

# Grading of Peripheral Cytopenias due to Splenomegaly and Hepatitis B Cirrhotic Portal Hypertension

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## Abstract

**Background:** Splenomegaly due to hepatitis B cirrhotic portal hypertension is common in clinical practice, and it is often complicated by monolineage or multilineage cytopenias. We attempted to answer the following questions based on our 20 years of observation and research: can peripheral cytopenias be graded and what are the effects of peripheral cytopenia grades on clinical outcomes?

**Objectives:** This study aimed to investigate the grading of peripheral cytopenia in patients with splenomegaly due to hepatitis B cirrhotic portal hypertension and its effect on clinical outcomes.

**Methods:** Data from 330 patients with splenomegaly due to hepatitis B cirrhotic portal hypertension were collected from January 1991 to December 2011. All data were analysed with SPSS 13.0. Univariate and multivariate analyses were performed. The various forms of cytopenia were scored and graded according to the F value of the multiple linear regression equation. Depending mainly on the severity, cytopenia was graded as mild, moderate, or severe, and was given a total score of <2 points, 2-3 points, and >3 points, respectively. Their relationships with clinical outcomes on follow up (cured, improved, no change or dead) were then compared.

**Results:** All patients in this study were treated with splenectomy +/- devascularization or total porto-systemic shunting operation. Of 330 patients, 99 (30%) patients had monolineage cytopenia, 118 (35.8%) bilineage cytopenia, and 113 (34.2%) trilineage cytopenia. On univariate analysis, severity of erythropenia was related to a significant difference in surgical outcome on intra-group comparison ( $P<0.05$ ). On multivariate analysis, thrombocytopenia was related to a significant difference in surgical outcome when compared with leukopenia and erythropenia ( $P<0.05$ ). A significant difference in surgical outcome existed among the three grades (mild, moderate, and severe) of cytopenia ( $P<0.05$ ).

**Conclusion:** Peripheral cytopenias had significant impact on clinical outcomes. The more severe the cytopenias, the worse the surgical outcomes. Thrombocytopenia was a major factor affecting surgical outcomes. The thrombocytopenia-based three-level grading of cytopenia provided a basis for analyzing individual patients, planning treatment, and assessing prognosis in clinical practice.

**Keywords:** Cirrhotic portal hypertension; Cytopenia; Grading; Clinical significance

## Introduction

Peripheral cytopenia is a reduction in number of blood cells in peripheral blood, including a leukocyte (WBC) count of  $<4.0 \times 10^9/L$ , an erythrocyte (RBC) count of  $<4.0 \times 10^{12}/L$ , and/or a platelet (PLT) count of  $<100 \times 10^9/L$ . Peripheral cytopenia is common in patients with splenomegaly as a consequence of hepatitis B cirrhotic portal hypertension. Peripheral cytopenia plays a significant role among many factors which affect surgical outcomes in these patients [1]. In this study, peripheral cytopenias were graded, and the relationship of the grade with surgical outcomes and its clinical significance were investigated.

## Clinical Data

### General information

This is a retrospective study. Of 330 patients with splenomegaly due to hepatitis B cirrhotic portal hypertension complicated by peripheral cytopenias operated between January 1991 to December 2011, there were 225 males and 105 females, making a male to female ratio of 2.2:1. The patients' ages ranged from 15 to 79 (mean 45) years. Hepatitis B cirrhosis was confirmed by histopathology on hepatic biopsy specimens taken during operations (Figure 1). The average spleen size was 224 mm×159 mm×95 mm, as measured by ultrasound or computed

tomogram (CT) scan. Upper gastrointestinal imaging and endoscopy revealed medium-to-severe varices in distal esophagus and gastric fundus. Sixty-seven patients (20.3%) were admitted into hospital for gastrointestinal hemorrhage, and 224 (67.9%) had a previous history of haemorrhage. Splenectomy was carried out after blood transfusion to supplement the deficient white blood cells (WBC), red blood cells (RBC) or platelet (PLT). In addition, 306 patients received extensive devascularization around the cardia (plus a splenorenal vein shunt in 54 patients), five received a mesocaval shunt, and five received a portacaval shunt. Thus, 14 patients received splenectomy only.

### Statistical analysis

All data were analysed using SPSS 13.0. Statistical significance was assessed using the chi-square test for univariate analyses or multiple

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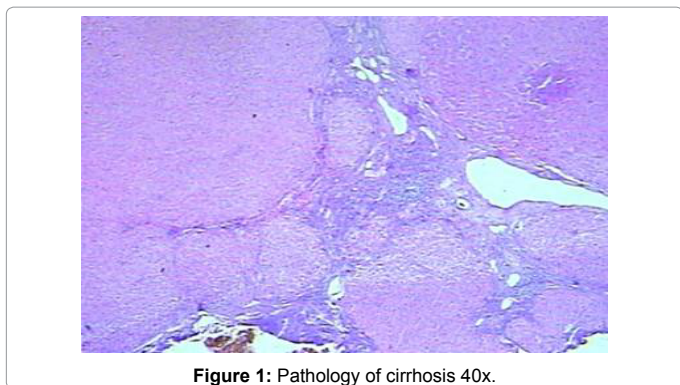


Figure 1: Pathology of cirrhosis 40x.

linear regression for multivariate analyses; a P value <0.05 was considered significant.

