Long-term complications of splenectomy in adult immune thrombocytopenia

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Abstract
The recent large decrease in splenectomy use for chronic immune thrombocytopenia (ITP) is partly due to still-unsolved questions about long-term safety. We performed the first single-center exposed/unexposed cohort study evaluating the long-term incidence of splenectomy complications in patients with primary ITP. Overall, 83 patients who underwent splenectomy more than 10 years ago (exposed) were matched with 83 nonsplenectomized patients (unexposed) on the date of ITP diagnosis ±5 years, age and gender. After a median follow-up of 192 months (range 0.5–528), 43 patients (52%) achieved overall response after splenectomy. Splenectomized patients experienced more venous thromboembolism (VTE) than controls (n = 13 vs n = 2, P = 0.005). On multivariate analysis, splenectomy was an independent risk factor of VTE (hazard ratio = 4.006, P = 0.032 [95% confidence interval: 1.13–14.21]). Splenectomized patients presented more severe infections on long-term follow-up: all required hospitalization, and 5/26 (19%) infections led to severe sepsis or septic shock and to death for 3 cases (none in controls). However, the incidence of malignancy was similar in both groups, as was cardiovascular risk, which appeared to be related more to ITP than splenectomy. Finally, splenectomy did not significantly decrease overall survival. Despite the risk of thrombosis and severe sepsis, splenectomy remains an effective and curative treatment for ITP.

Abbreviations: CR = complete response, CV = cardiovascular, DVT = distal venous thrombosis, ITP = immune thrombocytopenia, NR = nonresponse, OPSI = overwhelming postsplenectomy infections, PE = pulmonary embolism, R = response, Tpo-Ras = thrombopoietin-receptor agonists, VTE = venous thromboembolism.

Keywords: complications, immune thrombocytopenia (ITP), long-term, splenectomy, thromboembolism, treatment

1. Introduction
Primary immune thrombocytopenia (ITP) is an acquired bleeding disorder characterized by antibody-mediated destruction of platelets and impaired thrombopoiesis. The spleen plays a major role in ITP pathogenesis because it is the main site of platelet destruction and autoantibody production. Thus, splenectomy was long considered the gold standard treatment for severe chronic ITP, with sustained platelet response in two-thirds of patients.[1]

However, the emergence of new efficient drugs, first the monoclonal anti-CD20 antibody rituximab, then thrombopoietin-receptor agonists (Tpo-Ras), has deeply modified the therapeutic strategy by enhancing the generalized tendency to avoid or delay splenectomy.[2] Indeed, the 2010 International Consensus on ITP diagnosis and treatment considered these treatments as a reasonable alternative to splenectomy as second-line treatment.[3]

The large decrease in splenectomy incidence in Europe and the United States may also be due to some concerns about its long-term safety for ITP despite decades of experience.[4]

The spleen is a major secondary lymphoid organ and contributes to both T-cell-dependent and -independent immune responses against bacterial agents, especially encapsulated bacteria. Accordingly, splenectomy is associated with a particular risk of overwhelming postsplenectomy infections (OPSI), mostly due to Streptococcus pneumoniae,[5] but also an overall increased risk of infection.[6,7] The spleen also plays an important role as a filter for platelets and senescent red blood cells, which explains that splenectomy could be associated with increased risk of venous thromboembolism (VTE)[2,8] and cardiovascular (CV) events such as myocardial infarction and stroke.[18–10] Moreover,
patients undergoing splenectomy may be at increased risk of cancer,[9] although still controversial.[10] Of note, the type and incidence of such complications may differ depending on the indication for splenectomy.[6,7]

In the setting of ITP, population-based and large retrospective cohort studies suggested that splenectomy could be associated with increased risk of VTE and infections. However, ITP per se could be an independent risk factor of thrombosis.[13–16]

To address these important questions, we investigated the long-term complications of splenectomy in a single-center cohort study comparing long-term outcome in adults with ITP who were exposed and not exposed to splenectomy.

2. Patients and methods

The study was approved by our local institutional review board (Comité de Protection des Personnes Île de France-IX) and was conducted in accordance with the Helsinki Declaration.

