Curr Surg Rep (2022) 10:95–102
https://doi.org/10.1007/s40137-022-00316-x

Splenectomy of Immune Thrombocytopenic Purpura in the Era of New Medical Therapies: A Retrospective Cohort Study from a Tertiary Cancer Center in Egypt

Amr Abouzid[1] · Ahmed Setit[1] · Shaimaa El-Ashwah[2] · May Denewer[2]

Accepted: 2 April 2022 / Published online: 14 May 2022

Abstract

Purpose of the study Splenectomy is considered generally as a second-line therapy in refractory ITP patients and in relapsed patients after an initial response to medical treatment. About 80% of the patients respond adequately to splenectomy, with long-term remission in 66% without the need for any further treatment.

Patients and Methods This retrospective cohort study was done in Oncology Center, Mansoura University, Egypt and included patients with refractory ITP to medical therapies between 2004 and 2021 with the assessment of their response rate after splenectomy and its surgical and hematological outcomes.

Results Seventy-five patients with refractory ITP underwent splenectomy, 48 patients underwent open splenectomy and 27 patients underwent laparoscopic splenectomy. Forty-three patients had complete response (CR), eight patients had partial response (PR), and twenty-three patients had non- response (NR). About 88.4% of patients with achieved CR have maintained their response throughout the follow-up period and 9.8% of the patients had a relapsed disease. The median duration to loss of response after surgery was 23 months (range: 5–58 months).

Conclusion Splenectomy, especially the laparoscopic approach, is a safe and effective line of treatment for refractory ITP patients, despite newer lines of therapy have been evolved and becoming more widely used in recent years.

Keywords Immune thrombocytopenic purpura · Splenectomy · Response rate · New medical therapies

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease caused by autoantibody destruction of circulating platelets and suppression of platelet production that can lead to symptoms of bleeding or bruising [1]. ITP may be idiopathic or occurs secondary to other diseases, such as malignancy, immunological disorders, viral infections, or certain drugs [2]. ITP is defined as a reduced platelet count below than 100,000/mL and the patients commonly presented with cutaneous and mucosal bleeding, although many patients remain asymptomatic for a long period of time [3].

Since 1950, oral corticosteroids have been the first-line of therapy for ITP patients [4]. Medical treatment has been progressed in recent years to include Rho(D) immunoglobulin and intravenous immunoglobulin (IVIg) [5], and recently, rituximab and thrombopoietin receptor agonists (TPO-RAs), these developments have made splenectomy to be used rarely in the early phase of the disease course [6]. Patients usually have initial response to medical treatment without sustained response with the long-term use of steroids and other lines of medical treatment [7]. Therefore, splenectomy is considered generally the second line of therapy in refractory ITP patients to steroids and in

This article is part of the Topical collection on *Surgical Oncology*.

✉ Amr Abouzid
amrahmedabouzid@mans.edu.eg

[1] Department of Surgical Oncology, Oncology Center, Mansoura University (OCMU), 101 Gihan St., 35516 Mansoura, Egypt

[2] Department of Internal Medicine, Clinical Hematology Unit, Oncology Center, Mansoura University (OCMU), 101 Gihan St., 35516 Mansoura, Egypt

those who develop relapse after an initial response [8]. About 80% of the patients respond adequately to splenectomy, with long-term remission in 66% without the need for any further treatment [9, 10].

The relapse rate after splenectomy usually occurs in 20–30% of ITP patients, especially in the first 2 years. So, other medical therapies are given to these patients; but they are sometimes refractory to these medical agents and experience high rates of morbidity and mortality [11].

Laparoscopic splenectomy (LS) has become a popular approach for ITP patients in recent years [12]. The benefits of laparoscopic splenectomy in ITP patients include less blood loss, shorter hospital stay, and a reduction in morbidity and mortality rates. Moreover, the laparoscopic assessment helps complete visualization of the potential sites for accessory spleens to avoid disease recurrence [13].

This study aims to assess splenectomy as a 2nd effective line of treatment for ITP patients and assess the response rate through the review of the patients presented to our center over the past 17 years.

