Long-term outcomes after splenectomy in children with immune thrombocytopenia: an update on the registry data from the Intercontinental Cooperative ITP Study Group

by Maria L. Avila, Nour Amiri, Eleanor Pullenayegum, Victor Blanchette, Paul Imbach, and Thomas Kühne and Intercontinental Cooperative ITP Study Group

Haematologica 2019 [Epub ahead of print]


Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in print on a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Title: Long-term outcomes after splenectomy in children with immune thrombocytopenia: an update on the registry data from the Intercontinental Cooperative ITP Study Group

Authors: María L. Avila¹²; Nour Amiri¹; Eleanor Pullenayegum²; Victor Blanchette¹; Paul Imbach³; Thomas Kühne⁴, on behalf of the Intercontinental Cooperative ITP Study Group

¹ Department of Pediatrics, University of Toronto, Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada

² Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, ON, Canada

³ Prof. Emeritus of the Medical Faculty, University of Basel, Switzerland

⁴ UKBB Universitäts-Kinderspital, Oncology/Hematology, Basel, Switzerland

Running title: Splenectomy in Pediatric ITP

Key words: Child, platelet count, immune thrombocytopenia, splenectomy, registries

Total text word count: 1,500

Number of figures: 2

Number of tables: 1

References: 15

Correspondence: Thomas Kühne, Division of Oncology/Hematology, University Children’s Hospital Basel, Postfach, Spitalstrasse 33, CH-4031 Basel, Switzerland. E-mail: thomas.kuehne@ukbb.ch
Immune thrombocytopenic purpura (ITP) is an acquired immune-mediated disease characterized by a decrease in platelet count due to antiplatelet autoantibody-mediated increased platelet destruction and, in some cases, associated impaired platelet production.

There has been a decline in the number of splenectomies performed as a second-line treatment after the introduction of new therapies, such as thrombopoietin-receptor agonists. However, the current availability of long-term data on these new second-line therapeutic options seems to suggest that splenectomy remains the more effective second-line intervention in ITP. Therefore, data on long-term outcomes of splenectomy in children are relevant.

The Splenectomy Registry of the Intercontinental Cooperative ITP Study (ICIS) Group collects information regarding children who underwent splenectomy to treat ITP, including perioperative management and follow-up data. A report of the first 134 patients was published in 2007. The present study aims to update the findings of the ICIS Splenectomy Registry by analyzing over a decade of new data, with a focus on long-term outcomes of children with primary ITP.

Details of the data collection forms of the Splenectomy Registry have been previously described. Investigators included patients with ITP in whom splenectomy was planned. For the analysis, we excluded records in which splenectomy was not reported or no platelet counts were available at follow-up. Investigators sought local ethics approval prior to patient entry, according to the regulatory requirements of each institution. Response to splenectomy was classified as a complete response (CR), response (R), or no response (NR). CR was defined as $\geq 60\%$ of platelet counts performed $\geq 1$ month post-splenectomy that were $\geq 100 \times 10^9$/L; R was defined as $\geq 60\%$ of platelet counts $\geq 1$ month post-splenectomy that were $\geq 30 \times 10^9$/L; NR was defined as $< 60\%$ of platelet counts $\geq 1$ month post-splenectomy that were $\geq 30 \times 10^9$/L. At least two counts after the first month post-splenectomy were
required for outcome assessment. Refractoriness was defined as either the failure to achieve at least $R$ or loss of $R$ after splenectomy and clinically relevant bleeding $^5$.

Bleeding events were classified as major and clinically relevant non-major (CRNM) according to current definitions of the International Society on Thrombosis and Haemostasis for patients on anti-coagulants $^6,7$.

The trajectory of platelet counts over time was investigated using generalized estimating equations (GEE) models with basic splines to accommodate for the non-linear shape of the regression line. Predictors of response to splenectomy were explored using logistic regression analysis. Predictors associated with the outcome at a $p \leq 0.20$ in univariable analysis were considered for multivariable modelling. For model performance, simple bootstrap with 200 replications was used to estimate the optimism corrected (internally validated) area under the Receiver Operating Characteristic (ROC) curve. Significance was set at an alpha of 0.05. Analysis was performed in R.

A total of 267 patients were entered in the Registry between June 1997 and September 2017 by 82 investigators from 63 institutions and 26 countries. Seventeen records were excluded due to incompleteness and 11 due to secondary ITP diagnosis. Hence, 239 patients were included in the analysis. Eighty of those patients (80/239, 33%) came from a single institution [The Hospital for Sick Children (SickKids), Toronto]. Patients at SickKids were identified using the ICD-9-CM and ICD-10-CA codes, which explains the large number of participants identified in this institution.

