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Original Article

Safety and efficacy of splenectomy in immune thrombocytopenia

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Abstract: Background: Immune Thrombocytopenia (ITP) is characterized by low platelet counts. Splenectomy has been in practice for the treatment of ITP since the early 20th century. We aimed to analyze the data of ITP patients from our hospital who underwent splenectomy and further present the long-term outcome and safety profile in these patients. Method: This study was a single-center, registry based study conducted at a tertiary care hospital in Northern India. Patients aged 18 years or more, who underwent splenectomy after at least one line of therapy, were included in the study. The primary outcome was the overall response rate (ORR) at one month after splenectomy. Secondary outcomes were sustained response, relapse-free survival, factors affecting the ORR, and adverse events after splenectomy. Results: Forty-five patients of ITP were included in the study. Thirty-six patients underwent splenectomy in the first half (2001-2010), of the study period. The median age of the patients was 38 (19-56) years. The median duration from diagnosis to splenectomy was 1.76 (0.47-2.58) years. The median number of therapy received before splenectomy was 3 (1-6). The overall response rate (ORR) post-splenectomy at day 30 was 89.2% with 61.8% complete response (CR). The ORR was 88.5% at 1-year, with 48.8% CR. The relapse-free survival (RFS) at 5-years was 57.38% (95% Confidence Interval 40.59-71.02%), There was no effect of duration of disease, age, gender, and prior therapy received, on the ORR at one-month. At one year, the platelet response was significantly better in patients who had a CR at one-month than patients who had a partial response at one month. The relapse-free survival was better in patients who achieved CR after 1-month of splenectomy. During the median follow-up of 5.02 (1 month-20 years) years, there were five cases of overwhelming post-splenectomy infection (OPSI). There was no recorded incidence of perioperative mortality, deep vein thrombosis, or mesenteric thrombosis. Discussion: Despite the variation in outcome from different studies, splenectomy gives the best possible long-term treatment-free remission amongst all the available second-line agents. It is also, one of the most financially affordable therapies. Despite advantages, the number of ITP patients undergoing splenectomy has been on the decline and largely attributable to the newer and more effective second-line therapies. There is no pre-surgery variable predicting the ORR after splenectomy. Conclusion: Splenectomy in ITP offers a long-term sustained response at an economical cost.

Keywords: Splenectomy, thrombocytopenia, resource constraint settings, ITP, chronic ITP, second-line therapy

Introduction

Immune Thrombocytopenia (ITP) is a benign hematological disorder, which is characterized by low platelet counts in peripheral blood [1, 2]. Low platelet counts in circulation result from either destruction of platelets or low platelet production or both [3]. Low platelet count in ITP

clinically manifests as mucocutaneous bleeding however, rarely can it present with life-threatening bleeding complications [4, 5]. Bleeding manifestations in ITP are predominantly seen with platelets counts below 30,000/μL and necessitates initiation of therapy [6, 7]. However, platelet function defects in ITP may also contribute to the bleeding manifestation [8, 9]. Corticosteroids are usually the first line therapy, but 40-80% of patients ultimately require second-line therapy due to steroid-dependent, refractory, or relapsed disease [10, 11].

Thrombopoietin receptor agonists (TPO-RAs), rituximab, and splenectomy are the preferred second-line therapy options for ITP [6, 7]. TPO-RAs (eltrombopag and romiplostim) and rituximab therapy have good overall response rates (50%-80%) but sustained response after drug discontinuation in low (10-25%) [12, 13]. However, financial burden, need for prolonged duration of therapy, and limited durability of treatment responses are some of the limitations which particularly affect the decision-making in developing countries [11-14]. Hence, the role of splenectomy and other second-line agents comes into consideration [15, 16]. Splenectomy has been in practice for the treatment of ITP since the early 20th century [17]. However, due to newer and effective drug development, the treatment with splenectomy has been on a gradual declining trend for the last two decades [18]. With regard to consideration as a treatment option, apart from being a second-line option, splenectomy also offers a single time measure to correct the disease. It is particularly useful for patients who reside in remote rural areas with difficulties in regular follow-up and collection of drugs [7]. However, during earlier times, associated perioperative mortality was a concern but with recent advancements, it has come down to as low as 0% in some studies [19]. Overwhelming post-splenectomy infection (OPSI) and thrombosis have been two long-term concerns after splenectomy. However, the incidence of OPSI has decreased considerably to 3-5% with pre-operative vaccination and antibiotic prophylaxis [20].

