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Laparoscopic splenectomy for immune thrombocytopenia (ITP): long-term outcomes of a modern cohort

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Abstract

Background The advent of newer second-line medical therapies (SLMT) for immune thrombocytopenia (ITP) has contributed to decreased rates of splenectomy, following a trend to avoid or delay surgery. We aimed to characterize the long-term outcomes of laparoscopic splenectomy (LS) for ITP at our institution, examining differences in LS efficiency when performed before or after SLMTs.

Methods Adults with primary ITP who underwent LS between 2002 and 2016 were identified. Retrospective review of electronic medical records was supplemented with telephone interviews. Treatment response was defined according to current guidelines as complete responders (CR), responders (R), and non-responders (NR). Kaplan–Meier estimates assessed relapse-free rates, and predictors of long-term response were investigated using logistic regression.

Results 109 patients met inclusion criteria, from which 42% were treated with an SLMT before referral to LS. LS was completed in all cases, with no conversions or intraoperative complications. The perioperative morbidity was 7.3%, including 3 deep vein and 2 portal vein thrombosis, one reoperation for bleeding, and no mortalities. Splenectomy was initially effective in 99 patients (CR + R = 90.8%), and 10 patients were NR. At a median 62-month follow-up, 25 patients relapsed, resulting in a 68% CR + R rate. Proportion of CR + R was similar in patients who previously received SLMT and those who did not (61 vs. 76.7%, $p = 0.08$). CR + R patients were younger (45 vs. 53, $p = 0.03$), had higher preoperative platelet counts (36 vs. 19, $p = 0.01$), and experienced a higher increment in platelet counts during hospital stay (117 vs. 38, $p < 0.001$) as well as 30-days postoperatively (329 vs. 124, $p < 0.001$). Only a robust response in platelet count at 30-days postoperatively was independently associated with long-term response (OR 1.005, $p = 0.006$).

Conclusion LS was curative in 68% of patients, with no statistically significant difference when performed before or after SLMTs. Outcomes remain challenging to predict preoperatively, with only a robust increase in platelet counts on short term being associated with long-term response.

Keywords Splenectomy · Laparoscopic splenectomy · Immune thrombocytopenia · ITP

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by immunologically mediated platelet destruction in the reticuloendothelial system resulting in thrombocytopenia and a variable tendency towards bleeding [1–3]. Corticosteroids are universally considered to be the first-line therapy and are indicated in the presence or risk for bleeding (platelet counts below 30×10^9/L) [2, 3]. Although 50–75% of patients initially respond to steroids [4], relapses upon tapering or discontinuation of treatment are frequent. In this scenario, second-line therapies are indicated. Over the past several decades, splenectomy was the mainstay second-line treatment for ITP because (1) it is the only potentially curative option for ITP as the main site of

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platelet destruction is removed, (2) there is ample literature reporting sustained responses at long-term follow-up for over 60% of these patients [1–6], and (3) implementation of the laparoscopic platform has contributed to decreased morbidity of the procedure while conferring equivalent hematological outcomes when compared to open surgery [7–10].

Nevertheless, splenectomy has been less frequently performed for ITP [5] due to the emergence of new drugs such as anti-CD20 monoclonal antibodies (Rituximab) and thrombopoietin-receptor agonists (TPO-ras), which can be used as second-line modalities. The availability of such newer treatment options significantly influenced on second-line management of ITP, contributing to a tendency to avoid, or at least delay splenectomy. As such, the choice of a second-line therapy is now based on patient preference, lifestyle, potential side effects of each modality, and costs [1]. Consequently, modern cohorts are now evaluating the outcomes of splenectomy as a third-line therapy, or as a modality for ITP management on medically refractory patients.

We sought to investigate the long-term outcomes of laparoscopic splenectomy (LS) for primary ITP looking at our institutional, single-surgeon experience with a particular interest in (1) long-term relapse-free rates, (2) predictors of a sustained response after LS, (3) differences in hematological outcomes of LS when performed before or after treatment with medical second-line therapies, and (4) perioperative and long-term complications of LS.

Methods

Patient identification/inclusion criteria

Following Institutional Review Board (IRB) approval, all patients aged 18 or older, who have undergone LS for treatment of primary ITP performed by the senior author, from May 2002 through June 2016, were identified in a prospectively maintained database. Our analysis included all patients who had undergone surgery due to newly diagnosed (0–3 months duration), persistent (3–12 months of duration), or chronic ITP (> 12 months duration). Patients with secondary ITP (those associated with another autoimmune disease, HIV, HCV, or lymphoproliferative disorders) were excluded as the medical management in these instances is generally based on the underlying disorder [11]. Similarly, patients undergoing accessory splenectomy and those with presumed ITP whose ultimate splenic pathology revealed a non-ITP diagnosis were excluded from this analysis.

