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SURGICAL ENDOSCOPY
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Predictive factors for successful laparoscopic splenectomy in immune thrombocytopenic purpura

Study of clinical and laboratory data

C. Balagué,[1] S. Vela,[1] E. M. Targarona,[1] I. J. Gich,[2] E. Muñiz,[3] A. D'Ambra,[1] A. Pey,[1] V. Monllau,[1] E. Ascaso,[1] C. Martinez,[1] J. Garriga,[1] M. Trias[1]

[1] Service of Surgery, Hospital de Sant Pau, C/Padre Claret 167, 08025, Barcelona, Spain
[2] Service of Epidemiology, Hospital de Sant Pau, C/Padre Claret 167, 08025, Barcelona, Spain
[3] Service of Haemathology, Hospital de Sant Pau, C/Padre Claret 167, 08025, Barcelona, Spain

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Abstract
Background: Laparoscopic splenectomy (LS) offers better short-term results than open surgery for the treatment of immune thrombocytopenic purpura (ITP), but long-term follow-up is required to ensure its efficacy. The remission rate after splenectomy ranges from 49 to 86% and the factors that predict a successful response to surgical management have not been clearly defined. The goal of this study was to determine the preoperative factors that predict a successful outcome following LS.
Methods: From February 1993 to December 2003, LS was consecutively performed in a series of 119 nonselected patients diagnosed with ITP (34 men and 85 women; mean age, 41 years), and clinical results were prospectively recorded. Postoperative follow-up was based on clinical records, follow-up data provided by the referring hematologist, and a phone interview with the patient and/or relative. Univariate and multivariate analyses were performed for clinical preoperative variables to identify predictive factors of success following LS.
Results: Over a mean period of 33 months, 103 patients (84%) were available for follow-up with a remission rate of 89% (92 patients, 77 with complete remission with platelet count $>150{,}000$). Eleven patients did not respond to surgery (platelet count $<50{,}000$). Mortality during follow-up was 2.5% (two cases not related to hematological pathology and one case without response to splenectomy). Preoperative clinical variables evaluated to identify predictive factors of response to surgery were sex, age, treatment (corticoids alone or associated with Ig or chemotherapy), other immune pathology, duration of disease, and preoperative platelet count. In a subgroup of 52 patients, we also evaluated the type of autoantibodies and corticoid doses required to maintain a platelet count $>50{,}000$. Multivariate analysis showed that none of the variables evaluated could be considered as predictive factors of response to LS due to the high standard error.
Conclusion: Long-term clinical results show that LS is a safe and effective therapy for ITP. However, a higher number of nonresponders is needed to determine which variables predict response to LS for ITP.

Key words: Laparoscopic splenectomy — ITP — platelet count

Correspondence to: C. Balagué

Immune thrombocytopenic purpura (ITP) is the most common and well studied of the benign hematologic diseases, with an estimated incidence of 4.5 per 100,000 for men and 7.4 per 100,000 for women [9]. It is a disorder of immune regulation entailing accelerated phagocytosis of platelets by the reticuloendothelial system [8]. The spleen is the primary site of platelet destruction and anti-platelet antibody production. ITP may be treated with one of several immune-modulating agents, with varying degrees of success. The mainstay of medical therapy is bolus corticosteroids followed by a tapering dose. However, because few chronic ITP patients achieve remission with medical therapy (only 20–25% in adults), splenectomy is the main treatment. Historically, there has been a 49–86% successful remission rate after splenectomy. However, there is no definitive evidence concerning the optimal timing for splenectomy [1, 9]. Many investigators have documented variables that may predict a successful response to splenectomy for ITP, which include younger age [8, 9], successful response to preoperative steroids [20], a

Table 1. Univariate analysis of 103 patients related to response to splenectomy

	All patients	Responders	Nonresponders	*p* value
N	103	92	11	—
Age				
< 45 yr	63	58	5	
> 45 yr	40	34	6	0.330
Female/male	73/30	65/27	8/3	0.886
Associated immune pathology				
No	94	83	11	
Yes	9	9	0	0.592
Duration of disease (mo)	50 ± 56	50 ± 58	46 ± 46	0.992
Medical treatment (n = 94)				
Steroids	67	61	6	
Steroids + other	27	22	5	0.285
Preoperative platelet count				
< 20,000	16	12	4	
> 20,000	87	80	7	0.066

shorter interval from diagnosis to splenectomy [34], splenic sequestration, response to intravenous IgG, and preoperative platelet counts [8].