Considering the advancement in surgical methods, infection and thrombosis prevention and management, splenectomy can be one of the relatively safe and suitable second-line treatment options for ITP. The same is reflected in the recently published guidelines and updates [6, 7]. However, most of the available data are from the developed countries where despite improvement in splenectomy outcomes, splenectomy is on the decline [15, 18]. Following the trends from the developed countries, the incidence of splenectomy is on decline in developing countries as well. We aimed to analyze the outcomes of ITP patients from our hospital who underwent splenectomy and further present its long-term effectiveness and safety profile in these patients.

Methods

This study was a single-center, registry based study conducted at a tertiary care hospital in Northern India. This hospital is one of the busiest tertiary cancer care centre located in New Delhi, and caters to a huge population from all but not limited to the states from northern and central India. The study was approved by the Institutional review committee. An informed written consent was taken from the patients or relatives. Medical treatment details of the patients' were accessed from the outpatient department (OPD) files, and inpatient hospital admission and discharge summaries. The information was entered in a pre-defined excel sheet. Being a retrospective study, the attempts were made to minimize the missing data by interviewing patients and their family members through follow up phone calls via secure and confidential tele communication line.

Inclusion and exclusion criteria

Patients were diagnosed with ITP as per the International Working Group Criteria (IWG) [21]. Patients aged 18 years or more, who underwent splenectomy after at least one line of therapy were included in the study. Patients with secondary ITP, unwilling to give consent, unavailability of data for response and safety assessment were excluded from the study.

Outcome

The primary outcome was the overall response rate (ORR) at 30 days after splenectomy. Overall response rate was determined from the proportion of patients achieving a platelet count equal to or more than 30,000/μL or double from the

no active bleeding manifestations. Secondary outcomes were sustained response, event-free survival, factors affecting the ORR, and adverse events after splenectomy. Sustained response was determined from the proportion of patients maintaining a platelet count equal to or more than 30,000/μL or double from the baseline with no active bleeding manifestations and it was determined at one-year and 5-year after splenectomy. All adverse events were noted and graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [22].

Definitions of outcomes for the study [7, 21]

The response was assessed as IMWG criteria [21]. -Partial Response (PR) was defined as a platelet count equal to or more than 30,000/μL or double from the baseline till 100,000/μL with no active bleeding manifestations. -Complete response (CR) was defined as a platelet count of equal to or more than 100,000/μL with no active bleeding manifestations. -Overall response rate (ORR = CR + PR) was defined as the proportion of patients achieving complete response (CR) or partial response (PR). -No response was defined as a platelet count below 30,000/μL or less than double from the baseline or having active bleeding manifestations requiring another line of therapy. -Relapse was defined as any new-onset bleeding manifestation necessitating therapy or drop in platelet counts below 30,000/μL or patients who were started on another line of therapy for low platelet counts after achieving response with splenectomy. Response duration was defined as time duration from splenectomy to the day of documented relapse.

Statistical methods

The baseline characteristics were summarised using mean and standard deviation (or median and range) for continuous variables and proportion for categorical variables. The age at disease onset, gender of patient, duration of disease before splenectomy and whether rituximab was given or not and number of prior treatments were used as baseline explanatory variables. The variables were standardised (with respect to mean and standard deviation) before analysing their effect on outcomes. Remission status at 1 month was used as short-term outcome measure and remission status at 12 months, overall survival and relapse free survival were used as long-term outcomes. The outcomes were summarised and association were assessed with explanatory variables using linear regression and logistic regression analysis in Bayesian statistical framework using PyMC3 python package [23]. Vaguely informative prior distributions were chosen for analyses. The corresponding effects were summarised using 94% credible interval. The time to event outcomes were summarised using Kaplan-Meier analysis.

Results

Demographics and baseline laboratory parameters

After screening the data for inclusion criteria, 45 ITP patients, who underwent splenectomy from 2001 to 2020 were included in the present study. While 36 patients underwent splenectomy in the first half (2001-2010), only nine patients underwent splenectomy in the second half (2011-2020) of the study period. The median age of the study population was 38 years (range 19-56 years) and 22 patients (48.89%) were males. The median duration from diagnosis to splenectomy was 1.76 (0.47-2.58) years. The median number of therapies received before splenectomy was 3 (range 1-6). The median platelet count before splenectomy was 8000/μL (range 1000-28000/μL). The baseline characteristics and pre-splenectomy laboratory parameters of the patients are summarised in **Table 1**.