2.1. Study population

2.1.1. Splenectomized ITP patients (exposed). We first identified all ITP patients seen in the department of internal medicine of Henri-Mondor university hospital, the French national referral center for adult cytopenias, and registered from 1990 in a database. From 827 ITP patients treated in our institution, we selected those with definite primary ITP (n = 678) who underwent splenectomy before 2004. We excluded patients with systemic lupus diagnosed according to American College of Rheumatology criteria[17] and patients with malignant hematopathies. For exhaustivity, we also screened the database from the department of pathology of our institution for records from 1990 to 2004 by using the key words “splenectomy” and “ITP.” Clinical data were retrospectively collected from medical charts; all patients were interviewed by phone by 2 authors (LT, MMA) who used a standardized questionnaire. Information was systematically completed with the help of the general practitioner and/or medical care center if necessary, especially for deceased patients. The number of patients lost to follow-up was reduced by contacting the patient’s family, regular physicians, and/or the city records office of the place of birth in case of death.

2.1.2. Nonsplenectomized ITP patients (unexposed controls). Splenectomized ITP patients were matched in a 1:1 ratio to nonsplenectomized patients (screened from the database and drawn by lot) with primary ITP on the date of ITP diagnosis ≥5 years, age at diagnosis and gender. The same procedures used for splenectomized patients were used to collect data for controls.

2.2. Patients and criteria of response

The response to splenectomy was assessed postoperatively within 1 month after the procedure and at the last follow-up and was defined according to standardized international criteria: complete response (CR), platelet count >100 × 10^9/L; and response (R), platelet count >30 × 10^9/L, with at least a doubling of the baseline value. Nonresponse (NR) was defined as not achieving a platelet count ≥30 × 10^9/L with at least a doubling of the baseline count or requiring rescue therapy (intravenous immunoglobulin and/or corticosteroids). A hemorrhagic event was considered severe if visceral (cerebral, pulmonary, digestive, urinary, gynecological).

2.3. Definition of clinical outcome

VTE was defined by the presence of a clot in a deep vein, an abdominal vein (splenic or intrahepatic) and/or pulmonary arteries by Doppler ultrasonography and/or enhanced CT scan. CV events were defined as transient ischemic attacks (TIAs), ischemic stroke, or acute myocardial infarction according to the World Health Organization definition.[18,19] Infectious events were considered only with clinical symptoms suggesting a bacterial infection requiring antibiotics (suspected infections) or when a bacteria was identified; viral infections were excluded. To assess the incidence of VTE related to splenectomy and/or disease activity, we systematically screened potential confounding risk factors of VTE (antiphospholipid antibodies, underlying malignancy, prolonged immobilization) and CV disease (male gender, age ≥65 years, smoking, hypertension, diabetes, hypercholesterolemia, obesity, and family history of CV disease before age 45). Cancer was assessed from medical records and phone interview. Death was assessed by contacting regular physicians and/or the city records office of the place of birth in case of absence of recent follow-up.

2.4. Data analysis

Data were presented as number and percentages for categorical variables and median with interquartile range (IQR) for continuous variables. Comparison between groups involved Fisher exact test for qualitative variables and nonparametric Mann–Whitney test for continuous variables. Cumulative incidence of VTE, CV, infection, and cancer events was estimated by the Kaplan–Meier method with the rank test for comparing splenectomized and nonsplenectomized patients. We considered VTE, CV, infection, and cancer events that occurred after the date of splenectomy or the theoretical date of splenectomy for controls as corresponding to the date of surgery for the splenectomized matched patient. The Cox proportional hazards model was used for multivariate analysis; hazard ratios (HR) are presented with their 95% confidence intervals (95% CIs). Survival estimates were determined by the Kaplan–Meier method and compared by log-rank test. Data were standardized by using French mortality tables to estimate the expected mortality of a cohort of same age distribution and gender. The numbers of expected and observed deaths were compared by the Breslow and Day test. We calculated a propensity score to allow for comparison between splenectomized and nonsplenectomized ITP groups. A propensity score takes into account the factors that may have influenced the treatment allocation. The propensity score calculation included the variables age, gender, hemorrhagic event (see below), and number of treatment lines.

3. Results

3.1. Patient selection

We identified 94 patients who underwent splenectomy for primary ITP in our department. Among the splenectomized ITP patients, 11 were excluded because of early lost to follow-up (<1 year after splenectomy) or missing data. Thus, the final analysis was based on 83 splenectomized patients and 83 matched controls (nonsplenectomized). Patients who had died at follow-up were included in the final analysis.

