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Laparoscopic splenectomy for medically refractory immune thrombocytopenia (ITP): A retrospective cohort study on longtime response predicting factors based on consensus criteria

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HIGHLIGHTS

- The study follows consensus definitions of ITP, enabling proper comparison with medical studies.
- Response to splenectomy was achieved in 87.5% of the patients.
- Loss of response occurred in 30.2% of the patients in median after 3 (range 2–42) months.
- Response to preoperative steroids and postoperative rise in platelets predict long term response.
- Laparoscopic splenectomy is an effective and safe treatment option in patients with ITP.

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ABSTRACT

Background: Laparoscopic splenectomy has been proposed to be the standard therapy for adult patients with medically refractory immune thrombocytopenia (ITP). However, due to inconsistent definitions of response, variable rates of long term response have been reported. Furthermore, new medical treatment options are currently challenging the role of splenectomy. The aims of this study were to (1) analyze long term response after splenectomy according to recently defined consensus criteria, (2) identify possible predictive response factors. **Methods**: A case series of 72 consecutive patients with ITP undergoing laparoscopic splenectomy was retrospectively studied using univariate and multivariate analysis as well as logrank tests. **Results**: Median follow-up was 32 (2–110) months. Mortality was 0% and morbidity was 8.2%. Response to splenectomy was achieved in of 63/72 patients (87.5%). Loss of response occurred in 19/63 (30.2%) in median after 3 (range 2–42) months. Preoperative platelet counts after boosting with steroids and immunoglobulins as well as the postoperative rise in platelet counts were statistically significant factors for response upon both univariate and multivariate analysis, whereas age, gender, body mass index, ASA classification, disease duration, accessory spleens, splenic weight, conversion to open surgery, or perioperative complications were not. Patients with a postoperative rise in platelet counts >150,000/μL had a significant better chance on stable long term response than those with a smaller increment ($P < 0.001$). **Conclusions**: Laparoscopic splenectomy is an effective and safe treatment option in order to obtain stable long term response in patients with ITP. Perioperative platelet counts are predictive factors of long term response.

1. Introduction

Primary immune thrombocytopenia (ITP), formally known as idiopathic thrombocytopenic purpura or Morbus Werlhof, is an acquired autoimmune disorder leading to enhanced thrombocyte degradation in the reticuloendothelial system. As recently emerged, a further pathogenic mechanism for ITP is an

Abbreviations: ITP, immune thrombocytopenia; CR, complete response; R, response; NR, non-response; IgG, immunoglobulin; ASA, American Society of Anesthesiologists; BMI, body mass index.

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immunologically mediated reduction of platelet production in the bone marrow [1]. ITP is defined by a reduced platelet count lower than 100,000/μL without any other detectable reason [2]. ITP patients predominantly develop skin and mucosal bleeding, but many patients remain asymptomatic for long time. Though a major concern, the total risk for fatal hemorrhagic complications is low with reported bleeding associated mortality rates of 0.3–10% [3]. The bleeding risk and the hemorrhagic lethality rate increase with the patient's age [4,5]. In patients with platelet counts lower than 30,000/μL, first line medical treatment consists in corticosteroids [6], possibly in combination with intravenous immune globulins. Splenectomy is proposed as second line therapy for ITP [6]. Approximately 80% of the patients respond to splenectomy, among which approximately 66% experience long term remission without further therapy [7–16]. Therefore, prediction of the hematological outcome after surgery is important when referring ITP patients for splenectomy. The laparoscopic approach is advantageous in terms of shorter hospital stay, less postoperative pain, and lower complication rates [17–19]; however, hematological outcomes are not different to conventional splenectomy [8,15,20,21]. Numerous clinical studies on splenectomy for ITP have been published, but results are hardly comparable since there is a lack of consensus on standardized definitions and outcome criteria. The present study follows the definitions and response criteria as stated by the Vicenza Consensus Conference 2007 [2]. In this conference the major goal for treatment of ITP was defined as to provide a safe platelet count rather than correcting the platelet count to normal levels [2]. Therefore earlier studies on laparoscopic splenectomy for ITP using older and individual definitions for remission might give delusive results. In the light of these differently defined criteria of response, the aims of this retrospective cohort study were to (1) analyze long term response after splenectomy according to consensus criteria, (2) identify possible predictive response factors.

