Predictive Factors for Successful Laparoscopic Splenectomy in Patients With Immune Thrombocytopenic Purpura

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Hypothesis: Younger patients with immune thrombocytopenic purpura (ITP) and high preoperative platelet counts successfully respond to laparoscopic splenectomy (LS).

Design: Case series.

Setting: Private, tertiary care referral center.


Interventions: Laparoscopic splenectomy.

Main Outcome Measures: A successful response to LS was defined as a postoperative platelet count greater than $100 \times 10^3/\mu L$ without medical therapy. Failures were classified as refractory or recurrent. Patients considered refractory to surgery did not achieve a platelet count greater than $100 \times 10^3/\mu L$ without medical therapy. Patients with recurrent ITP initially achieved a platelet count greater than $100 \times 10^3/\mu L$, but thrombocytopenia subsequently recurred.

Results: Both univariate and multivariate analyses were performed for 13 preoperative variables to identify factors predictive of success following LS. At a mean follow-up of 22 months, 43 patients (64%) had a successful response to LS, 14 (21%) were refractory, and 10 (15%) developed recurrent ITP. By univariate analysis, patients responding to laparoscopic splenectomy were younger ($P = .005$) and had a higher preoperative platelet count ($P = .005$). In multivariate analysis, younger age ($P = .005$) and a higher preoperative platelet count ($P = .007$) again predicted a successful response to LS.

Conclusions: A successful response to LS for ITP is expected in patients younger than 50 years and in those with preoperative platelet counts greater than $70 \times 10^3/\mu L$. These factors can be incorporated into an equation that yields a splenectomy prediction score, which predicts the success of LS for ITP.

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Immune thrombocytopenic purpura (ITP) is a disorder of immune sensitivity entailing an accelerated phagocytosis of platelets by the reticuloendothelial system. The spleen is the primary site of platelet destruction and antiplatelet antibody production. The mainstay of medical therapy is bolus corticosteroids followed by a tapering dose. However, long-term remission rates are only 20% to 25% in adults.\(^1,2\) Alternatively, surgical management historically reports a 49% to 86% successful remission rate after splenectomy.\(^3\)

**See Invited Critique at the end of article**

However, defining a successful response to splenectomy remains unclear. Multiple investigators previously documented variables that predict a successful response to splenectomy for ITP. These factors include younger age,\(^1,4-9\) a successful response to preoperative steroids,\(^10-13\) shorter interval from diagnosis to splenectomy,\(^10,14-16\) splenic sequestration,\(^7,17,18\) response to intravenous IgG,\(^19-22\) and preoperative platelet counts.\(^18,22-24\) Since the first laparoscopic splenectomy (LS) was reported in 1992, there has been renewed interest in managing hematologic disorders with minimally invasive surgical techniques.\(^25-28\) Laparoscopic splenectomy results in less pain, shorter hospital stay, faster return to full activity, and superior cosmesis compared with open techniques.\(^29\) However, long-term follow-up is required to document the efficacy of LS for ITP. To date, few large series of LS for ITP are reported.\(^23,24,30,31\) This study seeks to determine the preoperative factors that predict a successful outcome following LS. Furthermore, a formula is presented that enables the stratification of patients into low, moderate, or high probability of successful outcome after LS.
**RESULTS**

Between August 1995 and August 2001, 67 LSs were performed for ITP. There were 25 males (36%) and 42 females (63%). The mean duration of disease was 29.2 months (range, 1–348 months). The mean age of the patients was 48 years (range, 9–87 years). The mean preoperative platelet count was $77 \times 10^3/\mu L$ (range, $1 \times 10^3/\mu L$ to $276 \times 10^3/\mu L$). There were no conversions to open splenectomy. Accessory spleens were identified in 7 patients (10%).

At a mean follow-up of 22 months, 43 patients (64%) had a successful response to LS, 14 patients (21%) were refractory to LS, and 10 patients (15%) developed recurrent ITP. All recurrences underwent radionuclide spleen scans. One patient had an accessory spleen identified 2 years postsplenectomy that was successfully removed laparoscopically. This patient remains in remission.

