Splenectomy and the Incidence of Venous Thromboembolism and Sepsis in Patients with Immune Thrombocytopenia

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KEY POINTS

After splenectomy patients with ITP have higher risk of venous thrombosis and sepsis than patients with ITP who do not undergo splenectomy.

ABSTRACT

Patients with immune thrombocytopenia (ITP) who relapse after an initial trial of corticosteroid treatment present a therapeutic challenge. Current guidelines recommend consideration of splenectomy, despite the known risks associated with surgery and the post-splenectomy state. To better define these risks, we identified a cohort of 9,976 patients with ITP, 1,762 of whom underwent splenectomy. The cumulative incidence of abdominal venous thromboembolism (AbVTE) was 1.6% compared to 1% in patients who did not undergo splenectomy; and venous thromboembolism (VTE) (deep venous thrombosis and pulmonary embolus) after splenectomy was 4.3% compared to 1.7% in patients who did not undergo splenectomy. There was increased risk of AbVTE early (< 90 days) [HR 5.4 (CI, 2.3-12.5)], but not late (≥ 90 days) [HR 1.5 (CI, 0.9-2.6)] after splenectomy. There was increased risk of VTE both early [HR 5.2, (CI, 3.2-8.5)] and late [HR 2.7 (CI, 1.9-3.8)] after splenectomy. The cumulative incidence of sepsis was 11.1% amongst ITP patients who underwent splenectomy and 10.1% among the patients who did not. Splenectomy was associated with a higher adjusted risk of sepsis both early [HR 3.3 (CI, 2.4-4.6)] and late (HR 1.6 or 3.1, depending on co-morbidities). We conclude that ITP patients post-splenectomy are at increased risk for AbVTE, VTE, and sepsis.
INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by the antibody and cell-mediated destruction of platelets in conjunction with impaired thrombopoiesis and an increased risk of bleeding. ITP can be associated with other autoimmune disorders such as systemic lupus erythematosus (SLE), lymphoproliferative disorders, or infections, or can develop without obvious underlying illness (idiopathic).

Diagnosis is based on exclusion of other causes with the typical clinical picture of isolated thrombocytopenia and relatively mild bleeding manifestations. Because serious spontaneous bleeding is rare with platelet counts greater than 30 X 10^9/L, the current treatment guidelines recommend maintaining the platelet count greater than 30 x 10^9/L to avoid bleeding complications, while trying to minimize the adverse effects of therapy.

Initial therapy for ITP is corticosteroids or, for patients who are actively bleeding or who have a contraindication to steroids, intravenous immunoglobulin or anti-D globulin. Although corticosteroids induce an initial response in 70-90% of patients, the majority will relapse when steroids are tapered or stopped.

Second-line therapies include rituximab, cyclophosphamide, azathioprine, and the newer thrombopoietic agents romiplostim and eltrombopag. Splenectomy has been considered a standard therapy in the management of patients who are refractory to corticosteroids and is
highly efficacious, with approximately two-thirds of patients subsequently achieving a normal platelet count 10.

Although the development of laparoscopic splenectomy has lowered the immediate post-operative risks 11, barriers to more frequent use of splenectomy include the unpredictability of response 12, reluctance to perform splenectomy on patients with thrombocytopenia, and the hesitancy of patients to undergo an invasive procedure. Hematologists may be less inclined to recommend this therapy due to reported higher risk of both sepsis and VTE.

However, the incidence of post-splenectomy sepsis and VTE in patients with ITP is not well defined. Although patients with ITP have a greater risk of VTE as compared to the general population 13, little data exists on the incidence of VTE after splenectomy for ITP. Likewise, post-splenectomy sepsis remains a significant concern, but the absolute incidence of post-splenectomy sepsis has been difficult to quantify 14. Larger series have reported the incidence of post-splenectomy sepsis or serious infection in the range of 2-8% 15 16 17. In examining the risk of infection after splenectomy in ITP patients, most studies are small series and have demonstrated either no or minimal increased risk of infection 6 18 19 20 21 22 23 24 25.

