

## Long Term Outcome of Splenectomy in Chronic Immune Thrombocytopenic Purpura

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**Conflict-of-interest statement:** The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: July 8, 2016

Revised: August 29, 2016

Accepted: September 1, 2016

Published online: September 7, 2017

### ABSTRACT

**AIM:** Splenectomy is the accepted second-line treatment in chronic immune thrombocytopenic purpura after corticosteroids fail. Splenectomy has a success rate of 50-60% in achieving complete remission. However, true long-term outcome is unknown since most of the follow-ups are around five years, according to other given publications. This retrospective review of adult patients with chronic ITP analyses true long term outcome of splenectomy over a long period and also examines for predictors of response to splenectomy.

**METHODS:** We retrospectively reviewed the medical records of 49 patients who had undergone splenectomy for chronic ITP from 1982 to 2015 [Range 2 - 396 months (33 years)] in a premier institute in south India. The mean follow-up period was 75.71 months.

**RESULTS:** Response to splenectomy gradually declined from 83.3% (five out of six patients) at one year to 25% (one out of four patients) when observed beyond 15 years, following splenectomy. Out of several factors studied like age, gender, initial response to steroids (pre-operative) and post-operative platelet count, there was no factor found to be statistically significant to predict long term remission. However, patients with post-splenectomy relapse could be managed with a significantly lower dose of prednisolone of 16.7 mg/day compared to their pre-splenectomy average requirement of 47.5 mg/day.

**CONCLUSION:** Although splenectomy normalizes platelet count acutely, sustained long term remission decreases with passage of time, to an extent only one-third of patients may remain in remission by 10 years of surgery. Further, there was no factor which could predict response to splenectomy.

**Key words:** Immune thrombocytopenic purpura; Splenectomy; Platelet count

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Dutta TK, Diljith H, Vishnu VY, Verma SP, Charles D, Vinod KV, Basu D. Long Term Outcome of Splenectomy in Chronic Immune Thrombocytopenic Purpura. *International Journal of Hematology*

Research 2017; 3(1): 164-167 Available from: URL: <http://www.ghmet.org/index.php/ijhr/article/view/1780>

## INTRODUCTION

Splenectomy is conventionally considered second line of treatment in chronic immune thrombocytopenic purpura (ITP) once steroids fail. Used since 1913, it is known to have cured substantial number of ITP patients who had not responded to steroids<sup>[1]</sup>. However, reports on long term effect of splenectomy on immune thrombocytopenic purpura (ITP) have been confusing. This is largely because of different duration of follow-up periods in different series, most of which range around five years following splenectomy<sup>[2-4]</sup>. Further, prognostic factors which determine long-term outcome are also not clearly known.

### Objectives

Objectives of the study were: (1) To evaluate the long term effect of splenectomy in chronic immune thrombocytopenic purpura (ITP); (2) To study the factors, if any, which predict long term remission in chronic immune thrombocytopenic purpura (ITP).

## MATERIALS AND METHODS

We retrospectively reviewed the medical records of 49 adult patients of ITP, diagnosed as per standard guidelines<sup>[5]</sup>, who had undergone splenectomy in our hospital, a premier institute in south India, from 1982 to 2015 [Range 2 -396 months (33 years)]. The average admission of ITP patients annually is about 60 patients in our hospital.

Response to splenectomy was categorized as follows<sup>[6]</sup>:

Patient belonging to first two categories [(i.e. Complete response (CR) + Response(R))] were considered as having responded to splenectomy (Table 1).

Primary outcome measure – Complete response/Response (CR/R)

Statistical analysis was done using SPSS version 19.0.

## RESULTS

Forty nine adult patients of chronic ITP had undergone splenectomy during the study period. There were 38 female and 11 male patients. The mean age was 32.1 ± 11.4 years. The mean time from diagnosis to splenectomy was 41.1 ± 55.7 months.

