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# Changes of Peripheral Blood Cells in Patients with Cirrhotic Portal Hypertension

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## 1. Introduction

Hemocytopenia is very common in patients with cirrhotic portal hypertension. These patients experience complications of monolineage or multi-lineage peripheral cytopenias. However, the range of variation of these cytopenias is unclear, and the question of whether they affect all patients remains uncertain. In general, it is believed that such cytopenias are caused by hypersplenism; however, this may not always be the case as numerous factors that cause hemocytopenia exist, and hypersplenism is only one of them. Patients with hypersplenism experience hemocytopenia, but not all cytopenias are caused by hypersplenism.

Can cytopenias be graded? How do cytopenias affect prognosis? According to the observation of clinical cases, cytopenias may, in fact, influence prognosis. These questions will be discussed in this chapter, which integrates clinical data from 366 cases investigated by the author.

## 2. Changes of peripheral blood cells

It has been accepted that "all patients with splenomegaly due to cirrhotic portal hypertension will manifest cytopenias in peripheral blood [1]; however, certain limitations were noticed in the traditional opinion by the author after studying clinical data from 366 cases.

This study included 250 male patients and 116 female patients (a total of 366 patients), and the ratio of males to females was 2.2:1. The patients' ages ranged from 5 to 79 years, with an average of 43 years. All the patients had hepatic cirrhosis and an enlarged spleen. The average spleen size was 224mm×159mm×95mm, as measured by B ultrasound or CT scan. Upper gastrointestinal imaging and gastroscopy revealed that there were medium-to-severe varices in the distal esophagus and gastric fundus (Figure 1). Seventy-four patients (20.2%) were hospitalized for gastrointestinal hemorrhage, and 248 (67.8%) patients had previously experienced hemorrhaging.Thirty-six patients (9.8%) had a normal blood cell count and 330 patients had peripheral cytopenias, in which mono-lineage cytopenias accounted for 30% (99/330), bi-lineage cytopenias accounted for 35.8% (118/330) and tri-lineage cytopenias accounted for 34.2% (113/330).The range of variation of hemocytopenia is listed in Table 1. Two-hundred ninety-seven cases underwent bone marrow aspiration, in which 155 cases (52.2%) showed moderate proliferation. The remaining cases were normal.

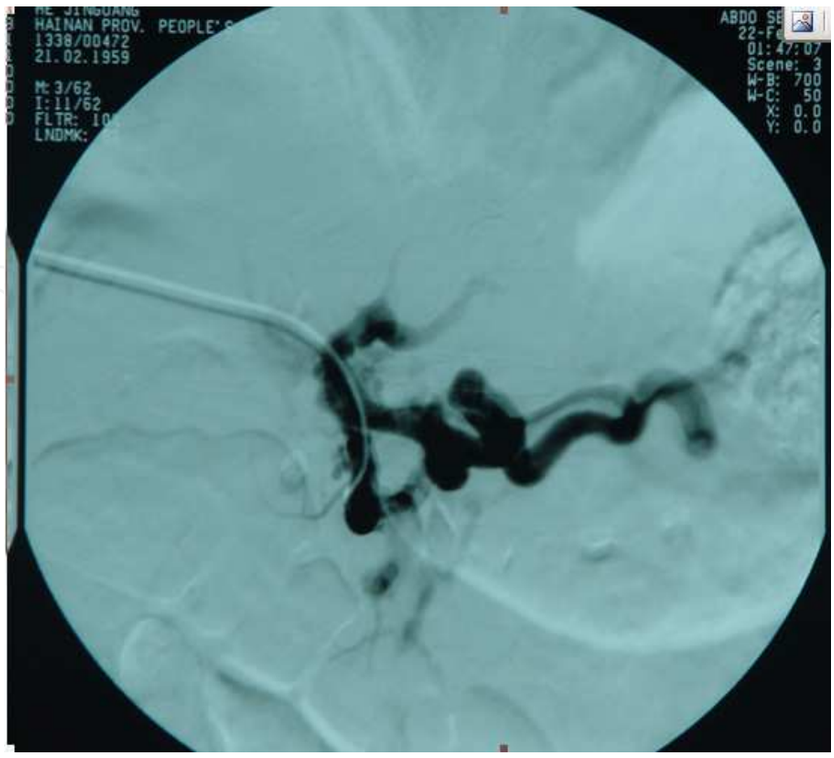


Fig. 1. severe varices in the distal esophagus and gastric fundus.