2. Patients and methods

The study was approved by the ethics committee of Muenster University (AZ 2009-490-f-S). Between 2001 and 2009, 96 consecutive patients underwent laparoscopic splenectomy for various hematological and oncological disorders at Muenster University Hospital. Among these, 73 patients with medically refractory ITP were identified. Patient characteristics and postoperative courses were studied from patient charts and the clinical data base system retrospectively. 37 patients were males (50.7%) and 36 (49.3%) females with a mean age of 50.6 ± 19.7 years (range 16–83) and a body mass index (BMI) of 27.0 ± 4.5 kg/m^2 (range 16.6–36.3). Median time from the first diagnosis of ITP and surgery was 11.5 months (range 3 months–33 years). Indications for splenectomy included patients who no longer responded to medical therapy (73/73), those with platelet counts < 10,000/μL (26/73), and those with recurrent bleeding (58/73; patients frequently had more than one indication for surgery). Preoperative medication included steroids (100%, 73/73), immunoglobulins (52%, 38/73), anti-D (6.8%, 5/73), rituximab (2.7%, 2/73), cyclosporine A (1.3%, 1/73), and azathioprine (1.3%, 1/73). 15 patients were preoperatively classified according to the American Society of Anesthesiologists (ASA) class I (20.6%), 37 patients ASA II (50.7%), 20 patients ASA III (27.4%), and one patient ASA IV (1.3%). All patients were vaccinated against pneumoccus, menigococcus, and haemophilus influenzae perioperatively.

2.1. Surgical procedure

All patients received single shot antibiotic prophylaxis with cefuroxime 1.5 g i.v. at least 30 min before skin incision. Laparoscopic splenectomy was performed in a standardized three-trocar technique. After dissection of the colosplenic, gastrosplenic, and splenophrenical ligaments, the splenic pedicle was divided with a laparoscopic stapler in accordance to the hanging-spleen-maneuver [22]. Capsule tearing and spillage of splenic tissue was carefully avoided. The spleen was removed using an extraction bag in which the spleen was morcellated. The entire abdomen including the lesser sac and the splenic cavity were thoroughly examined for accessory spleens, which were removed if present. A drainage tube as an indicator for postoperative bleeding or pancreatic fistula was placed in left upper quadrant routinely. These tubes were removed when lipase in the secretion was negative.

2.2. Follow up

Most patients (60.3%, 44/73) had a regular follow up at the Department of Hematology and Oncology of Muenster University Hospital. From patients that were followed by their general practitioners (39.7%, 29/73), a written informed consent was obtained and the follow up data were inquired from the general practitioners according to a standardized questionnaire. Hallmarks for follow up were splenectomy-related mortality and morbidity, post-splenectomy infections, course of platelet counts, occurrence of bleeding, and the need for further medical therapy related to thrombocytopenia.

2.3. Response and relapse criteria

Response and loss of response were related only to the event of laparoscopic splenectomy and were defined according to recent consensus criteria [2]:

Complete response (CR) Defined as a normal platelet count of >100,000/μL at day 30 after splenectomy, and discontinuation of medication. Spontaneous bleeding must be absent.

Response (R) Defined as a rise in platelet counts > 30,000/μL and <100,000/μL at day 30 after splenectomy, and at least the doubling of the baseline platelet count in absence of spontaneous bleeding, and discontinuation of medication.

Non-response (NR) Defined as a missing rise in platelet counts > 30,000/μL or an initial rise but return to values < 30,000/μL within 30 days postoperatively. The need to continue or to restart medical therapy such as steroids or others to sustain on normal platelet counts is also considered as non-response. Spontaneous bleeding within 30 postoperative days is considered as non-response.

Loss of response (only patients that initially reached CR or R) Every thrombocytopenic event with platelet counts < 100,000/μL (from CR) or < 30,000/μL (from R) or less than 2-fold level of platelet count compared to baseline (from R) is classified as a loss of response. Occurrence of spontaneous bleeding or the need for medication is also considered as loss of response.