Response rate

The overall response rate (ORR) after splenectomy at day 30 was 89.2%, with 61.8% patients in complete response (CR) (**Table 2**). From the baseline, the mean platelet counts increased by 15 times (94% credible interval of 10.134-23.07) (**Figure 1**). The ORR subsequently declined to 88.5% at 1-year, with 48.8% complete response (CR). The relapse-free survival (RFS) at 5-years was 57.38% (95% Confidence Interval 40.59-71.02%), while the median RFS has not been reached (**Figure 2**). The overall

Table 1. Demographic profile and baseline clinical characteristics of ITP patients who underwent splenectomy

Variable Median (range)	
Evaluable patients	45
Males	22 (48.89%)
Age (years)	38 (19-56)
Interval from ITP diagnosis to splenectomy (years)	1.756 (0.47-2.58)
Number of prior therapies	3 (1-6)
Less than three lines	15 (33.33%)
Three lines	16 (35.56%)
More than three lines	14 (31.11%)
Different therapies received prior to splenectomy	
Corticosteroid	45 (100%)
IVIG	20 (44.44%)
Anti-RhD Immunoglobulin	5 (11.11%)
Rituximab	15 (33.33%)
Eltrombopag	5 (11.11%)
Azathioprine	4 (8.89%)
Dapsone	29 (64.44%)
Danazol	14 (31.11%)
Vincristine	4 (8.89%)
Baseline Hemoglobin (g/dL)	13.1 (10-16.3)
Baseline WBC (/μL)	9000 (2400-15900)
Baseline Platelet count (/μL)	8000 (1000-28000)

survival (OS) at 5-years was 92.64% (95% Confidence Interval 73.46-98.12%) (**Figure 3**).

Factors affecting the response to splenectomy

After standardizing all the variables the effects of variables on the platelet count at 30 days were analyzed. On performing univariate and multivariate analysis, there was no effect of duration of disease, age, gender, and prior therapy received, on the overall response at day 30 post-splenectomy in our study cohort (**Figure 4**; **Tables 3**, **4**). At one year, the difference in platelets with gender (male versus female), rituximab (yes versus no), the response at day 30 (CR versus PR), and number of therapies (3 versus <3 and >3 versus <3), expressed as times showed the platelet response was significantly better in patients who had a complete response at 30 days than patients who had a partial response at 30 days (**Tables 5**, **6**). Patients with CR had mean platelets of 2.36 (94% credible Interval 1.33 to 4.07) times better than patients with PR (**Figure 5**). The longer duration of disease and more number of prior therapies negatively affected the platelet response. The relapse-free survival was better in patients who achieved CR at 30 days post-splenectomy (**Figure 6**).

Post-splenectomy adverse events

There were no perioperative complications during the procedure. During the median follow-up of 5.02 years (range 1 month-20 years), there were five cases of overwhelming post-splenectomy infection (OPSI) and one case of right middle cerebral artery thrombosis (i.e. ischaemic stroke). Two patients with OPSI and one patient with stroke died in hospital while the rest of the patients recovered. There was no recorded incidence of perioperative mortality, deep vein thrombosis, or mesenteric thrombosis.

Discussion

We observed the best overall response rate (ORR) of 89.2% after splenectomy at one-month in our study population. The ORR slightly decreased at one year (88.5%) and the five-year relapse-free survival was 57.38%. Our findings are consistent with the published studies reporting almost 80% platelet response immediately after splenectomy, with long-term ORR being 50-70% [15, 24]. However, some studies have published different results as compared to our study. In a systematic review analyzing 1223 patients from 23 studies, the ORR was 72% at five years [25]. Another study reported 90.8% ORR at initial evaluation post-splenectomy and 68% long-term ORR (median follow-up 62 months) [26]. The CR rates in our study at 30 days and after one-year post-splenectomy were 61.8% and 48.8% respectively. They are lower in comparison to 66% complete response rate [median follow-up 28 months (range 1-153 months)] reported in a systematic review analyzing the published literature from 1966-2004, including 135 case series [27].

One of the reasons for the lower sustained response in our cohort can be attributed to the

Table 2. Response to splenectomy in ITP patients

Variable	n (%) or median (range)	94% credible interval
Overall response rate		
At day 30 of Splenectomy	41 (89.2%)	80.9-96.8%
At one-year of Splenectomy	37 (88.5%)	79.9-97.1%
Complete response rate		
At day 30 of Splenectomy	28 (61.8%)	48.6-74.8%
At one-year of Splenectomy	20 (48.8%)	34.4-63.2%
Follow up (years)	5.02 (1 month-20 yr)	-
Relapse free survival	Not reached	-
Relapse free survival rate		
At 5 years	28 (57.38%)	40.59-71.02% (95% Confidence Interval)
Overall Survival		
At 5 years	42 (92.64%)	73.46-98.12% (95% Confidence Interval)