Patients and Methods

This retrospective cohort study was done in Oncology Center, Mansoura University, Egypt and included patients with refractory ITP to medical therapies between 2004 and 2021 with assessment of their response rate after splenectomy and the surgical and hematological outcomes. This study was done after approval of the Institutional Research Board of the Faculty of Medicine, Mansoura University with the code number (R.20.12.89).

Between 2004 and 2021, 75 patients underwent splenectomy for ITP. Data collected included the date of diagnosis, comorbidities, duration, and types of preoperative therapy, pre- and postoperative platelets count, operative outcomes and postoperative complications that were assessed according to the Clavien–Dindo classification. Written informed consent was obtained from all patients who underwent splenectomy in this study.

The patient's response was defined as complete response (CR) when the postoperative platelet counts are greater than 100×10^9/L without development of bleeding events. Partial response (PR) was considered when the platelet count ranged between 50 and 100×10^9/L without any attacks of bleeding. Non- response (NR) was defined as the failure to reach a platelet count of 50×10^9/L or continuous attacks of bleeding after surgery. Relapse of the disease occurred when the platelet count has dropped less than 50×10^9/L or development of bleeding symptoms in patients with a history of initial response.

Statistical Analysis

The data were analyzed using *Excel* (Microsoft office 2013) program and *SPSS* (Statistical Package for Social Science) program (SPSS, Inc, Chicago, IL) version 20. The normality of the data was assessed using *Kolmogorov–Smirnov test*. Qualitative data were presented as frequency and percentage. Comparison between groups was done using the *Chi-square test*. Quantitative data were presented as median and range, mean and standard deviation. For comparison between two groups, the *Mann–Whitney test* (for non-parametric data) was used. For comparison between more than two groups; one-way ANOVA for (parametric data) was used and *Kruskal–Wallis* for (non-parametric data) was used. *Friedman test* was used for comparison of non-parametric data within the same group. *Kaplan–Meier curves* were used for survival. *P* values were significant at ≤ 0.05 with a confidence interval 95%.

Results

This retrospective study was conducted on 75 patients with refractory ITP who underwent splenectomy between 2004 and 2021. Clinical and demographic data were reported in (Table 1). This study included 15 male and 60 female patients. The median age of our patients was 31 years old (range: 8–72 years). The patients were classified according to the platelet response to splenectomy into 3 groups; 43 patients with complete response (CR), 8 patients with partial response (PR), and 23 patients with non- response (NR). During the study period one patient died from postoperative bleeding.

The median duration of preoperative medical treatment in complete, partial, and non-responder were 16, 38.5 and 17 months, respectively. The median number of medical agents received in the preoperative period with complete response group was 1, while it was 2 in partial and non-response groups. Steroids were used in all patients in the preoperative period, immunosuppressive drugs were used in 18 patients with complete response, 5 patients with partial response and in 15 patients with non-response. Thrombopoietin agonists were used in 3 patients of complete responders, 1 patient of partial responders and 1 patient of non-responders. Complications of preoperative treatment were observed in 48 patients, in the form of high arched palate with café au lait like patches, infections, steroid-induced diabetes, cushioned faces, osteoporosis and combined complications.

The median PLT count on admission for surgery was 50×10^9 L (range: 3–229 $\times 10^9$ L). It was 39×10^9/L in patients underwent open splenectomy and it was 60×10^9/

Table 1 Clinical and demographic data for patients who underwent splenectomy for immune thrombocytopenic purpura (ITP)