Preoperative variables predictive of a successful response to LS were examined by univariate and multivariate analyses (Table 1). Univariate analysis revealed that patients with successful responses to LS were younger (mean age, 43 vs 59 years; $P = .005$) and had a higher mean preoperative platelet count ($98 \times 10^3/\mu L$ vs $48 \times 10^3/\mu L$; $P = .005$) compared with those in whom LS failed. These patients also initially responded to steroid treatments but relapsed with tapering (70% vs 38%; $P = .004$) when compared with patients in whom LS failed. Multivariate logistic regression analysis revealed that age was significantly younger and preoperative platelet counts were significantly higher in patients who had successful outcomes after LS vs patients who did not have successful outcomes.

Patients with refractory disease were older (mean age, 55 vs 44 years; $P = .05$), had lower preoperative platelet counts ($98 \times 10^3/\mu L$ vs $36 \times 10^3/\mu L$; $P < .001$), and did not respond to preoperative intravenous IgG ($P = .03$) compared with patients with a successful outcome on univariate analysis (Table 2). Multivariate analysis revealed that only older age and lower preoperative platelet counts were significantly different in patients with refractory disease when compared with patients with a successful outcome after LS. Meanwhile, patients with recurrent ITP were older (mean age, 64 vs 44 years; $P = .01$) on univariate and multivariate analysis compared with patients who responded successfully (Table 3).

Multivariate analysis revealed that age and preoperative platelet levels were significant prognostic indicators of successful outcome after LS. An age younger than 50 years had a sensitivity of 72%, a specificity of 68%, a positive predictive value of 58%, and a negative predictive value of 77%. A preoperative platelet count greater than $70 \times 10^3/\mu L$ had a sensitivity of 72%, a specificity of 62%, a positive predictive value of 56%, and a negative predic-

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**Table 1. Analysis of Preoperative Variables in Patients With Immune Thrombocytopenic Purpura**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful Failure</th>
<th>$P$ Value†</th>
<th>$P$ Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>43.6</td>
<td>59.0</td>
<td>.006</td>
</tr>
<tr>
<td>Duration of disease, mo</td>
<td>32.5</td>
<td>25.5</td>
<td>.16</td>
</tr>
<tr>
<td>Preoperative platelet count, $1 \times 10^3/\mu L$</td>
<td>98.6</td>
<td>48.5</td>
<td>.005†‡</td>
</tr>
<tr>
<td>Successful response, %</td>
<td>0</td>
<td>&gt;.99</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0</td>
<td>30.0</td>
<td>.12</td>
</tr>
<tr>
<td>IV IgG</td>
<td>54.5</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Steroids, %</td>
<td>37.5</td>
<td>50.0</td>
<td>.09</td>
</tr>
<tr>
<td>Nonresponsive</td>
<td>30.3</td>
<td>25.0</td>
<td>.07</td>
</tr>
<tr>
<td>Stopped responding</td>
<td>69.7</td>
<td>37.5</td>
<td>.02†</td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenous.
*Significance set at $P < .05$.
†Significant on univariate analysis.
‡Significant on multivariate analysis.

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**METHODS**

From August 1995 to August 2001, 190 LSs were performed at the Cleveland Clinic Foundation for various hematologic diseases, including ITP. A series of 67 consecutive patients undergoing LS for ITP was collected prospectively and analyzed retrospectively. The diagnosis of ITP was established according to criteria published by the American Society of Hematology. These criteria include isolated thrombocytopenia, normal findings on a peripheral blood smear, normal bone marrow aspirate, no splenomegaly, and no other associated benign or malignant diseases that could have induced the thrombocytopenia. Indications for LS included patients who no longer responded to glucocorticoid therapy, those with platelet counts less than $10 \times 10^3/\mu L$, and those actively bleeding, with platelet counts below $10 \times 10^3/\mu L$ for 3 months. Patients not responding to steroids were unable to maintain platelet counts above $100 \times 10^3/\mu L$ despite maximum medical therapy. Patients who failed to tolerate a steroid taper or who developed recurrent thrombocytopenia after discontinuing steroid treatments were considered to have relapsed. Operative data included operative time as measured from the first skin incision to the application of dressings, estimated blood loss, presence of accessory spleens, and morcellated splenic weight. Postoperative follow-up was obtained through medical record reviews of surgery and hematology clinic notes. Relevant information included platelet counts, medications, and management of recurrent disease. When medical records were not available or patients were lost to follow-up, the patients were contacted by telephone and underwent a standardized interview.

