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**Laparoscopic splenectomy for primary immune thrombocytopenia: Current status and challenges**

Zheng D *et al.* Laparoscopic splenectomy for primary ITP

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**Abstract**

Primary immune thrombocytopenia (ITP) is an immune-mediated disorder affecting both adults and children, characterised by bleeding complications and low platelet counts. Corticosteroids are the first-line therapy for ITP, but only 20%–40% achieve a stable response. Splenectomy is the main therapy for patients failing respond to corticosteroids for decades, about two-thirds of patients achieve a long-lasting response. Although some new drugs are developed to treat ITP as second-line therapies in recent years, splenectomy is still the better choice with less cost and more efficiency. Laparoscopic splenectomy (LS) for ITP is proved to be a safe technique associated with lower morbidity and faster recovery and similar hematological response when compared to traditional open splenectomy. Based on the unified hematological outcome criteria by current international Consensus, the response rate of splenectomy should be reassessed. So far, there is not widely accepted preoperative clinical indicators predicting favorable response to LS. Since the patients undergoing surgery should take the risk of complications and poor hematological outcome, the great challenge facing the doctors is to identify a reliable biomarker for predicting long-term outcome of splenectomy which can help making the decision of operation.

**Key words:** Immune thrombocytopenia; Laparoscopic splenectomy; Open splenectomy; Corticosteroids; Hematological outcome; Predictor; Biomarker

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**Core tip:** Despite of the new drugsdeveloped to treat primary immune thrombocytopenia,splenectomy is still the main therapy for patients who fail corticosteroid treatment. Laparoscopic splenectomy is proved to be a preferable technique comparing to open splenectomy. The response rate of splenectomy should be reassessed based on the unified outcome criteria by current international Consensus. So far, there is not widely accepted preoperative indicators predicting response to laparoscopic splenectomy. The challenge facing the doctors is to identify a reliable predictor for long-term outcome of splenectomy which can help making the decision of operation.

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**INTRODUCTION**

Primary immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura or primary immune thrombocytopenic purpura, is an immune-mediated disease characterized by bleeding complications and low platelet counts in both children and adults[1]. ITP occurs at an annual rate of 1.9 to 6.4 per 100000 children and 3.3 per 100000 adults[2]. Bleeding symptoms are highly variable in primary ITP. According to a newly published systematic review that enrolled all prospective ITP studies with 20 or more patients, weighted proportions for intracerebral hemorrhage (ICH) were 0.4% for children and 1.4% for adults. And severe (non-ICH) bleeding was 20.2% for children and 9.6% for adults[3]. The term “purpura” was inappropriate because bleeding symptoms are absent or minimal in a large proportion of cases[4,5]. Therefore an International Working Group (IWG) of recognized experts suggested to replace the original term “idiopathic thrombocytopenic purpura” or “immune thrombocytopenic purpura ”with the term “immune thrombocytopenia”[1]. The new term was only accepted by the American Society of Hematology (ASH) and the newly ASH guidelines[6].

Corticosteroids were introduced in the 1950s to treat ITP[7]. Until now, Corticosteroids are still recommended as the first-line therapy in primary ITP by current international consensus[8]. However, only 20%–40% patients can achieve a stable response with steroid treatment[9,10]. Splenectomy is recommended as the main second-line method for patients who don’t respond to steroid or relapse for a long time[1]. Since the first laparoscopic splenectomy (LS) was reported by Delaitre and Maignien[11] in 1991, this technique has gradually replaced traditional open splenectomy (OS) in surgical treatment of ITP. The following is our review in the current status and challenges of LS for ITP.

**OVERVIEW OF PATHOPHYSIOLOGY OF ITP**

Understanding of the immunopathogenesis of ITP is very important for treatment of this disease. The mechanisms which cause the accelerated platelet destruction and the inhibited platelet production are very complicated and intricate, for several abnormalities are involved in its immunopathogenesis. In terms of humoral immune dysregulation, the increased expression of B cell-activated factor (BAFF) and cyclophilin ligand interactor (TACI) can prolong the survival and enhance the proliferation of B cells[12], and B cells can produce substantial antiplatelet autoantibodies directed against GPIIb/IIIa and GPIb/IX[13]. Macrophages in spleen and liver can destroy those autoantibody-combined platelets, causing the accelerated platelet destruction. Besides that, autoantibodies can also inhibit megakaryocyte production and maturation and platelet release, thus leading to the decreased platelet production[14]. As for cellular immune dysregulation, multiple cell types are involved in the development of ITP. CD4+CD25+ regulatory T cells (Treg cells) which can depress T cell responses are found quantitatively and functionally impaired[15]. In patients with ITP, the considerably high Th1/Th2 ratios[16], the increase of Th17 and Th22 cells[17], and the augment of CD3+ cytotoxic T cells (CTLs) have been found[18]. Dysfunctions of macrophages and dendritic cells also take part in the immune disequilibrium of ITP patients[19].