Data collection/assessment of response to splenectomy

Electronic medical records (EMR) were retrospectively reviewed to complement database information, and telephone interviews were performed to obtain long-term follow-up when necessary. Patient demographics, details regarding diagnosis and previous pharmacologic management of ITP, operative details, perioperative complications, length of stay, unplanned readmissions, reoperations, and 30-day mortality were recorded. Platelet counts were documented immediately before splenectomy, at the time of hospital discharge, during postoperative visits, and at the last follow-up available. Bleeding symptoms were characterized according to the International Working Group standardization [12]. Steroid dependence was defined as the need for ongoing or repeated administration of corticosteroids for more than 2 months in order to maintain a platelet count $> 30 \times 10^9$/L or to avoid bleeding. The lack of an increase in platelet counts despite a high-dose corticosteroid regimen was considered resistance. Toxicity is recognized when any patient-reported or diagnosed adverse event is determined to be related to steroid use and therefore results in modification or discontinuation of the steroid regimen.

Response to treatment is defined according to criteria of the International Working Group [13], endorsed by the American Society of Hematology guidelines [3]. Complete response (CR) is a platelet count higher than 100×10^9/L measured on 2 occasions, more than 7 days apart and in the absence of bleeding. A postoperative platelet count lower than 100×10^9/L measured more than a week apart yet still found to be twice as high as preoperatively, and still measured to be higher than 30×10^9/L in the absence of bleeding is defined as a response (R). No response (NR) is defined as a platelet count $< 30 \times 10^9$/L or less than a twofold increase in platelet count from baseline, or the presence of bleeding. Loss of CR occurred when the platelet count decreased to $< 100 \times 10^9$/L or the presence of bleeding. Similarly, a loss of R was defined as a platelet count drop to $< 30 \times 10^9$/L or the presence of bleeding.

Response to splenectomy was determined within 30 days after surgery and reassessed at the last available follow-up. Time to response was calculated as the period between the splenectomy date and achievement of either complete response (CR) or response (R). Duration of response was measured from the time of CR or R until loss of CR or R.

During telephone interviews, patients were queried regarding current or past bleeding symptoms, latest platelet counts, eventual current treatments for ITP, or splenectomy-related complications. Splenectomy-related

complications were defined as severe infection requiring hospitalization and diagnosed venous thromboembolic events, including portal vein thrombosis, deep vein thrombosis, and pulmonary embolism.

Statistical analysis

Data were described using mean and standard deviation, or median and interquartile ranges for continuous variables and counts and percentages for categorical variables. Comparisons on demographic information, preoperative variables, and short-term hematologic outcomes were performed among the group of complete responders and responders (CR + R) versus the group of non-responders and relapses during follow-up (NR + Relapses) using Chi-Square, Fischer's exact, and *t* tests. A multivariate logistic regression model was built to identify predictors of sustained CR or R on long-term follow-up, where all significant variables on univariate analysis were included in the model as identified confounding factors. Kaplan–Meier estimations were used to assess relapse-free survival rates. The analysis was performed on a complete case basis. All tests were two-tailed and performed at a significance level of 0.05. R.3.3.1 Software (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

Results

During the study period, 128 patients who underwent LS due to a preoperative diagnosis of ITP were identified. Nineteen patients were excluded from the analysis, as depicted in Fig. 1. Therefore, 109 patients remained for analysis and are detailed in Table 1.

The majority of our study population was female (60.5%) and Caucasian (78%). All patients were initially treated with steroids, of which 92 (84.4%) responded and 17 (15.6%) were considered to be refractory to steroids. Among the initial 92 responders, 85 (92.3%) relapsed after steroid taper and were considered steroid dependent. Forty-six patients (42.2%) had been treated with second-line therapies before being considered for splenectomy, with Rituximab (39.5%) and the TPO-ra Eltrombopag (8.25%) being the most frequently used medications. Seven patients in this series (6.4%) were treated sequentially with more than one second-line drug before undergoing splenectomy. Response to any second-line treatment was seen in 22 patients (47.8%), but over 95% of the responders relapsed upon treatment discontinuation and therefore were referred for splenectomy. For the entire cohort, the median duration of drug treatment until splenectomy was 13.7 months (IQR 4.8–41.2 months), and this duration was significantly longer in patients who were previously treated with second-line therapies when compared to those who were not (median 24.2 vs. 8.3 months, $p < 0.001$).

