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Predictors of splenectomy response in patients with immune thrombocytopenia

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Προγνωστικοί παράγοντες της ανταπόκρισης στη σπληνεκτομή σε ασθενείς με ανοσιακή θρομβοκυτταροπενία

Περίληψη στο τέλος του άρθρου

OBJECTIVE **To evaluate the predictors of the response to splenectomy in patients with immune thrombocytopenia.** METHOD **The medical records were reviewed retrospectively of patients who had undergone total splenectomy for immune thrombocytopenia at a tertiary center between January 2009 and December 2019.** RESULTS **This study included 40 patients (28 females and 12 males) with immune thrombocytopenia. A complete response was obtained in 31 (77.5%) patients, with 9 (22.5%) patients failing to respond to splenectomy. The response was stable in 25 patients (62.5%), and 5 patients (12.5%) had a recurrence. The postoperative mortality rate was 2.5%; one patient developed an ischemic stroke and died. Multivariate analysis demonstrated that an extended time from diagnosis to splenectomy, a lower demand for transfusion of blood components, and a shorter length of hospitalization were positively associated with a complete response.** CONCLUSIONS **Splenectomy should be considered as the therapeutic approach to immune thrombocytopenia, with a high curative potential in suitable patients. An extended time from diagnosis to splenectomy, lower demand for transfusion of blood components, and shorter length of hospitalization were found to be positively associated with a complete response after splenectomy.**

Key words

Immune thrombocytopenia
ITP
Prognosis
Relapse
Splenectomy
Splenectomy response

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Immune thrombocytopenia (ITP) is an acquired form of thrombocytopenia characterized by autoantibody-mediated destruction of platelets and suppression of platelet production.[1] As part of the reticuloendothelial system, the spleen is concerned with both anti-platelet antibody formation and antibody-sensitized platelet destruction.[1,2] Although splenectomy was adopted as the gold-standard treatment for severe ITP from the 1910s until to 1940s,[3–5] since the 1940s, with the introduction of corticosteroids, splenectomy ceased to be recommended as a first-line therapy for ITP,[4,5] but it has not waned in popularity, as it delivers a better outcome than any other approach.[1] Today, splenectomy is generally reserved for patients who have failed to respond to multiple attempts at medical treatment, as it poses both short- and long-term risks.[1] Although efforts have been made to predict which patients are more likely to respond to splenectomy, these have not been fully successful.[1,4,6–10]

This study aimed to evaluate the predictors of response to splenectomy in patients with ITP.

MATERIAL AND METHOD

The medical records were retrospectively reviewed of patients who underwent total splenectomy for ITP at a tertiary center between January 2009 and December 2019. Exclusion criteria included patients younger than 18 years of age, and those with severe heart, lung or liver disease, and malignant diseases. Patients for whom there were no follow-up laboratory findings were also excluded from the study.

The diagnosis of ITP was based on isolated thrombocytopenia in the absence of other causes of thrombocytopenia. This was a diagnosis of exclusion, and anti-platelet antibodies were not evaluated. In cases where the platelet count was less than 30×10^9/L and or the patients had signs and symptoms of bleeding, first-line therapy was administered with oral methyl prednisolone, 1 mg/kg/day. In addition to steroid therapy, some patients had variously been prescribed danazol, azathioprine, cyclosporine, cyclophosphamide, vincristine, thrombopoietin receptor agonists (TPO-RAs) and intravenous immunoglobulin (IVIG). The patients who had not responded to multiple medical forms of treatment underwent splenectomy.

The following criteria were used for the classification of splenectomy response, depending on the platelet count and clinical

findings at the end of the 1st and or 6th month after surgery: (a) Complete response (CR): platelet count >100×10^9/L, and the absence of bleeding without any treatment after splenectomy; (b) partial response (PR): platelet count between 30×10^9 and 100×10^9/L, and at least a doubling of the baseline count, without bleeding and with no treatment after splenectomy; (c) non-response (NR): platelet count <30×10^9/L, or non-doubling of the baseline count, or the presence of bleeding with the need for other therapies; (d) stable response (SR): when CR or PR was never lost, and was maintained without the need for any therapy after splenectomy; and (e) recurrence: platelet count <100×10^9/L in patients with a CR, or <30×10^9 in patients with a PR, confirmed by at least two measurements.

The data recorded included demographic characteristics, clinical findings, laboratory findings, and therapeutic interventions.