2.4. Potential predictive factors

In order to obtain factors which might influence the long term hematological outcome of laparoscopic splenectomy in patients with ITP, the following variables were implicated for analysis: Age, gender, BMI, ASA classification, duration of the disease (defined as time from first diagnosis until laparoscopic splenectomy), response to preoperative IgG and/or steroid boosting (reflected as platelet count on admission according to the fact that all patients received a preoperative boost with IgG and/or steroids), presence of accessory spleens, splenic weight, conversion to open surgery, perioperative complications, postoperative rise in platelet counts.

2.5. Statistics

For continuous variables with normal distribution, mean and standard deviation are given, for continuous variables with skewed distribution median and range are given, respectively. Univariate statistical evaluations were performed using Fisher's exact test and *t*-test where appropriate. Multivariate analysis was performed by multiple logistic regression analysis. *P*-values < 0.05 were considered significant. Kaplan–Meier curves were created and log rank tests were performed using SSPS 17.0.

3. Results

A total of 73 patients were included. One patient was discharged on the fifth postoperative day after an uneventful laparoscopic splenectomy with a regular postoperative rise in platelet counts, but the patient was lost to further follow up. Therefore this patient's data were included in the surgical results ($n = 73$) but not in the hematological long term results ($n = 72$).

3.1. Surgical results

Median operation time was 123.5 min (range 28–241) including conversions. Conversion rate was 9.6% (7/73). Reasons for conversion were bleeding (6/7), severe obesity (3/7), and severe adhesions after previous surgery (1/7). In most cases a three trocar technique was used (77%, 56/73) while in 17 patients (23%) an additional trocar was inserted. Median spleen weight was 145 g (range 70–350). Single or multiple accessory spleens (1–3) were found in 10/73 patients (14%). Pathology results revealed no malignancies or other specific findings. 34/70 (48.6%) specimens showed a hyperplasia of the red pulpa and 16/70 (22.9%) a fibrosis of the splenic capsula. There was no perioperative mortality. Complications occurred in 6/73 patients (8.2%), which were mostly due to postoperative bleeding. 5 patients (6.8%) required surgery for bleeding control. The sources of bleeding were splenic veins in 3 patients, whereas 2 patients had bleeding from a trocar site in the abdominal wall. One patient had an epifascial wound infection after conversion. Pancreatic fistulas or intraabdominal abscesses did not occur. Limited pleural effusion developed in one patient. 9 patients (12%) were transfused perioperatively (units of erythrocytes: range 0–6 units). Median hospital stay was 6 days (range 3–17). In patients receiving long term steroids preoperatively, steroids were tapered quickly after surgery. There were no further postoperative platelet-specific or immunosuppressive medications.

3.2. Short term hematological results

Platelet count responses after laparoscopic splenectomy were observed immediately after the operation. The mean postoperative platelet count rose from 89,000 ± 72,000/μL preoperatively to 321,000 ± 237,000/μL within 5 days after surgery. Complete response (CR) was achieved in 56/72 patients (77.8%), whereas response (R) was observed in 7/72 patients (9.7%). Taking patients with CR and R together, a total of 63/72 patients (87.5%) responded after laparoscopic splenectomy according to consensus criteria [2] However, 9 patients (12.5%) showed non-response (NR).

3.3. Long term hematological results

The duration of follow up for all patients with CR and *R* ($n = 63$) was in median 32 (2–110) months. Among the 56 patients with initial CR, 18 patients (32.1%) had a loss of response during the follow up period. One patient with R (1/7, 14.3%) had a loss of response during follow up. This resulted in a total loss of response rate of 30.2% (19/63). Loss of response occurred in median after 3 (range 2–42) months. The latest loss of response was observed after 42 months. With regard to these long term results, a total of 44/72 (61.1%) patients had stable remission and no need for further therapy for ITP after laparoscopic splenectomy. These results are depicted as a Kaplan–Meier curve for all patients in Fig. 1. Estimated endurance of achieved response for all patients was 66.3 ± 5.6% after 1 year, 63.0%, ±5.8% after 2 years, and 60.6% ± 6.0% after 5 years. In two patients, a documented common cold preceded the loss of response. One patient developed a lymphoma and one other patient autoimmune hemolysis before loss of response. None of the patients experienced splenectomy related mortality or severe infectious events during the follow up period.