Thirteen preoperative variables were examined by univariate analysis and then subjected to multivariate logistic analysis. A successful response to LS was defined as a postoperative platelet count greater than $100 \times 10^3/\mu L$ without medical therapy. Patients failing to respond to LS were further classified into refractory and recurrent disease. Patients considered refractory to LS did not achieve a platelet count greater than $100 \times 10^3/\mu L$ without medical therapy 6 weeks postoperatively. Patients with recurrent ITP achieved a platelet count greater than $100 \times 10^3/\mu L$ when medical treatment was stopped, but subsequently became thrombocytopenic (<$100 \times 10^3/\mu L$). Initially, these groups were compared by Wilcoxon rank sum tests for continuous variables and $\chi^2$ or Fisher exact tests for categorical variables. Subsequently, multivariate logistic regression was used to assess risk factors with stepwise procedures. Significance was assessed with 2-tailed tests at $P < .05$, and all calculations were performed with SAS version 8.0 software (SAS Institute Inc, Cary, NC).
tive value of 71%. Based on these results, a multivariate equation was created to stratify the likelihood of a successful outcome to LS (Figure). The splenectomy prediction score is obtained by the following equation:

\[
\text{Splenectomy prediction score} = 0.039 + \{[\text{Age (Years)} \times 0.047] - [\text{Preoperative Platelet Count} \times 0.018]\}\]

All patients receive a score between -4 and +4. A negative score predicts a successful outcome after splenectomy, and a positive score indicates an increased risk of a failed response. Patients are subsequently classified into 3 categories. Patients with a negative score (<0) (n=10) had a 100% success rate following LS. Patients with a moderate score (0-2) (n=26) had a 65% rate of success, and patients with a high score (2-4) (n=31) achieved a successful outcome in only 40% of cases. For example, a 50-year-old patient with a preoperative platelet count of 15 \times 10^3/µL would have a score of 2.11, correlating to a 40% success rate.

### COMMENT

In 1735, British physician Paul Gottlieb Werlhof first described a female patient with blue-black spots on her neck and arms and hematemia and epistaxis. Originally called morbus haemorrhagicus maculosus, it serves as the first description of ITP.32 Currently, approximately 16,000 new cases of ITP are reported annually in the United States.33 Open splenectomy was the initial treatment for ITP; however, medical therapy replaced surgery as the first-line therapy after corticosteroids were introduced in 1958.20,34,35 Medical therapy provides durable remission rates of only 25%, while surgical management has historically reported a 49% to 86% remission rate.3 The recent emergence of minimally invasive techniques has broadened interest in splenectomy for a variety of hematologic illnesses, including ITP.28

Many investigators have long sought preoperative variables that might predict a successful outcome following splenectomy. Factors evaluated have included age, response to corticosteroids, site of splenic sequestration, response to chemotherapy or other pharmacologic agents, and duration of disease (Table 4). Our study shows that younger age and higher preoperative platelet counts are predictive of a successful response to LS. A limitation of all such analyses is the lack of a standardized and precise preoperative regimen.

Patient age is the most widely acknowledged variable predicting a successful response to splenectomy.7,8,40 Most series demonstrate that age between 30 and 45 years is an independent prognostic determinant of a successful response to splenectomy.5,9,39,40 Other investigators, however, have not found age to correlate with successful response to splenectomy.10,19,20,22,23,37 In our study, multivariate logistic regression analysis revealed that a younger age predicted a successful response to LS. Conversely, refractory as well as recurrent disease were seen in older patients. Specifically, a successful response to LS for ITP was seen in patients younger than 50 years.