| Item | N | % | WBC ($\times10^9$/L) | RBC ($\times10^{12}$/L) | PLT ($\times10^9$/L) |
|---|---|---|---|---|---|
| Pancytopenia | 113 | 34.2 | 2.35±0.76 (median 2.36) | 2.99±0.64 (median 3.00) | 58.6±19.8 (median 57.8) |
| WBC+PLT | 30 | 9.1 | 2.76±0.71 (median 2.73) | ---- | 56.9±21.2 (median 53.8) |
| RBC+PLT | 48 | 14.5 | ---- | 2.83±0.20 (median2.63) | 67.2±21.3 (median 62.5) |
| WBC+RBC | 40 | 12.1 | 2.85±0.76 (median 2.68) | 3.11±0.30 (median 2.96) | ----- |
| PLT | 27 | 8.2 | ---- | ---- | 66.2±23.3 (median 61.7) |
| WBC | 14 | 4.2 | 2.98±0.65 (median 2.82) | ----- | ----- |
| RBC | 58 | 17.6 | ---- | 2.71±0.50 (median 2.56) | ---- |

Note: The difference in WBC was significant between Group 1 and Group 2, 4 and 6 ($P<0.05$), and not significant between Group 2 and Group 4 and 6 ($P>0.05$); The difference in RBC was significant between Group 1 and Group 7, between Group 3 and Group 4, and between Group 4 and Group 7 ($P<0.05$), not significant between Group 1 and Group 3 and 4 ($P>0.05$), and not significant between Group 3 and Group 7 ($P>0.05$); And the difference in PLT was not significant when the 4 groups were compared ($P>0.05$, $F=1.61$).

Table 1. Hemocyte decrease (mean±SEM) in 330 cases ($\bar{x}\pm s$)

## 3. Causes of hemocytopenia in peripheral blood

There are numerous causes for cytopenias in patients with hepatocirrhotic portal hypertension, including the toxic effects of hepatic viruses and alcohol on the bone marrow, hypofunctioning of the liver [2], splenomegaly, hypersplenism, gastrointestinal bleeding, and hematopoietic dysfunction caused by malnutrition. In most cases, cytopenias are caused by multiple factors.

### 3.1 Toxic effects of hepatic virus

Hepatic viruses can directly suppress the differentiation and proliferation of hemopoietic stem cells and progenitor cells [3]. (2) Hepatic virus can cause disorders of cellular immunity and humoral immunity in vivo, to compromise the body's capacity to eliminate the viruses. The constant presence of viruses damages the hemopoietic functioning of the bone marrow [4]. (3) Viruses can impair the activity of bone marrow stromal cells to reduce the secretion of cytokines and to affect the proliferation of hemopoietic cells. (4) During pathogenesis caused by cytokines, the increase in the γ- interferon level and decrease in the interleukin-6 and erythropoietin levels, can affect the proliferation of hemopoietic cells [5]. The hepatitis B virus (HBV) and hepatitis C virus (HCV) can suppress the bone marrow, and affect the growth of all karyocytes in the bone marrow. This may lead to hypoplastic anemia, and patients must undergo a bone marrow transplant to survive.

The liver and bone marrow are target tissues of HBV. This virus can kill or injure hemopoietic cells directly, causing myelosuppression, and leading to leukopenia and reduction in the detoxification ability of the liver. This renders the body more sensitive to certain medicines, toxins and environmental pollutants, and cause hypofunctioning of bone marrow hematopoiesis. Leukopenia further damages immunity to cause the active replication of HBV, forming a vicious cycle. Currently, antiviral therapy is the first choice for chronic hepatitis B patients; however, antiviral medications also lead to myelosuppression. Therefore, monitoring leukocytes in the peripheral blood is conducive to the regulation of antiviral therapy. If the leukocyte count is lower than $2\times10^9$/L, antiviral therapy should be discontinued. Both HBV and HCV can induce suppression of the precursor cells of the bone marrow, and affect the lymph cells, causing lymphopenia and hypofunctioning of the bone marrow.