Figure 1 is a flow chart showing long-term response to splenectomy in 49 patients. Mean follow-up period was 75.7 ± 76.06 months [(Range 2 - 396 months (33 years)]. However, longest follow-up was for more than 15 years in four patients, and in one of them for 396 months (33 years). The rate of response to splenectomy steadily declined over years, and was observed only in one of four patients

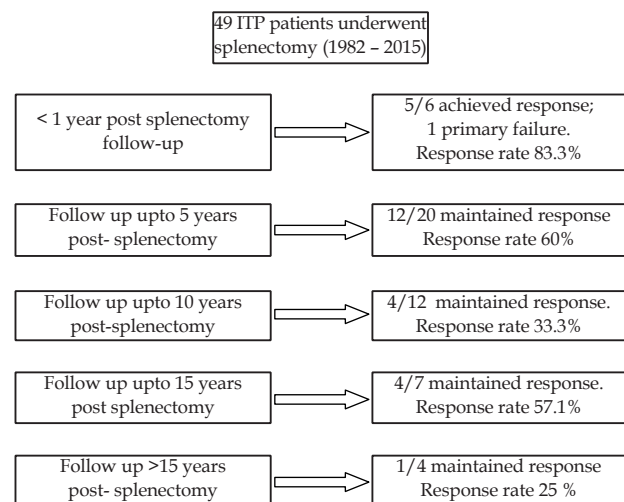
who were followed beyond 15 years. Substantial number of patients i.e. 23 patients were followed for 10 years or beyond. Overall, 26 patients (53.1%) patients had response to treatment. Twenty patients belonged to Complete response (CR) category, and six to Response (R) category as per new guidelines<sup>[6]</sup>. Twenty three patients (46.9%) had failed splenectomy.

Not surprisingly, number of patients for long-term follow up decreased with passage of time, and only four patients were available for the category of ‘follow up beyond 15 years’.

Tc 99 m sulphur colloid scan screening for accessory spleen was done in 20 non-responder patients; accessory spleen was detected in four patients. Removal of accessory spleen was performed in all of them, two patients achieved CR after the procedure, two continued to have low platelet count even after the procedure. Three non-responders could not be screened.

Various factors to predict response to splenectomy were also analysed in all the patients (Table 2). There was no ‘predictor of response’ found; splenectomy response could not be correlated with age, gender and post-operative platelet count. However, initial response to steroid (pre-operative) appeared close to predicting good response, (but, did not achieve statistical significance).

All the 23 non-responders were given various third line drugs namely azathioprine, dapsone, cyclophosphamide, rituximab and danazol empirically. Eighteen of them had to be finally put on prednisolone (to achieve remission). However, prednisolone requirement was significantly reduced to about 15 mg/day as compared to about 50 mg/day in the pre-splenectomy state (pre-splenectomy prednisolone dose 47.5 ± 26.30 mg/day vs. post-splenectomy prednisolone dose 16.66 ± 10.98 mg/day, *p* < 0.0001).



**Figure 1** Long term platelet response in 49 patients who underwent splenectomy for chronic ITP (1982-2015). Response to treatment included ‘Complete Response (CR) and Response (R) categories’.

**Table 1** Definitions of response to treatment by ITP\*.

Complete response (CR)	A platelet count ≥ 100 × 10 <sup>9</sup> /L measured on 2 occasions > 7 days apart and the absence of bleeding.
Response (R)	A platelet count ≥ 30 × 10 <sup>9</sup> /L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions > 7 days apart and the absence of bleeding.
No response (NR)	A platelet count < 30 × 10 <sup>9</sup> /L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.
Loss of complete response	A platelet count < 100 × 10 <sup>9</sup> /L measured on 2 occasions more than a day apart and/or the presence of bleeding.
Loss of response	A platelet count < 30 × 10 <sup>9</sup> /L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.

\* Based on the recommendations of the International Working Group.

Patient belonging to first two categories (i.e. CR + R) were considered as having responded to treatment.

