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Impact of total splenectomy on peripheral lymphocytes and their subsets in patients with hypersplenism associated with cirrhotic portal hypertension

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To study the impact of total splenectomy (TS) on peripheral lymphocytes and their subsets in patients with hypersplenism associated with cirrhotic portal hypertension (CPH). We studied 102 consecutive patients who received TS from January 2008 to January 2020 due to CPH-related hypersplenism. A similar number of healthy individuals are used as healthy controls (HC). The total lymphocyte counts and their percentages of B lymphocytes, total T lymphocytes (cluster of differentiation (CD)3⁺) and their subsets (CD4⁺, CD8⁺), and natural killer (NK) cells in preoperative peripheral blood samples in hypersplenism patients were significantly lower than that of the HCs (both $P < 0.05$). The total lymphocyte counts and percentages of B lymphocytes in peripheral blood were significantly increased 1 week and 1 month after TS when compared with the pre-TS values ($P < 0.05$). There was no significant difference in the percentages of NK cells before or after surgery ($P > 0.05$). However, the percentages of CD3⁺ cells was significantly higher 1 month after than before surgery ($P < 0.001$). The percentages of CD4⁺, and CD8⁺ T lymphocytes were significantly lower 1 week after surgery ($P < 0.05$), but they were significantly higher 1 month after surgery ($P < 0.01$). The CD4⁺:CD8⁺ ratio was not significantly different from those before surgery, and 1 week or 1 month after surgery ($P > 0.05$). Patients with hypersplenism associated with CPH were significantly immunosuppressed preoperatively. After TS, the total lymphocyte count and percentages of B lymphocytes, and total T lymphocytes and their subsets increased significantly, resulting in improved immune functions.

Hypersplenism associated with cirrhotic portal hypertension is a common condition that is often complicated by peripheral cytopenias¹. The more spectrum of peripheral blood cytopenia affects, the worse the prognosis, and may even endanger the life of the patient². Peripheral cytopenias can be caused by hypersplenism, non-hypersplenism, and a combination of other factors, though hypersplenism is still the major contributing factor³.

The definition of hypersplenism was controversial until in 1955, Dameshek⁴ defined hypersplenism by presence of four conditions: (a) splenomegaly; (b) mono-lineage or multi-lineage cytopenias; (c) normal status or hyperplasia of bone marrow; (d) correction of cytopenias after splenectomy. Strictly speaking, it is not appropriate to correct hypocytopenia after splenectomy as one of the criteria for diagnosing hypersplenism. Because various shunts can also correct hypocytopenia, indicating that dredging venous blood flow is the key. It can be speculated that the retention of blood cells in the spleen may be the main reason for the reduction of peripheral blood cells. However, the lack of such reports in the literature is collectively referred to as hypersplenism. The ideal diagnosis of hypersplenism in cirrhosis and portal hypertension should have three: First of all, non-hypersplenism factors that cause peripheral cytopenias such as toxic effects of hepatitis viruses on bone marrow⁵⁻⁷, gastrointestinal bleeding⁸, Severe infection, immunocompromised status^{9,10}, drug toxicity¹¹⁻¹³, platelet destruction in peripheral circulation¹⁴, Blood disease, and hematopoiesis disorders caused by deficiency of vitamins and nutrients^{2,15,16} should be excluded. (1) The spleen enlarges, the blood storage function of the spleen and the function of destroying blood cells through phagocytosis, production of abnormal antibodies and immune imbalance are enhanced, resulting in an increase in the number of blood cells stored and destroyed in the spleen. (2) There is a decrease

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in one or more blood cell components in the blood. This diagnosis does not include splenectomy and shunt to eliminate the content of peripheral blood cell reduction because they have to wait for surgery to be diagnosed, and hypersplenism should be diagnosed before surgery or patients without surgery, and use it to guide treatment.

The spleen is the largest lymphoid organ. Lymphocytes in the spleen account for approximately 25% of all the lymphocytes in the body. The spleen forms an important part of the whole immune system. T lymphocytes, B lymphocytes, and natural killer (NK) cells are the main immune cells in the spleen. The immune cells and factors in the spleen undertake non-specific immune functions through phagocytosis, and they also carry out specific immune functions through cellular and humoral immunity mediated by T and B lymphocytes. The spleen also participates in the immune response by adjusting the proportion of immune cells within the spleen and in peripheral blood¹⁷. Lymphocytes are a type of immune cell in the circulation, and are composed of T and B lymphocytes, the latter being the main humoral immune cells. NK cells are the main effectors of innate immune response¹⁸, and they mediate innate immune responses. They do not rely on antibodies or complements, but can kill target cells directly, thus playing a part in resisting infection and immune regulation/surveillance^{19,20}.