### 3.2 Toxic effects of alcohol

In the 1980s, studies of patients with alcoholic liver disease reported that neutrophil granulocytes demonstrated retarded growth and delayed release in the bone marrow. Later studies showed increased apoptosis of neutrophil granulocytes. Patients with end-stage cirrhosis complicated with neutropenia underwent Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) therapy for 7 days, and the leukocyte count increased more than 100%. However, the increased leukocytes could not be destroyed in the spleen, for no leukocyte fragments were found in the spleen. Ethanol can suppress or stimulate cellular proliferation, but in most cases, it suppresses cellular growth and increases cytotoxic effects. Its mechanism includes retarded cellular proliferation and induced apoptosis and necrosis [6-8]. A foreign study reported [9] that long-term alcoholism could cause abnormalities in the bone marrow and peripheral blood. In that study, 91% patients manifested changes in the

peripheral blood including granulopenia, thrombopenia, etc., and changes in bone marrow included highly-differentiated hemopoietic tissue and myelofibrosis. Long-term alcohol consumption can reduce the absorption of folic acid and vitamin $B_{12}$, which impairs the synthesis of erythrocytes. Djordjevic et al [10] believed both that hepatic viruses and alcoholism were able to cause cytopenias.

### 3.3 Hypofunctioning of liver

Hypofunctioning of the liver reduces degradation of toxic metabolites by liver cells; in this case, the liver cannot detoxify the toxins that suppress the bone marrow, thus affecting hemopoietic function. The incidence of liver disease combined with thrombopenia is 15% - 70%. It is usually at mild or moderate level, and its severity is a prognostic indicator. In liver diseases, thrombopenia is closely related to hepatocirrhosis, anti-platelet autoantibodies [11], bone marrow suppression caused by HBV and HCV, and toxic effects from excessive alcohol consumption [12]. The discovery of thrombopoietin (TPO) in 1994 ushered in a new era in the study of cirrhotic thrombopenia. TPO is almost exclusively produced in liver cells; a small proportion of TPO is produced in the kidneys, bone marrow stromal cells and muscle. The production of TPO depends on the function and amount of liver cells. In cirrhosis, functional liver cells become less able to decrease the secretion of TPO. A study by Wolber et al. [13], of cirrhotic patients developing from the compensation to decompensation stage, demonstrated that the expression or serum level of TPO changed from an increase to a decrease, and that the platelet count decreased gradually. The decrease in liver function, to some extent, was related to hemocytopenia and bone marrow dysfunction. Forbes et al. [14] suggested that hepatic exogenous myofibroblasts played an important role in hepatic fibrosis. In hepatic fibrosis, bone marrow stem cells differentiate into hepatic endothelial parenchymal cells but not into myofibroblasts. This indicates that the change in hemopoietic function and inner environment of the bone marrow might be somehow related to or interactive with the occurrence and development of hepatic fibrosis or even hepatic cirrhosis. These observations suggest that changes in the bone marrow of cirrhotic patients do not result from one single factor but a combination of multiple factors, with a complicated regulation mechanism. The changes in bone marrow might be directly or indirectly related to the severity of hepatic cirrhosis and changes in liver or spleen function. Their relationship and the detailed mechanism remain to be further explored. Solving this puzzle will be of significant importance to clinical practice.

### 3.4 Splenomegaly and hypersplenism

Hypersplenism is secondary to splenomegaly. Two mechanisms for splenomegaly caused by liver diseases exist. The first mechanism is expansionary splenomegaly, including congestive splenomegaly caused by increased venous pressure and hyperemic splenomegaly caused by increased splenic arterial flow; the former is the main cause. The second mechanism is hypertrophic splenomegaly, including: (1) Hepatic virus antigen and exogenous antigens unprocessed by the liver due to a shunting procedure, can stimulate the spleen and lead to hypertrophy of the immune tissue in the spleen (splenic corpuscle, periarterial lymphatic sheath, marginal zone). (2) In hepatic cirrhosis, increased necrotic cells and hypofunctioning of the hepatic reticuloendothelial system promote compensatory hypertrophy and lead to hyperfunctioning of the splenic reticuloendothelial system. (3) Increased intrasplenic pressure, stasis of blood circulation, change in the metabolic

environment and other factors can cause fibroplastic proliferation. Generally speaking, intrasplenic immune tissues show obvious hypertrophy during hepatitis, and middle or end stage cirrhotic patients mainly manifest splenic sinus dilation, hypertrophy of reticuloendothelial system and fibrous tissues.