Since the first laparoscopic splenectomy (LS) was reported in 1992 [6], there has been renewed interest in managing hematologic disorders with minimally invasive surgical techniques [19, 30]. Laparoscopic splenectomy is less painful, requires a shorter hospital stay, allows a faster return to full activity, and provides superior cosmesis compared to open techniques [32, 37]. However, long-term follow-up is required to confirm its efficacy in ITP. To date, few large series of LS for ITP have been reported. This study seeks to determine the preoperative factors that predict a successful outcome following LS.

Materials and methods

From February 1993 to December 2003, 260 LSs were consecutively performed at two university hospitals by the same surgical team for various hematologic diseases, including ITP, and data were collected prospectively. A series of 119 consecutive patients (34 men and 85 women, with a mean age of 41 years) underwent LS for ITP. Inclusion criteria for the diagnosis of ITP were platelet count less than 100×10^9/L for at least 6 months, normal or increased number of megakaryocytes at bone marrow examination, no medications known to cause thrombocytopenia, increased splenic sequestration, and no other associated benign or malignant diseases that could have induced thrombocytopenia.

Indications for LS included patients who no longer responded to glucocorticoid therapy and who required glucocorticoid therapy 10-15 mg/day to maintain platelet counts over $30 \times 10^3/\mu l$.

Long-term postoperative follow-up evaluation was obtained from clinical records, the referring hematologist follow-up visits, and phone interviews with both the patients and the referring hematologist. ITP remission was defined as complete remission (CR) when platelet count increased to $> 150 \times 10^9$/L, partial remission (PR) when it was 50–150 $\times 10^9$/L, or absent if otherwise.

Clinical data concerning age (younger or older than 45 years), sex, associated immune pathology, duration of disease, medical treatment (steroids alone vs steroids associated with other treatments), and preoperative platelet count (above or below 20,000 platelets) were analyzed as predictive factors of success by univariate and multivariate analysis.

In a subgroup of 52 patients, data were also obtained concerning the type of autoantibodies, clinical presentation, doses of steroids required to reach platelet counts > 50,000, and duration of steroid treatment. These data, together with those for the global group, were also analyzed as predictive factors of success by univariate and multivariate analysis.

Statistical analysis

The results are given as number of cases and percentage for categorical data and as mean and standard deviation for quantitative data. The relationship between the variables was evaluated initially by univariate analysis, contingency table, and chi-square or Fisher's exact test for categorical data and *t*-test for quantitative data. According to the results of the first analysis, the multivariate approach using logistic regression analysis with the forward stepwise method and likelihood ratio was then employed.

The variables used in the process were age (younger or older than 45 years), sex, associated immune pathology, duration of disease, medical treatment (steroids alone vs steroids associated with other treatments), preoperative platelet count (below or above 20,000 platelets), type of autoantibodies, clinical presentation, doses of steroids required to obtain platelet levels > 50,000, and time of steroid treatment. Data analysis was performed using SPSS software version 11.5 (SPSS, Chicago, IL, USA).

Results

Response to splenectomy

Over a mean period of 33 months, 103 patients (87%) were available for follow-up. The remission rate was 89.3% (92 patients), with CR in 77 cases (74.8%). Eleven patients (10.7%) did not respond to surgery (platelet count < 50,000). Mortality during follow-up was 2.5% (two cases not related to hematological pathology and one case without response to splenectomy).

Univariate analysis

No factor correlated with response to LS during follow-up in the total group. Patient characteristics related to response to splenectomy and results of the univariate analysis are reported in Table 1.