The aim of this study was to better define the incidence and risks factors associated with AbVTE, VTE, and sepsis in adult patients with ITP following splenectomy compared to ITP patients who did not undergo splenectomy.
METHODS

Cohort Definition

The State of California Office of Statewide Health Planning and Development (OSHPD) maintains records of all patients hospitalized in non-federal hospitals in the state, called the Patient Discharge Database (PDD). Since July 1990, the State of California has required that these hospitals report the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes corresponding to medical diagnoses and procedures performed on every patient. Data is encrypted and linked to a master death registry. The State of California Committee for the Protection of Human Subjects and the University of California, Davis Institutional Review Board approved this project.

To identify a cohort of adult cases with ITP, we identified all cases 18 years of age or older that had a diagnosis of ITP in the principal (first) position from January 1990-November 2009. We excluded patients with SLE or chronic lymphocytic leukemia (CLL). In a separate step, all cases discharged with a principal procedure code for splenectomy were ascertained. The datasets were then merged using unique record linkage numbers that allow longitudinal tracking of serial admissions for individual cases.

To compare ITP cases that underwent or did not undergo splenectomy, we first identified and excluded those ITP cases that underwent splenectomy during the index admission or during any prior hospitalization back to 1990. Because ITP is known to have a variable clinical phenotype
and this database does not have laboratory data, we reasoned that including cases that required hospital admission specifically for ITP would generate a more homogeneous cohort of cases that had similar disease severity. Therefore, we excluded patients with less severe disease who did not require hospital admission prior to splenectomy to enrich for a population for whom the disease was severe enough to require hospitalization for ITP rather than for splenectomy alone. Using this cohort definition we then identified the ITP cases that did or did not undergo splenectomy at some time after the index hospitalization.

Outcomes

Incident VTE was defined as cases admitted with a diagnosis of lower extremity acute deep-vein thrombosis (DVT) or pulmonary embolism (PE) using 14 specific ICD-9-CM codes for DVT and 3 for PE in the principal or second position. Incident intra-abdominal VTE (AbVTE) was defined as thrombosis occurring in the mesenteric, portal, or hepatic veins using one of 5 specific ICD-9-CM codes. Previous studies have shown high positive predictive value for VTE (>87%) for cases with these codes in the first or second position. Sepsis was defined by one of 25 specific ICD-9-CM codes, which code for sepsis, septicemia, and systemic inflammatory response syndrome. We selected cases with any of these sepsis codes in only the principal, second or third position.

Comorbidity

Presence of 29 potential chronic co-morbidities was determined using the Elixhauser co-morbidity index using comorbidities listed for the index ITP admission.

Data Analysis

The characteristics of the cases that underwent or did not undergo splenectomy were compared using bivariate statistics. The risks of AbVTE, VTE and sepsis were compared using Cox
proportional hazard analysis, with splenectomy as a time-dependent covariate. A risk factor was considered significant if the p value was < 0.01.

The cumulative incidences of AbVTE, VTE, and sepsis were determined for the entire ITP cohort. To illustrate the comparison between splenectomy cases and non-splenectomy cases for the incidence and time course of AbVTE, VTE and sepsis, a matched Kaplan-Meier time-to-event analysis was generated. Non-splenectomy cases were matched 2:1 with splenectomy cases based on: age (within 2 years), sex, number of co-morbidities, race/ethnicity, and year of index admission. Each non-splenectomy case selected had to have duration of follow-up equal to or greater than the time between the index ITP admission and the date of splenectomy. Incidence of AbVTE, VTE, or sepsis was then compared only during the comparable follow-up time period after the index hospitalization. On the Kaplan-Meier plots, the origin was the day of splenectomy or the equal follow-up time for each matched non-splenectomy cases.

Survival estimates were determined using the Kaplan-Meier method and compared using Log-rank. Logistic regression analysis was used to analyze predictors of death associated with incident AbVTE, VTE, or sepsis, adjusting for age (< 60 or ≥ 60 years), sex, co-morbidities, race/ethnicity, and splenectomy.

