# Adverse factors responsible for below-normal platelet count after laparoscopic splenectomy and azygoportal disconnection

*Dou-Sheng Bai[1]\* ID, Wen-Yu Shao[2]\* ID, Chi Zhang[1] ID, Ping Chen[1] ID, Sheng-Jie Jin[1] ID, Guo-Qing Jiang[1] ID*

[1]Department of Hepatobiliary Surgery, Clinical Medical College of Yangzhou University, Yangzhou, China
[2]Key Laboratory of Living Donor Liver Transplantation, Department of Liver Transplantation Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

## ABSTRACT

**Background/Aims:** Splenectomy is regarded as an effective curative treatment for thrombocytopenia caused by hypersplenism in patients with cirrhosis. However, in clinical practice, thrombocytopenia is not resolved by splenectomy in all patients. This study aimed to evaluate the adverse factors responsible for platelet (PLT) counts below the normal lower limit following laparoscopic splenectomy and azygoportal disconnection (LSD).

**Materials and Methods:** We retrospectively evaluated the outcomes of 123 cirrhotic patients with portal hypertensive bleeding and secondary hypersplenism, who underwent LSD and who had PLT counts <125×109/L (non-normal group) or ≥125×109/L (normal group) at the postoperative month (POM) 3, between April 2014 and March 2017.

**Results:** Sixteen patients (13.01%) had PLT counts <125×109/L at POM 3 after LSD, while the remaining 107 patients had normal counts. We analyzed 25 perioperative variables in both groups. A logistic multivariate regression identified age (relative risk [RR] 1.082, 95% confidence interval [CI] 1.018-1.150) and longitudinal spleen diameter (RR 0.977, 95% CI 0.955-1.000) as significant independent factors for the PLT count <125×109/L at POM 3. Bivariate correlation analysis showed that age >50 years and longitudinal spleen diameter ≤160 mm were threshold values for an increased risk of the PLT count <125×109/L at POM 3 after LSD.

**Conclusion:** Age was an independent positive predictor and longitudinal spleen diameter an independent negative predictor of PLT count <125×109/L at POM 3 after LSD.

**Keywords:** Platelet, splenectomy, laparoscopy, cirrhosis, portal hypertension

## INTRODUCTION

The high incidences of chronic hepatitis B and C virus infections worldwide are associated with increased incidences of hypersplenism, with splenomegaly secondary to cirrhotic portal hypertension. Splenectomy is regarded as a first-line curative treatment for thrombocytopenia and leukopenia resulting from hypersplenism in patients with cirrhosis. It also has been shown to improve coagulation and liver function, and it plays an important role in the surgical strategy for hepatocellular carcinoma by alleviating thrombocytopenia in cirrhotic patients (1-5). Furthermore, the Hassab procedure (splenectomy and azygoportal disconnection) is a common treatment strategy for patients suffering from hypersplenism together with esophagogastric variceal bleeding in Asia.

Splenectomy is always followed by increased blood viscosity as a result of high platelet (PLT) and leukocyte counts secondary to the absence of splenic breakdown. Previous studies reported that the mean postoperative PLT count usually increased to 231-399×10⁹/L after splenectomy or the Hassab procedure (6-8), which was within normal limits. However, thrombocytopenia is not resolved by splenectomy in all patients in clinical practice; some patients maintain a postoperative PLT count below the normal lower limit (125×10⁹/L) despite splenectomy, suggesting that this procedure may not be suitable in all cases. This may result in patient dissatisfaction, and even medical violence, in some countries (9,10). It is therefore necessary to determine the factors responsible for this treatment failure and to identify those patients at risk of maintaining a low postoperative PLT. We aimed to identify the adverse factors associated with a PLT count below the normal lower limit after splenectomy. We conducted a retrospective study to compare the demographic, preoperative, and intraoperative characteristics between pa-

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tients with PLT counts ≥125×10$^9$/L and those with counts <125×10$^9$/L at postoperative month (POM) 3 after laparoscopic splenectomy and azygoportal disconnection (LSD) for portal hypertensive bleeding and secondary hypersplenism.