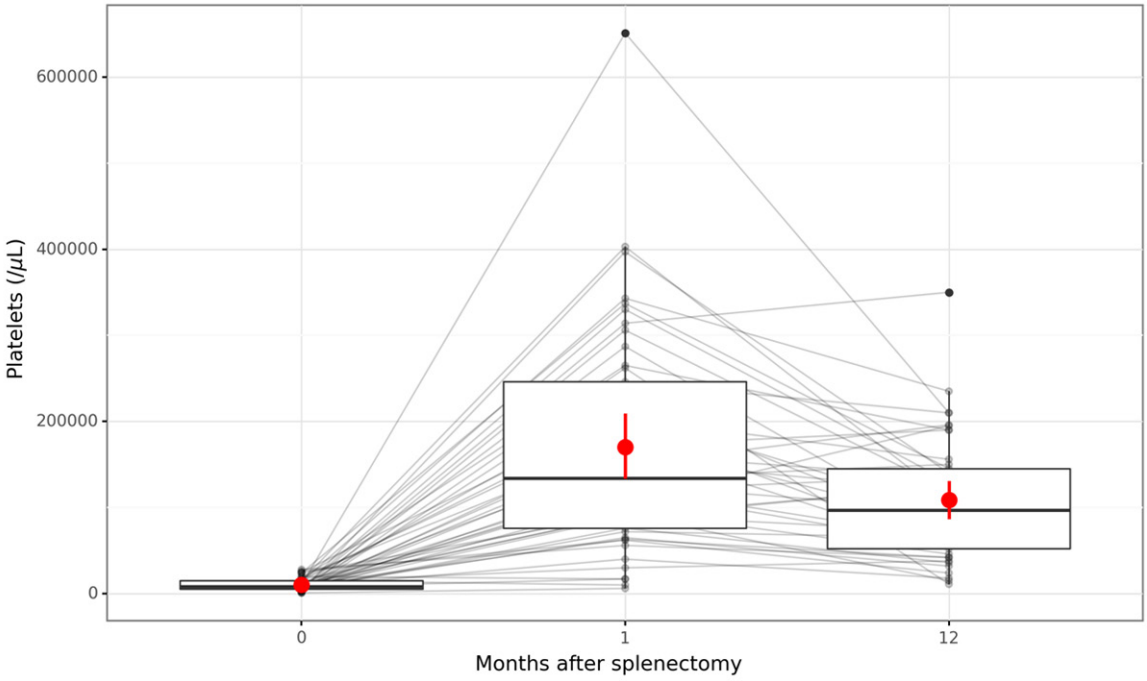

Figure 1. The figure shows the distribution of platelets (in/μL) at baseline, 1 month and 12 months post-splenectomy. The red dot represents the mean platelets and red line represents the 95% confidence interval.

higher number of therapies before splenectomy in our cohort (**Table 1**). Despite the variation in outcome, splenectomy gives the best possible long-term treatment-free remission amongst all the available second-line agents [7, 12, 13, 16]. It is also, one time therapy and one of the most financially affordable therapies [28].

We also noted that the number of ITP patients undergoing splenectomy has been on decline at our center during the study period. This is despite splenectomy being economical, providing a sustained response, and being recommended as second-line therapy in ITP [6, 7, 15, 28]. This declining trend for splenectomy in ITP is global and largely attributable to the availability of newer and more effective second-line therapies that have come up in the last couple of decades [15]. The patient preference for non-surgical treatment modalities is another major reason for reluctance for splenectomy in ITP.

We did not find any pre-surgery variable affecting the overall response rate after splenecto-

