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# Corticosteroid response predicts success of laparoscopic splenectomy in treating immune thrombocytopenia☆

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ABSTRACT

*Background:* Laparoscopic splenectomy is a second-line therapy for immune thrombocytopenia with a sustained success rate of 66%. In a climate of new available medical therapies for immune thrombocytopenia, the comparative safety and efficacy of laparoscopic splenectomy are worthy of attention. The purpose of this study is to identify factors predictive of laparoscopic splenectomy success that will enable preoperative prognostication.

*Methods:* A retrospective cohort study was conducted of patients undergoing laparoscopic splenectomy for immune thrombocytopenia. The data collected evaluated response to medical and surgical therapy, which was defined on a platelet level of $50 \times 10^9$/L with no bleeding events. Univariate and multivariate analyses were conducted to evaluate factors predictive of laparoscopic splenectomy success, with an additional subanalysis planned to assess for laparoscopic splenectomy safety in individuals ≥65 years.

*Results:* One hundred forty-one patients were reviewed. Operative outcomes showed a 3.6% conversion rate and 8.5% complication rate. Disease remission was achieved in 78.7% of patients. Response to initial corticosteroid therapy was associated with a laparoscopic splenectomy success rate of 90% and increased odds of surgical success by 5.58 over individuals with no response to corticosteroids. Age did not confer an increased risk of failure or complications.

*Conclusion:* Laparoscopic splenectomy is a safe and effective intervention for immune thrombocytopenia regardless of age. Initial response to corticosteroids is associated with laparoscopic splenectomy success rate of 90% and improved odds of surgical success. Laparoscopic splenectomy should be the standard second-line therapy for immune thrombocytopenia, especially in patients responding to corticosteroids.



The optimal therapeutic sequence in the management of immune thrombocytopenia (ITP) is controversial. Based on the American Society of Hematology 2011 guidelines, splenectomy is the recommended second-line therapy in patients who do not respond to or relapse after corticosteroid therapy (Grade 1B).[1] Some practitioners defer surgical referral to avoid perioperative morbidity and mortality despite a lack of evidence directly comparing nonoperative interventions to splenectomy.[2]

Modern laparoscopic techniques have made splenectomy a safe operation, demonstrating equal efficacy and a lower complication rate compared to open surgery,[3] as well as a lower adverse event rate than reported for common medical therapies.[4–6] To identify the patients that would benefit most from surgical intervention, observational studies have attempted to elucidate factors predictive of splenectomy success in the treatment of ITP.[7–15] The majority of these studies were small, assessed only open splenectomy (74%), and demonstrated heterogeneous results.[7]

The goals of this study were first, to assess the success and complication rate of laparoscopic splenectomy (LS) at our center given a large sample size compared to the existing literature, and second, to determine factors predictive of LS success that can guide therapeutic decision-making and prognostication. Identifying factors that enable prediction of surgical success preoperatively may change the second-line interventions patients are offered.

## Methods

All patients who underwent LS for ITP at London Health Science Centre (LHSC) from 2000 to 2015 were identified. LHSC is a quaternary care referral center with a catchment area of approximately

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1.6 million people. All diagnoses of ITP were made following consultation with hematologists at LHSC. Patients with a diagnosis of primary ITP (platelets $<100 \times 10^9$/L with no other causative process) were included in the analysis. Patients found postoperatively to have thrombocytopenia secondary to a separate disease process, such as lymphoma or a myeloproliferative disorder, were excluded. The morcellated spleen was sent to pathology following every operative case.

An electronic chart review was undertaken to extract information pertaining to patient demographics, operative details, and pre- and postoperative medical management. Paper charts were evaluated for data points prior to 2006. Preoperative platelet response to primary corticosteroid treatment was recorded. Platelet response to second-, third-, and fourth-line treatment regimens could not be established given the potential confounding effects of multiple medical therapies, and was therefore not reported. Platelet counts were recorded preoperatively and immediately postoperatively. Peak and trough platelet levels for the initial 72 hours postoperatively were documented, as were platelet levels at the time of each patient's most recent follow-up visit where available. Intraoperative and postoperative complications were identified. Medical therapies implemented postoperatively for refractory ITP were recorded. The electronic medical record allows capture of follow-up visits at LHSC and referring hospitals within the catchment area, as well as all laboratory results. Therefore, LS success or failure was determined at the time of data collection using the most recent patient information available.

