

# Long-term Relapse-free Survival Rate and Predictive Factors of Idiopathic Thrombocytopenic Purpura in Adults Undergoing Splenectomy

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**Background:** Our aim is to identify the long-term relapse-free rate and predictive factors of response to splenectomy in adults with idiopathic thrombocytopenic purpura (ITP).

**Methods:** Between 1999 and 2005, 54 patients of ITP, who underwent splenectomy in Chang Gung Memorial Hospital, Linkou, Taiwan were retrospectively reviewed. Various pre, intra and postoperative factors were analyzed to determine the predictive factors of response and long-term disease-free rate after splenectomy in adult patients.

**Results:** The relapse free survival rates in complete response patients of splenectomy at 1-, 3- and 5-yr are 91.9%, 88.4%, and 88.4%, respectively. Younger age, response to steroids, pre- and postsplenectomy high platelet counts were found to be have significant *p* value of < 0.05 as predictive factors in univariate analysis. In multivariate analysis, only pre-op and post-op platelet counts were significant.

**Conclusions:** Significant long-term relapse-free survival rate is achieved by splenectomy in adults with ITP. In univariate analysis, age, response to steroids, pre- and postsplenectomy platelet counts were the significant predictive factors of response. But in multivariate analysis, only pre-op and post-op platelet counts were significant. (*Biomed J* 2013;36:23-27)

**Key words:** idiopathic thrombocytopenic purpura, long-term relapse-free rate, platelet count, splenectomy

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by increased platelet destruction.<sup>[1]</sup> Autoantibodies are formed against platelet membrane proteins, most commonly the glycoprotein IIb/IIIa and Ib/IX complexes and platelet are destroyed by the reticuloendothelial system.<sup>[1]</sup> Spleen is the primary site of destruction of platelets.<sup>[2]</sup> Currently 30-40% of ITP patients are asymptomatic and incidentally diagnosed.<sup>[3]</sup> Medical therapy with steroids and other immunomodulatory agents constitutes the initial treatment option.

However, when the disease is refractory to medical therapy or the toxicity of the medication is unacceptable, splenectomy is usually offered.<sup>[2,4]</sup> Following splenectomy,

upto 80% of patients will have a response rate characterized by an elevation in platelet count.<sup>[5,6]</sup> Laparoscopic splenectomy (LS) was first reported in 1992.<sup>[7]</sup> Now LS is the standard procedure for many hematological diseases including ITP. Successful response to splenectomy in ITP is not very clear.

Multiple investigators previously documented factors that predict a successful response to splenectomy for ITP. These factors include younger age,<sup>[8,9]</sup> positive response to preoperative steroids,<sup>[10,11]</sup> shorter interval from diagnosis to splenectomy,<sup>[12,13]</sup> and different authors have different views. Few studies are available about the study of long-term relapse-free survival rate in adult patients with ITP undergo-

## At a Glance Commentary

### Scientific background of the subject

Splenectomy remains the last resort for management of idiopathic thrombocytopenic purpura (ITP) whenever the medical treatment fails.

### What this study adds to the field

The present study demonstrated a promising surgical result with a considerably long-term follow-up.

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ing splenectomy. The aim of our study is to analyze the predictive factors of response to splenectomy in adult patients with ITP and evaluate the long-term treatment outcome.

## METHODS

### Patient population

We have analyzed the medical records of 54 adult patients retrospectively, who underwent splenectomy for ITP at Chang Gung Memorial Hospital, Taipei, Taiwan from December 1999 to September 2005. 30 patients underwent LS and 24 patients underwent open splenectomy. Postoperative follow-up of these patients showed that 37 patients had complete response to splenectomy and 17 patients have no response to splenectomy. All the patients were evaluated according to the protocols of American Society of Hematology ITP protocols.<sup>[2]</sup>

### Selection of patients for splenectomy

When a patient was clinically suspected of ITP, the patient undergoes a series of investigations such as complete blood count, direct Coomb's test, bone marrow study, coagulation profile, liver function tests, HBsAg, anti-HCV Ab, antinuclear antibody, C3, C4, urease breath test to rule out autoimmune diseases, cirrhosis or *H. pylori* infection. Bone marrow study was done in almost our cases (48 patients, 88.9%) to rule out other causes of thrombocytopenia like myelodysplastic syndrome, aplastic anemia, SLE, occult bone marrow disease and megakaryocytopenic thrombocytopenia. We did not routinely check for the HIV status in our series. Megakaryocyte hyperplasia was recorded from the bone marrow study.