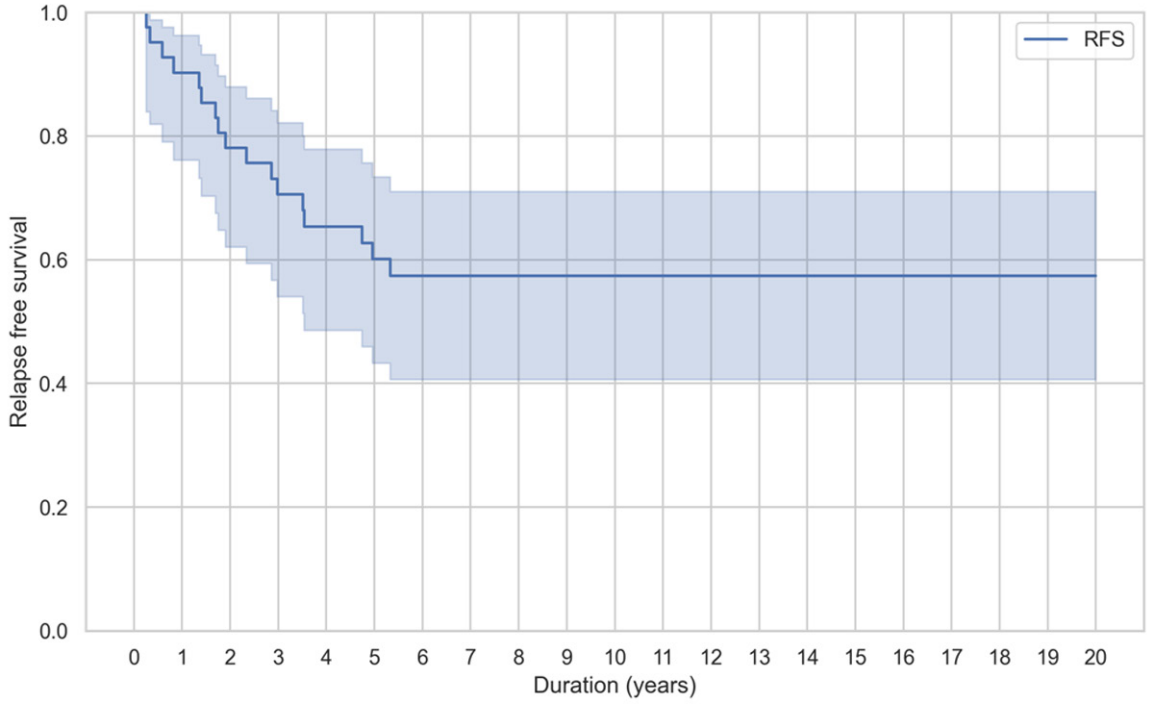

Figure 2. The figure shows relapse free survival in patients after undergoing splenectomy. The shaded interval represents 95% CI.

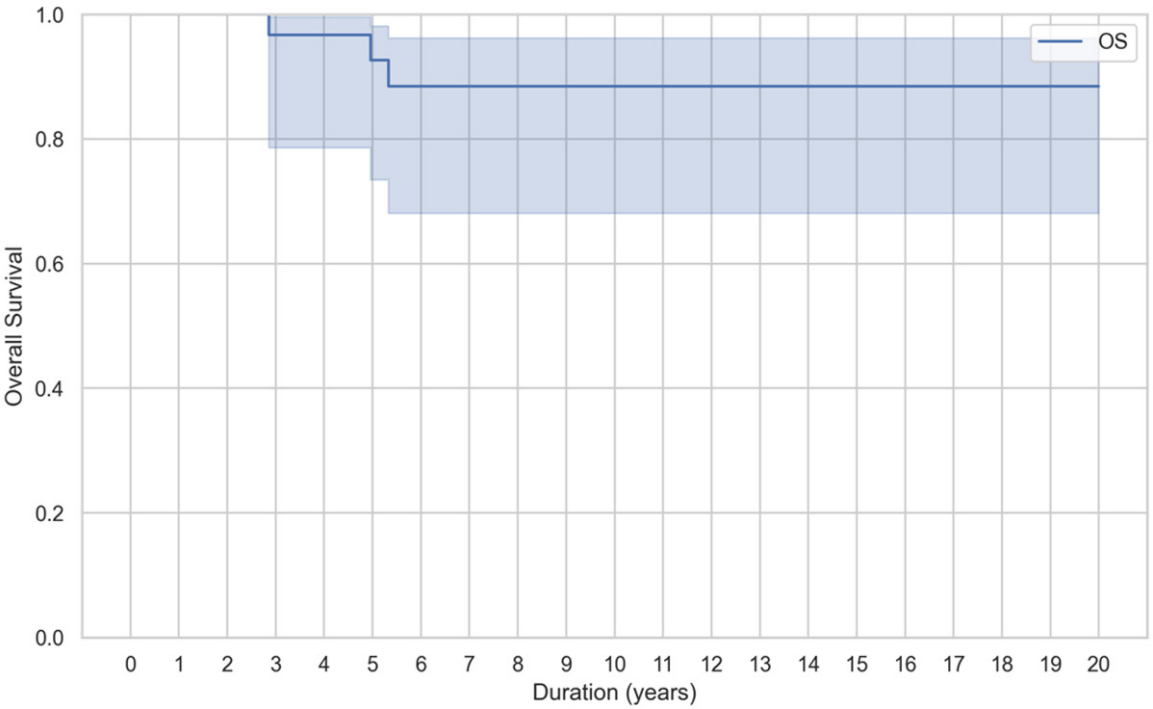

Figure 3. The figure shows the overall survival in patients after undergoing splenectomy. The shaded interval represents 95% CI.