**THE STATUS OF SPLENECTOMY IN THE ERA OF NEW SECOND-LINE THERAPIES**

Both intravenous Anti-D immunoglobulin (IV anti-D) and Intravenous immunoglobulin (IVIg) are recommended as first-line therapy of ITP in the international consensus report of IWG[1]. Either IV anti-D or IVIg produce short-term responses within 24-48 h in 60%-80% of patients. However, the responses are rarely durable beyond 4 wk[20-21]. In the past few decades, splenectomy is considered as the first choice for ITP after failure treatment of corticosteroids. In recent years, some new drugs are developed to treat ITP and recommended as second-line therapy. These drugs include the monoclonal anti-CD20 antibody rituximab, recombinant human thrombopoietin molecule (rhTPO), and thrombopoietin receptor agonists (TPO-RAs). Some promising results have been reported in the treatment of ITP with these drugs. Thus whether continuing to regard splenectomy as the main second-line therapy has evoked much controversy. Rituximab has a depleting effect on B lymphocytes. However, its long-term effect is modest, for no significant differences in treatment failure rate within 78 wk between rituximab and placebo had been found [32 (58%) of 55 *vs* 37 (69%) of 54][22]. RhTPO and TPO-RAs (Eltrombopag and Romiplostim) can considerably promote the platelet production, but ITP patients should rely on these medications, since these drugs only have short-term therapeutic effects[6,23]. Eltrombopag and Romiplostim were approved by Food and Drug Administration (FDA) for clinical use. While in many countries, these two drugs are unavailable. Splenectomy is also the second-line therapy for ITP patients who don’t response to first-line therapy. Percent of 80 of ITP patients respond to splectomy and about two-thirds achieve a lasting response with no additional therapy for at least 5 years[8]. A systematic review of 23 articles and 1223 patients showed that by the resection of the site of platelet destruction and antiplatelet antibody production, laparoscopic splenectomy can cure 72% of ITP patients with long-term response[24]. Compared with expensive therapies with these drugs, splenectomy is less costly and more efficient[25]. Therefore, splenectomy is the better choice of the second-line therapy for ITP patients, [especially](https://www.baidu.com/link?url=Idh1HQHNp6ccXUrE9XgZAPi27vEgIHQXAFED023kd0cUGIiC52mO2_F87hP_v9qP-jSXmmZkD_T5i3G0ShWya2drr9nWFAjZSJVMbFBr1bC&wd=&eqid=b1edd0c5001e16980000000656eccb48" \t "_blank) in the developing countries.

**TECHNIQUE ASPECTS OF LS**

The comparison of the long-term outcomes and safety between LS and OS is always an issue. One systematic review[26] published in 2004 and some case series[27-29] in the past decade suggested that the hematologic efficacy of LS is the same as OS, while LS had fewer complications and mortality than OS. The systematic review[26] including 47 case series reported that mortality was 1.0% with OS and 0.2% with LS. Complication rates were 12.9% with OS and 9.6% with LS. The common complications of splenectomy include bleeding, thrombosis, pancreatic leakage, infection, prolonged hospitalization, requirement for additional intervention and readmission to the hospital. But all the studies were retrospective. Randomized study is needed to confirm this conclusion. LS has other advantages such as less postoperative pain, shorter hospital stays and better cosmetic outcomes[27,30]. Therefore LS is preferred over OS for ITP by more and more surgeons.

In recent years, there are some case reports about the application of single-incision LS[31-33]. This technique emphasizes the concept of operation through one small transabdominal incision rather than the traditional multiple trocar sites, in order to show benefits of less pain and better cosmetics. However, because of the limited number of included patients in these studies, no obvious [advantage](http://www.baidu.com/link?url=oxQuN0Dz7WA4jIsnirflnw9O--w8RxKACfLvkZwqnqB0J-GkxPc6xRflf1qLfZkQ7VOsQm4bZ5svLEToYzj7CnMTq2SdxIox_7R4c_2VZGG" \t "_blank)s of this technique could be showed when comparing with traditional LS[31].