## Results

The surgical outcomes were classified as cured, improved, no change or dead. Those classified as cured met the following criteria: disappearance of ascites, abdominal distension, and hemorrhage, with increase in blood cell counts to normal, improvement in liver function, and no severe postoperative complications. Those who were classified as dead either died during hospitalization or on follow up. Those who showed no change in their clinical course, blood cell counts and liver function were classified as no change. All others were considered as improved. Scoring was as follows: a PLT count of  $>50 <100 \times 10^9/L$  was scored as 1,  $30-50 \times 10^9/L$  as 2, and  $<30 \times 10^9/L$  as 3; a RBC count of  $3-4 \times 10^{12}/L$  was scored as 0, and  $<3 \times 10^{12}/L$  as 1; a WBC count of  $2-4 \times 10^9/L$  was scored as 0, and  $<2 \times 10^9/L$  as 1. Therefore, peripheral cytopenias were graded as mild (<2), moderate (2-3) or severe (>3) (Table 1). The effects of the different total scores on surgical outcomes are shown in Table 2. Comparison of outcomes between the three grades revealed significant differences ( $P < 0.005$ ).

Comparisons of surgical outcomes for each patient with monolineage cytopenia are shown in Table 3. Patients with monolineage cytopenia had significantly better surgical outcomes than those with multilineage cytopenia (Tables 4 and 5).

Comparison among thrombocytopenia, leucopenia, and erythropenia revealed a significant difference, indicating that thrombocytopenia was the major influential factor of surgical outcomes (Table 6).

## Discussion

Over 90% of patients with splenomegaly due to hepatitis B cirrhotic portal hypertension are complicated with cytopenias [2], of which, 70% develop multilineage cytopenia and 30% develop monolineage cytopenia. The effect of mild peripheral cytopenia on a patient is usually not a matter of concern. However, severe leukopenia causes immune dysfunction and reduces the patient's resistance to infection. Severe erythropenia can result in ischemia, hypoxia, and even necrosis of tissues. Severe thrombocytopenia can result in reduced hemostasis and increased risk of bleeding, which can be life-threatening. In this paper, the causes of death of the patients included surgical wound bleeding, postoperative wound exudation, abdominal cavity infection and hepatic encephalopathy, but decreased peripheral blood cells is the basic and underlying factor. The greater the number of different types of decreased blood cells and the more severe the reduction, the greater is the risk to the patient.

In our study on monolineage cytopenia, only the severity of erythropenia was related to a significant difference in surgical outcomes on intra-group comparison ( $P < 0.05$ ). Although thrombocytopenia was not shown to be significant on univariate analysis, it was the only significant influential factor of surgical outcomes on multiple linear regression analysis ( $P < 0.005$ ).

The grading of cytopenias was based on: (i) the multiple linear regression equation  $\hat{Y} = 1.395 + 0.151 \text{PLT}$  which was obtained from the multiple linear regression analysis with a constant  $P = 0.001$ . This indicated that the multiple linear regression analysis was feasible in this study. The analysis demonstrated thrombocytopenia to be the main factor affecting surgical outcomes ( $P < 0.005$ ). Therefore, the grading was based on thrombocytopenia and a score of 1-3 was assigned to the different levels of thrombocytopenia. (ii) The significant difference on intra-group comparison of erythropenia in monolineage cytopenias with a  $P < 0.05$ . A RBC count of  $\leq 3 \times 10^{12}/L$  was given a score of 1. (iii) Although leukopenia was shown to have no significant difference on both univariate and multivariate analyses, in clinical practice patients with extremely low WBC are susceptible to serious infections resulting in adverse effects. Therefore, a WBC count of  $\leq 2 \times 10^9/L$  was given a score of 1. A total score of <2 indicated mild cytopenia, 2-3 indicated moderate cytopenia, and >3 indicated severe cytopenias. A comparison of surgical outcomes between the three grades revealed a significant difference ( $P < 0.005$ ), demonstrating that severe cytopenia have a significantly worse prognosis than mild cytopenia. Thus, it is scientific and feasible to grade cytopenia by this scoring method. If cytopenia is caused by hypersplenism, this grading can also be applied to grade hypersplenism or at least it can be used as a reference. Non-surgical treatment is preferred for mild cytopenia, while surgical treatment (splenectomy) is generally preferred for severe cytopenia. After removal of an enlarged spleen, blood count increased significantly [3]. In principle, non-surgical treatment is also preferred for moderate cytopenia, and surgical treatment should only be considered after failed non-surgical treatment for these patients.