### Table 2. Analysis of Successful vs Refractory Laparoscopic Splenectomy for Immune Thrombocytopenic Purpura

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful</th>
<th>Refractory</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>43.6</td>
<td>55.8</td>
<td>.056†</td>
</tr>
<tr>
<td>Spleen weight, g</td>
<td>181.8</td>
<td>204.5</td>
<td>.73</td>
</tr>
<tr>
<td>Duration of disease, mo</td>
<td>32.5</td>
<td>19.9</td>
<td>.05†</td>
</tr>
<tr>
<td>Preoperative platelet count</td>
<td>98.6</td>
<td>36.2</td>
<td>.001†</td>
</tr>
<tr>
<td>Successful response, %</td>
<td>0.0</td>
<td>0.0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>54.5</td>
<td>15.4</td>
<td>.03†</td>
</tr>
<tr>
<td>IV IgG</td>
<td>50.0</td>
<td>50.0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Danazol</td>
<td>38.5</td>
<td>25.0</td>
<td>.69</td>
</tr>
<tr>
<td>Steroids, %</td>
<td>27.3</td>
<td>57.1</td>
<td>.06</td>
</tr>
<tr>
<td>Nonresponsive</td>
<td>30.3</td>
<td>28.6</td>
<td>.92</td>
</tr>
<tr>
<td>Relapsed with tapering</td>
<td>69.7</td>
<td>21.4</td>
<td>.004†</td>
</tr>
</tbody>
</table>

### Table 3. Analysis of Successful vs Recurrent Laparoscopic Splenectomy for Immune Thrombocytic Purpura

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful</th>
<th>Recurrent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>43.6</td>
<td>63.9</td>
<td>.01†</td>
</tr>
<tr>
<td>Spleen weight, g</td>
<td>181.8</td>
<td>253.5</td>
<td>.59</td>
</tr>
<tr>
<td>Duration of disease, mo</td>
<td>32.5</td>
<td>33.9</td>
<td>.99</td>
</tr>
<tr>
<td>Preoperative platelet count</td>
<td>98.6</td>
<td>68.9</td>
<td>.49</td>
</tr>
<tr>
<td>Successful response, %</td>
<td>0</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>54.5</td>
<td>57.1</td>
<td>.93</td>
</tr>
<tr>
<td>Danazol</td>
<td>50.0</td>
<td>50.0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>WinRho‡</td>
<td>38.5</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Steroids, %</td>
<td>27.3</td>
<td>40.0</td>
<td>.46</td>
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<tr>
<td>Nonresponsive</td>
<td>30.3</td>
<td>20.0</td>
<td>.54</td>
</tr>
<tr>
<td>Relapsed with tapering</td>
<td>69.7</td>
<td>60.0</td>
<td>.59</td>
</tr>
</tbody>
</table>

*Significance set at P<.05.†Significant on univariate analysis.‡Manufactured by Nabi, Boca Raton, Fla.
Published series indicate that the identification of platelet sequestration by surface nuclear scanning may be the best predictor of response to splenectomy. In contrast, older patients with hepatic or mixed (liver and spleen) sequestration, respond successfully to splenectomy. Investigators argue that younger patients, who tend to have splenic sequestration rather than hepatic or mixed, will be the best predictor of response to splenectomy. Multivariate analysis revealed that higher platelet kinetics or platelet sequestration were evaluated as a predictive factor by several investigators. Additional studies report that 30% to 67% of patients with primarily hepatic sequestration tend to respond poorly to splenectomy. In our investigation, univariate analysis demonstrated that preoperative platelet levels were predictive of a successful response to LS regardless of how this level was achieved (ie, patients still receiving steroids or intravenous IgG). Furthermore, lower preoperative platelet levels were predictive of patients who would subsequently develop refractory ITP.