Parameter	CR (n = 43)	PR (n = 8)	NR (n = 23)	P
Age** (years) (Mean ± SD)	33.8 ± 12.1	30.1 ± 15.5	32.3 ± 13.4	0.720
BMI* kg/m^2[Median (range)]	32.0 (23–43)	29.0 (23–39)	30.0 (23–41)	0.452
Gender				
Male [No (%)]	12 (27.9%)	0 (0.0%)	2 (8.7%)	0.058
Female [No (%)]	31 (72.1%)	8 (100.0%)	21 (91.3%)	
ASA classifications*				
I [No (%)]	42 (97.7%)	8 (100.0%)	23 (100.0%)	
II [No (%)]	1 (2.3%)	0 (0.0%)	0 (0.0%)	
Comorbidity				
No [No (%)]	31 (72.1%)	4 (50.0%)	19 (82.6%)	0.150
DM [No (%)]	4 (9.3%)	1 (12.5%)	0 (0.0%)	
HTN [No (%)]	0 (0.0%)	0 (0.0%)	1 (4.3%)	
HTN/DM [No (%)]	3 (7.0%)	1 (12.5%)	1 (4.3%)	
SLE [No (%)]	1 (2.3%)	0 (0.0%)	0 (0.0%)	
Hepatic [No (%)]	4 (9.3%)	1 (12.5%)	0 (0.0%)	
Bronchial asthma [No (%)]	0 (0.0%)	1 (12.5%)	0 (0.0%)	
Epilepsy [No (%)]	0 (0.0%)	0 (0.0%)	1 (4.3%)	
Psychosis [No (%)]	0 (0.0%)	0 (0.0%)	1 (4.3%)	
Duration of preoperative medical therapy/months* [Median (range)]	16.0 (1–112)	38.5 (3–156)	17.0 (3–113)	0.184
No of agents received in preoperative period [Median (range)]	1.0 (1–3)	2.0 (1–3)	2.0 (1–2)	0.195
Preoperative steroids [No (%)]	43 (100.0%)	8 (100.0%)	23 (100.0%)	
Preoperative Immunosuppressive drugs [No (%)]	18 (41.9%)	5 (62.5%)	15 (65.2%)	0.156
Preoperative TPO agonists [No (%)]	3 (7.0%)	1 (12.5%)	1 (4.3%)	0.728
Complications of preoperative medical treatment				
No [No (%)]	17 (39.5%)	2 (25.0%)	7 (30.4%)	0.622
Yes [No (%)]	26 (60.5%)	6 (75.0%)	16 (69.6%)	
Duration from diagnosis to surgery/months [Median (range)]	16.0 (1–112)	38.5(3–156)	20.0 (3–113)	0.186
Platelet count on admission* [Median (range)]	65.0 (3–229)	41.5(7–94)	43.0(6–139)	0.276
Accessory spleen removed				
No [No (%)]	39 (90.7%)	6 (75.0%)	15 (65.2%)	0.038
Yes [No (%)]	4 (9.3%)	2 (25.0%)	8 (34.8%)	

CR Complete Response, *PR* Partial Response, *NR* Non-Response, *BMI* Body Mass Index, *ASA* American Society of Anesthesiology, *HTN* hypertension, *DM* Diabetes Mellitus, *SLE* Systemic Lupus Erythematosus, *TPO* Thrombopoietin agonists

Chi-Square test, one-way ANOVA**, Kruskal–Wallis*.*P* between 3 groups **significant (P value < 0.05)

L in those who had laparoscopic splenectomy with significant differences ($P = 0.017$). Forty-eight patients underwent open splenectomy while twenty-seven patients underwent laparoscopic splenectomy (Table 2). Conversion from laparoscopic to open splenectomy occured in 2 (7.4%) cases. The median operative duration in open splenectomy was 90 mins (range: 45–150 mins), while in laparoscopic splenectomy it was 130 mins (range: 60–190 mins) with a significant difference ($P < 0.001$). An accessory spleen was removed in 14 cases, fewer accessory spleens were removed in the CR group (9.3%) when compared to the PR (25%) and NR (34.8%) groups with significant difference ($P = 0.038$) (Table 1). Moreover, an accessory spleen was removed in 6 patients in the open splenectomy group, while it was removed in 8 patients of laparoscopic splenectomy group. The median estimated blood loss (EBL) was 110 ml (range: 60–200 ml) in open splenectomy, and it was 85 ml (range: 20–450 ml) in laparoscopic splenectomy. There was one case of intraoperative intestinal injury in open splenectomy. The median length of hospital stay was significantly lower in laparoscopic splenectomy as it was 4 days (range: 2–7 days), while in open splenectomy it was 5 days (range: 3–20 days) with ($P < 0.001$).