All analyses were done using SAS analysis software, version 9.3, Cary, NC.
RESULTS

A total of 13,804 cases were identified with a principal diagnosis code for ITP. We excluded 1059 cases with SLE or CLL, and cases that underwent splenectomy before (69) or during (2691) the index ITP admission. The analysis cohort included 9,976 ITP cases (Figure 1). The frequency of ITP as the principal diagnosis was 0.03% amongst the 36,099,198 unique cases hospitalized in California during the study period. The median age was 55 years.

The majority of cases were female (58.2%) and Caucasian (58.4%) (Table 1). Reflecting the demography of California, significant proportions were Hispanic and Asian. Cases that underwent splenectomy were younger, more often female, included a higher percentage of Hispanics, and had fewer co-morbidities. One thousand seven hundred and sixty-two (17.7%) of the ITP cases underwent splenectomy (17 had partial splenectomy). The median time from index hospitalization to splenectomy was 2.9 months (range 1-207). The rates of splenectomy over the twenty-year period are shown in Figure 2.

Abdominal and Peripheral Venous Thromboembolism

Abdominal VTE developed in 109 cases: 27 splenectomized cases (cumulative incidence 1.6%) and 82 non-splenectomized cases (cumulative incidence 1%), VTE developed in 215 cases: 75 splenectomized cases (cumulative incidence 4.3%) and 140 non-splenectomy cases (cumulative incidence 1.7%) with a median follow-up of 60 months. The corresponding Kaplan-Meier plots are shown in Figure 3. Fifty-one cases in the entire cohort were coded as having a
hypercoaguable state and 33 cases were coded as having the antiphospholipid antibody. Only 1 case with either of these conditions developed a VTE.

Because undergoing an operation may have provoked VTE, the hazards for “early” AbVTE and VTE (<90 days of splenectomy) and “late” (≥ 90 days) were separately determined (Table 2). Splenectomy was associated with increased hazard of early AbVTE [HR 5.4 (CI, 2.3-12.5)], but not late AbVTE [HR 1.5 (CI 0.9-2.6)]. Splenectomy was associated with increased early [HR 5.2 (CI, 3.2-8.5)], and late VTE [HR 2.7 (CI, 1.9-3.8)]. The median time from splenectomy to AbVTE was 9.3 months (range 0-158 months) and to VTE was 20.9 months (range 0-179 months). In the multivariable model, comorbid conditions predicted an increased risk of AbVTE and older age predicted an increased risk of VTE. Asian/Pacific Islanders had a lower risk of developing VTE consistent with previous epidemiologic data.28,29

Sepsis

Sepsis developed in 1016 cases: 191 splenectomized cases (cumulative incidence 11.1%) and 825 non-splenectomized cases (cumulative incidence 10.1%) with a median follow-up of 56 months. The corresponding Kaplan-Meier plots are shown in Figure 4. The cumulative incidence of early sepsis after splenectomy (< 90 days) was 2.6%, and of late sepsis (≥90 days) was 8.8%. Amongst the splenectomy cases the median time from splenectomy to hospitalization with sepsis was 35.5 months (range 0-219 months).

In the multivariable model for sepsis, splenectomy was a significant predictor of both early and late sepsis, with an over 3-fold higher hazard for early sepsis [HR 3.3 (CI, 2.4-4.6)]. For late
sepsis, there was an interaction between splenectomy and number of co-morbidities. Cases with none or one comorbidity had a HR of 1.6 (CI 1.3-2.0) and for cases with 2 or more co-morbidities the HR was 3.1 (CI, 2.2-4.4). There was also an interaction between age and number of comorbidities. In addition to splenectomy, age $\geq$ 60, presence of co-morbidities, non-Hispanic Blacks, and males were also significant predictors of sepsis (Table 3).

Mortality

The Kaplan-Meier 5- and 10-year survivals for the entire ITP cohort were 73% (CI, 72%-74%) and 64% (CI, 63-65%), respectively. For the cases that developed acute VTE, the corresponding K-M 5- and 10- year survivals rates were 62 % and 46%, respectively (CI could not be calculated). The AbVTE cases had 5-year survival of 38% (insufficient number of cases to calculate 10-year survival). For the cases that developed sepsis, the 5- and 10-year survival rates were 35% (CI, 32%-38%) and 27% (CI, 24%-30%).