Several investigators have examined patients’ preoperative responses to steroids, with conflicting results. In our series, univariate analysis demonstrated that younger patients who initially responded to steroids and then experienced recurrent thrombocytopenia with steroid tapering responded to LS. Steroid response, however, was not an independent predictor after multivariate analysis. These results are supported by some,5,10-12,42-45 while disputed by others. Several controversial factors used to predict successful response to splenectomy is a patient’s preoperative response to intravenous IgG. In the pediatric population, studies demonstrate a positive predictive value of 74% to 91% to splenectomy after successful response to intravenous IgG and a negative predictive value of 75% to 100%. With adult ITP patients, the ability to predict the success of intravenous IgG is more difficult. In adult patients, the sensitivity of intravenous IgG as a predictor of response to splenectomy is 71% to 88%, the speci-
ficity, 20% to 52%, the positive predictive value, 73% to 75%, and the negative predictive value, 16% to 75%. Other studies contend that a response to intravenous IgG has no prognostic value in predicting the response to splenectomy. In one study, 67% of patients in whom intravenous IgG therapy was unsuccessful responded to splenectomy. The discrepancy is most likely due to the different age populations studied and the varying length of follow-up. In our series, the only laparoscopic series investigating intravenous IgG, to our knowledge, successful response was significant in patients with refractory disease by univariate analysis only. There was no significance determined with recurrent ITP. Although the value of intravenous IgG appears promising, most reports of success are limited to pediatric patients and smaller cohorts. Presently, the relationship between the response to intravenous IgG and a sustained response to splenectomy in the adult patient is unclear.

There is no commonly accepted definition of the therapeutic success of splenectomy, yet our criteria were rigid. Consequently, our success rate is lower than that reported in many other series. In the absence of a standardized definition, interstudy comparisons may be unreliable. The practical importance of understanding the value of preoperative variables of an expected outcome might clarify postoperative expectations in patients with ITP. Our data and equation support a short trial of medical therapy in young patients with relatively higher platelet counts. If a short medical trial results in recurrent, refractory, or symptomatic thrombocytopenia, LS is indicated. Currently, at our institution, patients with ITP are being counseled prospectively using the splenectomy prediction score. The expected rates from the graph in the Figure are based on the expectations of a larger sample size. Although all of the patients in the low-score category in our series had a successful outcome, the logistic regression equation indicates that there is still a risk of failure at these levels.

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REFERENCES

T here has been a slow but steady change in attitude toward the application of minimally invasive surgery in the treatment of certain infrequent diseases for which surgery used to be considered an excessively aggressive alternative to medical or less invasive approaches. This change has had a great effect on the treatment policy for diseases such as achalasia, gastroesophageal reflux, and ITP. Once the feasibility and safety of the minimally invasive surgical alternative was demonstrated, the new-approach old-procedure surgery reclaimed its place as first-line therapy. This has been the case with LS for ITP, as recent reports demonstrate.1-5 Another advantage of LS is a “revisiting effect”; many of the surgical aspects of these diseases have been reanalyzed. For example, when the surgical approach is proposed as first-line treatment, it is investigated for its ability to replace the open approach on a long-term basis. Another aspect is how to select or predict the outcome of LS, especially in the context of a disease in which there are many dark areas and in which the result is still not entirely predictable.

In this area, Duperier et al have made several recent contributions, taking into account a series of clinical and surgical variables. However, preoperative prediction of outcome continues to be relatively inaccurate. The authors did not take into account the preoperative physiologic data (liver, spleen, or mixed sequestration, platelet kinetics, platelet half-life, type of antiplatelet antibodies, etc), which, in the context of an immunologic-based disease, may have provided clues that explained the apparently unpredictable differences in response in cases that were similar.

To achieve good long-term results and to ensure the safety of LS for ITP, the authors propose a procedure that aims, above all, to maintain an adequate level of platelets. The procedure requires excellent technical expertise and training. Surgeons need to be able to explore, recognize, and excise an accessory spleen as well to dissect and remove the organ while keeping the capsule intact and avoiding the spillage of tissue, as the latter may cause a relapse of the disease.6 This message should be transmitted to hematologists to persuade them of the advantages of more friendly, pain-free techniques. Laparoscopic splenectomy for ITP is a very good ambassador.

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