Table 2 Surgical data for patients who underwent splenectomy for immune thrombocytopenic purpura (ITP)

	Open Splenectomy (n = 48)	Laparoscopic splenectomy (n = 27)	P
Duration from diagnosis to surgery (months; Median, range)	15.5 (1.0–108)	24.0 (3.0–156)	0.157
PLT count in admission (Median, range)	39.0 (3.0–139.0)	60.0 (7.0–229.0)	0.017
Operative time (mins) (Median; range)	90.0 (45–150)	130.0 (60–190)	< 0.001
EBL in open (ml) (Median; range)	110 (60–200)	85 (20–450)	0.130
Accessory spleen *			
Negative	42 (87.5%)	19 (70.4%)	0.068
Positive	6 (12.5%)	8 (29.6%)	
Hospital stay (days) (Median; range)	5 (3–20)	4 (2–7)	< 0.001

Chi-square test*, Mann–Whitney test, P between 2 groups. **significant (P value < 0.05)

There were 11 (14.8%) cases with postoperative surgical complications (Table 3); 7 (9.4%) cases with Clavien–Dindo grade II complications, in the form of blood transfusion in 3 cases, postoperative small abdominal collection that required conservative treatment in 3 cases and 1 case developed deep venous thrombosis. Four cases (5.4%) had Clavien–Dindo grade III complications, 1 patient had an abdominal collection that required guided drainage, 1 patient required re-exportation for internal hemorrhage, 1 patient had a burst abdomen and 1 patient with an incisional hernia. We had one case with 30-day mortality from postoperative bleeding.

Table 4 demonstrates the comparison of postoperative platelet count of all studied groups. It showed a significant difference in the platelet count in the five PODs (Postoperative Days) between three groups ($P < 0.001$).

The follow-up period after surgery had a mean duration of 81.74 months (95% confidence interval

Table 3 Medication- related complications and postoperative complications for patients who underwent splenectomy for immune thrombocytopenic purpura (ITP)

Parameter	No (%)
Medication- related complications	48 (64%)
High arched palate with café au lait like patches	1 (1.3%)
Infections	2 (2.6%)
Cushioned	16 (21.3%)
Steroid- induced diabetes	2 (2.6%)
Osteoporosis	17 (22.6%)
Combined	10 (13.3%)
Postoperative complications according to Clavien-Dindo classifications	
Grade I	63 (85.1%)
Grade II (n = 7)	
Blood transfusion	3 (4.05%)
Small abdominal collection	3 (4.05%)
Deep venous thrombosis	1 (1.3%)
Grade III (n = 4)	
Burst abdomen	1 (1.3%)
Large abdominal collection	1 (1.3%)
Re-exploration for internal haemorrhage	1 (1.3%)
Incisional hernia	1 (1.3%)
Thirty-day mortality	1 (1.3%)

71.6–94.07 months). Of 74 patients, 58.1% achieved a complete response (CR) after splenectomy. About 88.4% of the patients have maintained response to splenectomy throughout the follow-up period and 9.8% of the patients had a relapsed disease (Table 5). The median duration to loss of response after surgery was 23 months (range: 5–58 months). The median platelet count of relapsed cases at admission for surgery was 77×10^9 L (range: 13–95 $\times 10^9$ L) compared to non-relapsed cases with a count of 64×10^9 L (range: 3–229 $\times 10^9$ L) with ($P = 0.894$). In the responder group, RFS (relapse-free survival) of studied ITP patients was 83.8% at 7- and 10-year intervals (Fig. 1). A 7-year RFS estimates of 82.6% for patients with open splenectomy compared to 83.3% for patients with laparoscopic splenectomy ($P = 0.541$) (Fig. 2). Relapsed cases were treated by steroids, immunosuppression and rituximab in 100%, 80% and 20% respectively. Non- and partial responder ITP (41.9%) patients were treated by single or combined regimens of steroids, immunosuppression, rituximab, TPO agonists.