In a logistic regression model adjusted for age, race/ethnicity, and number of co-morbidities, AbVTE was associated with increased odds ratio for death (OR 3.3; CI, 2.1-5.1), whereas VTE was not (OR 1.4; CI 1.0-1.9). Development of sepsis was associated with increased odds of death (OR 4.7; CI, 4-5.5), as were age $\geq$ 60 years and a higher number of co-morbidities (data not shown). In the adjusted model splenectomy was associated with a significant reduction in the odds of death (OR 0.8; CI, 0.7-0.9).
DISCUSSION

To our knowledge, this represents the largest population-based study that has examined the effect of splenectomy on the incidence of AbVTE, VTE, sepsis, and mortality in patients with ITP. Using a retrospective observational cohort design, we found that amongst patients who required at least one hospitalization for ITP, subsequent splenectomy was associated with an approximately 5-fold higher risk for early AbVTE and VTE, and a 3-fold higher risk for late VTE when compared to patients with ITP who not undergo splenectomy, after adjusting for potential cofounders. In contrast with other patient populations, the presence of medical co-morbidities did not increase the risk for VTE, although co-morbid conditions were shown to increase the risk for AbVTE.

Splenectomy was also associated with a higher risk of sepsis, both early and late after the operation. In addition to splenectomy, the risk of sepsis was associated with expected risk factors, including with older age, and the number of co-morbidities. We also found that male gender and Black ethnicity predicted for a high risk of sepsis. Despite a demonstrated increased risk for AbVTE, VTE, and sepsis, splenectomy was associated with a reduction in the odds of death (OR 0.8; CI, 0.7-0.9).

The major strengths of this report include the large number of cases (n = 9,976) and the long duration of follow-up (up to 228 months). Limitations include reliance on hospital discharge coding and lack of laboratory data. Reliance on hospitalization to identify ITP cases means that
our findings may not be generalizable to patients who can be managed exclusively in the outpatient setting or who require hospitalization only for splenectomy. The patients we analyzed likely represented the more severe cases of ITP. Because we did not analyze cases that underwent splenectomy during the index hospitalization, it is likely that all patients included in our cohort did have some initial response to treatment, and then subsequently failed treatment.

Although the accuracy of the ICD-9-CM coding in the PDD for ITP has not been validated, we only included patients hospitalized with a principal diagnosis of ITP. Our conservative definition might have resulted in undercounting the number of ITP cases, but our goal was not to estimate the incidence or prevalence of ITP, but rather to evaluate the effect of splenectomy. As splenectomy is almost exclusively an inpatient procedure, it is unlikely that a significant number of splenectomized patients were missed.

The outcome measures AbVTE, VTE, and sepsis were based on the presence or absence of specific ICD-9-CM codes. Although VTE codes have high positive predictive value when compared to abstracted chart documentation, codes for sepsis or AbVTE have not been similarly validated. We based the definition of “sepsis” on accepted coding guidelines, and included cases where a code corresponding to sepsis, septicemia, and systemic inflammatory response syndrome (SIRS) were present in one of the first three diagnostic positions.

The cumulative incidence of AbVTE and VTE were higher in cases that underwent splenectomy; Cox proportional hazard modeling showed splenectomy to be independently associated with
increased hazard of AbVTE and VTE. Cases undergoing splenectomy were younger and had fewer medical co-morbidities (Table 1); traits that have been shown in most studies to lessen the risk of thromboembolism. It is possible the increased risk associated with splenectomy was a post-operative phenomenon that might be seen with any major abdominal operation. As the risk for post-operative thromboembolism has been shown to vary by type of operation 31 the site of postoperative thrombosis (i.e. abdominal verses peripheral) might also vary in the early versus later postoperative period. Because AbVTE is typically thought of as a surgical complication, it is not surprising there was a 5-fold higher risk of AbVTE in the early postoperative period that did not persist. The cumulative incidence of 1.6% reported here is similar to that reported in other studies examining the rate of post-splenectomy portal vein thrombosis (PVT) 32,33 although none of the patients who developed PVT in those series had underlying ITP. A small series of patients with beta-thalassemia who underwent splenectomy reported an 8.3% incidence of post-splenectomy VTE 34, a difference likely due to the higher burden of hypercoagulability in patients with beta-thalassemia as compared to ITP.