Currently, there are several hypotheses concerning the mechanism of cytopenia: (1) The hypothesis of intrasplenic trapping[15]: After the formation of splenomegaly, blood volume in the spleen increases, and a great number of leukocytes, erythrocytes and platelets are trapped in the spleen. The ratio of trapped hemocytes compared with that in the normal spleen is 5.5- to 20-fold, resulting in hemocytopenia in the peripheral blood. (2) The hypothesis of cytophagy: There are a large number of mononuclear-macrophages in the spleen. Under pathological circumstances, mononuclear-macrophages demonstrate hyperfunctioning in cytophagy and destruction of hemocytes, especially erythrocytes [16]. Recently, a study using erythrocyte creatine (EC), the life-span sensitive marker of erythrocytes, revealed that the EC level was significantly increased in patients with splenomegaly due to post-necrotic cirrhosis compared with patients with hepatic cirrhosis with normal spleens ($P$<0.05). In addition, the same was observed compared with the normal control group but without a significant difference [17]. This suggested that splenomegaly accelerated the destruction of erythrocytes and the determination of the EC value could be used to evaluate the severity of cirrhotic splenomegaly [18]. (3) The spleen can produce excessive "splenic hormones" to suppress the hemopoietic function of the bone marrow, and accelerate the destruction of and trap produced hemocytes to prevent them from entering into blood circulation [19]. (4) The hypothesis of autoimmunity: The spleen is a large lymph organ that produces antibodies. Antigens unprocessed by the liver enter the marginal zones of splenic lymph follicles (splenic nodule) and activate the pro-lymphocytes and plasma cells to generate antibodies. These antibodies can destroy hemocytes causing hemocytopenia in the peripheral blood.

### 3.5 Gastrointestinal bleeding

Gastroesophageal fundus varices bleeding is a common complication for patients with cirrhotic portal hypertension. Gastrointestinal bleeding of any cause can directly lead to a decreased amount of hemocytes in the effective circulatory blood volume.

Chronic gastrointestinal bleeding can result in iron, folic acid and vitamin $B_{12}$ deficiencies, and insufficient material for the synthesis of erythrocytes. Massive loss of erythrocytes can lead to anemia in patients. A $Cr^{51}$ labeled-erythrocyte test demonstrated that only 20% of patients with cirrhosis complicated with anemia had increased erythrocytes in their spleens.

### 3.6 Malnutrition

Portal hypertensive gastropathy can cause malabsorption of hematopoietic growth factors and non-visible loss of nutrients necessary for hematopoiesis. Additionally, the lack of iron, folic acid and vitamin $B_{12}$ results in insufficient materials for the synthesis of erythrocytes, leading to decreased hematopoiesis.

The significance of exploring the causes of hemocytopenia in the peripheral blood in the patients with cirrhotic portal hypertension lies in its guidance for treatment and evaluation

for therapeutic effects. If hemocytopenia is caused by splenomegaly or hypersplenism, whether monolineage or multi-lineage, the decreased hemocytes will rise significantly after a splenectomy ($P$<0.01). The most sensitive is hemocyte is the platelet, which will increase half an hour after the operation, and reach the highest level in 2 weeks; afterwards it will decrease gradually and remain at a normal level. Leukocytes and erythrocytes would increase following the platelets. Hemocytopenia in the peripheral blood caused by non-splenic factors does not lead to a definite increase in hemocytes after splenectomy.