Table 5 Treatment of partial, non-responder and relapsed cases after splenectomy for immune thrombocytopenic purpura (ITP)

Parameter	*N* (%)
Treatment of (PR and NR)	31 (41.9%)
Steroids	29 (93.5%)
Immunosuppressive drugs	27 (87.1%)
Rituximab	1 (3.2%)
TPO agonists	7 (22.6%)
Relapsed cases and their treatment	5 (9.8%)
Duration of relapse/months (median, range)	23.0 (5.0–58.0)
Steroids	5 (100.0%)
Immunosuppressive drugs	4 (80.0%)
Rituximab	1 (20.0%)

Discussion

Splenectomy is considered the second line of therapy for patients with refractory ITP, it has more favorable outcomes and superior to other medical modalities, as it gives long-lasting responses in most of the patients [14]. For decades, long courses of corticosteroids are considered the first and the main line of treatment of ITP patients [15].

The American Society of Hematology 2019 guidelines have recommended the use of either splenectomy, Thrombopoietin receptor agonists (TPO-RA) or Rituximab in adult patients with ITP lasting $\geq$ 3 months and are corticosteroid-dependent or resistant. The choice of the second line is individualized, according to the disease duration, frequency of severe attack of bleeding and comorbidities. For example, patients who desire a long-lasting response prefer splenectomy or thrombopoietin receptor agonists (TPO-RAs), while patients who wish to avoid long-term medications and its side effects, splenectomy or rituximab may be indicated [16].

Splenectomy should be used as a line of ITP therapy after at least 1 year of the initial diagnosis to give the chance of spontaneous remission of the disease in the first year. The immune thrombocytopenia (ITP) management has been evolved in the past 25 years as new lines of treatments have been emerged. Despite such advances, splenectomy remains a viable choice of treatment. At our center, we used corticosteroid therapy as the initial and main line of treatment, and before 2018 splenectomy was the main second line of treatment. The use of THPO-RA agents and rituximab has been evolved in the recent years as an effective second line of therapy for ITP patients. The choice between medical therapies and splenectomy depended on disease course, patients' comorbidities, preferences, and drugs availability.

Table 4 Comparison of postoperative platelet counts for patients who underwent splenectomy for immune thrombocytopenic purpura (ITP)

Parameter	CR ($n = 43$)	PR ($n = 8$)	NR ($n = 23$)	*P*
POD1 Median (range)	101.0(31.0–360.0)	75.5 (43.0–231.0)	54.0 (8.0–232.0)	0.004
POD2 Median (range)	150.0 (27.0–824.0)	126.5 (22.0–380.0)	66.0 (4.0–185.0)	< 0.001
POD3 Median (range)	190.0 (34.0–979.0)	141.5 (45.0–560.0)	43.0 (3.0–537.0)	< 0.001
POD4 Median (range)	219.0 (36.0–1205.0)	175.0 (33.0–660.0)	48.0 (5.0–600.0)	< 0.001
POD5 Median (range)	271.0 (70.0–1300.0)	199.5 (50.0–720.0)	60.0 (6.0–612.0)	< 0.001
P value	$P^1 = < 0.001$	$P^2 = 0.010$	$P^3 = 0.014$	

P between 3 groups by Kruskal–Wallis. P^1, P^2, and P^3 within the same group by Friedman test