From the subgroup of 52 patients, the only factors that correlated with response in follow-up were the doses of steroids required to obtain platelet levels > 50,000, the treatment received (prednisone alone or

Table 2. Characteristics of patients related to response to splenectomy and results of univariate analysis in a subgroup of 52 patients

	All patients	Responders	Nonresponders	*p* value
N	52	46	6	—
Age				
< 45 yr	22	20	2	
> 45 yr	30	26	4	1
Female / male	33/19	30/16	3/3	0.656
Clinical presentation				0.935
Asymptomatic	12	11	1	
Mucocutaneous hemorrhage	21	17	4	
Digestive or gynecological hemorrhage	11	10	1	
Antiplatelet Ab	40	36	4	0.584
Negative	24	21	3	
IgG	8	8	0	
IgM	3	3	0	
IgG + IgM	5	4	1	
Other Ab	40	36	4	0.151
Negative	21	20	1	
ANA	13	10	3	
Others	6	6	0	
Medical treatment	50	44	6	**0.022**
Steroids	25	25	0	
Steroids + other	25	19	6	
Doses of steroids to maintain platelet levels > 50,000	41	35	6	**0.023**
< 40 mg/day	19	19	0	
> 40 mg/day	22	16	6	
Duration of disease (mo)		46.84	10.33	**< 0.005**
Time of steroid treatment (mo)		13.79	5	0.272
Preoperative platelet count		80,717	73,333	0.768

Ab, autoantibodies

Table 3. Results of multivariate analysis of global group

Variable	β	SE	*p* value
Age (dicotomic variable)	−66935.198	30858.386	0.034
Preoperative platelet count	0.583	0.269	0.034
Treatment received (prednisone alone or associated with other treatments)	−70369.848	33028.629	0.037

Table 4. Results of multivariate analysis of subgroup of 52 patients

Variable	β	SE	*p* value
Constant	−9.617	55.475	0.862
Doses of steroids to obtain platelet levels > 50,000	9.783	55.475	0.860
Treatment received (prednisone alone or associated with to other treatments)	−10.401	102.871	0.919
Evolution time of disease (mo)	−0.043	0.039	0.269

associated with other treatments), and the duration of the disease. The patients' characteristics in relation to response to splenectomy and the results of the univariate analysis are reported in Table 2.

Multivariate analysis

We used different statistical procedures for the multivariate analysis of the global group. Using multiple regression by stepwise Wald, we evaluated four factors: age (older vs younger than 45 years), sex, treatment received (steroids alone vs steroids associated with other treatments), and preoperative platelet count (above or below 20,000 platelets). For this analysis, we studied only the 94 patients for whom all the information for the variables evaluated was available. Only the preoperative platelet count proved to be a predictive factor of response ($p = 0.045$), but the standard error was too high (0.712). When we evaluated the entire group using the preoperative platelet count as the progressive variable, we observed that age, preoperative platelet count, and treatment were predictive factors of response but also the standard errors were too high (Table 3); thus, these variables could not be considered as predictive factors of response to splenectomy.

We also performed multivariate analysis in a subgroup of 52 patients. Three factors with significance in the univariate analysis were evaluated: the doses of steroids required to obtain platelet levels > 50,000, the treatment received (prednisone alone or associated with other treatments), and the duration of disease. None of these factors were statistically significant (Table 4).

Analysis of nonresponders cases

Eleven patients (eight women and three men; mean age, 48 years) did not respond to splenectomy and an immediate relapse occurred in five of them. Residual splenic tissue was evaluated by CT scan and scintigraphy in five of the 11 patients, and the results showed residual splenic tissue in one patient. Scintigraphy and CT scan also showed residual tissue in two patients with

Table 5. Results of nonresponders group

Patient no.	Age (yr)	Sex	Preoperative platelet count	Treatment	Immediate relapse	CT scan	Time, follow-up (mo)	Platelet count, follow-up	Mortality, follow-up
1	63	Male	5,000	PDN	No	Negative	104	45,000	No
2	19	Male	29,000	PDN	No	Negative	99	7,000	No
3	37	Male	5,000	PDN/CICLF	Yes	Negative	102	49,000	No
4	59	Male	19,000	PDN	Yes	No	78	30,000	No
5	31	Female	56,000	PDN	Yes	Negative	38	46,000	No
6	67	Female	79,000	PDN + Ig	Yes	Negative	1	42,000	No
7	79	Male	2,000	PDN + Ig	Yes	No	2	6,000	Yes (12/01)
8	54	Female	81,000	PDN	No	No	38	21,000	No
9	17	Male	128,000	PDN	No	No	1	48,000	No
10	64	Male	104,000	PDN + Ig	No	No	7	36,000	No
11	22	Male	81,000	PDN + Ig	No	No	46	20,000	No