## 4. Hemocytopenia in peripheral blood and its prognosis

The postoperative prognosis was classified as cured, improved or dead. There were few cases without any changes. In this analysis, cured meant meeting the following criteria: the disappearance of ascites, abdominal distension and hemorrhage, blood cell count increase and recovery, improvement in liver function, no severe postoperative complications, and meeting the criteria for being discharged from the hospital. On the other hand, dead meant that the patients died during hospitalization, or that the patients in critical condition died one week after early discharge from the hospital, as requested by the relatives. All others were considered improved. Comparison of the therapeutic effect between each mono-lineage cytopenia group is shown in Table 2. Comparison of the therapeutic effect between mono-lineage cytopenia and bi-lineage and comparisons of the therapeutic effect between the mono-lineage cytopenia and bi-lineage cytopenias, the mono-lineage cytopenia and multi-lineage cytopenias are shown in Table3 and Table 4, respectively.

| Group | Grade | Case number | Therapeutic effect | | | $\chi^2$, $P$ value |
|---|---|---|---|---|---|---|
| | | | Cured (%) | Improved (%) | Dead (%) | |
| WBC ($\times 10^9$/L, N=14) | <2 | 1 | 1 (100) | 0 | 0 | $\chi^2$=1.478, $P$=0.478 |
| | 2-3 | 10 | 6(60) | 4 (40) | 0 | |
| | 3-4 | 3 | 1 (33.3) | 2 (66.7) | 0 | |
| RBC ($\times 10^{12}$/L, N=58) | <2 | 4 | 3 (75) | 0 | 1 (25) | $\chi^2$=10.908 $P$=0.028<0.05 |
| | 2-3 | 20 | 16 (80) | 2 (10) | 2 (10) | |
| | 3-4 | 34 | 16 (47.1) | 16(47.1) | 2 (5.8) | |
| PLT ($\times 10^9$/L, N=27) | <30 | 3 | 1 (33.3) | 2 (66.7) | 0 | $\chi^2$=2.220, $P$=0.695 |
| | 30-50 | 1 | 1 (100) | 0 | 0 | |
| | 50-100 | 23 | 15 (65.2) | 7 (30.4) | 1 (4.4) | |
| HB (hemoglobin ) ($\times$g/L, N=366) | <30 | 78 | 32 (41) | 39 (50) | 7(9) | $\chi^2$=4.236, $P$=0.375 |
| | 30-70 | 52 | 28 (53.8) | 20 (38.5) | 4 (7.7) | |
| | >70 | 236 | 122 (51.7) | 89 (37.7) | 25 (10.6) | |

Note: Among the four mono-lineage peripheral cytopenia groups, only the RBC group demonstrated a significant difference in intra-group comparison ($p$<0.05); comparison among the four groups revealed no significant difference ($P$>0.05).

Table 2. Comparison of the therapeutic effect between each mono-lineage peripheral cytopenia group

Table 2 shows that only the RBC group demonstrated a significant difference ($P<0.05$) in the intra-group comparison among the mono-lineage cytopenia groups. According to Table 3 and Table4, there were significant differences ($P<0.05$) in the therapeutic effects between mono-lineage cytopenias and multi-lineage cytopenias, indicating that the more severe the cytopenia, the worse the therapeutic results appeared to be.

For the multi-lineage cytopenias(Table5), a multiple linear regression analysis was applied, and results revealed that thrombocytopenia was the major factor ($P<0.005$) influencing the therapeutic effect, while leukopenia, erythropenia and decreased hemoglobin showed no statistical significance, and should not be considered. Erythropenia showed significant differences in the intra-group comparison of mono-lineage cytopenias, but no difference compared to other mono-lineage cytopenia groups. This was possibly due to the small sample size in the mono-lineage cytopenia groups. Leukopenia showed no significant difference in the univariate analysis or the multivariate analysis, and had no influence on the therapeutic results. For example, 2 patients recovered and were discharged from the hospital though their leukocyte count was lower than $1\times10^9$/L; this may have been because they had no serious postoperative infection. Theoretically, anemia is related to the prognosis, but in this research it showed no statistical significance in the univariate analysis or the multivariate analysis; the reason for this may have been because the blood transfusions before and during operation had a favorable effect on the blood condition. Although thrombocytopenia had no statistical significance in the univariate analysis, in the multiple linear regression analysis it was indicated to be the most important influential factor with the increase in case load.