3.4. Determination of predictive factors for CR and R

Clinical findings and laboratory data as well surgical results underwent univariate analysis in relation to the achievement of response (Table 1). The only parameters with significant predictive value for CR or *R* were response to preoperative steroids and/or IgG reflected as platelet count on admission ($P = 0.046$) and postoperative rise of platelet count ($P < 0.0001$). The same parameters were analyzed by multivariate multiple logistic regression analysis (Table 2). Both platelet count on admission (odds ratio 1.353, 95% confidence interval 1.040–1.761, $P = 0.024$) and postoperative rise of platelet count (odds ratio 1.244, 95% confidence interval 1.053–1.470, $P = 0.01$) were found to be independent predictive factors for CR and R after laparoscopic splenectomy for ITP. Surgical complications or conversion to open splenectomy had no effect on hematological response. We analyzed the platelet counts on admission as a predictive value for response after splenectomy in order to predict the duration of response (CR + R). Patients with platelet counts on admission <40,000/μL (reflecting poor response to preoperative steroid or IgG boosting) had a significant lower rate of stable response than patients with platelet counts > 40,000/μL on admission reflecting a good response on steroid or IgG boosting

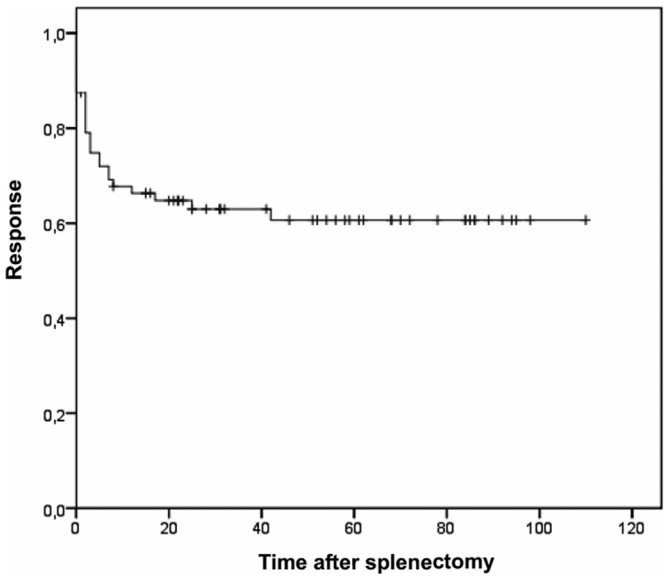

Fig. 1. Overall response [including complete response (CR) and response (R)] after laparoscopic splenectomy in patients with ITP (Kaplan–Meier-curve, $n = 72$). The *y*-axis indicates response levels in percent; the *x*-axis indicates time after splenectomy in months. Initial response rate (CR + R) 1 month after surgery was 87.5%. Approximately 61% of the patients achieved long term response (no loss of response during the follow-up period of median 32 months). Up to 3.5 years after surgery events of loss of response were observed, beyond this time point response rate was stable.

Table 1
Univariate analysis of possible predictive factors for complete response (CR) and response (R) versus non-response (NR) ($n = 72$).

Factor	CR + R	NR	*P* Value
Age (years)	49.4 ± 19.5	59.9 ± 20	0.171[a]
Gender (f: m)	32: 31	4: 5	1[b]
BMI (kg/m^2)	26.8 ± 4.4	27.7 ± 4.3	0.57[a]
ASA (I + II: III + IV)	45:18	6: 3	0.714[b]
Duration of disease (years in median (range))	0.9 (0.1–25)	0.7 (0.25–33)	0.462[a]
Thrombocyte count on admission (10^3/μl)[c]	94.1 ± 74.7	60.1 ± 48.8	**0.046**[a]
Accessory spleen (y: *n*)	9: 54	1: 8	1[b]
Splenic weight (g)	161.3 ± 61.7	148.7 ± 53.7	0.589[a]
Conversion to open surgery (y: *n*)	5: 58	2: 7	0.209[b]
Perioperative complications (y: *n*)	5: 58	1: 8	0.565[b]
Postoperative rise of thrombocyte count (10^3/μl)	257.1 ± 217.5	30.7 ± 68.0	< **0.0001**[a]

Values given as mean ± standard deviation, if not indicated otherwise.
BMI: Body mass index, ASA: American Society of Anesthesiologists.
Statisically significant values are printed in bold.
[a] *t*-test.
[b] Fisher's exact test.
[c] Reflecting the response to preoperative boosting with steroids and/or IgG.