CICLF, ciclofosfamide; PDN, prednisone

Table 6. Percentage of nonresponders and predictive factors of long-term response to splenectomy obtained by multivariate analysis in previous series

Author/year	*n*	No. of nonresponders (%)	Follow-up (mo)	Predictive factor	*p* value
Winde et al. [36]/1996	72	3 (4)	—	Splenic thrombocytolysis	—
				Hyperplasia megakaryocytopioiesis	—
Radaelli et al. [23]/2000	65	14 (21.5)	129.8	Response to steroids	<0.05
Fabris et al. [9]/2001	54	12 (33)	90	Age <40 yr	<0.005
Tsereteli et al. [34]/2001	35	5 (14)	16	Disease duration	RR = 1.083
Katkhouda et al. [16]/2001	67	15 (22)	38	Age <40 yr	OR = 7.65
				Steroid 40[a]	<0.018
Duperier et al. [8]/2004	67	24 (36)	22	Age <50 yr	<0.005
				Preoperative count platelet $>70 \times 10^3/\mu l$	<0.005

[a] Using prednisolone 40 mg/day as the cut point for maintaining the maximum platelet level

PR. Mortality was related to ITP in one case. Results for this group are shown in Table 5.

Discussion

ITP is the most frequent indication for LS. The prevalence of this disorder is high, the size of the spleen is usually normal, and the patient is healthy—features that facilitate the procedure.

Medical therapy tends to stabilize adult patients with ITP but permanent remission is unusual. Approximately 70% of patients eventually require splenectomy [29]. In several open splenectomy studies, remission rates of 60–90% have been reported, depending on the definition of recurrence criteria [21, 35]. LS has achieved immediate remission rates of 80–90% [14, 17, 33]. Although surgical failures have been reported up to 18 years later, most recurrences occur within the first 2 years after splenectomy and long-term follow-up is required to document the efficacy of LS for ITP. In our series, after a mean follow-up of 33 months, 89% of patients with ITP presented response, with a complete remission rate of 75%, similar to that obtained by other investigators [2, 17, 18].

Although good short-term results obtained after LS for ITP have renewed interest in surgery for this disorder, it would be helpful to establish preoperative clinical variables that could predict which patients are likely to benefit from splenectomy. Several studies have attempted to investigate the predictive factors for success after surgery [8, 9, 16, 34], but their results are not unequivocal (Table 6). The factors most frequently evaluated have been age, previous response to corticoids, interval between diagnosis and splenectomy, preoperative platelet counts, site of platelet sequestration, and platelet survival.

Patient age has been an important predictor of response to splenectomy in some studies [8, 10, 11]. Most series demonstrate that age between 30 and 45 years is an independent prognostic determinant of a successful response to splenectomy [7, 16, 28], but other researchers have not found this correlation [23, 27]. In our study, univariate and multivariate analyses using age as a dicotomic variable did not predict better results of surgical treatment in the younger group.

Some series have evaluated the preoperative prognostic value of the site of platelet sequestration and have considered that it may be the best predictor of response to splenectomy [11, 23]. In general, younger patients tend to have splenic sequestration rather than hepatic or mixed (liver and spleen) sequestration [11]. We did not evaluate platelet sequestration for several reasons; most patients in our study had predominantly splenic sequestration, isotope studies are expensive and time-consuming, and hematologists at our institution deemed them unnecessary, in agreement with the American Board of Hematology guidelines [12].

It is also frequently noted that the response to steroids predicts the response to splenectomy. Mintz et al. [20] observed a higher remission rate in patients who responded to steroids before surgery than in those who showed no response (92 vs 65%). However, these results have not been observed in other studies [2, 34]. In our study, when the global series was evaluated, we did not observe a correlation between the medical treatment received and the response to surgical treatment during follow-up. Although the corticoid dose required to reach platelet count levels $> 50{,}000$ had statistical significance in the group of 52 patients, this significance was lost in the multivariate analysis.