Reasons for the increased risk for VTE in splenectomized patients might include factors attributable to (1) ITP, (2) splenectomy, and/or (3) the more aggressive medical therapies to which patients with relapsed or refractory disease might be exposed. As smaller studies have suggested ITP itself to be a risk factor for thromboembolic events 23,35-37, it is possible that patients with more severe ITP, rather than the splenectomy, are at higher risk for VTE. Data from the Danish National Patient Registry 38 indicated the adjusted odds ratio for VTE in splenectomized patients was 32.6 versus the general population in the first 90 days post surgery, although the absolute incidence was low. Patients who developed thromboembolism post-
splenectomy were more likely to have an underlying hematologic malignancy, massive splenomegaly, thrombocytosis, or hemolytic anemia, features not commonly associated with ITP.

Within the ITP population, potential mechanisms by which splenectomy could increase the risk of VTE were recently reviewed and include loss of the spleen’s filtering activity, allowing for increased circulation and exposure of damaged red cells, cholesterol, and C-reactive protein. Animal models have suggested splenic macrophages regulate inflammation and mobilization of splenic macrophages could promote thrombosis. Candidates for splenectomy are likely to be patients with relapsed or refractory ITP, a cohort also likely to be receiving aggressive medical therapy, in the form of higher levels of immunosuppression and repeated hospitalization. It is possible that these risk factors increased the incidence of thromboembolism.

In a prospective analysis of 205 patients with ITP, Aledort et al. 2004 reported the cumulative incidence of VTE to be 5% in the adult patients. Fifty percent of the VTE cases were in patients who had undergone splenectomy. Bennett et al., using an insurance claims dataset, reported an overall rate of thromboembolism of 6.9% in a cohort of 2,783 patients with a median follow-up of 15 months. However, the events included stroke and myocardial infarction, there was no increased risk ratio for VTE, and there was no information on splenectomy. Another prospective analysis of 114 patients with ITP refractory to splenectomy reported an increased rate of VTE when compared to the expected rate of VTE in the general population; however this increase was not significant when patients with other VTE risk factors were removed from the analysis. In contrast, a more recent retrospective analysis of 233 patients with ITP who
underwent splenectomy revealed an 8% incidence of VTE in the 10-year period of follow up, a higher incidence than previously reported and herein.

In a study to evaluate the safety of romiplostim in patients with ITP, 4.9% of treated patients had a thrombotic event. Most patients who developed thrombotic events had preexisting risk factors for thrombosis before initiation of therapy. The same group reported a cumulative incidence of 2.4% for the entire study cohort, but did not specifically analyze the relationship of VTE to splenectomy.

The variable rates of VTE between these other studies and the present one are likely due to differences in case ascertainment; referral bias; cohort size and duration of follow-up; treatment, and other unaccounted for demographic factors. Given the large size and diversity of the hospitals included in the present study, it may more accurately reflect the incidence of VTE in across a range of practice settings.

It has been difficult to quantify the risk of infection for ITP patients who undergo splenectomy compared to those that do not. It should be noted that some studies have determined all serious infections while others have looked only at sepsis, as in the present report.

Routine therapy for ITP is immunosuppressive. Because splenectomy is highly effective therapy for ITP and response may obviate the need for further immunosuppressive therapy, the procedure might actually decrease the overall risk of infection in patients with ITP despite resultant loss of splenic function.
In an attempt to determine the attributable risk associated with splenectomy, a recent retrospective review analyzed the infectious outcomes of 3,812 patients who underwent splenectomy for a variety of indications. The study showed those who underwent splenectomy were at 4.6 fold (CI, 3.8 to 5.5) higher risk for infection when compared to the general population from days 91 to 365 days post-splenectomy. When compared to disease-matched controls, patients with ITP who underwent splenectomy had a trend towards increased rates of infection at >365 days post-splenectomy that was not statistically significant [HR 1.4 (CI, 1.0 to 2.0)]\(^\text{17}\).