## DISCUSSION

Thirty eight of 49 patients of ITP in the current study were female, which was an interesting observation. In literature, female preponderance of ITP is well known. Female-male ratio of 1.7: 1 has been observed in a report<sup>[7]</sup>. Ours was, however, 3.4: 1- almost twice the previous figure. But no clear explanation could be found for such a high incidence.

With the potential disadvantages of splenectomy like overwhelming post-splenectomy infection (OPSI) and inefficacy of anti-D globulin therapy being realized more often (besides, more effective drugs like cyclosporine, rituximab, eltrombopag etc. being available now), there has been a serious question mark on continuing to contemplate splenectomy as second line of treatment, without understanding the predictable factors for successful splenectomy.

We in this report have compiled the data of a much longer follow-up of 15 years or beyond than is available in literature. Maximum follow up was for 33 years in one patient, and for nearly 20 years in two patients. Our observation has been startling and much different from earlier reports i.e. a significant fall in CR from 83% at one year to 25% beyond 15 years).

Table 3 gives reports in different series. As evident from the table, the overall response in various series has been 50- 60%; however, follow-up period has been only 5-6 years in most of the studies.

There is one report from India with long term follow up – a report from Chennai which was a retrospective study from 1983 to 1996 of 364 patients. Seventy one patients underwent splenectomy. Average follow-up period was 58 months. CR was observed in 42% of patients at the end of 5 years. Factors studied with regard to good response were age, sex, initial response to steroids, time interval

between diagnosis and splenectomy. Good initial complete response to steroids and post-operative platelet count at discharge of  $> 300 \times 10^9/L$  were associated with good long term prognosis<sup>[3]</sup>.

Ours is the longest study of 33 years next only to a John Hopkins study of 37 years (Bell WR Jr. unpublished work)<sup>[1]</sup>. In our series, we could not correlate response favorably with any factor.

Further, at follow up beyond 15 years, there was only one of the four patients in remission.

There are potential disadvantages of splenectomy<sup>[1]</sup>: (1) As the time since splenectomy increases, the rate of excellent response decreases; (2) Opsonin (critical for the optimal killing of invasive micro-organisms by white blood cells) is manufactured only in the spleen. Patient may, thus, be prone to develop fulminant infection; (3) Despite pneumococcal vaccination prior to splenectomy, fatal fulminant sepsis is a distinct possibility; (4) Anti-D globulin, an excellent treatment option for ITP, is rendered ineffective once spleen is removed from the body.

Thus, a number of published studies, including the Johns Hopkins study, have questioned the long-term benefit of splenectomy<sup>[1]</sup>.

**Table 2** Predictors of response to splenectomy.

Parameter	Response group (n = 26)	Failed group (n = 23)	p value
Age in years	31.7 ± 12.05	32.69 ± 10.8	0.77
Gender	Male	5	0.56
	Female	21	
Initial Response to Steroid (pre-operative)	Good	15(57.7%)	0.055
	Poor	11(42.3%)	
Immediate Post-operative PLC	314 ± 175.9 x10 <sup>9</sup> /L	214.33 ± 172.06 x 10 <sup>9</sup> /L	0.11

Splenectomy response - could not be correlated with age, gender, initial response to prednisolone and immediate post-operative platelet count.