The median duration of follow-up was 25 months ($25^{th}-75^{th}$ percentile 7.8-53.4 months). One hundred and thirty-five patients (135/250, 54%) were females. Median age at the time of ITP diagnosis was 9.2 years ($25^{th}-75^{th}$ percentile 4.8-13.0 years).

Splenectomy was performed at a median age of 11.7 years ($25^{th}-75^{th}$ percentile 7.9-15.3 years). Sixty-two of the 239 patients (26%) had their splenectomy performed < 1 year of diagnosis (i.e., before
reaching chronic ITP status) and 10 of those 62 patients (16%) had their splenectomy performed < 3 months of ITP diagnosis (i.e., before reaching persistent ITP status).

There was one intra-abdominal bleeding event documented during surgery. Eleven patients (11/239, 5%), including the patient with intra-abdominal bleeding, received peri-procedural red blood cell transfusions. Twenty-four patients (24/239, 10%) had fever at a median of 41 hours post-procedure (range 6-99 hours). No deaths or episodes of sepsis in the immediate post-operative time were recorded.

One-hundred and eighty-six patients were followed up for > 6 months. No major bleeding events were reported on those patients. Sixteen patients (16/184, 8.7%) had a documented CRNM bleeding; all cases were classified as CRNM because of the need of hospitalization. Twenty patients (20/186, 11%) had at least one admission due to fever or infection and 5 patients (5/186, 2.7%) were reported to have had sepsis (one viral, one due to streptococcus B) on long-term follow-up. A systematic review of studies conducted between 1966 and 1996 reported an incidence of invasive infection of 2.1% among 484 patients with ITP, including adults and children. In comparison, a more recent report including nearly 10,000 adults with ITP estimated the cumulative incidence of sepsis at 11.1% in splenectomised vs 10.1% in non-splenectomised patients. Age and the number of co-morbidities and longer follow-up of these patients (median of 25 months of total observation in our study vs 35 months median time from surgery to sepsis in the adult study) were also associated with higher risk of sepsis and might explain the lower frequency seen in our study.

Trend of platelet count post-surgery in the first 30 days and up to 4 years post-surgery is shown in Figure 1. The peak platelet count after surgery was 549 x10^9/L (range 5-1944 x10^9/L) at a median of 7 days (range 1-35 days). The median platelet count between 30-60 days post-surgery was 337 x10^9/L (25th-75th percentile 128-493 x10^9/L). Generalized estimating equations showed a non-statistically
significant decline in platelet count over time of $0.56 \times 10^9/L$ per month, 95% CI $-1.15 - 0.04$, $p = 0.08$, after the first month post-splenectomy.

Frequency of CR/R/NR is shown in Figure 2. Overall, 93% of patients showed CR/R; this frequency is slightly higher than that reported among adult patients and might be explained by the high frequency of splenectomy performed before reaching chronic ITP status (26%) and by a relatively low number of patients who received second line therapy (51/239, 21%). In addition, we observed a significant difference on the median time to surgery from ITP diagnosis before and after 2009 (median time 1.7 years, 25th-75th percentile 0.9-3.1 years, before and including 2009 and 3.2 years, 25th-75th percentile 2.0-4.3 years after 2009), when standardized definitions for chronic and persistent ITP were published. Importantly, the higher frequency of bleeding documented as the response category decreases (Figure 2), suggests that the classification used in this study approximates clinically relevant outcomes.

Refractoriness was 1.7% (4/239) among all children and 2.6% (4/152) in children with ≥ 1 year of follow-up. These estimates of refractoriness are slightly lower than those for adult patients, as we did not take into account administration of platelet-enhancing therapy on follow-up since administration of platelet-enhancing therapy at the time of each platelet count was not reported in the Registry.

Results of simple logistic regression are shown in Table 1. In multivariable analysis, both age at the time of surgery and average platelet count on the first 30 days post-splenectomy predicted CR/R. For every year increase in age at the time of surgery, the odds of CR/R increased by 1.18 (95% CI 1.02-1.40) and for every $10^9/L$ increase in the average platelet count in the first month, the odds of response increased by 1.09 (95% CI 1.05-1.16). In terms of model performance, the optimism-corrected area under the ROC curve was estimated as 0.87.

Older age at the time of diagnosis was reported to be an independent predictor of CR in the previous analysis of this Registry and age at the time of diagnosis was highly correlated with age at the
time of splenectomy in the present study. Younger age is considered a predictor of CR/R in adult patients with ITP undergoing splenectomy \(^\text{11,12}\), perhaps indicating that there might be a more similar underlying mechanism among teenagers and young adults. Older age is also a predictor of chronic ITP in pediatrics \(^\text{13}\), further indicating a distinct pathophysiology in ITP affecting teenagers and young adults. It is also possible that patients who undergo splenectomy at a young age are also more refractory to treatment.