Patients diagnosed as ITP with symptoms or low platelet count ( $<3,000/\mu\text{L}$ ) were treated with prednisolone first, and add azathioprine, or vincristine, or intravenous immunoglobulin (IVIG) if failure of prednisolone treatment. Symptomatic ITP patients with failure of medical treatment and with a preoperative platelet count  $> 50,000/\mu\text{L}$  were considered for surgery. Patients who could not tolerate the side effect of steroid treatment were also candidates for splenectomy. Preoperative preparation of the patient included intravenous steroids, platelet transfusion and IVIG, if the platelet count was less than  $50,000/\mu\text{L}$ . No cases underwent emergency splenectomy.

We performed open splenectomy ( $n = 24$ ) for all cases operated on before 2000 and LS ( $n = 30$ ) beginning in 2000. Complete response to splenectomy was defined as rise in platelet count to more than  $100,000/\mu\text{L}$  after 3 months of splenectomy without any medical treatment or under tapering down the steroid treatment. No response was considered if patients had a relapse with platelet counts falling below  $100,000/\mu\text{L}$ , or if required medical treatment to keep platelet counts above  $100,000/\mu\text{L}$ .

Non-responders after surgery were treated either with

prednisolone or with a combination of corticosteroids and second line drugs like azathioprine, vincristine along with steroids. We followed up the platelet count at 1<sup>st</sup>, 2<sup>nd</sup> and 4<sup>th</sup> week, and thereafter once in every 3 months for 1 year and then annually.

### Statistical analysis

Medical records of all 54 patients were collected and survival time in each patient was defined as the interval between the date of splenectomy and that of the last follow-up. Median follow-up period was 31 months (2-84 months) until 31 December 2006. The long-term relapse-free survival rate was calculated using the Kaplan-Meier method.

The predictive factors of response to splenectomy were analyzed with Student *t* test or Chi-square test according to each parameter property. Then multivariate analysis was using logistic regression method. Statistical assessment is performed using SPSS 10.0J software package (SPSS, Japan Inc., Tokyo, Japan). *p* value  $< 0.05$  is considered as statistically significant.

## RESULTS

### Patient demographics

Retrospective analysis of 54 patients of ITP who underwent splenectomy revealed that the overall complete response rate was found in 37 (68.5%) patients whereas no response rate was found in 17 (31.5%) patients. In laparoscopic splenectomy group, 66.7% patients had complete response and 33.3% patients had no response. In open splenectomy group, 70.8% patients had complete response and no response was found in 29.2% patients. There is no significant difference between laparoscopy and open method.

### Patient outcome

In analysis of predictive factors of response to splenectomy, various pre and postoperative parameters were taken into consideration such as age, gender, time duration between the diagnosis and splenectomy, pre-op and post-op platelet count, splenic weight, megakaryocyte hyperplasia (recorded from bone marrow study), response to steroids, type of splenectomy (laparoscopic or open), blood loss and operative time. Mean follow-up period is  $35.1 \pm 24.0$  months. Female preponderance was found in our series constituting 89.2% and 82.4% of the patients in complete response and no-response groups, respectively.

Age, response to steroids, preoperative and postoperative platelet counts were found to be significant with a *p* value of 0.019, 0.045,  $<0.0001$  and  $<0.0001$ , respectively [Table 1].

In multivariate analysis of predictive factors, the pre-op

**Table 1:** Analysis of predictive factors of complete response (CR) to splenectomy in adults with idiopathic thrombocytopenic purpura

Factors	Complete response (%)	No response (%)	p value
	37 cases	17 cases	
Age (yrs, mean±SD)	34.7±14.1	44.9±14.8	0.019
Gender			0.665
Male (n=7)	4 (10.8)	3 (17.6)	
Female (n=47)	33 (89.2)	14 (82.4)	
Duration (months)	6.5±8.0	6.7±3.2	0.935
Platelet count (1000/μL)			
Pre-op	120.1±55.9	49.7±37.6	<0.0001
Post-op	326.8±105.6	102.6±90.3	<0.0001
Platelet count			
Pre-op>80,000/μL	29 (78.4)	3 (17.6)	<0.0001
Pre-op 80,000/μL	8 (21.6)	14 (82.4)	
Post-op>140,000/μL	34 (91.9)	3 (17.6)	<0.0001
Post-op 140,000/μL	3 (8.1)	14 (82.4)	
Splenic weight (grams)	100.4±32.9	106.3±49.9	0.626
Megakaryocyte hyperplasia			0.522
Yes (n=32)	23 (62.2)	9 (52.9)	
No (n=22)	14 (37.8)	8 (47.1)	
Response to steroid			0.045
Yes (n=20)	17 (45.9)	3 (17.6)	
No (n=34)	20 (54.1)	14 (82.4)	
Splenectomy			0.743
Laparoscopic (n=30)	20	10	
Open (n=24)	17	7	
Blood loss (ml)	159.2±383.1	173.5±205.2	0.886
Operation time (mins)	134.1±64.6	121.8±36.0	0.468