Thrombocytopenia is a significant and common complication of hepatitis B cirrhotic portal hypertension [4,5]. It is related not only to retention of blood cells in the spleen, blood cell aggregation, and enhanced phagocytosis by macrophages [6], but also to viral hepatitis infection and compensation and regulation of marrow [7]. Djordevic et al. [8,9] suggested that extreme thrombocytopenia can be a risk factor for decreased survival. A PLT count of  $<30 \times 10^9/L$  can cause variceal hemorrhage in distal esophagus and gastric fundus, and intraoperative and postoperative massive hemorrhage [10], which can be life-threatening. Therefore, PLT transfusion should be performed before or during operation to increase the PLT count to  $50 \times 10^9/L$ , to ensure safety of the patients. Transfusion should also be performed when bleeding occurs. Cui et al. [11] reported that combined transfusion of PLT and fibrinogen (FB) could achieve even better effect. Splenectomy should be carried out when the PLT count does not increase significantly after

Item	Mild	Moderate	Severe
PLT	>50	30-50	<30
(Score)	1	2	3
RBC	>3	02-Mar	<2
(Score)	0	1	1
WBC	>3	02-Mar	<2
(Score)	0	0	1
Total score	<2	02-Mar	>3

Table 1: Grading of peripheral cytopenias

Total score	Case number	Surgical outcome			χ <sup>2</sup> , P value
		Cured (%)	Improved (%)	No change/Death (%)	
0-1	205	118 (57.6%)	73 (35.6%)	14 (6.8%)	χ <sup>2</sup> = 104.775 P = 0.005
02-Mar	95	40 (42.1%)	43 (45.3%)	12 (12.6%)	
04-May	30	10 (33.3%)	14 (46.7%)	6 (20.0%)	

**Table 2:** Comparison of the influence of different scores on the therapeutic effect

Group	Scoring	Patient number	Surgical outcomes			χ <sup>2</sup> , P value
			Cured (%)	Improved (%)	No change/Dead (%)	
Leukopenia (×10 <sup>9</sup> /L, n = 14)	<2	1	1 (100)	0	0	χ <sup>2</sup> = 1.478, P = 0.478
	02-Mar	10	6(60)	4 (40)	0	
	03-Apr	3	1 (33.3)	2 (66.7)	0	
Erythropenia (×10 <sup>12</sup> /L, n = 58)	<2	4	3 (75)	0	1 (25)	χ <sup>2</sup> = 10.908, P = 0.028
	02-Mar	20	16 (80)	2 (10)	2 (10)	
	03-Apr	34	16 (47.1)	16(47.1)	2 (5.8)	
Thrombocytopenia (×10 <sup>9</sup> /L, n = 27)	3	3	1 (33.3)	2 (66.7)	0	χ <sup>2</sup> = 2.220, P = 0.695
	2	1	1 (100)	0	0	
	1	23	15 (65.2)	7 (30.4)	1 (4.4)	

Note: Among the three monolineage cytopenias, only the intra-group comparison of leukopenia revealed a significant difference between different severities (P<0.05); intra-group comparisons of the other two monolineage cytopenias revealed no significant difference (P>0.05).

**Table 3:** Comparisons of surgical outcomes for each monolineage peripheral cytopenia

Item	Patient number	Surgical outcome			χ <sup>2</sup> , P value
		Cured (%)	Improved (%)	No change/Dead (%)	
Monolineage cytopenias	99	60 (60.6%)	33 (33.3%)	6 (6.1%)	χ <sup>2</sup> = 7.446, P = 0.024
Bilineage cytopenias	118	51 (43.2%)	51 (43.2%)	16 (13.6%)	

**Table 4:** Comparison of surgical outcomes between monolineage cytopenias and bilineage cytopenias

Item	Patient number	Surgical outcome			χ <sup>2</sup> , P value
		Cured (%)	Improved (%)	No change/Dead (%)	
Monolineage cytopenias	99	60 (60.6)	33 (33.3)	6 (6.1)	χ <sup>2</sup> = 7.819 P = 0.02
Multilineage cytopenias	231	103 (44.6)	102 (44.2)	26(11.2)	

Note: includes bilineage and trilineage cytopenias.

**Table 5:** Comparison of surgical outcomes between monolineage cytopenias and multilineage cytopenias

Item	T value	P value
Thrombocytopenia	2.827	0.005
Erythropenia	-0.439	0.661
Leukopenia	1.516	0.13
Constant	1.395	0

**Table 6:** Multiple linear regression analysis of cytopenias in 330 patients

transfusion of 12-24 units of PLT or decreases to the original lowest count 1-2 days after the transfusion [12]. Mastuura et al. [13] suggested that a high postoperative PLT count was also a risk factor of decreased survival, and therefore the patient should be closely monitored for a high PLT count postoperatively [14,15] and appropriate treatment should be administered immediately when necessary.

The main limitations of this study are that it is a retrospective study, the data came from a single center and all patients in this study had hepatitis B cirrhosis. Whether the results of this study can be applied to other patients require further studies.

All patients who were enrolled in this study underwent splenectomy, though it might be performed for a variety of reasons such as gastrointestinal bleeding, splenomegaly or hypersplenism.

Cytopenia grading is of clinical significance in disease severity assessment, academic communication, communication

with patients and their relatives, choosing treatment, and deciding on perioperative management in the future.

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