Other studies have demonstrated an increased risk of post-splenectomy bacteremia and infection \(^\text{43}\), with reported rates of 2.3 to 3.2% \(^\text{15,16}\). The present study also demonstrates that patients with ITP who underwent splenectomy were at higher risk for both early and late sepsis compared to non-splenectomized ITP patients.

It is worth noting that the cumulative incidence of sepsis in the non-splenectomized ITP patients (10.1%), although lower than for those that had undergone splenectomy (11.1%), was not trivial. As would be expected, older age and presence of co-morbidities were also associated with increased risk for sepsis. Interestingly, female gender was associated with a lower risk of sepsis. Being of Black ethnicity was associated with a slightly increased risk of sepsis.

Sepsis and abdominal VTE were associated with an increased OR for death, but VTE was not. Interestingly, splenectomy was associated with decreased odds of death in the same model.
Splenectomy patients were younger and had less co-morbidity. However, the odds of death were reduced even when adjusted for age, co-morbidities, gender, ethnicity, and incident AbVTE/VTE/sepsis. We believe that patients selected for splenectomy are overall healthier, but cannot exclude the possibility that splenectomy was somehow protective of death in this cohort. When compared to a population-based comparator group, Yong et al. demonstrated a higher relative risk for death in the 90-day period following splenectomy (RR 2.3) that decreased to 0.5 in days 91-365, and decreased further to 0.4 in days > 365 post splenectomy. Taken together, this data imply that, while patients are at higher risk for AbVTE, VTE, and sepsis following splenectomy, they might have a reduced long-term risk of death.

In the present report, 5- and 10- year K-M survival rates for the entire cohort (73% and 64% respectively) were lower than previously reported. In a retrospective review of 152 patients with ITP, only 24 patients died during a 20-year follow up period (84% survival). Of the entire cohort, the HR for death was 1.5 (CI, 1.1-2.2) when compared to the general population. When patients with secondary ITP were excluded, the HR was 1.3 (CI, 0.89-2.0). However, patients with severe ITP (defined as persistent thrombocytopenia of < 30.0 x 10^9/L two years after diagnosis) had a HR for death of 4.2 (CI, 1.7-10). Differences from our study may be due to the present cohort being older (median age 55 vs. 39) with more co-morbidities and more likely to have severe disease.

In the 2011 updated treatment guidelines for ITP, the American Society of Hematology recommends splenectomy be considered in patients who fail front-line therapy with corticosteroids (Grade IB evidence). The authors noted that paucity of evidence prevents them
from making specific recommendations regarding second line therapies, although recommended thrombopoietin receptor agonists for patients at risk of bleeding who relapse after splenectomy, have a contraindication to splenectomy, or who have failed at least one other line of therapy (Grade 1A recommendation). The authors suggest use of thrombopoietin receptor agonists for patients at risk for bleeding who have failed one prior line of therapy prior to splenectomy (Grade 2C recommendation). They note that only splenectomy is likely to provide sustained remission off treatment beyond 1 year 4.

The International Working Group (IWG) recognized that many patients and physicians prefer to delay or avoid splenectomy when patients relapse after front line therapy. The panel stated that splenectomy should not be performed in patients who are too ill or frail, but the curative potential of splenectomy is superior to other available treatments 2. The IWG panel did not provide specific recommendations for sequencing of second line therapies.

Despite the efficacy of splenectomy, the rate of splenectomy decreased during the period of this analysis. Possible reasons for this decline include physician and patient preference for medical over surgical therapy, as well as an increased awareness of the possible risks associated with splenectomy.

Patients with ITP refractory to primary therapy and contemplating splenectomy should be made aware of both short and longer term complications. The risk of AbVTE, VTE, and sepsis were increased in patients who underwent splenectomy, with cumulative incidences of 1.6%, 4.3%
and 11.1%, respectively. The increased risk of AbVTE, VTE and sepsis must be weighed against the efficacy of splenectomy for long-term disease control.