**Table 2:** Multivariate analysis of predictive factors

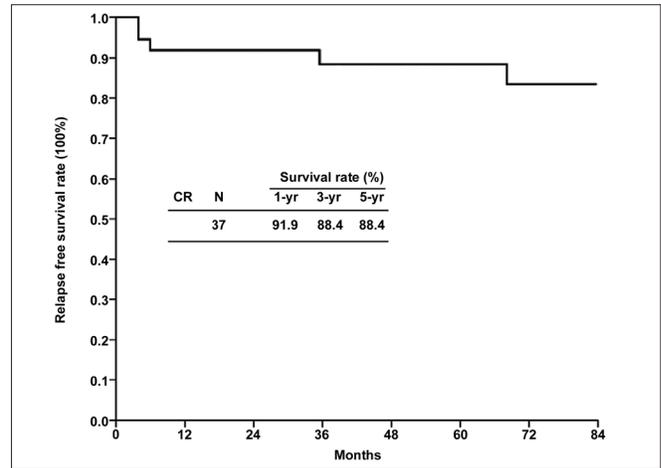
Factors	Odds ratio	95% C.I. of odds ratio	p value
Age	0.969	0.903-1.040	0.384
Pre-op platelet count (1000/μL) >80/ 80	10.537	1.465-75.799	0.019
Post-op platelet count (1000/μL) >140/ 140	24.178	2.824-207.006	0.004
Response to steroid	0.771	0.072-8.272	0.83

platelet count more than 80,000/μL and the post-op platelet count more than 140,000/μL are independent factors for good response to splenectomy [Table 2].

Three patients had surgical complications, one had intra-abdominal abscess, one had pulmonary atelectasis with pleural effusion and one had salmonella sepsis. There were no overwhelming sepsis, malignancy, ITP or splenectomy-related death in long-term follow-up. No surgical mortality was seen in our series.

### Long-term period

The 1-, 3- and 5-years relapse-free survival rates in



**Figure 1:** Long-term relapse-free survival rate in complete response ITP patients after splenectomy

complete response group (n = 37) are 91.9%, 88.4%, and 88.4%, respectively. [Figure 1].

## DISCUSSION

In univariate analysis, our study revealed that age is a predictive factor to splenectomy in ITP patients. Patients in complete response group have younger mean age (34.7 ± 14.1) than no response group (44.9 ± 14.8) (p < 0.05); similar to earlier reports.<sup>[8,14]</sup> Age of the patient was reported to be a significant predictor of complete response to splenectomy in ITP patients.<sup>[6,8,14]</sup> Younger age group i.e., 30-45 years had a favorable prognosis to splenectomy,<sup>[6,8,14]</sup> but another study had not reported it as a predictive factor.<sup>[15]</sup>

Our results indicated that an initial response to steroid during the time period between diagnosis and splenectomy is a positive predictor of complete response to splenectomy in univariate analysis. This correlation also reported by Mintz *et al.*,<sup>[15]</sup> who observed a higher remission rate in patients who responded to steroids prior to surgery than those without response (92% vs. 65%). However, another study failed to show similar association.<sup>[6]</sup>

In our study preoperative platelet count >80,000/μL had a better response rate (90.6%) to splenectomy similar to Duperier *et al.*,<sup>[14]</sup> who observed a successful response to laparoscopic splenectomy for ITP in patients with preoperative platelet counts above 70,000/μL. However, most series have failed to show that preoperative platelet counts as a predictor of response for splenectomy.<sup>[9,16,17]</sup> Our analysis also shows that postsplenectomy platelet count > 140,000/μL is also found to be a predictor of complete response to splenectomy in ITP, similar to earlier reports.<sup>[14,16,17]</sup> Our study suggests that lower platelet count ≤ 80,000/μL before and ≤ 140,000/μL after splenectomy is a predictor of poor

response or refractoriness to splenectomy. Davis *et al.*,<sup>[18]</sup> reported that the non-responders/refractory patients would slowly achieve stable remission over a long period of time. These controversies in different groups regarding the predictive factors of complete response may be due to inclusion of different study groups related to age, treatment options, timing of splenectomy and length of follow-up.