my. Younger age at splenectomy has been reported as a pre-surgery variable, which predicts a better response after splenectomy [26]. However, in a large systematic review, none of

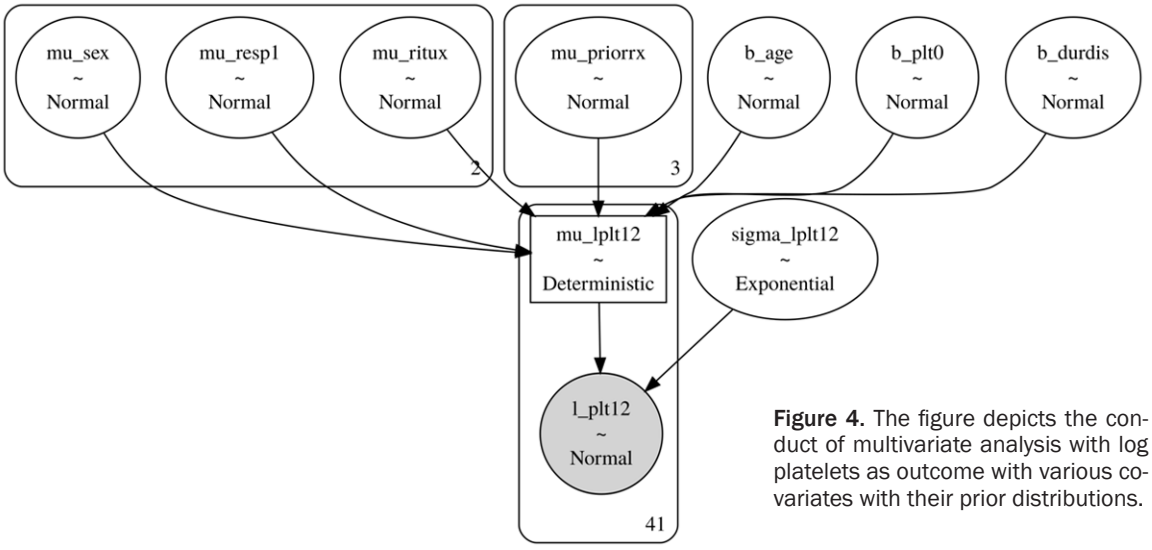

Figure 4. The figure depicts the conduct of multivariate analysis with log platelets as outcome with various covariates with their prior distributions.

Table 3. Univariate analysis for response assessment at day+30 after splenectomy

Variable	Mean effects of logit overall response rate (ORR)	94% credible interval
Standardised duration of disease	0.810	0.209-2.005
Standardised Age	-0.045	-0.931-0.860
	ORR	94% credible interval
Sex		
Male	83.2%	70-97.3
Female	91.9%	81.9-99.8
Prior treatment		
<3	88.3%	74.9-99.2
3	77.7%	60.7-95.5
>3	93.8%	82.8-100
Rituximab		
Yes	87.7%	76.9-96.9
No	88.4%	75.3-99.7

Table 4. Multivariate analysis for response assessment at day+30 after splenectomy

Variable	Mean effects of logit overall response rate (ORR)	94% credible interval
Standardised age	-0.014	-0.656-0.731
Standardised duration of disease	0.512	-0.451-1.406
Standardised baseline platelet	-0.144	-0.877-0.584
Sex (male:female)	-0.257	-1.310-0.684
Rituximab (yes:no)	-0.243	-1.258-0.791
Prior therapy		
three lines: <3 lines	0.305	-1.298-0.819
>3 lines: <3 lines	0.007	-1.270-1.171

the pre-surgery variables were found to be significantly affecting the post-splenectomy response [27]. Reports have been published regarding the possible role of splenic sequestration in pre-surgery response prediction [29]. However, not much significance was found in a systematic review [27]. The long-term platelet response or relapse-free survival was strongly

Table 5. Univariate analysis for platelet response at one-year after splenectomy (the variables in bold have significant effect on the outcome)