AUTHORSHIP

Contribution: S.B. and T.W. had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. T.W. and R.W. contributed to study concept and design. A.B. did statistical analysis. S.B drafted the manuscript and final revision. T.W. and R.W. provided critical revision of the manuscript.

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Table 1. Characteristics of the cohort

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<tr>
<td><strong>Race/Ethnicity (vs. NH White)</strong></td>
<td>NH Black 0.8 (0.4, 1.7) 0.5049</td>
<td>1.0 (0.6, 1.7) 0.9936</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hispanic 0.6 (0.3, 1.0) 0.0410</td>
<td>0.7 (0.5, 1.0) 0.0423</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NH Asian/PI 0.9 (0.5, 1.8) 0.8321</td>
<td>0.2* (0.1, 0.6) 0.0011</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2+ Comorbidities (vs. 0-1 comorbidities)</strong></td>
<td>2.4* (1.6, 3.6) &lt;0.0001</td>
<td>1.3 (1.0, 1.7) 0.1058</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spleenectomy vs. No Spleenectomy</strong></td>
<td>VTE within 90 days of splenectomy 5.4* (2.3, 12.5) &lt;0.0001</td>
<td>5.2* (3.2, 8.5) &lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VTE 90+ days after splenectomy 1.5 (0.9, 2.6) 0.1252</td>
<td>2.7* (1.9, 3.8) &lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*statistically significant at 0.05
Table 3. Cox Proportional Hazards for Post-splenectomy Sepsis

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% Confidence Limit</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>0.8*</td>
<td>(0.7, 0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age ≥ 60</td>
<td>3.2*</td>
<td>(2.7, 3.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Race/Ethnicity (vs NH White)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NH Black</td>
<td>1.4*</td>
<td>(1.1, 1.8)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.1</td>
<td>(1.0, 1.3)</td>
<td>0.1687</td>
</tr>
<tr>
<td>NH Asian/PI</td>
<td>1.2</td>
<td>(1.0, 1.5)</td>
<td>0.0964</td>
</tr>
<tr>
<td>Two or more Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 60</td>
<td>3.6*</td>
<td>(2.9, 4.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age ≥ 60</td>
<td>6.1*</td>
<td>(5.1, 7.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Splenectomy vs. No Splenectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis within 90 days of splenectomy*</td>
<td>3.3</td>
<td>(2.4, 4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sepsis 90+ days after splenectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 comorbidities</td>
<td>1.6*</td>
<td>(1.3, 2.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2+ comorbidities</td>
<td>3.1*</td>
<td>(2.2, 4.4)</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

*statistically significant at 0.05
Figure 1. Identification of the cohort

1991-2009 CA Patient Discharge Data
Accessed for eligibility (N=56,980,538)

ITP Admissions
(Principle Dx)
N=20,407 admissions; N=13,804 cases

Excluded:
SLE or CLL
N=1,059 cases

Excluded:
Splenectomy before the index ITP admission
N=69 cases

Excluded:
Splenectomy same day as the index ITP admission
N=2,601 cases

ITP and Splenectomy
N=4,522 cases

Analysis Cohort

Splenectomy after the index ITP admission
N=1,762 cases

ITP ONLY
N=8,214 cases
Figure 2. Decline in the rate of splenectomy over time
Figure 3a. Incidence of AbVTE by Splenectomy Status

Log-Rank P-value: 0.0544
Figure 3b. Incidence of VTE by splenectomy status

Incidence of VTE vs. Months after Splenectomy

- Controls: No Splenectomy
- Cases: Had Splenectomy

Log-Rank P-value: <0.0001
Figure 4. Incidence of sepsis by splenectomy status

Log-Rank P-value: < 0.0001

Incidence of Sepsis

0 0.05 0.1 0.15 0.2 0.25
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180
Months after Splenectomy

Control: No Splenectomy  Case: Had Splenectomy
Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia

Soames Boyle, Richard H. White, Ann Brunson and Ted Wun