The following characteristics were recorded:

- Demographic data: Age and gender
- Clinical findings: Comorbid factors, hospital stay, complications and bleeding tendency during postoperative follow-up
- Laboratory findings: Preoperative and postoperative complete blood counts (hematocrit, hemoglobin, white blood cell, platelet, and mean corpuscular volume (MCV), and percentages of neutrophils, lymphocytes, eosinophils, basophils, and monocytes) and inflammatory markers (neutrophil-to-lymphocyte ratio [NLR] and platelet-to-lymphocyte ratio [PLR]), which were calculated based on the complete blood count
- Radiological and or nuclear imaging findings: Preoperative and or postoperative ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and radionuclide scan findings, if available.
- Therapeutic interventions: Surgical techniques (open or laparoscopic), transfusion of blood components for preoperative preparation, and the need for medical therapy.

The study was conducted according to the principles set forth by the Helsinki Declaration of 1975. Approval from the Human Ethics Committee of the Institution was obtained.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS), version 17.0 for Windows. Continuous variables were presented as mean with standard deviation (mean±SD); categorical variables were presented as numbers with percentages. A logistic model was set up to describe the relationship between splenectomy response and variables associated with splenectomy response. The Shapiro-Wilk test was used to analyze the normality of the groups. For intergroup comparison, the Chi-squared test or Fisher's exact test was used for categorical variables. The Student's t-test was used for continuous variables with a normal distribution. The Mann-Whitney U-test was applied for non-normally distributed variables. Significant variables were included in multivariate binary logistic regression analysis. A bivariate correlation test was used to determine whether there was a relationship between the independent variables to be analyzed before multivariate binary logistic regression analysis. In multivariate binary logistic regression analysis, a backward stepwise method with likelihood ratio (LR) was used. The level of significance used for the entry criterion of the variables was 0.05; the level of significance used for exit was 0.1. The level of significance used in testing the model, in general, was 0.05.

RESULTS

The study included 40 patients, of which 70% were women, who had undergone splenectomy for ITP. Their mean age was 39.1±14.5 years, range 18–72 years, and the mean follow-up was 44.1±36.7 months, range 1.5–116 months. Of the 40 patients, 9 (22.5%) had one or more systemic diseases, including hypertension (n=4), diabetes mellitus (DM) (n=3), atrial septal defect (n=1), hypothyroidism (n=1), systemic lupus erythematosus (SLE) (n=1), and multiple sclerosis (MS) (n=1). Preoperative abdominal ultrasound (US) was conducted in all cases, but abdominal CT, MRI, and or scintigraphy were not used routinely.

Laparoscopic techniques were employed in 82.5% of cases. An accessory spleen, located near the spleen, was also excised during laparoscopic surgery in 3 patients (7.5%), one of which had been identified on preoperative CT. Transfusion of blood components was required in 25% of cases. The mean length of hospitalization was 4.15±2.28 (range: 2–12) days (tab. 1).

One or more of the following complications developed in 7 (17.5%) patients: Pulmonary complications (n=2), subphrenic abscess (n=1), portal venous system thrombosis (PVST) (n=1), postoperative bleeding (n=2), incisional hernia (n=2), myocardial infarction (n=1) and ischemic stroke (n=1).

A complete response was obtained in 31 (77.5%) patients, with 9 (22.5%) patients failing to respond to surgery; 25 patients (62.5%) experienced a stable response, and 5 patients (12.5%) had a recurrence. The postoperative mortality rate was 2.5%; the patient who developed ischemic stroke died on the 42nd postoperative day.

Of the non-responders, two patients underwent a second operation for an accessory spleen and or splenosis, 13, and 98 months after the initial surgery. In one, the accessory spleen was detected as a nodular lesion in the pancreatic tail on both CT and MRI. Scintigraphy and CT identified the accessory spleen along the splenic artery and splenosis in the omentum in the other patient. One of the patients had developed a pancreatic leakage and died of cardiac arrhythmia on the 3rd postoperative day.

Table 1. Univariate analysis of the variables associated with splenectomy response in idiopathic thrombocytopenic purpura (n=40).