($P = 0.012$; Fig. 2). However, even patients with platelet counts <40,000/μL still had a 40% chance to achieve stable response. Unfortunately, a separate analysis for different single preoperative medications was not possible due to the heterogeneity of therapeutic regimes. The postoperative rise in platelet counts was found to be the strongest predictive factor for the achievement of response (CR + R). In reflection to stable long term response the postoperative rise in platelet counts was tested using the log rank method (Fig. 3). Patients with a postoperative rise in platelet counts >150,000/μL had a significantly higher chance to achieve long term stable response compared to those with a lower rise of platelets ($P < 0.001$). Nevertheless, patients with a rise in postoperative platelet counts of 51,000–150,000/μL still achieved long term stable response in approximately 50% and those with a rise in postoperative platelet counts <50,000/μL of approximately 28%.

3.5. Rebound thrombocytosis and thrombotic complications

Reactive or rebound thrombocytosis is generally addressed to as platelet counts >500,000/μl after splenectomy for any indication. It is observed after medical therapy for ITP as well. 15/72 patients (20.8%) had rebound thrombocytosis at the time of discharge (median 711,000/μl, range 530,000–1,000,000/μl). Upon follow-up, reactive thrombocytosis persisted resp. occurred in 6 patients (range 693,000–858,000/μl), from which one patient had no

Table 2
Multivariate analysis of possible predictive factors for complete response (CR) and response (R) versus non-response (NR) ($n = 72$).

Factor	OR (Exp (B))	95% CI	*P* value[a]
Age	0.926	0.828–1.036	0.179
Gender (male)	0.459	0.031–6.751	0.57
ASA classification			0.32
Duration of disease	1.006	0.990–1.022	0.48
Thrombocyte count on admission[b]	1.353	1.040–1.761	**0.024**
Accessory spleen	11.978	0.167–859.985	0.255
Conversion to open surgery	0.041	0.000–4.140	0.175
Perioperative complications	0.145	0.001–17.969	0.433
Postoperative rise of thrombocyte count	1.244	1.053–1.470	**0.01**

Interpretation of Odds ratios:
"Age" – odds ratio for one additional year of lifetime.
"Duration of disease" –odds ratio for one additional month disease duration.
"Thrombocyte count on admission" and "Postoperative rise of thrombocyte count" – odds ratio for an increment of 10,000/μl, respectively.
OR: Odds ratio, CI: Confidence interval, IgG: Immunoglobulins, ASA: American Society of Anesthesiologists.
Statisically significant values are printed in bold.
[a] Multiple logistic regression analysis.
[b] Reflecting the response to preoperative boosting with steroids and/or IgG.

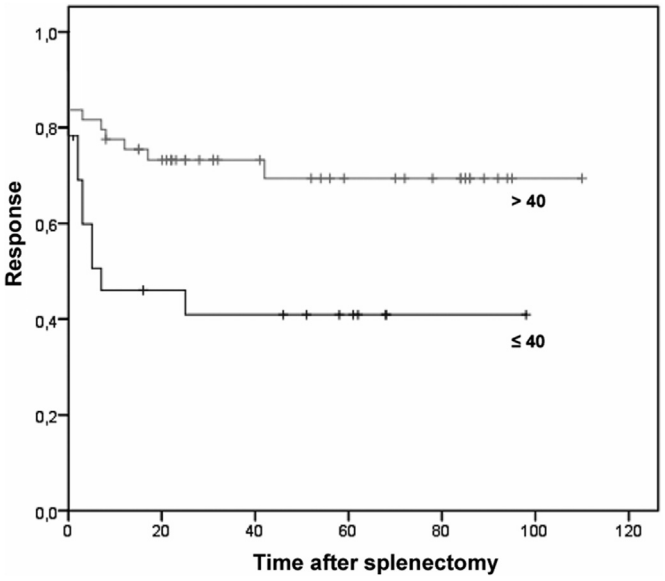

Fig. 2. Platelet count on admission predicts long-term response (CR + R) after splenectomy (Kaplan–Meier-curve, $n = 72$). The *y*-axis indicates response levels in percent; the *x*-axis indicates time after splenectomy in months. Black curve: platelet count on admission ≤40.000/μL (indicating poor response to preoperative boosting), grey curve: platelet count on admission > 40.000/μL (good response to preoperative boostering); $P = 0.012$ (log rank test). Patients with a good response to preoperative boosting with steroids and/or IgG (increment of thrombocytes > 40.000/μl) have a better chance to achieve stable long term response after laparoscopic splenectomy.