## MATERIALS AND METHODS

### Patients
Patients were included in the study if they met the following criteria: diagnosed with cirrhosis of any etiology; aged 18-80 years; had a history of esophageal/gastric variceal bleeding and secondary hypersplenism; liver function Child-Pugh A or B; hypersplenism with a PLT count <100×10$^9$/L; no portal vein system thrombosis proved by ultrasonographic evaluation on admission; underwent LSD; and completed a 3-month follow-up.

Patients were excluded for the following reasons: any malignancy; hypercoagulable state not resulting from liver disease; management with oral contraceptives, anticoagulation agents, or antiplatelet agents; uncontrolled hypertension or peptic ulcer disease; hemorrhagic stroke; or human immunodeficiency virus infection.

A total of 123 patients satisfied the inclusion criteria between April 2014 and March 2017, and they were diagnosed with esophageal/gastric variceal bleeding and secondary hypersplenism due to cirrhotic portal hypertension in our department. All the patients underwent LSD. All operations were performed by the same experienced surgical team. The LSD procedure was carried out as described previously (11,12). The clinical characteristics of the patients were analyzed retrospectively. This study was approved by the Ethics Committee of our institution. Written informed consent was provided by each patient. The methods were performed in accordance with the relevant guidelines and regulations.

Clinical data were collected retrospectively. Preoperative patient data included age, gender, etiology of cirrhosis, hypertension, diabetes mellitus, Child-Pugh classification, the longitudinal spleen diameter, the main portal vein diameter, spleneolus, hemoglobin levels, the PLT count, prothrombin time, and levels of total bilirubin, plasma albumin, alanine aminotransferase, blood urea nitrogen, creatinine, laminin, precollagen III, collagen IV, and hyaluronidase. Intraoperative data included the operation time, intraoperative blood loss, and intraoperative blood transfused. Postoperative data included the PLT count on postoperative days (POD) 7 and 10, and at POM 1 and

3. Patients with a PLT count at POM 3 below the normal lower limit (125×10$^9$/L) were classified as the non-normal group (n=16) and those with a PLT count ≥125×10$^9$/L were placed in the normal group (n=107).

### Statistical analysis
All statistical analyses were performed using the SPSS 22.0 software (IBM Corp.; Armonk, NY, USA). p values <0.05 were considered statistically significant. Data are presented as mean (standard deviation), median (range), or percentage. Group means were compared using Student's $t$-tests or Mann-Whitney U tests, as appropriate. Percentages were compared using $\chi^2$ tests. Bivariate correlation was used to determine the significance levels of patient age and longitudinal spleen diameter. Multivariate regression analysis was performed with forward stepwise elimination of nonsignificant variables.

## RESULTS

### Baseline patient characteristics
The non-normal group included 16 (13.01%) patients (6 males, 10 females; mean age, 60.8±8.2 years; range, 44-73 years) with portal hypertensive bleeding and secondary hypersplenism due to liver cirrhosis. These patients had been admitted because of variceal bleeding. All 16 patients suffered from splenomegaly, with a longitudinal spleen diameter of 99-207 mm. The non-normal group included the remaining 107 (86.99%) patients (72 males, 35 females, mean age, 52.0±10.2 years; range, 21-77) with PLT counts ≥125×10$^9$/L at POM 3. These patients were also admitted because of variceal bleeding and had spleen diameters of 132-300 mm.

### Adverse factors responsible for below-normal platelet count
The 25 analyzed variables in the non-normal and normal groups are shown in Table 1. The variables shown to differ significantly between the two groups were gender, age, and longitudinal spleen diameter. These significant variables were regarded as independent variables, and PLT count <125×10$^9$/L at POM 3 as a dependent variable. Multivariate logistic regression identified age (relative risk [RR] 1.082, 95% confidence interval [CI] 1.018-1.150) and longitudinal spleen diameter (RR 0.977, 95% CI 0.955-1.000) as significant variables affecting the risk of PLT count <125×10$^9$/L at POM 3 (Table 2).