Thirty-day outcomes

The mean age at the time of surgery was 47.5 years (SD ± 20.5), and patients presented to surgery with a median platelet count of 33×10^9/L (IQR 14.5–65.5), thus reflecting platelet counts after a preoperative boost with steroids, IVIg, or both. LS was successfully performed in all cases. There were no conversions to open surgery nor any intraoperative complications in this cohort. Perioperative complications and 30-day outcomes are detailed in Tables 2 and 3. Patients were discharged home after a median 2 days (IQR2-3) length of stay. Perioperative complications were seen in 8 patients (7.3%) and are detailed in Table 2. One patient (0.9%) required reoperation on postoperative day 2 due to postoperative bleeding. Upon exploration, hemoperitoneum was evacuated, but no evidence of active bleeding was identified. This patient was refractory to all first-line treatments and had a platelet count of 9×10^9/L just prior to the operation, which might have contributed to this complication. Furthermore, this patient did not respond to splenectomy, was started on Romiplostim (TPO-ra) during the hospital stay, and was discharged on postoperative day 17 without other complications. The most frequent complications associated with this population were venous thromboembolic events (VTE), which comprised three deep vein thrombosis (diagnosed on postoperative days 12, 13, and 36) and two symptomatic portal vein thrombosis (diagnosed on postoperative days 7 and 9, respectively). Unplanned 30-day readmissions rate was 5.5%, and no 30-day mortality was seen in this cohort.

Median platelet count at the time of discharge was 156×10^9/L (IQR 65–227). Ninety-nine (90.8%) patients achieved a postoperative response at 30-days after surgery, of which 81 (74.3%) were CR and 18 (16.5%) revealed an R. Ten patients (9.2%) did not respond to splenectomy.

Long-term outcomes

Figure 2 represents the relapse-free survival rates postoperatively. After a median follow-up of 62 months (IQR 29–115), 74 of the 99 patients sustained their initial response in the long-term, accounting for a 67.9% (74/109) response rate among the entire cohort (Table 3). Twenty-five (25.25%) initial responders relapsed during follow-up. This patient population included 17.3% of initial complete responders (14 of 81 patients) and 61.1% of responders (11 of 18 patients). Over 90% of the relapses (23 patients) occurred within the first 2 years of the surgery, 19 of which were diagnosed within the first year. Only two patients relapsed more than 2 years after splenectomy (39 and 109 months, respectively). Table 4 details the comparisons on short- and