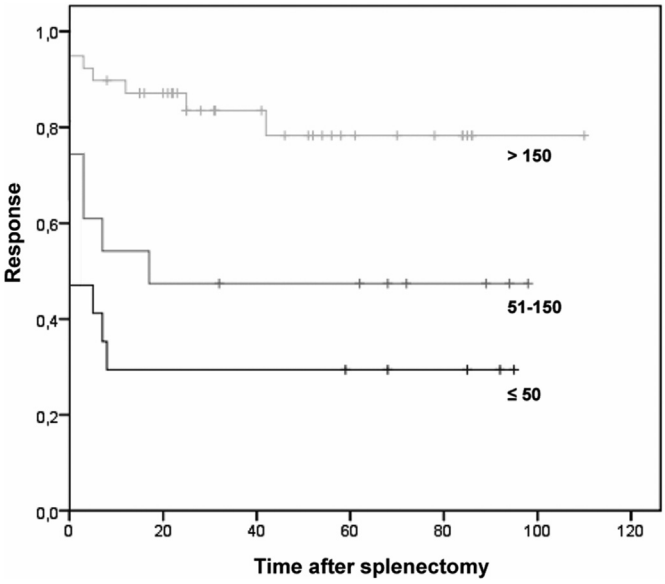

Fig. 3. Postoperative platelet count (measured during hospital stay) predicts long-term response (CR + R) after splenectomy (Kaplan–Meier-curve, $n = 72$). The *y*-axis indicates response levels in percent; the *x*-axis indicates time after splenectomy in months. Black curve: postoperative platelet counts 0–50.000/μL, dark grey curve: postoperative platelet counts 51.000–150.000/μL, light grey curve: postoperative platelet counts >150.000/μL. Patients with a postoperative rise in platelet counts >150.000/μL have a significantly better chance on stable long term response than those with a smaller rise; $P < 0.001$ (log rank test).

thrombocytosis at discharge. Long term thrombotic complications after splenectomy occurred in 6 patients (8.3%), although 5/6 had no thrombocytosis at the time of occurrence. 3 patients experienced deep vein thrombosis, with one developing consecutive pulmonary embolism. Two patients, both with loss of response, developed a stroke after media infarction. There were no cases of postoperative portal or mesenterial vein thrombosis, although there was no systematic postoperative surveillance program for this condition. However, one 20-year old patient with postoperative thrombocytosis and concomitant APC-resistance developed a Budd–Chiari syndrome, leading to successful liver transplantation 26 months after splenectomy.

4. Discussion

This study shows that laparoscopic splenectomy is a safe procedure in patients with ITP with no mortality and a low morbidity rate. Main limitations of this study are its retrospective single centre design and the inhomogeneity of preoperative medications. However, long-term response with an increase of quality of life and discontinuation of medication was achieved by laparoscopic splenectomy in approximately two thirds of our patients. Both preoperative response to steroid and IgG boosting (as reflected by preoperative increment of platelet counts) and the postoperative rise in platelet counts were found to be predictive factors for long term response after splenectomy. This study uses the consensus criteria as defined in 2007 and shows that these definitions are applicable on surgical studies. Older studies might have to be re-evaluated according to these definitions to avoid false impressions on the efficacy of splenectomy in ITP.