### Postoperative PLT count changes with time
The mean PLT count changes from admission to POM 3 fluctuated widely (p<0.001; Figure 1), with the peak

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**Table 1.** Demographic, preoperative, and intraoperative characteristics of patients with platelet counts ≥ or <125×10⁹/L at the postoperative month 3

| Variable | Non-normal (n=16) | Normal (n=107) | p |
|---|---|---|---|
| Sex (female/male) | 10/6 | 35/72 | 0.021 |
| Age (years) | 60.8±8.2 | 52.0±10.2 | 0.001 |
| Etiology[a] | 11/1/1/1/1/1 | 72/7/4/3/9/12 | 0.957 |
| Hypertension | 3 | 15 | 0.904 |
| Diabetes mellitus | 3 | 16 | 0.983 |
| Child-Pugh classification (A/B) | 10/6 | 60/47 | 0.628 |
| WBC (×10⁹/L) | 3.17±1.87 | 3.00±2.43 | 0.779 |
| Hb (g/L) | 109.1±17.4 | 103.1±28.2 | 0.250 |
| PLT (×10⁹/L) | 40.2±17.1 | 46.7±14.7 | 0.110 |
| PT (s) | 15.93±1.59 | 16.29±1.96 | 0.484 |
| TBIL (μmol/L) | 23.74±9.87 | 22.50±11.82 | 0.692 |
| ALB (g/L) | 37.13±4.47 | 39.14±6.15 | 0.213 |
| ALT (U/L) | 30.3±21.2 | 27.7±16.6 | 0.586 |
| BUN (mmol/L) | 6.03±2.21 | 5.65±2.11 | 0.507 |
| Cr (μmol/L) | 73.12±19.32 | 73.78±20.36 | 0.903 |
| Spleneolus | 0 | 4 | 0.975 |
| Longitudinal spleen diameter (mm) | 165.1±29.7 | 184.8±27.8 | 0.010 |
| Main portal vein diameter (mm) | 13.3±2.8 | 14.3±2.5 | 0.112 |
| Laminin (μg/L) | 46.06 (9.39-1000) | 46.88 (2.0-1000) | 0.682 |
| Precollagen III (μg/L) | 61.28±39.86 | 52.32±28.48 | 0.270 |
| Collagen IV (μg/L) | 55.98±30.21 | 57.71±34.02 | 0.847 |
| Hyaluronidase (μg/L) | 189.18±131.49 | 165.95±159.43 | 0.580 |
| Operation time (min) | 162.8±48.0 | 174.8±42.4 | 0.303 |
| Estimated blood loss (mL) | 114.4±123.6 | 159.3±249.1 | 0.481 |
| No. of blood transfusions | 1 | 3 | >0.99 |

Data are given as mean±standard deviation, median (range), or number of patients, as indicated. WBC: white blood cells; Hb: hemoglobin; PLT: platelets; PT: prothrombin time; TBIL: total bilirubin; ALB: albumin; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cr: creatinine

[a]Hepatitis B/hepatitis C/schistosomiasis/alcohol/autoimmunity/idiopathic cirrhosis

mean PLT count occurring on POD 10. The mean PLT count on POD 10 (383.5±186.9×10⁹/L) was significantly higher than on POD 7 (271.1±135.6×10⁹/L), POM 1 (276.1±154.5×10⁹/L), or POM 3 (245.9±115.0×10⁹/L) (all p<0.001). There was no significant difference in the mean PLT count between POM 1 and POM 3 (p>0.05).