3.2. Characteristics of splenectomized patients and controls

Splenectomized patients and controls were similar in the matching variables sex and median age at ITP diagnosis and median duration of follow-up after ITP diagnosis. As expected,
Clinical characteristics of patients with immune thrombocytopenia (ITP) who underwent splenectomy matched with controls.

|                        | Splenectomized patients, n=83 | Controls, n=83 | P       |
|------------------------|-------------------------------|---------------|---------|
| Male/female, no.       | 23/60                         | 23/60         |         |
| Age at ITP diagnosis, years, median (range) | 37 (3–92) | 38 (3–93) | 0.765   |
| Duration of follow-up after splenectomy, months, median (range) | 192 (1–528) | 192 (2–528) | —       |
| Severe hemorrhagic event (visceral hemorrhage), no. (%) | 22 (26) | 7 (6) | 0.004   |
| No. of ITP treatments, median (range) | 4 (1–7) | 2 (1–6) | <0.001  |
| Medical treatment, no. (%) | 29 (35) | 5 (6) | 0.008   |
| Immunosuppressive treatments | Rituximab | 11 (13) | 11 (13)  |
| TPO receptor agonists | 8 (23) | 7 (6) |         |
| Ongoing treatment at the last visit in living patients, no. (%) | 10/66 (15) | 16/74 (21) | 0.387   |
| Platelet count at the last follow-up in living patients, no. (%) | >100 x 10^9/L | /66 |         |
|                       | ≥30 x 10^9/L | 46 (70) | 52 (70) | 0.941   |
|                       | <30 x 10^9/L | 19 (29) | 20 (27) |         |

**Table 1**

**Clinical characteristics of patients with immune thrombocytopenia (ITP) who underwent splenectomy matched with controls.**

**3.3. Characteristics of splenectomized patients and response to splenectomy**

Most splenectomized patients were females (n=60, 72%), the median age was 37 years (range 3–92) at ITP diagnosis (Table 1). Splenectomy was performed after a median time of 16 months (range 2–140) after ITP diagnosis, by laparotomy in 50 cases (62.5%) or laparoscopy in 30 (37.5%) (3 missing data). The 3-year-old patient eventually underwent splenectomy at age 13 years. In total, 14 patients (17%) had 16 early postoperative complications, including hemorrhagic events (n=9/16), VTE (n=5/16), and infections (n=2/16). The proportion of early postoperative complications was double the rate for laparotomy (11 patients [22%], presenting 4 VTE, 7 hemorrhagic events and no infection) versus laparoscopy (3 patients [10%], presenting 1 VTE, 1 hemorrhagic event and 2 infections) (Supplemental Table 1, http://links.lww.com/MD/B405). Overall, 73 patients (88%) had an initial response after splenectomy. One patient with refractory disease died from hemorrhage within 1 month after splenectomy. Six other patients died within the 10 years after the splenectomy. After a median follow-up of 192 months (range 0.5–528) after splenectomy, 43 patients (52%) achieved long-term sustained response (39 CR and 4 R). At last follow-up, 66/83 patients (80%) were alive; 10 (15%) were still receiving treatment for ITP, and only 1 had a platelet count <30 x 10^9/L.

**3.4. VTE**

During the follow-up period, 13 (16%) splenectomized patients and 2 (2%) controls presented at least 1 VTE (P=0.005) (Table 2, Fig. 1A). The cumulative incidence of VTE at 10, 20, and 30 years after splenectomy or after the theoretical date of splenectomy in the 2 groups is in Supplemental Table 2, http://links.lww.com/MD/B405. The number of patients with VTE presenting at least 1 associated confounding risk factor of VTE did not differ between the 2 groups (Table 2). No patient had thrombocytosis at the time of VTE. Three cases presented a postoperative symptomatic portal vein thrombosis that led to a portal cavernoma despite curative anticoagulation therapy. Beyond the postoperative period, on long-term follow-up, VTE occurred more frequently in splenectomized patients than controls (n=10 vs n=2, P=0.032) (Supplemental Table 2, http://links.lww.com/MD/B405). Postembolic pulmonary arterial hypertension developed in 2 cases and 1 control. Responders and nonresponders to splenectomy did not differ in number of VTEs (Table 3; Supplemental Fig. 1A, http://links.lww.com/MD/B405). As expected, risk factors of VTE (antiphospholipid antibodies, underlying malignancy, prolonged immobilization) were strongly associated with VTE on multivariate analysis (HR=7.54 [95% CI: 2.79–20.40], P<0.001). Splenectomy was also associated with increased risk of VTE, independent of classical VTE risk factors (HR=4.01 [95% CI: 1.13–14.21], P=0.032). After adjustment on the propensity score, splenectomy was independently associated with VTE (HR=4.32 [95% CI: 1.19–15.67], P=0.026).