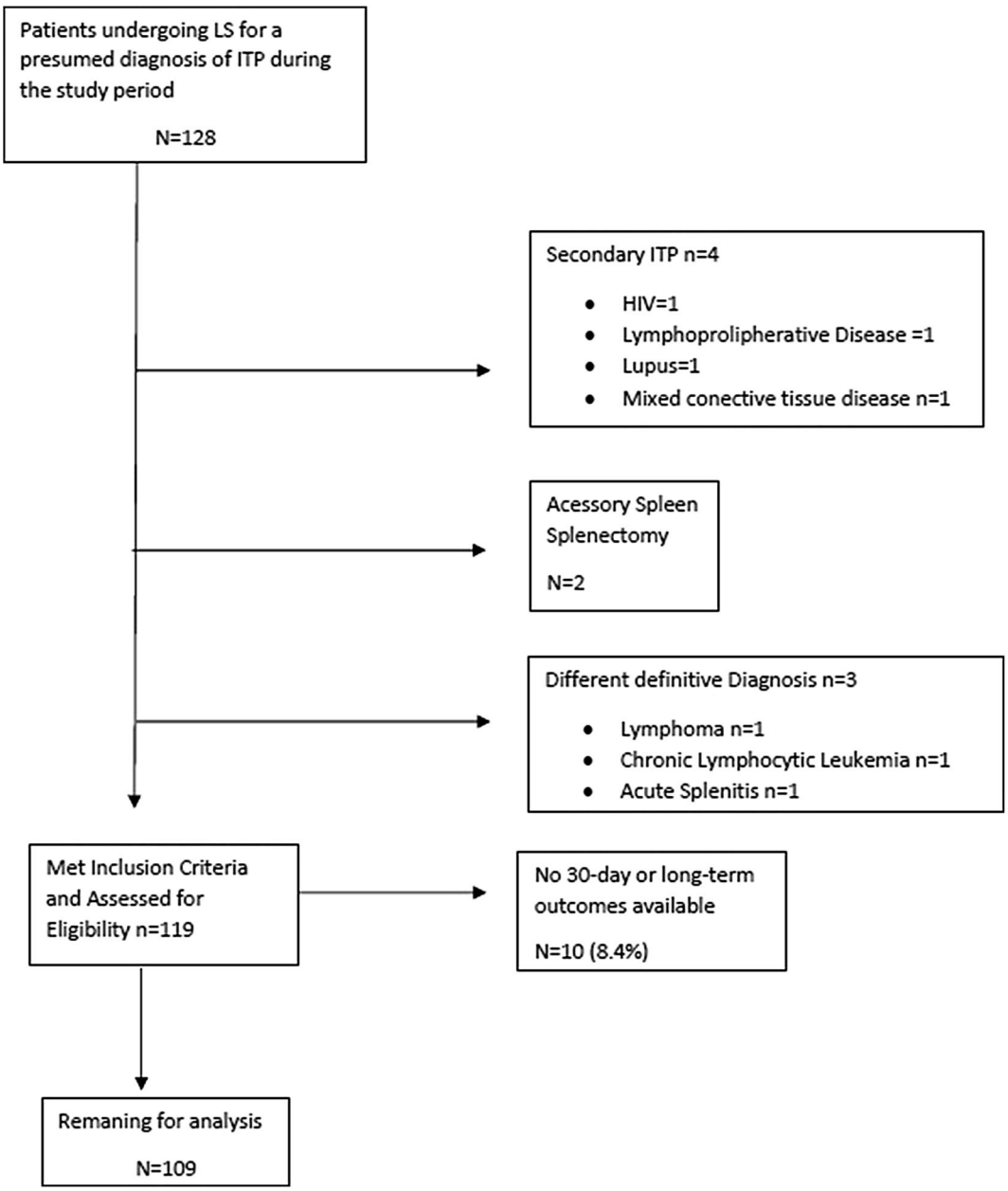

Fig. 1 Study population

long-term hematological outcomes between patients who were previously treated with medical second-line therapies (PSLT) and those who were not (No PSLT). On long-term follow-up, no statistically significant difference in the proportion or CR + R between groups was seen (PSLT 61% vs. No PSLT 76.7%, $p = 0.08$). With regards to long-term complications, one patient (0.91%) experienced post-splenectomy sepsis 4 years after the operation, that was complicated by septic shock leading to a prolonged ICU stay. No other venous thromboembolic events were detected during long-term follow-up. One of the non-responders died 3 months after surgery as a consequence of intracranial hemorrhage in the setting of refractory ITP.

Predictors of sustained complete response or response

On univariate analysis (Table 1), patients who sustained long-term CR or R were younger (44.7 years ± 20.6 vs. 53.4 years ± 19.5, $p = 0.037$), had higher preoperative platelet counts (36.5×10^9/L vs. 19×10^9/L, $p = 0.01$), and had higher platelet counts upon hospital discharge (169×10^9/L

Table 1 Univariate comparisons and demographic, clinical, and outcomes information

	Total	CR + R	NR + Relapses	*P* value
N	109	74	35	
Age at splenectomy, years, mean (± SD)	47.5 (± 20.5)	44.7 (± 20.6)	53.4 (± 19.5)	**0.037**
Gender *n* (%)				0.77
Female	66 (60.5)	46 (62.2)	20 (57.1)	
Male	43 (39.4)	28 (37.8)	15 (42.9)	
Ethnicity/Race, *n* (%)				0.11
Caucasian	85 (78)	56 (75.8)	29 (82.9)	
African American	12 (11)	6 (8.1)	6 (17.1)	
Other	12 (11)	12 (100)	0	
Platelet count at diagnosis, $\times 10^9$/L—median [IQR]	10 [4–24]	10 [4–25]	10.5 [4–20]	0.90
Previous Bleeding Symptoms, *n* (%)	72 (66)	48 (64.86)	24 (68.57)	0.87
Steroid dependents, *n* (%)	85 (78)	56 (89)	29 (100)	0.093
Steroids refractory, *n* (%)	17 (15.6)	11 (14.9)	6 (17.1)	0.98
Toxicity to Steroids, *n* (%)	33 (30.3)	20 (27)	13 (37.1)	0.40
Previous Second-Line treatments, *n* (%)	46 (42.2)	28 (37.8)	18 (51.4)	0.26
Rituximab	43 (39.5)	27 (96.4)	16 (88.9)	0.55
Eltrombopag	9 (8.25)	4 (14.3)	5 (27.8)	0.28
Romiplostim	1 (0.91)	0	1 (5.6)	0.39
Response to 2nd-line therapies, *n* (%)	22 (47.8)	14 (50)	8 (44.5)	0.95
Relapse after 2nd-line therapies, *n* (%)	21 (95.4)	13 (92.9)	8 (100)	> 0.99
Toxicity to 2nd-line therapies, *n* (%)	3 (6.5)	1 (3.6)	2 (11.1)	0.55
Duration of medical treatment until splenectomy, months, median [IQR]	13.7 [4.8–41.2]	11.9 [4.8–37.9]	14.8 [6.8–40.3]	0.69
Preoperative platelet count, $\times 10^9$/L—median, [IQR]	33 [14.5–65.5]	36.5 [23.25–77.5]	19 [6.5–47]	0.010
Platelet count at discharge, $\times 10^9$/L—median, [IQR]	156 [65–227]	169 [135.5–245.2]	65 [33–146]	< 0.001
Platelet count on 30 day follow-up, $\times 10^9$/L—median, [IQR]	259 [88–493]	339 [184–535]	84 [27–227]	< 0.001
In-hospital platelet count increase, $\times 10^9$/L— median, [IQR]	98 [35–161]	117 [61–186]	38 [3.5–99.5]	< 0.001
Postoperative platelet increase[a], $\times 10^9$/L—median, [IQR]	215 [65–430]	329 [277–381]	124 [78–180]	< 0.001
Time to achieve response (days)[b]	12 [7–18]	11 [7–17]	13 [10–18]	0.14
Spleen weight, grams, mean, (± SD)	186 ± 111	195.5 ± 122.5	168.5 ± 81.7	0.17