### Association between age, longitudinal spleen diameter, and PLT count <125×10⁹/L at POM 3

Bivariate correlation analysis was performed to analyses the relationship between these significant variables and the occurrence of a PLT count <125×10⁹/L at POM 3. The variables were age and longitudinal spleen diameter. Age and longitudinal spleen diameter were divided into groups. According to the correlation coefficient, the threshold values for a PLT count <125×10⁹/L were age >50 years (Table 3) and longitudinal spleen diameter ≤160 mm (Table 4).

Patients were divided into the following age groups: 21-35 years, 36-50 years, 51-65 years, and 66-80 years. The PLT count at POM 3 decreased gradually with increasing
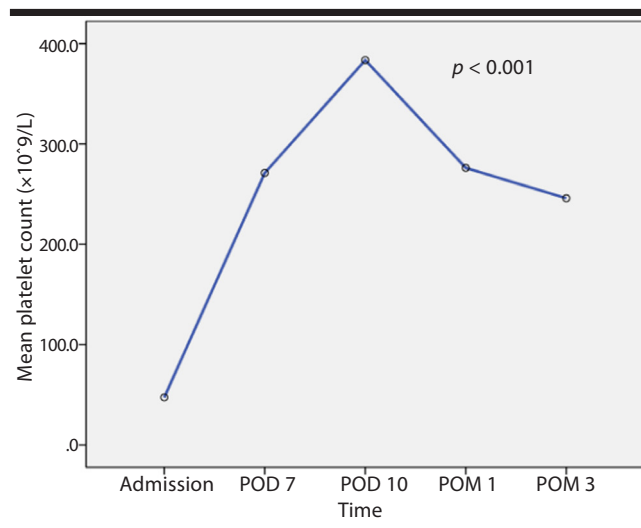


**Figure 1.** Changes in mean platelet counts
POD: postoperative day; POM: postoperative month

**Table 2.** Multivariate logistic regression analysis

| Independent variables | B | SE | Wald | df | Sig | Exp (B) | 95%CI |
|---|---|---|---|---|---|---|---|
| Age | 0.079 | 0.031 | 6.383 | 1 | 0.012 | 1.082 | 1.018-1.150 |
| Longitudinal spleen diameter | -0.023 | 0.012 | 3.713 | 1 | 0.054 | 0.977 | 0.955-1.000 |

SE: standard error; CI: confidence interval

age, as shown in Table 5. The overall difference among these measures were significant (p=0.004; Table 5; Figure 2). The incidences of a PLT count $<125\times10^9$/L at POM 3 increased gradually with increasing age as shown in Table 5. The overall differences among these incidences were significant (p=0.001; Table 5).

Similarly, all patients (except 1 with a spleen diameter of 99 mm) were divided into groups according to longitudinal spleen diameter as follows: 121-160 mm, 161-200 mm, and ≥201 mm groups. The PLT count at POM 3 increased gradually with increasing spleen diameter as shown in Table 6. The overall comparison of these measures was significant (P=0.003; Table 6, Figure 3). The incidences of a PLT count $<125\times10^9$/L on POM 3 decreased gradually with increasing spleen diameter, as shown in Table 6. The overall comparison of these incidences was significant (P=0.016; Table 6).

**Table 3.** Bivariate correlation analysis of the relationship between age and platelet count $<125\times10^9$/L at the postoperative month 3

| Correlation Factor | Correlation Coefficient | p |
|---|---|---|
| Age (years) | | |
| >45 | -0.152 | 0.093 |
| >50 | -0.251 | 0.005 |
| >55 | -0.270 | 0.002 |
| >60 | -0.266 | 0.003 |
| >65 | -0.225 | 0.012 |

**Table 4.** Bivariate correlation analysis of the relationship between longitudinal spleen diameter and the platelet count $<125\times10^9$/L at the postoperative month 3

| Correlation Factor | Correlation Coefficient | p |
|---|---|---|
| Longitudinal spleen diameter (mm) | | |
| >170 | 0.158 | 0.081 |
| >165 | 0.176 | 0.051 |
| >160 | 0.231 | 0.010 |
| >155 | 0.182 | 0.044 |
| >150 | 0.166 | 0.067 |