| Item | Total case number | Therapeutic effect | | | $\chi2$, $P$ value |
|---|---|---|---|---|---|
| | | Cured (%) | Improved (%) | Dead (%) | |
| Mono-lineage cytopenia | 99 | 60 (60.6%) | 33 (33.3%) | 6 (6.1%) | $\chi2=7.446$, $P=0.024$ |
| Bi-lineage cytopenia | 118 | 51 (43.2%) | 51 (43.2%) | 16 (13.6%) | |

Table 3. Comparison of the therapeutic effect between the mono-lineage cytopenia and bi-lineage cytopenia

| Item | Total case number | Therapeutic effect | | | $\chi2$, $P$ value |
|---|---|---|---|---|---|
| | | Cured (%) | Improved (%) | Dead (%) | |
| Mono-lineage cytopenia | 99 | 60 (60.6) | 33 (33.3) | 6 (6.1) | $\chi2=7.819$, $P=0.02$ |
| Multi-lineage cytopenia | 231 | 102 (44.2) | 102 (44.2) | 27 (11.6) | |

Table 4. Comparison of the therapeutic effect between the mono-lineage cytopenia and tri-lineage cytopenia

Thrombocytopenia is a significant and common complication in posthepatitic cirrhotic portal hypertension[20-21]; it is related to not only retention of blood cell in the spleen, blood cell aggregation and enhanced phagocytosis of macrophages[22], but also HBV infection, and compensation and regulation of marrow[23]. Djordevic et al[10]. proposed that extreme

thrombocytopenia was life-threatening. A PLT count of < $30x10^9$/L can cause variceal hemorrhaging in the distal esophagus and gastric fundus, and intraoperative and postoperative massive wound hemorrhaging, which can be life-threatening. Therefore, PLT transfusions should be performed before an operation to increase the PLT count to $50\times10^9$/L to ensure the safety of the patient. Cui et al[24]. reported that PLT transfusions combined with plasma fibrinogen transfusions led to better results. In some cases, after transfusion of 12-24 units of PLT, the PLT count did not increase obviously, or decreased to the previous lowest count after 1-2 days. These types of patients are suitable for splenectomy[25]. Mastuura et al.[26]suggested that the excessive postoperative PLT count was also a life-threatening factor, so the condition of the patient should be closely monitored[27-28] when there is excessive platelet count, appropriate treatment should be administrated immediately.

| Item | T value | *P* value |
|---|---|---|
| PLT | 2.827 | .005 |
| RBC | -.439 | .661 |
| WBC | 1.516 | .130 |
| HB | 0.628 | 0.531 |
| Constant | 1.395 | .000 |

Note: Regression equation $\hat{Y}$ =1.395+0.151 PLT

Table 5. Multiple linear regression analysis of blood cells in 366 cases

## 5. Grading of hemocytopenia

In 1907, Chauffard proposed the term 'hypersplenism' for the first time[29]. After further research, in 1949, Doan[30] proposed the criteria for hypersplenism: 1. enlarged spleen 2. mono-lineage or multi-lineage cytopenias 3. normal or proliferative bone marrow 4. disappearance of the pathological changes in the blood components after splenectomy. While these four criteria are indispensable for the diagnosis of hypersplenism, peripheral cytopenia and an increase and recovery in blood cell count after a splenectomy are the major criteria for assessing hypersplenism due to cirrhotic portal hypertension. This is because splenomegaly in itself is a necessary criterion for the cirrhotic portal hypertension.

It is of vital significance to formulate a grading method, like the Child-Pugh Classification for liver function, to evaluate hypersplenism. However, grading of hypersplenism is extremely difficult for many reasons. 1) Some patients show decreased monolineage cytopenias and others show bi-lineage cytopenias. Even patients with pancytopenia barely meet the grading criteria. 2) There are many causes of hemocytopenia, but no examination can ascertain whether it is caused by splenomegaly or hypersplenism. A definite diagnosis would be made only when hemocytes returned to a normal level after splenectomy.