**Table 3** Response to splenectomy in ITP in different studies.

Study	Patients undergoing splenectomy	Response
Williams EJW et al, 1958 [8] (earliest study)	52 of 93 patients underwent splenectomy	Immediate – 60% excellent response 1 year follow up – Good (not excellent)
Carpenter AF et al, 1959 [9]	45 (of 85 patients) underwent splenectomy	1 year follow up - 25 (55%) complete response (CR)
Meyers MC et al, 1961[10]	46 of 54 patients underwent splenectomy	All had excellent response for months (details not available)
Thompson RL et al, 1972 [11]	35 patients underwent splenectomy	5 year follow up -26 (74%) had excellent response. 23% - No response
Ikkala et al, 1978 [12]	41 patients underwent splenectomy	6 year follow up - 54% had excellent response
Picozzi V et al, 1980 [13]	37 of 57 patients underwent splenectomy	(1) Immediate post-operative - 73% had complete remission; (2) 18 months later - response dropped to 49%
DiFino SM et al, 1980 [14]	36 of 38 patients underwent splenectomy	5 year follow up - 50% remission, but 1- 12 years on 23% had relapse, only 36% remained in remission
Pizzuto J et al, 1984 [15]	399 of 943 patients underwent splenectomy	Six months follow up - 65% had very good remission (authors also opined – early vs. late splenectomy: response same)
BellWR Jr., 2000 [1](Johns Hopkins study)	647 splenectomy patients	6 months to 37 years follow up - 615 (95%) relapsed, was the most disappointing result (unpublished data)
Kumar S et al, 2002 [4]	140 patients underwent splenectomy	5 year follow up - 75% relapse free survival. Young age and increased post-splenectomy platelet count - found favorable prognosticators. However, there were 25 deaths during the period (2 - postoperative complications, 1 - gastrointestinal bleed due to thrombocytopenia, 1 - overwhelming sepsis)
Schwartz et al, 2003 [2]	75 patients underwent splenectomy	5 year or longer follow up (median 7.5 years) - 57% in remission
VianelliHematologica 2005 [16]	345 patients underwent splenectomy	79 (23%) patients relapsed, mostly 80% within 48 months
VianelliHematologica 2013 [17]	233 patients underwent splenectomy.	10 yr followup: Sixty-eight of 206 (33%) responsive patients relapsed, mostly (75%) within four years from first response. Splenectomy achieved a long-term stable response in about 60% of cases.
A meta-analysis of 18 published reviews (BellWR Jr., 2000)[1]	Response to splenectomy	Initial response - 60%
Current study	49 patients underwent splenectomy	1 year follow-up – 83.3% CR; 5 year follow up - 60% CR; 10 year follow up - 33.3% CR; >15 year follow up - 25% CR

To conclude, there is an acute response to splenectomy in ITP in terms of normalisation of platelet count; however, longer the follow-up lower is the response rate. Sustained long term remission was observed only in one of four patients after 15 years. Nevertheless, patients with post-splenectomy relapse could be managed with a very low dose of prednisolone of 16.7 mg/d compared to their pre-splenectomy average requirement of 47.5 mg/d.

It further appears logical, more potent third line drugs now available like rituximab, cyclosporine, eltrombopag etc. should be first tried before resorting to a drastic step like splenectomy.

#### Strengths and limitations of the study

**Strength:** It is a study with a very long study period, one next to John Hopkins study [(Bell WR Jr. Long-term outcome of splenectomy for idiopathic thrombocytopenic purpura. *Semin Hematol.* 2000; 37(Suppl 1): 22-5].

**Limitation:** (1) It being a retrospective study spread over 33 years, some cases of splenectomy could have been inadvertently missed out. However, results are still clear enough to reflect the current overall status of long term outcome of splenectomy in chronic ITP. (2) There were 23 non-responders to splenectomy; however, 20 patients only could be screened for accessory spleen. Two out of four accessory spleen patients failed to respond to removal of accessory spleen; (3) Three non-responders could not be screened. Screening them, however, could not have significantly altered the result; (4) Due to very limited number of patients with a follow up of 15 years or more, data analysis and interpretation of result were hampered in those groups of patients.

## ACKNOWLEDGEMENTS

We acknowledge the help rendered by Dr. Harichandra, Assistant Professor of Biostatistics, JIPMER, Puducherry, India in carrying out the statistical analysis.

#### Contributor Statement

Dr. T.K. Dutta and Dr. D. Basu designed the study. Further, Dr. Dutta prepared the manuscript. Dr. Hitha Diljith, Dr. Shailendra Prasad Verma and Dr. Deepak Charles were involved in data collection and literature search. Dr. Venugopalan Y Vishnu and Dr. Kolar Viswanath Vinod apart from other things reviewed the manuscript and offered constructive criticisms.

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**Peer reviewer:** Mudi Misgav