**Figure 2.** Changes in mean platelet counts at the postoperative month 3 in different age groups

**Table 5.** Changes in the platelet count at the postoperative month 3 in different age groups

| | 21-35 years | 36-50 years | 51-65 years | 66-80 years | 21-80 years | p (Total) |
|---|---|---|---|---|---|---|
| n | 3 | 52 | 53 | 15 | 123 | |
| PLT count ($\times10^9$/L) | 398.3±94.4 | 261.2±117.9 | 235.6±104.8 | 198.8±117.9 | 245.9±115.0 | 0.004 |
| No. with PLT count <125 ($\times10^9$/L) | 0 (0.0%) | 2 (3.8%) | 9 (17.0%) | 5 (33.3%) | 16 (13.0%) | 0.001 |

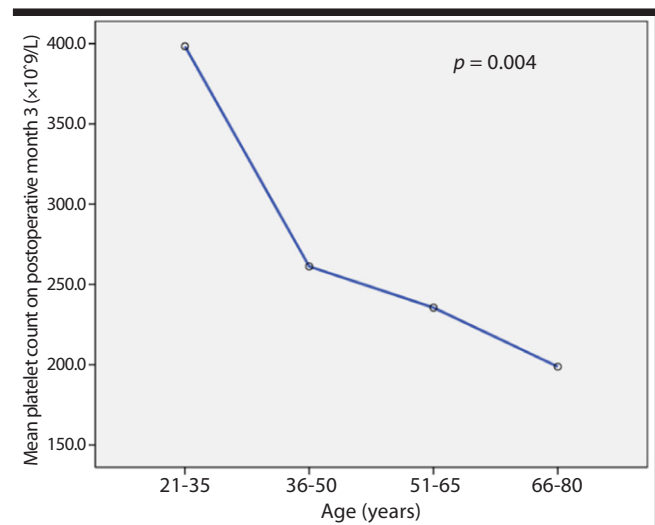Data are given as mean±standard deviation, or number (percentage) of patients, as indicated
PLT: platelets

**Table 6.** Changes in the platelet count at the postoperative month 3 in patients with different longitudinal spleen diameters
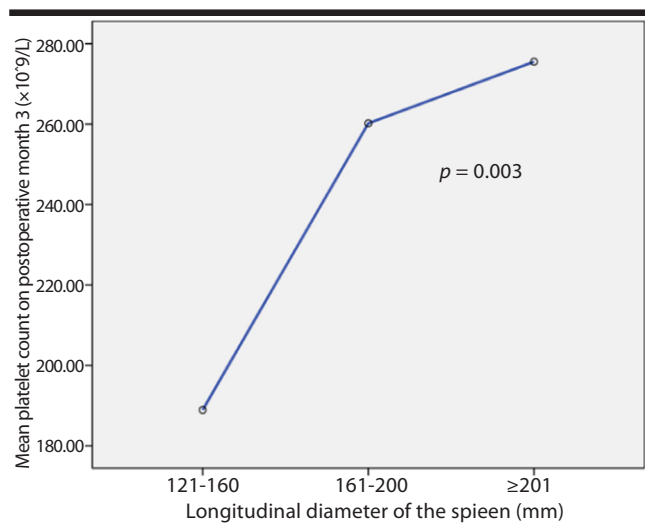
| | 121-160 mm | 161-200 mm | ≥201 mm | ≥121 mm | p (Total) |
|---|---|---|---|---|---|
| n | 29 | 63 | 30 | 122 | |
| PLT count ($\times10^9$/L) | 188.9±78.5 | 260.2±122.4 | 275.5±111.3 | 247.0±114.8 | 0.003 |
| No. with PLT count <125 ($\times10^9$/L) | 7 (24.1%) | 7 (11.1%) | 1 (3.3%) | 15 (12.3%) | 0.016 |