When comparing medical and surgical treatment for ITP, it has to be considered that most patients receiving surgery have already failed in several medical attempts, causing a bias for therapy-refractory cases. In adults, long-term remission rates on standard medical therapy such as corticosteroids or immunoglobulins vary between 20 and 70% [7,11,23]. However, adverse effects such as osteoporosis or infections often outweigh their benefits, excluding corticosteroids as a long term treatment option [6]. 50% of the patients experience a relapse after discontinuation of steroids [24]. Response rates to rituximab (anti-CD20) were reported to be 44–58% in patients without splenectomy, with a mortality rate of 2.9% in a pooled analysis [25–27]. With the introduction of the novel thrombopoetin receptor agonists romiplostim and eltrombopag achieving response rates from 38 to 60% [28,29], the indication for surgical therapy of ITP has to be re-evaluated. However, thrombopoiesis stimulating drugs might not be a causal therapy for ITP. Although expectations on these new drugs are high, long term remission rates and possible side effects have to be awaited for [30]. Economical aspects of long term medical therapy should be also taken into account.

No response or loss of response after splenectomy occurred in approximately one third of our patients. This failure rate is higher than commonly reported in surgical studies. Beside the spleen, anti-thrombocytic antibodies can be produced in other tissues as well and thrombocytic breakdown is not limited to the spleen either; this can lead to persistent thrombocytopeniea despite splenectomy. Some patients were successfully treated with immunosuppressive or thrombopoetic medications after loss of response despite of medically refractory thrombocytopenia before surgery. This might have been a potential benefit of splenectomy. However, the reason for loss of response in previously long term stable patients is not clarified yet.

A major concern is to evaluate risk factors for the failure of splenectomy in order to identify those patients, which might benefit from the operation. Although numerous predictive factors such as age, response to steroids, duration of the disease, spleen weight, or postoperative platelet counts have been proposed [7,10,13,14,16,23,31–34], these factors were not consistently confirmed. The most cited predictive factors are response to preoperative boosting therapy and the postoperative platelet counts. These factors were also found in this study, which is consistent with recently published studies [13,14,16]. However, these predictors do not lead to the decision whether to perform surgery or not, since patients lacking these predictors still have a reasonable chance of response. The patients should be informed about their chances of long term response after surgery, which can be crucial for patients with a long history of disappointing medical therapies.

Laparoscopic splenectomy is a well evaluated treatment option with a low complication profile. In a systematic review by Mikhael et al., splenectomy has been shown to be effective for patients with ITP with an approximate failure rate of 28% at five years [12]. This is confirmed in the present study when applying consensus definitions. Therefore splenectomy is still an important option in the treatment of patients suffering from ITP, especially in those refractory to medical therapy. Given the low risk and the fact that splenectomy is a one-time therapy in contrast to repeated antibody infusions, laparoscopic splenectomy should be discussed with ITP patients by both hematologists and surgeons before escalating medication.

There is no further debate whether splenectomy should be performed laparoscopically or in an open fashion in patients with ITP. Although there are no prospective randomized trials available on this question, the laparoscopic approach is safe in experienced hands and offers a shorter hospital stay and a good cosmetic result [15,20,21]. Conversion to open surgery, which is necessary in 0–22 % [12,17,21], does not jeopardize the hematological outcome as conversion was not a negative predictor. Complications of laparoscopic splenectomy in our series were mostly related to bleeding; however, this is not surprising as 63% of our patients hat platelet counts <100,000/μl at the time of surgery. On the other hand, there was no perioperative mortality, showing that the laparoscopic approach is safe even in patients with severe thrombocytopenia.

5. Conclusion

In summary, laparoscopic splenectomy is still a valuable and effective option in the treatment of patients with ITP. Uniform definitions of response rates do not put the results of former surgical studies in question, since we could confirm long term response rates in more than 60% of all patients undergoing laparoscopic splenectomy. Identifying patient related predictive factors of response to either medical or surgical therapy might facilitate the choice of optimal therapy for the individual patient in the future.

Ethical approval

The study was approved by the ethics committee of Muenster University (AZ2009-490-f-S).

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None.

Author contribution

All authors listed contributed substantially to the preparation of this manuscript. Their work included in particular:

Study conception and design: ER, RM, GB, MB.

Acquisition of data: ER, KK, RM, GB, SM.

Analysis and interpretation of data: ER, RM, SM, KK, MB, NS, GB.

Drafting of manuscript: ER, RM, SM, MB, NS.
Critical revision of manuscript: ER, RM, GB, SM, KK, MB, NS.

Conflict of interest

None.

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