**HEMATOLOGICAL OUTCOME CRITERIA**

The response rate of splenectomy for ITP in different studies differs from each other. Case series[29,34-42] reporting 50 or more patients conducted splenectomy for ITP that contain platelet count response were listed in Table 1. All these data were published in recent ten years and searched from PubMed database. One of the main reason for the discrepancies of hematological outcomes is the different definitions and clinical criteria which were used in different studies[9,43,44]. Fortunately, the standard terminology, definitions and outcome criteria for ITP have been unified[1,6]. In the new guidelines updated by ASH[6], a platelet count less than 100 × 109/L was diagnosed as thrombocytopenia and a platelet count more than 100 × 109/L or 30 × 109/L was diagnosed as complete response or partial response after splenectomy. The recommendations for using 100 × 109/L as an upper-threshold were based on 3 reasons: over 10 years of follow-up, only 6.9% patients with a platelet count between 100 and 150 × 109/L may develop a persistent platelet count of less than 100 × 109/L[45]. In some non-western healthy individuals, platelet count values may be between 100 and 150 × 109/L[46-48]. Using 100 × 109/L as a threshold would reduce inclusion of most women with pregnancy-related thrombocytopenia[49]. The new guidelines will provide the evidence-based guidance for the diagnosis and therapy of ITP, as well as unified criteria for evaluating treatment outcome.

**PREDICTORS OF SPLENECTOMY**

Splenectomy is benefit for most of the patients, but there are still some patients have a poor long-term response. They should also take the risk of surgery, in the worst case, even death. So the choice of surgery is a deliberate decision. Many studies have attempted to determine reliable predictors of hematological response to splenectomy. Some factors including younger age[50,51], preoperative platelet count after using steroids and immunoglobulins[40,42], response to preoperative steroids[52,53], shorter disease duration (from diagnosis to splenectomy)[51], and splenic sequestration[54,55] have been reported as successful predictors to splectomy for ITP. But all the above conclusions can’t be verified in other studies. So far, there is not widely accepted preoperative clinical indicators predicting response to splenectomy. Identifying a preoperative biological or immunological marker to predict long-term results of LS for patients with primary ITP will be the focus of future research. Our team have made preliminary progress toward this goal[56]. In our study, we showed that the preoperative heptoglobin in serum may be a favourable predictor for the long-term response to splenectomy in ITP. Further studies with long-term follow-up and larger sample size are needed to confirm the findings. With the efforts of hematologists and surgeons, identifying biomarkers for favorable hematological outcome of ITP patients undergoing splenectomy and therefore avoiding invalid operation may come true in the future.

In summary, although some new drugs are developed as second-line therapies for primary ITP, splenectomy is still recommended as the first choice for patients who fail corticosteroid therapy. LS is a good alternative to OS for treatment of ITP. The great challenge facing the doctors is to identify a reliable predictor for long-term outcome of splenectomy which can help making the decision of operation.

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**Table 1 Case series reporting 50 or more patients conducted splenectomy for immune thrombocytopenia that contain platelet count response**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Publication**  **Date** | **Accrual**  **years** | **Ref.** | **Country** | **No.**  **Patients** | **Operation**  **method** | **CR rate** | **R rate** | **NR rate** | **Relapse** |
| 20061 | 1993-2003 | Balague *et al*[28] | Spain | 103 | LS | NA | NA | 4.9% | 6.1% |
| 20072 | 1988-2006 | Sampath *et al*[29] | Canada | 105 | LS, OS | NA | NA | NA | 21.6% |
| 20071 | 1994-2004 | Kang *et al*[30] | South Korea | 59 | LS | 47.5% | 40.7% | 11.9% | 15.2% |
| 20113 | 2005-2010 | Chen *et al*[31] | China | 81 | LS | 88.9% | 8.6% | 2.5% | NA |
| 20114 | 1999-2006 | Zheng *et al*[32] | China | 127 | LS | 79.5% | 9.5% | 11% | 9.7% |
| 20133 | 1982-2011 | Gonzalez-Porras *et al*[33] | Spain | 218 | LS, OS | 80.7% | 8.3% | 11.0% | 36.1% |
| 20143 | 1995-2012 | Montalvo *et al*[34] | Mexico | 150 | LS | 88.7% | 2.7% | 8.6% | NA |
| 20143 | 2001-2009 | Rijcken *et al*[35] | Germany | 72 | LS | 77.8% | 9.7% | 12.5% | 30.2% |
| 20143 | 2010-2012 | Cai *et al*[36] | China | 88 | LS | 77.3% | 19.3% | 3.4% | NA |
| 20153 | 1992-2013 | Navez *et al*[37] | Belgium | 82 | LS | 72.0% | 24.4% | 3.6% | NA |

OS: Open splenectomy; LS: Laparoscopic splenectomy; CR: Complete response; R: rEsponse; NR: No response. 1Remission was defined CR when platelet count increased to more than 150 × 109/L, R when it was 50-150 × 109/L; 2 The criterian of ITP remission was not mentioned in the study; 3Remission was defined CR when platelet count increased to more than 100 × 109/L, R when it was 30-100 × 109/L; 4Remission was defined CR when platelet count increased to more than 100 × 109/L, R when it was 50-100 ×109/L.