Data are given as mean±standard deviation, or number (percentage) of patients, as indicated PLT: platelets

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**Figure 3.** Changes in mean platelet counts at the postoperative month 3 in patients with different longitudinal spleen diameters

## DISCUSSION

Platelet counts are known to decrease progressively with age in the general population (13-16), with a mean decrease of $6-9 \times 10^9$/L with every additional 10 years of aging (15,16). However, the reasons for this age-related effect are presently unexplained. The decrease in the PLT count during aging may reflect a reduced hematopoietic stem cell reserve or decreased proliferation and differentiation capabilities of hematopoietic stem cells in older people. However, further investigations are required to explore the mechanisms underlying these age-related changes.

The above hypotheses may at least partly explain why age was an independent risk factor for PLT count $<125 \times 10^9$/L at POM 3 after LSD in the present study. Furthermore, a bivariate correlation analysis also identified age >50 years as a threshold value for an increased risk of a lower PLT count and a PLT count $<125 \times 10^9$/L at POM 3. Consistently, the mean PLT counts at POM 3 in patients aged 51-65 and 66-80 years were lower than those in patients aged 21-35 and 36-50 years, and below the total mean PLT count at POM 3. In addition, PLT counts $<125 \times 10^9$/L at POM 3 were more frequent in patients aged 51-65 and 66-80 years compared with patients aged 21-35 and 36-50 years, and more frequent than the total mean incidence of PLT count $<125 \times 10^9$/L at POM 3.

The spleen is an immune-system center containing large numbers of lymphocytes and macrophages, with bigger spleens having more macrophages. Thrombocytopenia is known to result from hypersplenism due to excessive phagocytosis of macrophages that engulf PLTs, and a larger spleen thus leads to increased phagocytosis and fewer PLTs. Removal of the enlarged spleen should thus allow PLT numbers to recover, and postoperative PLT numbers may be positively associated with the spleen size. Smaller spleen may be more inclined to have a lower PLT count after LSD. Accordingly, the current study found that longitudinal spleen diameter was an independent positive predictor of the PLT count $<125 \times 10^9$/L at POM 3.

A bivariate correlation analysis in the present study also revealed that the longitudinal spleen diameter ≤160 mm was a threshold value, below which patients were more likely to have a lower PLT count and a higher risk of a PLT count $<125 \times 10^9$/L at POM 3. Consistently, the mean PLT count at POM 3 in patients with a spleen diameter of 121-160 mm was lower than that in patients with diameters of 161-200 and ≥201 mm, and lower than the total mean PLT count at POM 3. Furthermore, the incidence of a PLT count $<125 \times 10^9$/L at POM 3 was higher among patients with spleen diameters of 121-160 mm compared with those with diameters of 161-200 and ≥201 mm, and higher than the total mean incidence of the PLT count $<125 \times 10^9$/L at POM 3.

In the present study, 5 of the 21 (23.8%) patients with a PLT count $<125 \times 10^9$/L at POM 3 were aged age >50 years and had a longitudinal spleen diameter ≤160 mm. This suggests that patients older than 50 years who also have a longitudinal spleen diameter ≤160 mm may be at increased risk of having a PLT count $<125 \times 10^9$/L at POM 3 after LSD.

It is necessary to warn patients preoperatively of the possibility of having a PLT count below the normal lower limit after surgery, especially in the case of patients older than 50 years and/or those with a longitudinal spleen diameter ≤160 mm, to avoid postoperative patient dissatisfaction (17).

This retrospective observational study showed that age is an independent positive predictor, and longitudinal spleen diameter is an independent negative predictor of having a PLT below the normal lower limit after LSD. This study also identified age >50 years and a longitudinal spleen diameter ≤160 mm as threshold values for increased risks of a lower PLT count and a PLT count below the normal lower limit at POM 3 after LSD. This study may be limited by its small sample size. Prospective trials with a large sample size are required to confirm these findings.

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