**3.5. CV events**

CV events occurred in 10 (12%) splenectomized patients and 4 (5%) controls (P=0.143) (Table 2, Supplemental Table 2, Supplemental Fig. 1B, http://links.lww.com/MD/B405). In total, 10 patients had 12 CV events after splenectomy, and 4 controls had 5 CV events. The number of CV risk factors did not differ between the 2 groups with a CV event. The number of myocardial infarction events did not differ (n=3 in each group), but the number of splenectomized patients with ischemic stroke or TIA events was greater, although not significantly, than controls (n=7 vs n=2) (P=0.106) (Table 2). Of note, the number of nonresponders with CV events was greater, although not significantly, than responders (n=7/40 vs n=3/43, P=0.085) (Table 3).

**3.6. Infection events**

The proportion of patients presenting at least 1 suspected or proven bacterial infection did not differ between splenectomized patients and controls (n=18 [22%] vs n=12 [14%], P=0.335) (Table 2, Supplemental Table 2, http://links.lww.com/MD/B405;
Fig. 1C). However, the total number of bacterial infections was greater among splenectomized patients than controls (n = 26/18 vs n = 13/12). Infections in splenectomized patients were mainly pneumonia (n = 14, 54%); 5 cases were due to encapsulated bacteria (S pneumoniae, n = 4; Haemophilus influenzae, n = 1). Two of the 4 patients with S pneumoniae infection were correctly vaccinated and 1 received prophylactic antibiotherapy. Importantly, infections were more severe in splenectomized than nonsplenectomized patients because they all required hospitalization (n = 26/26 vs n = 8/13, P = 0.002); 5/26 cases of infection (19%) led to severe sepsis or septic shock and was fatal for 3 (vs no death caused by an infection among controls) (Table 2). The causative bacteria were S pneumoniae in 2 cases. One pulmonary infection fulfilled the criteria of OPSI caused by S pneumonia and occurred in a 21-year-old patient, more than 10 years after splenectomy. The 3 patients who died were 64, 70, and 73 years old, and all had at least 1 associated comorbidity (i.e., lymphoma, massive ischemic stroke, or bleeding complication related to ITP relapse). Patients with and without response did not differ in incidence of infections (Table 3; Supplemental Fig. 1C, http://links.lww.com/MD/B405).

3.7. Malignancies

Splenectomized patients and controls were similar in number with a cancer diagnosis during follow-up (n = 12 [14%] vs n = 10 [12%], P = 0.789) (Table 2); the median age at the time of cancer diagnosis was 67 (range 51–92) and 74 (range 49–85) years, respectively (P = 0.468) (Table 2).

3.8. Mortality

The number of deaths did not differ between splenectomized patients and controls (n = 17 [20%] vs n = 9 [11%], P = 0.206) (Fig. 1D). However, as mentioned previously, 3 cases died from infection, with none in controls. Mortality was higher, although not significantly, in nonresponders than responders to splenectomy and controls (n = 11/40 [27.5%] vs n = 6/43 [14%] and
n = 9/83 [11%], P = 0.134) (Table 3), mainly because of some fatal hemorrhages in 5 patients who did not achieve response after splenectomy. The cumulative incidence of overall survival at 30 years was 58 ± 11% and 79 ± 8% for nonresponders and responders, respectively (Supplemental Fig. 1D, http://links.lww.com/MD/B405). The standardized mortality ratio was 1.465 and was not significantly different from 1 (P = 0.17).

4. Discussion

Splenectomy is an effective therapeutic option for adult chronic ITP. However, evaluating the long-term safety is crucial for both clinicians and patients now that new alternative therapies are available. VTE, CV disease, infection, and cancer have been found or suspected as potential long-term adverse effects of splenectomy,[6–10] but in the setting of ITP, some of these events could also be related to the disease.[2,11,13] To address the question of long-term safety of splenectomy in ITP, we report the data from the first single-center cohort study comparing ITP patients with or without splenectomy.