POD Postoperative day

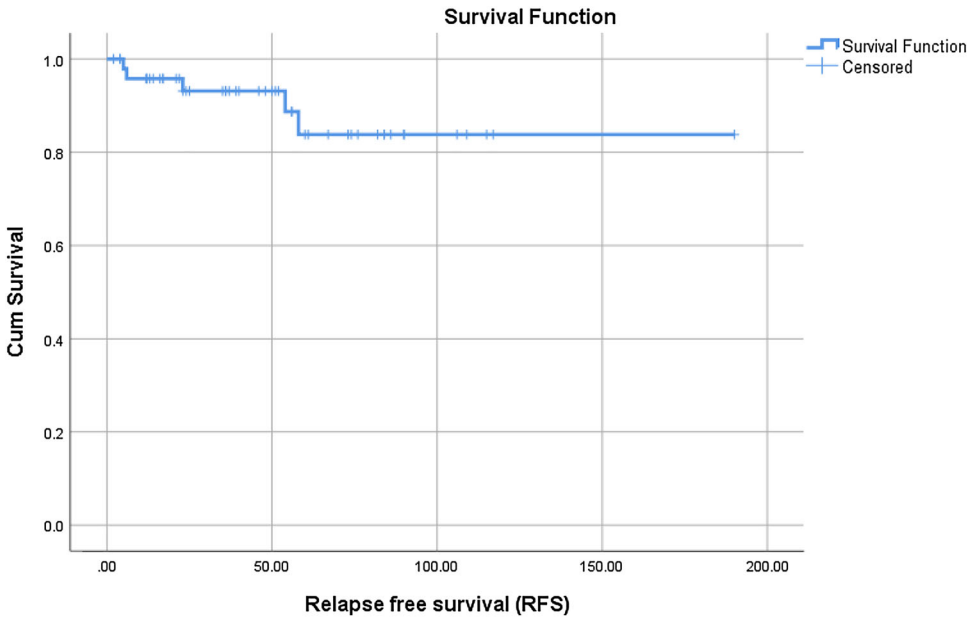

Fig. 1 Relapse-free survival of studied ITP patients with complete and partial response at 7- and 10-year intervals

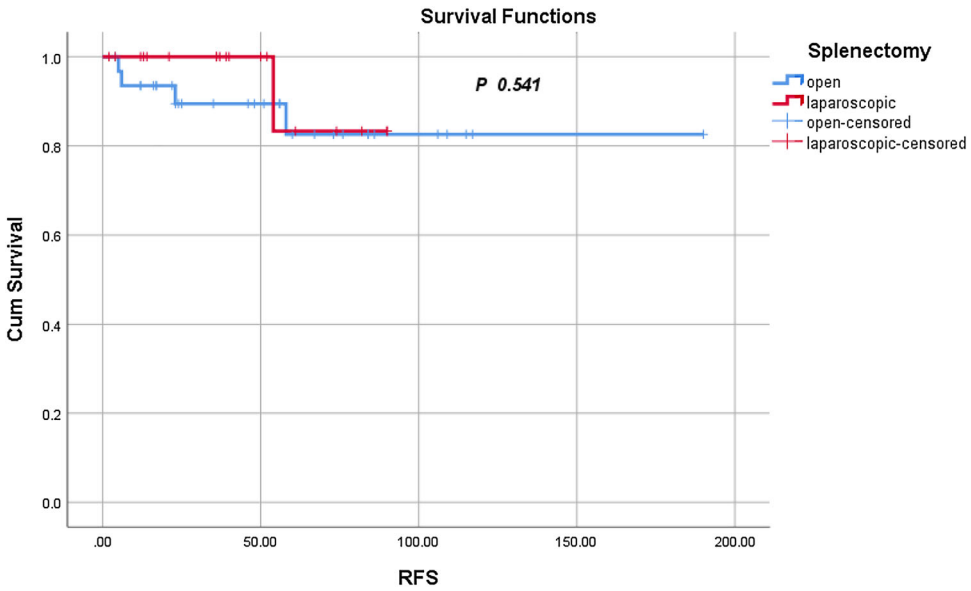

Fig. 2 Relapse-free survival at 7 years for patients underwent open and laparoscopic splenectomy

The platelet count of the patients on admission for splenectomy in CR, PR and NR was (65, 41.5 and 43 $\times$ 10^9 L, respectively). A study by Rijcken et al. reported platelet count on admission in groups with complete and non-response (94.1 and 60.1 $\times$ 10^9 L, respectively). [17] Forty-eight patients had an open splenectomy and twenty-seven patients had a laparoscopic splenectomy, with significant difference regarding the operative time, blood loss and hospital stay as most of patients who had laparoscopic splenectomy were discharged after 4 days. Conversion from laparoscopic to open splenectomy occured in 2 cases due to severe intraoperative bleeding that was difficult to be controlled laparoscopically. We started laparoscopic splenectomy in our center in 2013 and with the improvement in the laparoscopic instruments and laparoscopic splenectomy skills, it has become a standard approach for any case with ITP indicated for splenectomy and we did not have any conversion rate in the last 5 years. Tada et al. reported 10 cases with open splenectomy and 22 cases with laparoscopic splenectomy with a significant difference regarding the operative time, blood loss, and the hospital stay [18].