The total number of clusters of differentiation (CD)³⁺ cells reflects the total number of T lymphocytes which can be divided into two subsets, CD4⁺ and CD8⁺, according to their phenotypes and functions. The T-lymphocyte subsets are the most important cell populations in the immune system. CD4⁺ cells are mainly T helper (Th) cells which secrete interleukins, tumor necrosis factor and other cytokines, and express different surface molecules. They play an important part in regulation of specific and non-specific immunity, as well as cellular and humoral immunity²¹. CD8⁺ cells exert cytotoxicity to inhibit T lymphocytes¹⁸ and are the main effectors of the immune system to eliminate virus-infected cells¹⁷. Appropriate immune functions are maintained through the interaction of the T-lymphocyte subsets¹. The CD4⁺:CD8⁺ ratio is an important indicator that reflects directly a balanced immune function of host T cells.

Most patients with cirrhosis and portal hypertension and hypersplenism can be treated non-surgically. However, a small number of patients require surgical treatment based on total splenectomy due to factors such as severe hypersplenism, repeated gastrointestinal bleeding, or a huge spleen that affects the quality of life, or poor results of non-surgical treatment. In the past, people did not know enough about the peripheral lymphocytes and their subgroups in patients with cirrhosis and portal hypertension and hypersplenism. In particular, there was almost no report on the impact on them after total splenectomy, so we conducted the research.

Patients and methods

The study cohort. Ethical approval for this research project was obtained from the Ethics Committee of Hainan General Hospital (Hainan, China) (Ethical Lot Number: Med-Eth-Re [2021] 003). Consecutive patients with hypersplenism associated with cirrhotic portal hypertension who underwent TS at Hainan General Hospital (Hainan, China) from January 2008 to January 2020 were enrolled in this study. These patients formed the “TS group”.

All methods were performed in accordance with the relevant guidelines and regulations/Declaration of Helsinki. Informed consent obtained from all patients in every research.

The control cohort. During the study period, a volunteer group of the same number of healthy individuals matched with age and gender with the TS group was recruited to form the control group.

Treatment. All patients in the TS group underwent total splenectomy as a part of the surgical treatment. The control group of individual did not receive any medical or surgical treatment, and they were completed healthy individuals.

Blood taking for cell counts. In the TS group of patients, peripheral blood was taken preoperatively to determine the total lymphocyte count, the percentages of B lymphocytes, NK lymphocytes, total T cells (CD3⁺) and T-cell subsets (CD4⁺ and CD8⁺), as well as counts of white blood cells (WBCs), red blood cells (RBCs) and platelets. These tests were repeated 1 week and 1 month after surgery. In the control group of normal and healthy individuals, peripheral blood was taken for the same preoperative blood tests as in the TS group of patients.

Statistical analyses. The collected data were entered into Epidata 3.1, analyzed using SPSS 26 (IBM, Armonk, NY, USA) and Rstudio 1.1.456 (R Project for Statistical Computing, Vienna, Austria), and visualized using Prism 8.2.1 (GraphPad, San Diego, CA, USA). Measurement data were expressed as mean ± standard deviation. Count data were expressed as percentages. A $P < 0.05$ was considered significant.

Results

The TS group consisted of 102 patients, with 57 men and 45 women. The mean age ± standard deviation was 43.6 ± 5.9 years. The underlying etiologies of liver cirrhosis were hepatitis B virus (HBV) infection in 61 patients (59.8%), hepatitis C virus (HCV) infection 15 patients (14.7%), alcoholic hepatitis 11 patients (10.8%), cholestasis 7 patients (6.9%) and other causes 8 patients (7.8%). Overall, 81 patients (79.4%) had Pugh-Child grade A cirrhosis and 21 (20.6%) had grade B cirrhosis. TS was carried out in these patients as a part of the operations for massive gastrointestinal bleeding of ≥ 500 ml (n = 54), a low platelet count of ≤ 5 × 10⁹/L (n = 31) and splenomegaly (n = 17). In addition, 91 of these 102 patients underwent pericardial devascularization. There were 102 healthy individuals included into the control group which consisted of 58 males and 44 females, with a mean ± standard deviation age of 44.13 ± 3.6 years. There were no significant differences between groups in age and