CR complete response, *R* response, *NR* no response

[a]Postoperative platelet increase (platelet count at 30 days—preoperative platelet count)

[b]From splenectomy until response

Table 2 Perioperative complications

Perioperative complications, *n* (%)	8 (7.3)
Deep vein thrombosis	3 (2.7)
Portal vein thrombosis	2 (1.8)
Bleeding	1 (0.9)
Pneumonia	1 (0.9)
Bacteremia	1 (0.9)
30-day unplanned readmissions	6 (5.5)
VTE[a]	5
Fever/bacteremia	1
30-day unplanned reoperations[b]	1
30-day mortality	0

[a]Venous thromboembolic event

[b]30-day unplanned reoperations

Table 3 Long-term outcomes—response to splenectomy

	30-days *n* (%)	Last follow-up *n* (%)
Complete response or response (CR + R)	99/109 (90.8)	74/109 (67.8)[a]
No response (NR)	10/109 (9.17)	10/109 (9.17)
Relapses	–	25/99 (25.25)

[a]Five patients turned from responders to complete responders during follow-up

vs. 65×10^9/L, $p < 0.001$) and at first follow-up (339×10^9/L vs. 84×10^9/L, $p < 0.001$), thus reflecting a more pronounced increment in platelet counts after splenectomy in the short term. There were no other significant differences on univariate analysis between groups. On multivariate analysis

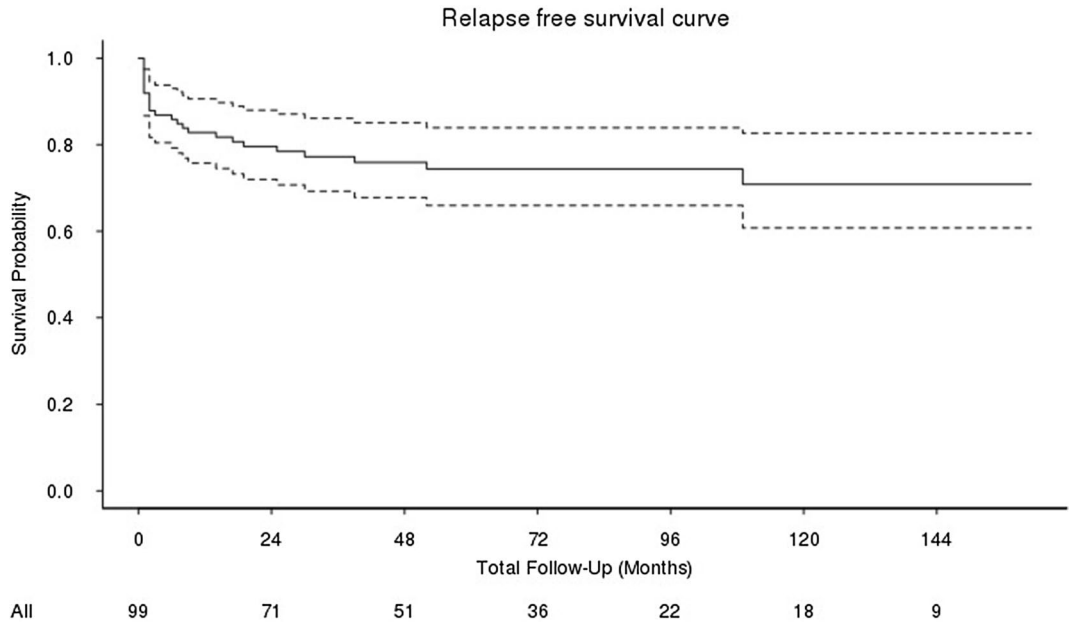

Fig. 2 Relapse-free survival plot of 99 patients who achieved complete response or response following surgery