Characteristics	Total (n=40) mean±SD or n (%)	Complete response (n=31) mean±SD or n (%)	Non-response (n=9) mean±SD or n (%)	(p)
Age (years)	39.1±14.5	39.03±13.3	39.3±19.0	0.957
Gender				
Male	12 (30.0)	8 (25.8)	4 (44.4)	0.411
Female	28 (70.0)	23 (74.2)	5 (55.6)	
Time from diagnosis to splenectomy (months)	36.3±41.7	41.6±43.7	18.1±29.0	0.048
Laboratory findings				
Hematocrit	39.6±5.5	39.9±4.98	38.7±7.56	0.582
Hemoglobin	13.0±1.87	13.1±1.65	12.8±2.6	0.707
Platelet count	129.1±103.2	146.3±107.5	70.0±58.6	0.046
White blood cell count	11.88±473	11.6±3.82	12.7±7.2	0.783
Neutrophil count	8.3±4.84	8.05±3.88	9.2±7.5	0.884
Lymphocyte count	2.55±0.8	2.66±0.77	2.14±0.95	0.097
Neutrophil percentage	65.8±15.7	66.3±12.1	64.1±25.4	0.758
Lymphocyte percentage	24.2±10.1	25.1±9.8	20.9±10.8	0.281
Eosinophil percentage	1.2±1.49	1.21±1.3	1.28±2.1	0.378
Basophil percentage	0.49±0.33	0.47±0.33	0.55±0.35	0.459
Monocyte percentage	7.0±2.79	6.77±2.21	7.76±4.34	0.307
Neutrophil-to-lymphocyte ratio	3.96±3.5	3.62±3.07	5.14±4.83	0.507
Platelet-to-lymphocyte ratio	54.1±48.1	51.1±8.53	35.2±31.2	0.124
Mean corpuscular volume	83.7±6.7	83.2±6.6	85.5±7.36	0.377
Surgical technique				
Open surgery	7 (17.5)	5 (16.1)	2 (22.2)	0.645
Laparoscopic	33 (82.5)	26 (83.9)	7 (77.8)	
Transfusion of blood components				
Yes	10 (25.0)	5 (16.1)	5 (55.6)	0.029
No	30 (75.0)	26 (83.9)	4 (44.4)	
Length of hospitalization (days)	4.15±2.28	3.74±1.98	5.55±2.78	0.039

The other patient had developed PVST and was treated with anticoagulation therapy.

The mean time interval between diagnosis and splenectomy was 36.3±41.7 months. The interval was 41.6±43.7 months in complete responders and 18.1±29 months in non-responders. The mean duration was 42.8±46.6 months in patients who experienced a stable response and 43±38.6 months in patients who had a recurrence. The mean time interval between the splenectomy and the recurrence was 22.2±11.18 (range: 4–32) months. One of 5 recurrent cases resolved spontaneously, 3 patients required steroid therapy and one patient required both steroid and TPO-RA therapy. Of the recurrent cases, 80% responded to medical therapy.

Univariate analysis showed that preoperative platelet count, time from diagnosis to splenectomy, transfusion of blood components for preoperative preparation, and length of hospitalization were all significantly associated with splenectomy response (tab. 1). In multivariate analysis, an extended time from diagnosis to splenectomy, decreased demand for transfusion of blood components, and a shorter length of hospitalization were shown to be positively associated with a complete response (tab. 2).

DISCUSSION

Apart from its potential risk of complications, sple-

Table 2. Multivariate analysis of the variables associated with splenectomy response in idiopathic thrombocytopenic purpura (n=40).

Characteristics	(p)	OR	95% CI	
			Lower	Upper
Time from diagnosis to splenectomy	0.074	0.960	0.917	1.004
Transfusion of blood components	0.086	5.115	0.795	32.9
Length of hospitalization	0.047	1.632	1.006	2.647

95% CI: 95% confidence interval

nectomy is the most effective treatment for ITP.[1] Almost two-thirds of splenectomized patients remain stable and require no further treatment.[11] In the current study, similarly to previous reports,[7,11] most patients (77.5%) achieved a complete response, and 62.5% sustained a stable response. Post-splenectomy relapses occur in 4% to 30% of patients, usually within the first 1–2 years.[12,13] In the current study, 12.5% developed a recurrence within 3 years of surgery, but most of them improved with conservative management and or medical treatment.

Despite intense efforts to identify suitable candidates, there is no consensus as to which patients are more likely to respond to splenectomy. Conflicting results may be due partly to differences in study design and to the response definitions used. Age is one of the variables with contradictory results,[6,12,14–17] but we found that age did not predict splenectomy response, and in concordance with previous studies,[14,18] gender did not affect the prognosis.

In contrast to previous studies, which concluded that time from diagnosis to splenectomy was not associated with splenectomy response,[6,7,9,14] we found that a shorter time interval resulted in a poorer response. The early need for surgery may be a reflection of disease severity. The longer length of hospitalization and increased demand for blood products for preoperative preparation may be indicative of the severity of the disease and its lack of response to any medical therapy. Underlying pathology may differ between non-responders and responders. The exact mechanism of ITP may be more complex than presently understood, and research on non-responders may facilitate a better understanding of ITP. There is no specific test for ITP, which is a diagnosis of exclusion, and the possibility of misdiagnosis should be kept in mind in non-responders.