### *Definitions*

Platelet response to therapy was determined on a threshold of $50 \times 10^9$/L. This was the generally acceptable threshold for proceeding with surgical intervention at the time of data collection and was the most agreed-upon value for corticosteroid nonresponsiveness used in the literature.[16]

Success of LS was defined as the achievement of a platelet count of greater than $50 \times 10^9$/L with no need for postoperative medical management during the follow-up period. Failure of LS was defined as a persistent postoperative platelet level of less than $50 \times 10^9$/L or thrombocytopenia with bleeding symptoms requiring medical intervention. Any requirement for postoperative medical intervention was considered a failure. LS success or failure was determined by the authors at the time of data collection given the most recent information available in the patient's chart rather than at the time of last follow-up. Thus, any LS successes are considered to have sustained remission to date based on the most recent electronic data.

Use of medical interventions for ITP at our center has corresponded with the evolution of medical therapies and evidence-based recommendations for their use. At our institution, preoperative corticosteroids are administered as per ASH guidelines for individuals with platelet counts lower than $30 \times 10^9$/L as standard first-line therapy. Prednisone is typically the therapy of choice at our institution with a starting dose of approximately 1mg/kg/day. Primary dexamethasone is used rarely. Rate of taper depends on patient factors including patient response and toxicity. In our study, corticosteroid response was stratified based on response to the first course of corticosteroids received after diagnosis: complete initial responders maintained a platelet count of $>50 \times 10^9$/L for any length of time after corticosteroid therapy was stopped. Transient responders achieved a platelet count of $>50 \times 10^9$/L but fell below $50 \times 10^9$/L while still on corticosteroid therapy. Nonresponders failed to demonstrate an increase in platelet count above $50 \times 10^9$/L at all. The first course of corticosteroids was assessed because 98% of patients received corticosteroids as first-line therapy. Later courses of corticosteroid therapy were not assessed given the confounding effects of other interventions.

Length of follow-up was defined as the time between surgery and the last recorded clinic visit. Incidence of overwhelming post-splenectomy infection (OPSI) was also determined at this time point. However, success or failure of LS was determined at the time of data collection based on the patient's most recent laboratory values and electronic clinical data, rather than at the time of last follow-up.

### *Statistical analysis*

Descriptive statistics were completed using means with standard deviations, medians with interquartile ranges, and frequencies where appropriate. Univariate analyses were conducted to assess differences between LS failure and LS success groups using Student's $t$ test or Mann-Whitney $U$ tests for continuous data and Pearson $\chi^2$ statistic or Fisher exact test for categorical variables. The number of preoperative medical therapies was analyzed as a discrete nominal variable. The platelet counts included in the analyses were those measured immediately preoperatively and immediately postoperatively.

Preoperative data was subjected to multivariate logistic regression analysis to identify factors independently associated with failure of laparoscopic splenectomy for the treatment of ITP. Thirty LS failures were identified and therefore we included 3 variables, each with 10 events and 10 nonevents per covariable. Variables were identified a priori as age, response to initial course of corticosteroid therapy, and number of preoperative medical therapies. Age was analyzed as a continuous variable without cutoff values. Response to corticosteroids was analyzed as a categorical variable with stratifications as described above. Postoperative data were collected and reported; however, these were not subjected to regression analysis as they cannot contribute to preoperative prognostication.

An additional subanalysis was completed comparing individuals $<65$ years to those $\geq 65$ years with respect to complication rate, rate of conversion to open, and success of LS for treatment of ITP using a Pearson $\chi^2$ statistic. Significance was determined using Fisher exact test. A cutoff age of 65 was chosen to ensure comparability with other studies assessing safety and efficacy of LS that used age 65 as a threshold.

All statistical analysis was completed using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY).

## Results

From 2000 to 2015, 141 patients underwent an attempted laparoscopic splenectomy for ITP. Of those, 39.7% were male. Mean age at the time of surgery was 49 years. In 96.4% of cases, splenectomy was completed laparoscopically as planned. There was no significant difference in age, gender, American Society of Anesthesiologists class, or time from diagnosis to surgery between LS success and LS failure groups (Table 1). Those refractory to splenectomy had significantly longer length of stay ($P < .05$) and follow-up period ($P < 0.05$) compared to LS success group. It should be noted that the mean length of follow-up in the LS success group was still greater than 1 year. Preoperative platelet measures were significantly higher in the LS success group ($P < .01$) (Table 1). Overall, successful LS requiring no further medical management was observed in 111 patients (78.7%).

Conversion from laparoscopic to open occurred in 5 patients (3.6%). Two cases were converted due to technical difficulties attributed to the patients' body habitus. One was for control of active hemorrhage. One was for difficulty with a concomitant laparoscopic cholecystectomy. The last was to facilitate a thorough

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