Table 4 Hematological outcomes: LS after prior second-line therapies (PSLT) vs. LS without prior second-line therapies (No PSLT)

	30-day CR + R, *n* (%)	*p* value	Last follow-up CR + R, *n* (%)	*p* value
PSLT[a] *n* = 46 (42.2%)	39 (84.8)	0.061	28 (61)	0.08
No PSLT[b] *n* = 63 (57.8%)	60 (95.2)		46 (76.7)	

[a]PSLT median follow-up: 48 months (IQR 29–78)

[b]No PSLT median follow-up: 76 months (29–121)

Table 5 Multivariate logistic regression results

Variable	Odds ratios	95% CI	*p* value
Age	0.991	(0.968–1.014)	0.438
Preoperative platelet count[a]	1.008	(0.997–1.022)	0.202
In-hospital platelet count increase[a]	1.003	(0.997–1.012)	0.385
Postoperative platelet count increase[a]	1.005	(1.0016–1.0085)	0.006

[a]Odds ratios presented per unit of platelet count $\times 10^9$/L

(Table 5), only the degree of postoperative platelet count increase was independently associated with sustained complete response or response on long-term follow-up (OR 1.005—95% CI 1.0016, 1.0085, $p < 0.01$)—(OR presented per unit of platelet count $\times 10^9$/L).

Discussion

In this study we present our 15-year, single-surgeon institutional experience with LS for primary ITP. After a median 62-month follow-up, essentially two-thirds (68%) of the patients experienced a sustained response and were treatment-free. With overall low morbidity and no mortality, we found that LS remains an effective second-line therapy for ITP, with similar hematological outcomes when performed before or after treatment with current second-line drug regimens such as Rituximab or TPO-ras. However, despite results that cannot be matched with any other therapy, splenectomy seems to have fallen out of favor to newer treatment modalities. Presumably, this change is due to the concerns about surgical intervention and hematologic outcomes which have been difficult to predict preoperatively. In our study, only a short-term increase in platelet counts after

splenectomy was independently associated with long-term sustained response.

The laparoscopic platform has been successfully implemented to splenectomy, contributing to decreased morbidity, shorter length of hospital stay, and faster recovery while conferring equivalent hematologic outcomes when compared to open surgery [10]. Ahad et al. [14] compared open and LS using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) and found that open surgery had a longer length of hospital stay (3 vs. 6 days, $p < 0.001$) and was independently associated with increased odds for serious complications (OR 1.95) and overall morbidity (OR 1.76) after adjusting for identified confounding factors on patient demographic and clinical characteristics. Pooled data from 51 studies in a systematic review published by Winslow and Brunt [15] found that the laparoscopic approach was associated with shorter length of stay, fewer pulmonary, wound, and infectious complications when compared to open surgery. Indeed, in our study, LS was performed uneventfully in all cases with a 7.3% overall morbidity rate. As compared to nationwide NSQIP data [14], this is a lower rate (12%) but types and frequency of complications are similar, with VTEs (3%), pneumonia (2.1%), and bleeding requiring transfusion (2.8%) being the most frequent complications. Nevertheless, our data are representative of a single surgeon with extensive experience in LS, and additionally, our case series is limited to splenectomies for ITP where spleen size is usually small, facilitating the operation and patient recovery.

Although LS is a safe procedure with low morbidity as reinforced by our data, surgery carries an inherent risk for perioperative complications and spleen removal results in a life-long risk for infectious complications which is increased from one- to three-fold [1]. As such, all patients should receive preoperative vaccines for encapsulated bacteria. All patients in this study received vaccinations according to institutional protocols. Although vaccination protocols have changed during the study period, our current institutional recommendation is for all patients to receive vaccination at least 2 weeks prior to the operation. The scheme includes quadrivalent coverage for Neisseria meningitidis (Menveo®, GSK Vaccines, Srl, Sovicille, Italy), Haemophilus influenzae b (Act-HIB®, Sanofi Pasteur SA, France), and Streptococcus pneumoniae (Prevnar 13®, Pfizer, Philadelphia, PA). Boosters are administered at 2 months and 5 years postoperatively. In the rare instances where splenectomy is performed emergently for ITP, patients are vaccinated immediately prior to the operation and 2 months postoperatively. A particularly important factor is the increased risk for venous thromboembolic events. In our study, five patients developed VTEs. Other studies have demonstrated that the risk for portal or splenic vein thrombosis after splenectomy is estimated to be 0.1–4/100 patient-years [1]. In a study by Thai et al. [16], ITP patients who underwent splenectomy had a 16% VTE rate when compared to a 2% rate on a matched cohort that was not treated with surgery. In the same study, splenectomy was shown to be an independent risk factor for VTE (HR 4.0). The occurrence of post-splenectomy thromboembolic events has been well documented, and a multitude of factors are deemed to contribute for such increased risk, namely, hypercoagulability, platelet activation, disturbance of the endothelium, and changes in portal circulation flow [17, 18]. Another factor that might play a role in such complications is the occurrence of reactive thrombocytosis after the operation. Although extreme platelet counts can be seen after splenectomy, this is a rare occurrence in ITP patients. In addition, none of the patients who experienced a thrombotic complication had abnormally high platelet counts at time of diagnosis. In our cohort, there were three patients whom their platelet counts during 30-day follow-up were noted to be twice higher than the upper limit ($\geq 800 \times 10^9$/L). For such patients, no intervention was necessary, with platelet counts normalizing on further assessments. Nevertheless, the use of anti-aggregation agents and platelets apheresis in the management of uncontrolled reactive thrombocytosis was previously described [19]. Our current protocol for prophylaxis of VTE includes a combination of mechanical and pharmacological measures. Sequential compression devices are used both intra- and postoperatively during the entire hospital stay. Patients are started on a prophylactic dose of low molecular weight heparin (Enoxaparin sodium injection, Lovenox®, Sanofi-Aventis, Bridgewater, NJ) upon arrival to the floor and this is continued until hospital discharge. Patients are educated about clinical signs of VTEs and encouraged to return promptly to our institution if any symptoms arise. No other agents are used for prevention of VTE's unless clinically indicated.