The systematic review of splenectomy complications reported by Kojouri et al suggested that the frequency of death and complications was significantly greater for laparotomy than laparoscopic splenectomy. In our cohort, most laparotomies had been performed before the 2000s. The number of early VTE and hemorrhagic events differed, although not significantly, between

### Table 3

| Long-term morbi-mortality by response to splenectomy and comparison with controls. |
|---------------------------------|-----------------|-----------------|-----------------|
| Response (n=43) | Refractory or relapsed disease (n=40) | Controls (n=83) | \( P^* \) | \( P^{**} \) |
|-----------------|-----------------|-----------------|-----------------|
| Patients, no. (%) | | | | |
| VTE | 8 (19) | 5 (12.5) | 2 (2) | 0.396 | 0.028 |
| CV event | 3 (7) | 7 (17.5) | 4 (5) | 0.158 | 0.085 |
| Infectious event | 8 (19) | 10 (25) | 12 (14) | 0.394 | 0.409 |
| Deaths, no. (%) | 6 (14) | 11 (27.5) | 9 (11) | 0.141 | 0.134 |
| Age at death, years, median (range) | 75 (57–95) | 62 (21–94) | 81 (51–94) | 0.305 | 0.284 |
| Cause of death, no. | | | | |
| Hemorrhage | 1 | 5 | 0 | | |
| Infection | 1 | 2 | 0 | | |
| VTE | 0 | 0 | 0 | | |
| CV disease | 0 | 2 | 1 | | |
| Cancer, malignant hemopathy | 3 | 1 | 2 | | |
| Other | 1 | 1 | 4 | | |
| Unknown | 0 | 1 | 2 | | |

\( CV = \) cardiovascular, VTE = venous thromboembolism.

* Comparing response and refractory or relapsed to splenectomy.

** Comparing the 3 groups.
cases with laparotomy and laparoscopy. However, on long-term follow-up, the frequency of complications did not differ between these 2 groups; the effect of the surgery was probably less important at that time.

The main finding of this study is that splenectomy is an independent risk of VTE. Beyond postoperative VTE of the portal vein system, VTE was more common in splenectomized patients than matched controls over the study period. The proportion of VTE in splenectomized patients (16%) was higher than previously reported by Vianelli et al.[11] (8%) and Boyle et al.[22] (4.3%). Of note, Boyle et al used a coding database to identify major VTE events requiring hospitalization, which could have underestimated the number of events. The observed incidence rate of VTE among controls (2%) agreed with the 1.4% to 2.9% found by others[3,12-14] and was higher than the 1% in the general population.[13] As previously reported, the occurrence of VTE did not appear to be related to platelet count or number of treatment lines.[1] Interestingly, the incidence of VTE was similar between responders and nonresponders to splenectomy, which strongly suggested that VTE was related more to the splenectomy than the disease course or to the different treatment lines. Adjustment on the propensity score showed that the number of treatments lines and bleeding score were not confounding factors. The mechanisms that may promote VTE in splenectomized patients are unclear; endothelium activating factors, increased platelet activation and/or released microparticles may be involved.[20,21] Genetic screening of heritable thrombophilia in the general population is still debated and was not performed in our study.[22] The relevance of such screening in the setting of splenectomy remains to be determined. The number of splenectomized patients receiving TPO-receptor agonists in our series was too small to assess whether this could be an additional risk factor of thrombosis in this population.[23] From these results, splenectomy should be considered an independent risk factor of VTE throughout life, and appropriate prophylaxis should be started in patients with additional risk factors of thrombosis (i.e., immobilization, surgery, etc.).

Schilling[10] reported an increased risk of CV disease in patients undergoing splenectomy for hereditary spherocytosis mostly associated with increased hemoglobin level after splenectomy. More recently, Ruggeri et al.[12] also found more CV events with than without splenectomy. However, in an epidemiological analysis of a large cohort of US veterans who underwent splenectomy after trauma, the rate of myocardial infarction and ischemic stroke did not differ from that in nonsplenectomized controls (relative risk 0.97 and 1.06, respectively), but the risk of dying from such complications was increased after splenectomy.[8] Finally, Vianelli et al.[11] observed a 4.5% rate of CV events after a minimum follow-up of 10 years after splenectomy in their cohort of ITP patients. In the present study, the incidence of CV events was very high in both splenectomized and nonsplenectomized patients (12% vs 5%), probably because of the extended follow-up. Despite the lack of power of our study for formal conclusions, we observed a tendency toward more CV events in nonresponders than responders to splenectomy. This observation questions the effect of disease activity and/or therapy on the risk of CV disease. A strong association between autoimmune diseases and morbidity due to CV disease has been shown in several diseases, particularly systemic lupus erythematosus and rheumatoid arthritis.[24,25] In a large population-based data-source study performed in the United Kingdom with 1070 ITP patients matched (1/4) with 4280 disease-free subjects, risk of CV events was slightly increased, with an adjusted HR of 1.37 (95% CI: 0.94–2.00) for ITP patients.[14] Overall, although the association of CV events and splenectomy remains unclear, primary and secondary prevention of CV disease should be carefully monitored in splenectomized ITP patients.

