 382)	1.00	11 (6 – 20)	1.00
Cardio-pulmonary disease	68 (26 – 181)	0.38 (0.14-1.06)	11 (3 – 45)	0.72 (0.15-3.40)
No connective tissue disease	264 (209 – 333)	1.00	11 (6 – 19)	1.00
Connective tissue disease	108 (27 – 433)	0.53 (0.12-2.31)	20 (3 – 141)	1.72 (0.21-13.85)
No moderate to severe renal disease	257 (204 – 324)	1.00	12 (7 – 20)	-
Moderate to severe renal disease	131 (19 – 932)	0.94 (0.12-7.45)	0	--
No hepatic disorder	255 (203 – 322)	1.00	11 (7 – 19)	-
Hepatic disorder	175 (25 – 1240)	0.53 (0.07-3.82)	0	
No diabetes	266 (211 – 336)	1.00	9 (5 – 17)	1.00
Diabetes	95 (24 – 379)	0.58 (0.14-2.47)	53 (17 – 165)	3.02 (0.75-12.18)

* Adjusted for age, gender, disease severity, year of cITP diagnosis, and co-morbidity index level.
§ Adjusted for age, gender, disease severity, year of cITP diagnosis, and the comorbidity groupings, except for the one under interest.

Appendix

Translation of disease categories of chronic diseases into discharge diagnoses in ICD-8 and ICD-10

Disease category	Diseases	ICD-8	ICD-10
Cardio-pulmonary disease	Acute myocardial infarction, congestive heart disease, peripheral vascular disease and cerebrovascular disease	410; 427.09; 427.10; 427.11; 427.19; 428.99; 782.49; 440-445; 430-438. 490-493; 515-518	I21-I23; I50; I11.0; I13.0; I13.2; I70-I74; I77; I60-I69; G45-G46.
	Emphysema, asthma and chronic obstructive lung disease		J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective Tissue Disease	Diffuse connective tissue disease, rheumatoid arthritis and other inflammatory polyarthropathies and polymyalgia rheumatica	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30-M36; D86
Moderate to severe renal disease	Glomerulonephritis, nephropathies and end-stage renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Hepatic disorder		570-577	K70-K77
Diabetes		249, 250	E10, E12, E11