Despite significant heterogeneity in the criteria used to define response in the published literature, short and long-term response rates of splenectomy for ITP remain consistent over time and our long-term results are in concordance with previously published data. With the standardization of response criteria proposed by the International Working Group [13], comparisons between studies have become more reliable. Table 6 summarizes case series [20–28] reporting hematologic outcomes of LS for ITP using such response criteria.

Also consistently shown in the literature is the fact that hematologic outcomes of laparoscopic splenectomy are hard to predict preoperatively. Several studies have examined potential predictive factors of complete response and response after splenectomy [21, 23–25, 27, 29–32] and the majority of the studies report that only younger age, higher preoperative platelet counts, and higher postoperative platelet counts are the factors associated with long-term sustained response. Our results on multivariate analysis also match

Table 6 Case series of Laparoscopic splenectomy for immune thrombocytopenia reporting response rates according to the response criteria of the International Working Group [13]

Author (year)	Surgical approach	Number of patients	Complete response (CR)	Response (R)	No response (NR)	Relapse	Relapse-free survival	Follow-up, months
Gonzalez Porras et al. (2013) [20]	LS, OS	218	176 (80.7%)	18 (8.3%)	24 (11%)	70 (32.6%)	124 (56.9%)	85/62 (median)
Wang et al. (2013) [21]	LS	92	49 (53.3%)	21 (22.8%)	8 (8.7%)	14 (15.2%)	70 (76.1%)	21 (median)
Montalvo et al. (2014) [22]	LS	150	133 (88.7%)	4 (2.7%)	2 (8.7%)	NR	137 (91.3%)	12[a]
Rijcken et al. (2014) [23]	LS	72	56 (77.7%)	7 (9.7%)	9 (12.5%)	19 (30.2%)	44 (61.1%)	32 (median)
Navez et al. (2015) [24]	LS	82	58 (70.7%)	20 (24.4%)	3 (4%)	6 (7.3%)	72 (87.8%)	57 (median)
Ahmed et al. (2016) [25]	LS, OS	254[b]	189 (74.4%)	40 (15.8%)	25 (9.8%)	51 (20.1%)	178 (70.1%)	54 (median)
Xu et al. (2016) [26]	LS	114	30 (26.3%)	57 (50%)	27 (23.7%)	10 (8.8%)	77 (68%)	NR
Guan et al. (2016) [27]	OS	174	101 (58%)	21 (12.1%)	20 (11.5%)	32 (20.8%)	122 (70.1%)	100 (median)
Tada et al. (2018) [28]	LS, OS	32	26 (81.2%)[c]	NR	6 (18.7%)	4 (12.5%)	22 (68.7%)	183/92 (mean)

LS laparoscopic splenectomy, *OS* open splenectomy

[a]Assessment at 1-year after splenectomy

[b]167 adults and 87 children

[c]CR and R reported combined

the findings of these studies. Ultimately, our study confirms the findings of previously published literature where initial platelet count response after surgery is a consistent predictive factor of splenectomy success on long-term [21, 23, 30–32].