Variable	Mean platelets at 1-year	94% credible interval
Overall	82603/μL	62661-107646
Mean effect of logit platelet response rate at 1-year		
Standardised age	0.056	-0.05-0.163
Standardised duration of disease	-0.097	-0.203-0.003
Mean platelet count at 1-year (/μL)		
Sex		
Male	80352	56363-117760
Female	83368	60534-116949
Prior treatment		
<3	93540	65614-139315
3	112979	75857-170215
>3	51760	35563-76736
Rituximab		
Yes	61517	41879-95279
No	94188	68865-126182
Remission Status at one-month		
CR	112461	87096-141579
PR	42364	29922-63241

Table 6. Multivariate analysis for response assessment (log of platelet counts) at one-year after splenectomy

	Mean effect on log platelet counts at 1 year	94% Credible Interval
Standardised Age	0.029	-0.071-0.126
Standardised Duration of disease	-0.000	-0.113-0.123
Standardised baseline platelets	-0.017	-0.127-0.101
	Difference in mean of log platelet counts at 1 year (in multiplicative terms)	94% Credible Interval
Sex (Male:Female)	1.07	0.66-1.75
Rituximab (Yes:No)	0.78	0.45-1.36
Response at 1 month (CR:PR)	2.37	1.37-4.14
Prior treatment (3 cycles: <3 cycles)	1.10	0.63-1.88
Prior treatment (>3 cycles: <3 cycles)	0.93	0.47-1.95

predicted by a robust platelet response (CR) at day 30, lesser number of prior therapies, and lesser duration of disease in our study. These findings are consistent with previously published studies [15, 26, 28].

Overwhelming post-splenectomy sepsis (OPSI) was noted in five of our patients and two of them succumbed to infection. One patient died due to right middle cerebral artery thrombosis. During the median follow-up of 5.02 years (range 1 month-20 years), none of our patients developed venous thromboembolism (VTE). A decrease in life-threatening OPSI has resulted from routine pre-surgery vaccination. The reported rate of sepsis has been comparatively higher in the first 3 months after surgery, while it is comparable to non-splenectomized patients thereafter [30, 31]. Also, due to more awareness and better supportive care, the recovery rates following OPSI have improved. In two studies from Italy, among 612 patients who underwent splenectomy, there were no reported fatalities due to sepsis [32, 33]. Splenectomy has been reported as a risk factor for thrombosis [34-36]. A multifactorial mechanism has been proposed for the increased incidence of thrombosis in splenectomized patients. The

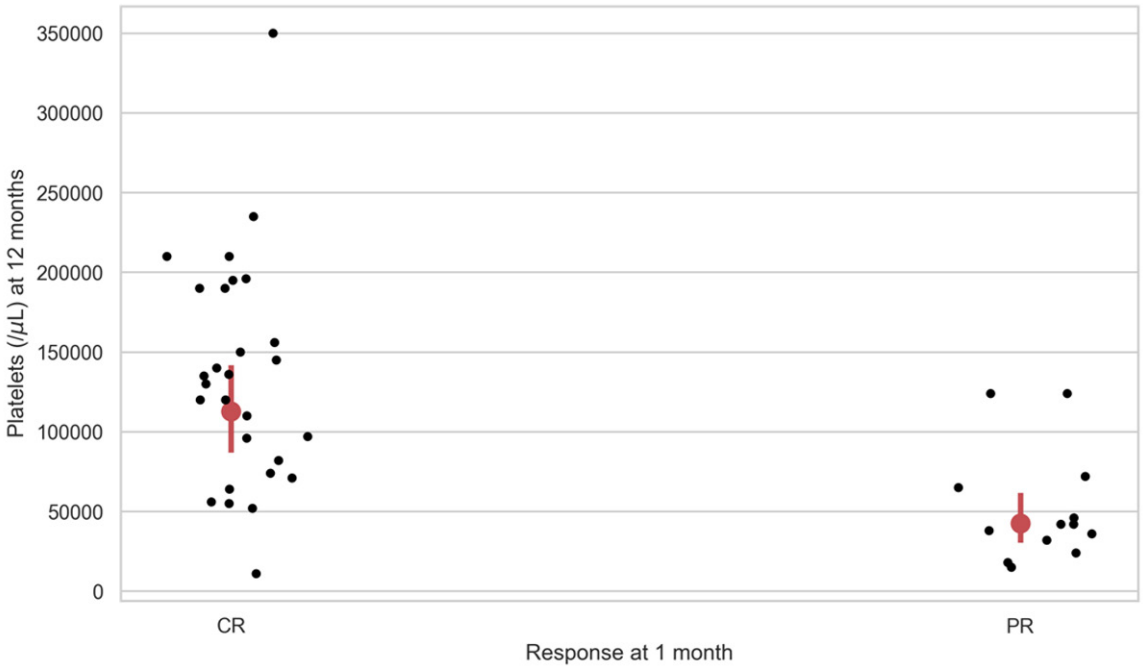

Figure 5. The figure shows the platelets at 12 months post-splenectomy in patients who achieved CR and PR after 1 month post splenectomy. The red point depicts the mean platelet count and the red line depicts the 94% credible interval.