There are a few of other predictors for the response to splenectomy for ITP patients published. Response to IVIG,<sup>[19]</sup> predominance of <sup>111</sup>In-labelled platelets sequestration,<sup>[20]</sup> short duration of illness,<sup>[12]</sup> and megakaryocyte hyperplasia<sup>[21]</sup> are predictors for good response to splenectomy. But there are also many other reports had no significant response difference in these predictors.<sup>[8,10,22]</sup> In our study, duration of illness, megakaryocyte hyperplasia showed no predictive value to splenectomy for ITP patients. We had no data about the <sup>111</sup>In-labelled platelets sequestration.

In multivariate analysis of predictive factors, only pre-op platelet count (greater than 80,000/ $\mu$ L) and post-op platelet count (greater than 140,000/ $\mu$ L) were independent predictive factors for complete response to splenectomy. The patient with platelet count greater than 80,000/ $\mu$ L can tolerate most of the invasive procedure and no need further blood transfusion. The platelet count greater than 140,000/ $\mu$ L is known as the lower limit of normal population. Duperier *et al.*,<sup>[14]</sup> reported the similar conclusion using multivariate analysis. They found a successful response to laparoscopic splenectomy for ITP is expected in patients with the pre-op platelet counts greater than 70,000/ $\mu$ L. Age was another independent factor in their multivariate analysis but not in our study. The post-op platelet count was a predictive factor for response in our study but not analyzed in their reports. Fenaux *et al.*,<sup>[23]</sup> found post-op platelet count and age retain an independent prognostic significance in multivariate analysis.

Natural course of ITP in adults is different from that in pediatric group. Spontaneous remission without treatment occurs in >80% and splenectomy is nearly always curative in pediatric patients.<sup>[18,24,25]</sup> But in adults, relapse is likely to occur even after medical treatment and splenectomy. There is no standardized definition for remission of ITP and duration of follow-up after which it can be defined as complete remission. Earlier studies defined remission as normalization of platelet count without need for future medical treatment. In our series, we defined disease remission as a sustained platelet count of >100,000/ $\mu$ L without the need for medical therapy at the end of 3 months postoperation.

The response rate to splenectomy for ITP is reported to be 64-90%.<sup>[8,14-16]</sup> In our study 68.51% had complete response and relapse-free survival rates in this group are 91.9%, 88.4% and 88.4% at 1-yr, 3-yrs and 5-yrs, respectively, at a mean follow-up period of 35.1 + 24.0 months,

which is close to earlier reports.<sup>[8,14,22,26,27]</sup> Vianelli *et al.*,<sup>[28]</sup> reported that 5-yr relapse-free rate was 75%; where as other study reported the complete response rate of 50%,<sup>[29]</sup> both slightly lower than our series.

Our study confirmed that adult population with ITP will have good response to surgical treatment in the form of splenectomy and is an effective modality of treatment for increasing the platelet count and achieving long-term relapse-free survival. Earlier authors reported LS as the standard procedure for ITP; however, there is no difference in the remission rate depending on the type of splenectomy (open vs. laparoscopy). But the overall complication rate is low in LS.<sup>[24,30]</sup> As our study, Tsereteli *et al.*,<sup>[31]</sup> did not find any significant difference between the open and laparoscopic procedures as a predictive factor of favorable outcome.

Our patients were all older than 17 years of age in our hematological service. The spleen plays no more important role in the host immune system. This could explain why there was no overwhelming sepsis in our study.

In our study, relapse occurred most within 3 years of splenectomy. Few studies reported relapse even after 15 years of follow-up.<sup>[32,33]</sup> Long-term follow-up in our series shows that risk of relapse is much decreased after 3 years of splenectomy, confirming the potential benefit of splenectomy to provide a long-term control of the disease. However, Kumar *et al.*,<sup>[34]</sup> reported that splenectomy often converts refractory patients into responding ones. Splenectomy is the only modality of treatment of ITP patients, which will give a sustained complete response in over 60%.<sup>[35]</sup>

In summary our study concludes that splenectomy provides significant long-term relapse-free survival in adult patients with ITP. In univariate analysis, younger age, platelet counts > 80,000/ $\mu$ L and >140,000/ $\mu$ L in pre- and postsplenectomy periods, respectively, and better response to steroids before splenectomy are the predictive factors of complete response for splenectomy. But in multivariate analysis, only pre- and postsplenectomy platelet counts were significant predictive factors.

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