The interval between diagnosis and splenectomy has also been evaluated. Tsereteli et al. [34] studied this variable and observed that it was a significant factor even in multiple logistic regression analysis, but the magnitude of the relative risk (1.083; confidence interval, 1.004–1.167) shows that disease duration is a weak predictor of outcome. In the group of 52 patients, we observed that the disease duration had a prognostic value in the univariate analysis but not in the multivariate analysis. Our results and those of other published studies do not indicate any difference in the effects of early and later splenectomy [11, 13, 15], but it seems reasonable to adopt a ''wait and see'' approach for 8–12 months after diagnosis in the case of patients at low hemorrhage risk because it has been reported that some of these patients respond to second-line medical therapies [23].

Duperier et al. [8] observed a successful response to LS for ITP in patients younger than 50 years and in those with preoperative platelet counts above 70,000/μl. However, most series [2, 10, 13, 15] have failed to show that preoperative platelet counts may be a predictor of response to splenectomy. A preoperative platelet count was used as the dicotomic variable in our series. Although the preoperative platelet count was initially a predictive factor in the multivariate analysis, it could not be used as a significant predictive factor due to the high standard error.

Because of the immunological implications of ITP, we also evaluated whether the association with other immune pathology could be a predictive factor of success. However, no significant differences between patients with or without associated immune pathology were observed.

Because ITP encompasses a variety of thrombocytopenias with different pathogenic mechanisms, the same prognostic factors cannot be applied to all patients. In a subgroup of 52 patients, we obtained a greater quantity of data and evaluated whether the type of autoantibodies and the doses of steroids required to obtain platelet levels $> 50{,}000$ could act as predictive factors. No influence was observed in reference to the type of autoantibodies, but the doses of steroids required to obtain platelet levels $> 50{,}000$ presented statistical significance in the univariate analysis. However, this was again without significance in the multivariate analysis.

Residual splenic tissue has been considered a possible cause of failure after splenectomy [26], and several authors have questioned whether or not accessory splenic tissue can be identified during laparoscopy. However, a review of the literature shows that accessory spleens are found in 4–27 % of open splenectomies for ITP [2, 5], whereas several laparoscopic studies have reported accessory splenic tissue localization in similar percentages of cases (11–21%) [14, 17, 24, 25, 29, 33, 35]. Careful, systematic dissection by laparoscopy allows accurate identification of accessory spleens and may improve detection. We found accessory spleens in 8.6% of patients. Tsereteli et al. [34] did not find a significant difference between the open and laparoscopic procedures as a prognostic factor predictive of a favorable outcome. Moreover, the significance of accessory splenic tissue is not fully defined, and long-term follow-up evaluation provides the only way to determine the effects of retained splenic tissue. In our series, 11 patients did not respond to splenectomy and CT scan was performed in five of them without evidence of residual tissue.

To date, the long-term data obtained indicate that LS is an adequate procedure for ITP patients. However, a meticulous technique must be used in order to avoid residual tissue or implants due to spleen fracture or spillage through the bag [31].

Overall mortality of splenectomized patients ranges from 0.2 to 4.2% [3] and was 2.5% in the current study (two cases not related to the hematological pathology and one case without response to splenectomy). Portielje et al. [22] reported that most adult patients with ITP had a good outcome with a low mortality. However, patients with platelet counts less than 30×10^9/L had an increased mortality risk compared to the general population and to patients with platelet counts higher than 30×10^9/L. This is in agreement with a previously published report [4].

Results in the literature concerning predictive factors of response to splenectomy are contradictory and mainly based on retrospective studies. Furthermore, platelet levels used to consider nonresponders differ, many groups are heterogeneous, and the number of nonresponders is low. The correlation between predictive factors may also influence results. Results from our statistical analysis suggest that no evaluated variable acts as a clear predictive factor and the previously mentioned variables influence our results.

Findings from various studies suggest that there are no conclusive results to date, and the response to splenectomy (laparoscopic and open surgery) in patients with ITP cannot be adequately predicted on the basis of presplenectomy clinical variables. However, as Tsereteli et al. [34] noted, disease duration and patient age should be taken into consideration when selecting patients for splenectomy. Further studies are needed to determine the biological parameters that may predict outcome and select the best cases for surgical therapy [16, 34].

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