Importantly, over 40% of the present cohort was previously treated with second-line therapies before being considered for splenectomy. The total median duration of drug treatment for 24 months confirms the current trend to attempt other second-line therapies upon steroid failure. The advent of Rituximab and more recently the TPO-ras has provided patients and physicians the opportunity of continuing ITP treatment without surgical intervention. This has led to a significant decrease in the number of splenectomies performed for ITP, especially in the United States and Europe, where access to second-line therapies is wider. Currently, it is estimated that only 25% of these patients are referred for splenectomy as the next step in management upon failing to attain a sustained response to steroids. This is a significant decrease in splenectomy rates from the 50–60% noted in previous data [10]. In addition to medical alternatives, a multitude of factors are responsible for the decrease in splenectomy rates, including patient preference, reluctance to undergo removal of a healthy organ, fear of surgical complications, and the possibility to avoid surgery with second-line therapies without affecting curative response rates if surgery is employed in the future [5].

There has been an increasing number of publications reporting the outcomes of Rituximab and TPO-ras as second-line therapies for ITP. Rituximab was shown to induce response in 40–60% of patients, but with response waning over time with only 21–26% of patients remaining disease-free at 5-years [33, 34]. Initial response rates with TPO-ras (defined as achieving a platelet count $\geq 50 \times 10^9$/L) ranged from 59 to 79% with Eltrombopag [34–36], and 38–92% with Romiplostim [34, 37, 38] have been reported. On long-term follow-up (≥ 3 years), Eltrombopag was shown to maintain a platelet count $\geq 50 \times 10^9$/L in 62% of patients receiving daily oral doses of the medication [34, 39]. Longer-term outcomes of the EXTEND study were recently published [40] and the median duration of Eltrombopag treatment was 2.37 years. 42% of these patients continuously treated with oral daily doses of the medication could sustain a platelet count $\geq 50 \times 10^9$/L in at least 75% of on-treatment assessments. An 8% rate of thromboembolic events was also reported. With respect to Romiplostim, weekly injections were reported to maintain platelet counts $\geq 50 \times 10^9$/L in all patients in a median of 92% of office-visit assessments [38].

Ultimately, similar to splenectomy, all second-line modalities in the management of ITP have inherent advantages and drawbacks. Drawbacks of splenectomy are mainly the intrinsic life-long increased risk of infection and thrombotic events and difficulty to predict response preoperatively. While Rituximab and TPO-ras provide the opportunity to delay or even to avoid surgery, it should be noted that response with TPO-ras relies on continuous administration and, with the exception of Rituximab (21–26% response at 5-years), none of these drugs have curative intent. Furthermore, one of the major shortcomings of such medical second-line therapies is the high cost. Treatment with TPO-ras is estimated to cost $2500–$4000 per month and each 4-infusion course of Rituximab is estimated to cost $50,000 [10], highly limiting its use in developing countries and rendering its widespread adoption difficult. Additionally, the need for ongoing treatment, monthly monitoring of blood counts and liver enzymes, and annual bone marrow and ophthalmologic exams are factors to influence the shared patient–physician decision-making process and favoring splenectomy.

Our study has several limitations that deserve mention. First and foremost, although all data corresponding to surgical outcomes were gathered prospectively, our study is retrospective in nature as data on prior treatments and follow-up information was abstracted retrospectively from electronic medical records and through telephone interviews. Therefore, our study is prone to all inherent biases of a retrospective study. Second, our data are limited to single-institution, single-surgeon experience, and therefore our surgical and long-term outcomes might not be applicable to the general population. While our findings report no statistically significant difference in long-term success rates between patients who underwent splenectomy as either second-line therapy or as third-line therapy, the lack of statistical difference might be due to power since there were fewer patients who were treated with second-line therapies before splenectomy. Additionally, as all patients in this study underwent splenectomy, we cannot assess superiority or inferiority of splenectomy related to hematological outcomes since our study lacks a comparative group of non-splenectomized patients treated with other second-line therapies, in order to determine response to such medications. Specifically, we were unable to assess the proportion of these medically managed patients who experienced spontaneous disease resolution over time and in whom splenectomy would not have been beneficial. Therefore, we are not able to draw any conclusions and it is not our intent to demonstrate the superiority of splenectomy vs. medical second-line therapies. More important, there is a lack of prospective studies directly comparing splenectomy to other second-line treatments. Instead, we feel strongly that further studies are needed to assess the overall value of LS vs. Rituximab or continuous medical treatment with TPO-ras.

Conclusion

In experienced hands, LS for ITP remains an effective treatment modality for ITP with a potential for a cure of the disease for up to 68% of patients. The efficiency of LS was similar when used before or after treatment with medical second-line therapies. While LS is safe and effective, outcomes remain challenging to predict preoperatively. Further prospective studies assessing the value of splenectomy vs. medical second-line therapies are necessary to determine an optimal approach for ITP upon steroids failure.

Compliance with ethical standards

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