The accessory spleen, which is found in 10–30% of the population, is a major concern in patients undergoing splenectomy for ITP.[6,14,19,20] The majority of accessory spleens are located in the splenic hilum (75%), adjacent to the pancreatic tail (20%), and along the splenic artery (5%).[19] It may also be encountered in the gastrosplenic, splenocolic, or gastrocolic ligament, and even in the adnexa, scrotum, or mediastinum.[19] Thus, if it is not looked for specifically, an accessory spleen may be overlooked during surgery, which leads to failure in response to removal of the primary spleen. The localization and excision of an accessory spleen may be more challenging in repeat surgery and give rise to further complications, as in the current study. Of the non-responders, two patients underwent a second operation for an accessory spleen and or splenosis (heterotopic auto-transplantation of splenic tissue following injury or surgery). One of them developed pancreatic leakage and died of cardiac arrhythmia; the other developed portal vein system thrombosis (PVST) and was treated with anticoagulation therapy. Surgeons should therefore try to find accessory spleens during primary surgery. When the expected benefit from splenectomy is not achieved, the possibility of an accessory spleen and or splenosis should be kept in mind. Although abdominal US is a sensitive and primary imaging technique for an accessory spleen, more advanced techniques such as CT and or MRI should be applied if required.[21–23] Although we did not use them routinely, liver-spleen radionuclide scans, not only make a definitive identification of an accessory spleen and or splenosis, but also determine the platelet sequestration/destruction site. This technique provides surgeons with an opportunity to perform splenectomy when the spleen is the only sequestration site, and to avoid splenectomy when the liver participates in sequestration.[24–26] Retrospective design and small case numbers were limitations of this study.

In conclusion, although 12.5% of the patients relapsed after splenectomy, the majority of those were balanced by late remissions, and 75% of all patients benefited from splenectomy. Thus, splenectomy should be considered the therapeutic approach with a higher curative potential in suitable patients. An extended time from diagnosis to splenectomy, decreased demand for transfusion of blood components, and shorter length of hospitalization were found to be positively associated with a complete response. To achieve an optimum response, preventable causes of surgical failure, such as an overlooked accessory spleen, should be minimized by a comprehensive evaluation of the abdominal cavity during surgery and or through the use of special preoperative imaging methods, including CT/MRI and radionuclide scan. Future research should focus on non-responders to splenectomy, to clarify the pathogenesis of ITP.

ΠΕΡΙΛΗΨΗ

Προγνωστικοί παράγοντες της ανταπόκρισης στη σπληνεκτομή σε ασθενείς με ανοσιακή θρομβοκυτταροπενία

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ΣΚΟΙΠΟΣ Αξιολόγηση των προγνωστικών της απόκρισης της σπληνεκτομής σε ασθενείς με ανοσιακή θρομβοπενία. **ΜΕΘΟΔΟΣ** Έγινε αναδρομική αξιολόγηση των ιατρικών αρχείων ασθενών που είχαν υποβληθεί σε ολική σπληνεκτομή για ανοσιακή θρομβοπενία σε ένα τριτοβάθμιο κέντρο από τον Ιανουάριο 2009 μέχρι τον Δεκέμβριο 2019. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Η μελέτη περιλάμβανε 40 ασθενείς (28 γυναίκες και 12 άνδρες). Πλήρης ανταπόκριση παρατηρήθηκε σε 31 (77,5%) ασθενείς, με 9 (22,5%) ασθενείς να μην ανταποκρίνονται στη σπληνεκτομή. Είκοσι πέντε ασθενείς (62,5%) παρουσίασαν σταθερή ανταπόκριση, ενώ 5 ασθενείς (12,5%) εμφάνισαν υποτροπή. Ένας ασθενής εμφάνισε ισχαιμικό εγκεφαλικό επεισόδιο με δυσμενή κατάληξη. Η μετεγχειρητική θνησιμότητα ανερχόταν στο 2,5%. Σε πολυπαραγοντική ανάλυση βρέθηκε ότι η πλήρης ανταπόκριση σχετιζόταν με τον παρατεταμένο χρόνο από τη διάγνωση έως τη σπληνεκτομή, τη μειωμένη ανάγκη για μετάγγιση συστατικών του αίματος και τη βραχύτερη διάρκεια της νοσηλείας. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η σπληνεκτομή θα πρέπει να θεωρείται η καταλληλότερη θεραπευτική προσέγγιση σε επιλεγμένους ασθενείς. Βρέθηκε ότι ο παρατεταμένος χρόνος από τη διάγνωση έως τη σπληνεκτομή, η μειωμένη ανάγκη για μετάγγιση συστατικών αίματος και το μικρότερο χρονικό διάστημα νοσηλείας σχετίζονται θετικά με πλήρη απόκριση.

Λέξεις ευρετηρίου: Ανοσιακή θρομβοπενία, Πρόγνωση, Σπληνεκτομή, Υποτροπή

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