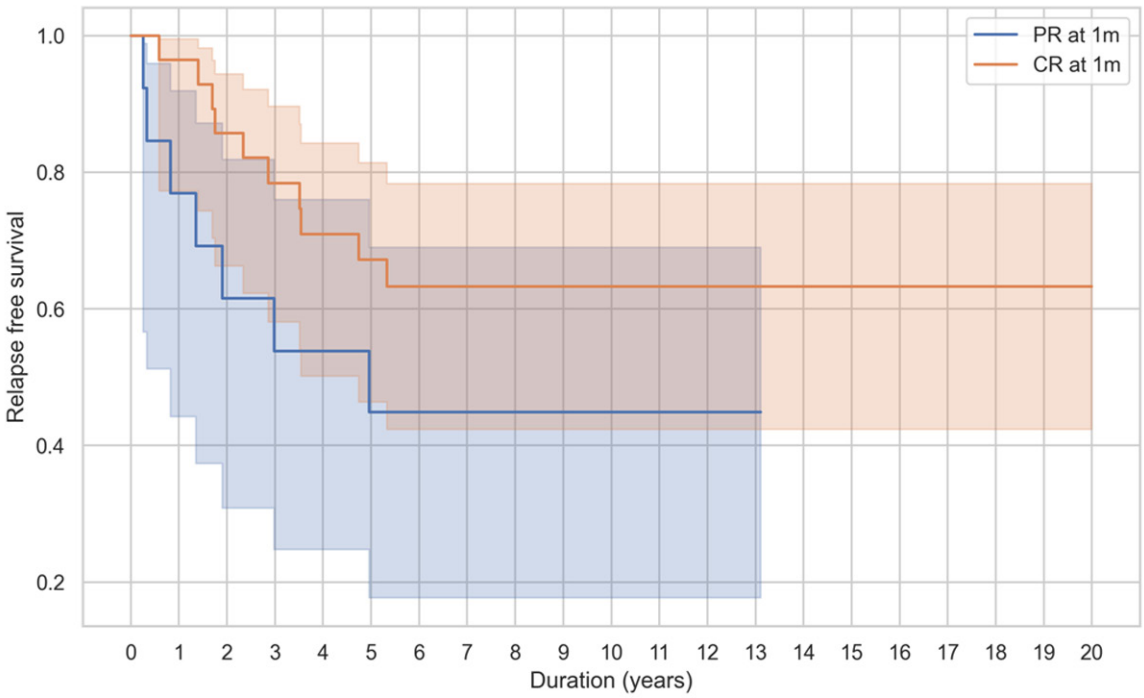

Figure 6. The figure shows the relapse free survival in patients who achieved CR and PR after 1 month post splenectomy. The shaded intervals represent 95% CI.

common pathogenetic mechanisms include persistent thrombocytosis, activation of endothelium, platelet activation, and changes in portal circulation [20, 30]. The incidence of venous thromboembolism (VTE) after splenectomy has been reported to be 10-16% [27, 35, 37].

However, consistent with our findings, a study with 109 ITP patients reported no incidence of VTE after long-term follow-up [26].

Our study had the limitations of retrospective analysis including missing data. However, we tried to minimize the missing data with best efforts. Though it has a small cohort of ITP patients, a long follow-up makes this study more informative.

At the time when splenectomy is on decline in ITP, our study is a timely reminder for the hematologists regarding importance of splenectomy. Despite long median follow up of 5 years (1 month-20 years), there were no evidence of statistically significant increase in mortality due to OPSI or thrombosis in our cohort. It adds to the growing evidence of long term safety of splenectomy in ITP patients. The EFS was 57.38% at 5 years confirming the effectiveness of the splenectomy. Moreover, our study fills the gap of data from developing country on efficacy and safety of splenectomy in ITP. This study highlighted that splenectomy is very good second line treatment in low to middle income countries where most of patients not affordable for TPO-agonists and unable to do regular follow up.

Conclusions

Splenectomy is effective second line therapy in the majority of the ITP patients. It is one time procedure, cost effective and still offers a long-term sustained response. With routine pre-procedural vaccination, advancement in sepsis management, and thrombosis care, it is also a safe option.

Disclosure of conflict of interest

None.

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