Higher platelet counts in the first month post-splenectomy was also an independent predictor of both CR/R in this population. Interestingly, higher platelet counts immediately before surgery, not having platelet counts below 100 x 10^9/L in the first 30 days post-splenectomy, and higher peak platelet count in the first 30 days post-splenectomy were predictors of CR/R in univariable analysis. Ahmed et al reported that platelet count at the time of splenectomy as one of the predictors of CR/R in a cohort of 254 patients that included 87 children \(^\text{14}\). In addition, high platelet count in the first week after splenectomy has been shown to predict response in some studies conducted in adult patients, although results are inconsistent \(^\text{10}\). A more recent study among 174 adults splenectomised for ITP showed that higher pre- and post-operative platelet count were predictors of response in univariable analysis \(^\text{12}\).

Importantly, pre-surgical and early post-surgical platelet counts may be influenced by platelet enhancing therapy administered pre-operatively in addition to the thrombocytosis seen after splenectomy. Taken together, these observations indicate that individuals able to increase and sustain platelet counts in response to an intervention are more likely to show CR/R in the long term.

There are limitations to the present study. For example, biases such as selection bias and information bias of an intercontinental registry cannot be ruled out. However, one third of the patients included in the Registry come from a systematic search at a single-center (SickKids) which could help in part overcome the issue of selection bias. In addition, the median follow-up time was 25 months, despite the fact that the registry has been open for two decades. Retention can be problematic in
registries, particularly when they are voluntary. However, there is benefit in the use of registry data, as registries are also characterized by strong external validity in view of the heterogeneous population it includes; thus better reflecting clinical practice. In addition, the differential diagnosis in terms of primary or secondary ITP was left to the decision of the treating physician, and therefore misclassification cannot be ruled out. However, the high frequency of response found herein suggests misclassification is unlikely and may not have impacted the results. Lastly, there was no specific protocol attached to the registry, and care of the patient was left to the discretion of the clinician, thus reflecting general practice.

In conclusion, splenectomy is a very effective approach for the management of selected children with primary ITP as evidenced by platelet count recovery. Although low, the risk of adverse events both peri-operative and in the long-term, should be carefully considered when indicating this therapeutic modality. The only predictor of response available prior to indication of splenectomy is patient age, the older the patient, the higher the odds of response.
References


Table 1: Simple logistic regression results for complete response or response to splenectomy in primary ITP

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male vs female)</td>
<td>0.94 (0.30-3.05)</td>
<td>0.92</td>
</tr>
<tr>
<td>Age at the time of ITP diagnosis, in years</td>
<td>1.12 (0.99-1.29)</td>
<td>0.09</td>
</tr>
<tr>
<td>Age at the time of surgery, in years</td>
<td>1.15 (1.01-1.33)</td>
<td>0.04</td>
</tr>
<tr>
<td>Time from diagnosis to surgery, in years</td>
<td>1.05 (0.86-1.41)</td>
<td>0.71</td>
</tr>
<tr>
<td>Number of previous treatment modalities</td>
<td>0.70 (0.41-1.24)</td>
<td>0.21</td>
</tr>
<tr>
<td>Second line therapy (yes vs no)</td>
<td>0.30 (0.09-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Steroids as part of initial therapy (yes vs no)</td>
<td>1.02 (0.05-5.83)</td>
<td>0.99</td>
</tr>
<tr>
<td>IVIG as part of initial therapy (yes vs no)</td>
<td>0.59 (0.03-3.25)</td>
<td>0.99</td>
</tr>
<tr>
<td>Platelet count immediately before splenectomy*</td>
<td>1.01 (1.01-1.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Average platelet count in the first 30 days post-splenectomy*</td>
<td>1.09 (1.04-1.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Any platelet count &lt;100 x 10⁹/L in the first 30 days post-splenectomy (no vs yes)</td>
<td>26.32 (6.62-176.30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak platelet count in first 30 days post-splenectomy*</td>
<td>1.03 (1.01-1.06)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Legend: ITP refers to immune thrombocytopenia; IVIG, to intravenous immunoglobulin

*for every 10 x 10⁹/L increase
Figure 1: Spaghetti plot showing platelet counts over time

Legend: Spaghetti plots of platelet count for each individual over time after splenectomy. The upper panel shows platelet counts in the first 30 days and the lower panel shows platelet counts in the first 50 months of follow-up. The blue solid line represents the regression line (loess)

Figure 2: Frequency of response and bleeding in primary ITP

Legend: CRNM refers to clinically relevant non-major bleeding. The column in the center shows the overall response category and percentage of patients in each one of them, the column to the left shows the frequency of bleeding and clinically relevant non-major bleeding according to response category, and the column to the right shows the frequency of patterns of response in each response category depending on whether the response was sustained or there were fluctuations over time