Although grading of hypersplenism is difficult, hemocytopenia could be graded. According to a multiple linear regression, thrombopenia is the major factor influencing the effect of surgery. The 330 cases of cytopenia scores were mainly based on thrombocytopenia combined with erythropenia, as well as clinical experience (leukopenia). Scoring was as follows: PLT＞50<$100x10^9$/L was scored as 1 point, 30-$50x10^9$/L was scored as 2 points, <$30x10^9$/L was scored as 3 points; RBC 3-$4x10^{12}$/L was scored as 0 points, and RBC<$3x10^{12}$/L was scored as 1 point; WBC 2-$4x10^9$/L was scored as 0 points, and

WBC<2x10$^9$/L was scored as 1 point. Except for 36 cases with normal blood cell counts and 69 cases with 0 points, the influences of scores on postoperative prognoses in 261 cases are shown in Table 6 (totally 105 cases). There were significant differences between the 3 groups ($P<0.05$). Therefore, peripheral cytopenias were graded as mild (<2), medium (2-3) or severe (>3) (Table 7).

Thus, only cytopenias can be graded. In the present study, the cases were scored and graded based on the accumulated scores. The scoring criteria used in this study were: 1.Analytical results of multiple linear regression: F value obtained from multiple linear regression equation was 7.993 ($P<0.005$), indicating that multiple linear regression was applicable. The equation $\hat{Y}$=1.395+0.151PLT indicated that thrombocytopenia was the major influential factor for postoperative prognosis. Therefore, according to the severity of the thrombocytopenia, 1 to 3 points was scored. 2. Intra-group comparison of erythropenia showed a significant difference ($P<0.05$), so an RBC count ≤3x10$^{12}$/L was scored as 1 point. 3. According to clinical experience, leukopenia can cause severe infection and lead to undesirable effects. A WBC of count ≤2x10$^9$/L was scored as 1 point, though leukopenia showed no statistical significance in either the univariate analysis or multivariate analysis. A total score of $<2$ points indicated mild cytopenia, 2-3 points indicated medium cytopenia and $>3$ points indicated severe cytopenia. If cytopenias are caused by hypersplenism, this grading standard could also be used for grading hypersplenism or as a reference.

| Item | Total case number | Therapeutic effect | | | χ2, P value |
|---|---|---|---|---|---|
| | | Cured (%) | Improved (%) | Death (%) | |
| 1 point | 136 | 80 (58.8%) | 43(31.6%) | 13 (9.6%) | χ2=10.163 P=0.034 |
| 2-3 points | 95 | 41 (43.2%) | 44 (46.3%) | 10 (10.5%) | |
| 4-5 points | 30 | 10 (33.3%) | 15 (50%) | 5 (16.7%) | |

Table 6. Comparison of the influence of different scores on the therapeutic effect

| Item | Mild | Medium | Severe |
|---|---|---|---|
| PLT | >50 | 30-50 | <30 |
| (Score) | 1 | 2 | 3 |
| RBC | >3 | 2-3 | <2 |
| (Score) | 0 | 1 | 1 |
| WBC | >3 | 2-3 | <2 |
| (Score) | 0 | 0 | 1 |
| Total score | $<2$ | 2-3 | $>3$ |

Table 7. Grading of peripheral cytopenias (hypersplenism)

Cytopenia grading could facilitate clinical practice in various aspects, including assessing the disease condition, representation and academic communication, communication with patients and their relatives to resolve or avoid medical disputes, choosing a suitable treatment plan (for example, splenectomy is suitable for severe cytopenia or hypersplenism) and taking preventive methods before an operation[16] to increase the curative rate.

## 6. Treatment

As to the patients with splenomegaly due to cirrhotic portal hypertension complicated with hemocytopenia in the peripheral blood, treatment should aim at both the causes and clinical symptoms, that is, the principle of treating the branch and the root simultaneously.