The rate of post-splenectomy complications in our study was 14.8%; most of them (9.4%) were with Clavien–Dindo grade II (3 cases with blood transfusion, 3 cases with - a small abdominal collection that required conservative

treatment, and 1 case with DVT). Four cases (5.4%) had grade III complications, (1 case with intra-abdominal fluid collection required guided drainage, 1 case with internal hemorrhage, 1 case with a burst abdomen, and 1 case with an incisional hernia). We had one case with 30-day mortality from postoperative bleeding. There was no case reported with post-splenectomy sepsis as all the patients were routinely vaccinated pre- or postoperative at our center. Guan et al. reported post-splenectomy complications in the form of subphrenic hydrops in 31 cases, pneumonia in 8 cases, wound infection in 3 cases, wound dehiscence in 2 cases, urinary infection in 1 case, 15 patients developed infections and 1 case with incisional hernia. Three cases died during the follow-up period from intracranial hemorrhage [19].

In the current study, post-splenectomy complete response was achieved in 58.1% of the patients, and about 88.4% of them have maintained their response during the follow-up period. There was a significant difference in the platelet count in the immediate five postoperative days in the three studied groups with a rising count in the complete and partial response groups. Another study reported that 80% of refractory ITP patients, have increased platelet counts immediately post-splenectomy, and 50% to 70% of them maintained their response [20].

A multicenter study included 402 patients and they had a complete response after splenectomy in 66%, partial response in 20% and 75% of cases maintained their responses within the follow-up period that was 92 months [21]. A case series that was published between 1966 and 2004, and reported that 1731 (66%) of 2623 adults patients have maintained their complete response within a follow-up period of 29 months [22]. Moreover, 72% of patients in another systematic review have maintained their response for 5 years [23]. A recent study reported the rate of post-splenectomy complete response is 83.5% of their patients and 81% of them have maintained this response during the follow-up period of 49.5 months [24].

We had 5 (9.8%) patients with a relapsed disease after complete and partial response within a median duration of 23 months (range: 5–58 months). The relapse rate in another study was 32.1% within a follow-up period of 32 months (range: 2–110 months) [17]. The relapse rate after splenectomy is usually (20–30%) and it occurs mostly within the first 24 months. These patients may respond to other medical modalities; however, some of these refractory ITP patients may not respond to these medical lines and experience high morbidity and mortality rates [25].

It is important to evaluate and predict the risk factors for the failure of splenectomy to select the patients who might benefit from this line of treatment. There are many factors involved such as age, response to steroids, disease duration, splenic size, or postoperative platelet counts. The most reliable predictive factors are the response to preoperative therapy and the postoperative platelet counts. However, patients without these predictors still have the chance of long-term response. [26]

There are some limitations in this study given that it is a single institution study, reporting its 17-years experience with ITP patients where the medical therapy has been changed and evolved. Moreover, the medical regimens used among our ITP patients were inhomogenous and have not been used regularly in our center till the past two years, which made the comparison between their effects with limited results.

Conclusion

Splenectomy, especially the laparoscopic approach, is an effective and safe line of treatment for refractory ITP patients, despite new lines of therapy have been evolved and become more widely used in recent years. Long-term medical therapy for ITP has significant complications, while early splenectomy, as a second-line treatment, is a good choice when medical therapy has failed.

Acknowledgements The authors of this study are grateful to their colleagues and patients in Oncology Center, Mansoura University.

Authors' Contributions All authors have made substantial contributions to formal analysis, writing and editing of this manuscript. All authors have approved the submitted version of the article.

Funding Not applicable.

Data Availability Are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Compilance with Ethical Guidelines

Conflict of interest The authors declare no conflict of interest.

Ethical Approval An approval was obtained from the Institutional Research Board (IRB) of the Faculty of Medicine, Mansoura University code (R.20.12.89).

Consent to Participate A written informed consent was obtained from all the patients included in this study.

Consent for Publication Not applicable.

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- • Of importance;
- •• Of major importance

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