Splenectomy is a well-established risk factor for some bacterial infections. Encapsulated bacteria such as S pneumoniae cannot be easily opsonized and are cleared by the spleen, involving macrophages and B cells from the marginal zone.[26] As a result, splenectomy leads to a life-long increased risk of life-threatening septicemia or meningitis (OPSI), with a high mortality rate (>50%).[15,26] We identified 4 cases of S pneumoniae infection; 2 occurred more than 10 years after splenectomy. One led to an OPSI in a 21-year-old female who had undergone splenectomy in childhood; she had received pneumococcal vaccine 3 years earlier but had stopped antibioprophylaxy a few months before OPSI developed. Thus, infections caused by S pneumoniae remain a severe complication that can occur at any age and even decades after splenectomy despite preventive measures. Among patients interviewed by phone, 63% were aware of the long-term risk of infection and 64% were correctly vaccinated against S pneumoniae (data not shown). This observation agrees with some recent data for 178 splenectomized patients reported in a French pharmacoepidemiological study, showing a 70.2% vaccination rate against S pneumoniae and a 47.0% rate against H influenzae b.[27] We also observed severe infections not related to S pneumoniae a long time after splenectomy, but all episodes occurred in patients >65 years old who had associated comorbidities. In light of these results, information about the long-term risk of severe infection is crucial for management after splenectomy, and pneumococcal vaccination coverage should be improved.

Regarding the potential risk of cancer after splenectomy, a study of US veterans almost 40 years ago did not find an increased risk of cancer related to splenectomy.[19] However, an overall increased risk of cancer due to malignant hemopathies was recently reported from a large medicoadministrative study of US veterans who underwent splenectomy for various diseases.[13] We did not confirm this result in the setting of ITP. Although our relatively low number of patients included does not allow for definite conclusions, our results suggest that splenectomy is not associated with a major risk of malignancies.[12]

Finally, splenectomy did not affect overall survival. This observation confirms the administrative data reported by Boyle et al.[22] However, although overall survival was similar for responders and controls, the mortality rate for nonresponders with true chronic refractory ITP tended to increase, mainly due to bleeding complications. This over-risk of mortality in patients with refractory ITP was previously reported.[28,29] In this regard, we observed a short- and long-term overall response to splenectomy that was comparable in historical studies. Overall, 88% of patients achieved immediate postoperative response, which was similar to previous reports.[30-32] The long-term sustained overall response was 52%, but when not considering relapses that required only transient corticosteroids, we found 60% long-term sustained response, which was close to the results of the largest literature review including more than 2600 splenectomized patients with ITP.[31] The main limitation of our study is its retrospective design, with potentially missed data, but a large prospective cohort study with more than 10 years of follow-up is unlikely to ever be conducted. To collect the maximum data and update the follow-up, all medical charts were closely reviewed by 2 of the authors, and all living patients and their general practitioners, when necessary, were interviewed. Thus, our data were collected in a
prospective manner, instead of from an epidemiological, numerical database. Another potential bias could be that ITP patients who underwent splenectomy had more severe disease than those who received only medical treatments. Moreover, because more than 70% of controls had a chronic ITP (i.e., ITP duration longer than 1 year), the duration of ITP may have influenced the results. However, by comparing responders and nonresponders, we were able to evaluate the part of active disease in terms of long-term complications and overall survival. Recording such information was by definition not possible in most of the published studies based on administrative data. Furthermore, the use of a propensity score helped in bias reduction.

To conclude, our study demonstrates that splenectomy in ITP is associated with an increased risk of VTE and confirms that splenectomized patients are at increased risk of severe infection, even in the long-term. We provide some reassuring data concerning the CV and cancer events risk even if the number of patients was too low to draw definite conclusions. Our data imply that despite the risk of thrombosis and sepsis, splenectomy remains an effective and curative treatment for ITP. Specific management for primary prevention of VTE and adapted preventive measures such as vaccination and information about the risk of OPSI are mandatory, and CV risk factors should be corrected in this population.

Acknowledgments

We are grateful for helpful discussions with GM. L-HT was supported in part by a fellowship from the “Société de Médecine Interne” (Bourse Marcel Simon).

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