### 6.1 Treatment of causes of disease

- Antiviral treatment: Patients with severe viral infection should take antiviral medicine for an extended time, and should be constantly monitored to protect liver function.
- Avoid drinking alcohol: Patients with alcoholic cirrhosis and post-hepatic cirrhosis should avoid drinking alcohol; otherwise, disease conditions may deteriorate. In addition, medications that affect liver function should be avoided.
- Correcting malnutrition: Patients with obvious emaciation and malabsorption should replenish nutrients, such as iron, folic acid and vitamin $B_{12}$ to avoid a shortage of materials for the synthesis of erythrocytes. Additionally, patients should undergo blood transfusions to treat anemia and increase the hemochrome level.

### 6.2 Treatment of symptoms

Different treatments should be applied according to the severity of the disease. Patients with mild hemocytopenia should be under close observation; for patients with moderate hemocytopenia, blood components or whole blood transfusions should be applied as well as hemocyte boosting medications. In severe cases, a splenectomy in the patients with splenomegaly should be considered. Theoretically, splenic arterial embolization can also achieve the same effect as a splenectomy, but this procedure tends to cause splenic infarction, splenic necrosis, splenic abscess and high fever. This method should only be attempted by experienced physicians.

In recent years, autologous stem cell transplantation has achieved good results in the treatment of cirrhotic portal hypertension complicated with hemocytopenia in the peripheral blood [17], but more research is needed to further its application in clinics.

### 6.3 Treatment of both the branch and root: Treating the causes and the clinical symptoms

1. Gastrointestinal bleeding: Gastrointestinal bleeding is not only a cause of hemocytopenia in peripheral blood, but also a complication of cytopenia. It is of vital importance to treat gastrointestinal bleeding; treatment measures include blood transfusion, fluid infusion, intravenous injection of antacid, administration of somatostatin (sandostatin and stilamin), endoscopic loop ligation of bleeding areas, sclerotherapy, and so on. Lecleire et al. [31] demonstrated that the success rate of endoscopic treatment could reach 80%. Intervention embolization can also be applied. Selective embolization can stop the bleeding in most cases. In recent years, with the improvement of coaxial catheter and embolization material, super-selective angiography and transcatheter embolization (SATE) is regarded as a safe and effective method to treat gastrointestinal hemorrhage[32]. It should be the first choice for patients suffering from post-operational massive hemorrhage, especially for the elderly or the sick. If the intervention fails, surgery should be performed.

If massive hemorrhage cannot be stopped using the measures mentioned above, emergency surgery should be performed, including pericardial devascularization and/or placement of a transjugular intrahepatic portal systemic shunt.

2. Liver transplantation: Schuppan et al. [33] concluded that liver transplantation was an effective method to treat cirrhotic portal hypertension, as it not only corrected liver problems, but also cured portal hypertension, and was likely an effective way to treat hemocytopenia. After transplantation, the TPO level increases immediately. In 2 or 3 days, the TPO level can be 5-10 times the level it was before the surgery. In about 6 days, the platelet count returns to the normal range, and anemia is corrected. Therefore, liver transplantation can treat both the branch and root simultaneously.

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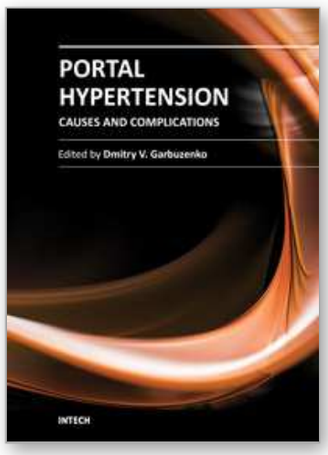


**Portal Hypertension - Causes and Complications**
Edited by Prof. Dmitry Garbuzenko

ISBN 978-953-51-0251-9
Hard cover, 156 pages
**Publisher** InTech
**Published online** 14, March, 2012
**Published in print edition** March, 2012

Portal hypertension is a clinical syndrome defined by a portal venous pressure gradient, exceeding 5 mm Hg. In this book the causes of its development and complications are described. Authors have presented personal experiences on conducting patients with various displays of portal hypertension. Moreover, the book presents modern data about molecular mechanisms of pathogenesis of portal hypertension in liver cirrhosis, the information about the original predictor of risk of bleeding from gastro-esophageal varices and new methods for their conservative treatment.



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