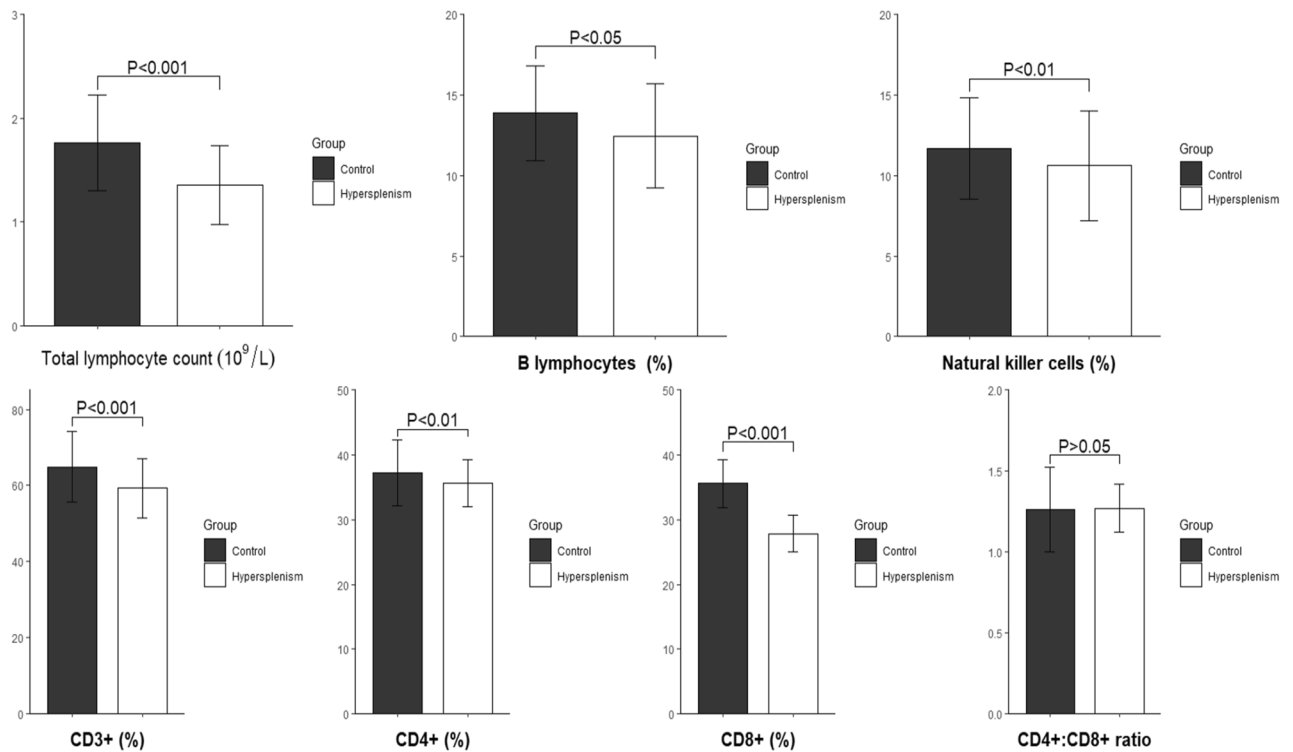


Figure 1. Comparison of peripheral lymphocytes and their subsets between the hypersplenism group and control group.

gender ($P > 0.05$). No healthy individuals in the control group had any history of liver diseases and they had not received any medical or surgical treatment for any associated medical conditions.

Before surgery, the total lymphocyte count and percentages of B lymphocytes and NK cells in peripheral blood were significantly lower in the TS group than those in the control group ($P < 0.05$). In the TS group, the total lymphocyte count and percentage of B lymphocytes in peripheral blood increased significantly 1 week and 1 month after surgery when compared with those before surgery (both $P < 0.05$) (Fig. 1). There was no significant difference in the percentage of NK cells before and after surgery ($P > 0.05$).

Before surgery, the percentages of total T lymphocytes ($CD3^+$) and their subsets ($CD4^+$ and $CD8^+$) in peripheral blood were significantly lower in the TS group than those in the control group ($P < 0.01$). In the TS group, when compared with the results before surgery, the percentage of $CD3^+$ lymphocytes increased significantly 1 month after surgery ($P < 0.001$). In addition, the percentages of $CD4^+$ and $CD8^+$ lymphocytes were significantly lower 1 week after surgery ($P < 0.05$), but they were significantly higher 1 month after surgery ($P < 0.01$) (Fig. 2). The $CD4^+ : CD8^+$ ratio showed no significant difference before or 1 month after surgery ($P > 0.05$).

Discussion

Chu and colleagues²² stated that further research is required to ascertain if subtotal splenectomy can improve the immune function of the residual spleen in patients with cirrhotic splenomegaly. In the present study, the total lymphocyte count and the percentages of B lymphocytes, NK cells, and total T lymphocytes and their subsets in the peripheral blood in patients with hypersplenism associated with cirrhotic portal hypertension before surgery were significantly lower than those of the control group. The reduction in the number of lymphocytes and their subgroups suggested an immunocompromised status of these patients, with consequent impairment of liver function or aggravations of the existing liver dysfunction. Thrombopoietin production by hepatocytes^{23–25} is reduced as a result and ultimately can lead to a decrease in platelet counts in the peripheral circulation. The compromised or disordered immune functional status can also lead to the production of autoantibodies to blood cells, resulting in accelerated blood cells destruction²⁶. The numbers of these cells and their subsets increase significantly to normal or above-normal levels after total splenectomy, which is similar to the relative increase in the number of T lymphocytes after splenectomy as reported by Graffner and coworkers²⁷. The explanation for this phenomenon is likely to be related to hypersplenism as hypersplenism can result in decrease in WBCs, RBCs, and platelets in peripheral blood. Lymphocytes are a type of WBC, and any decrease in WBC count leads to a decrease in lymphocytes and their subsets. Increase in WBC count after total splenectomy with increase in lymphocytes and their subsets²⁸, result in an improved immune functional status.

T lymphocytes play an important role in the immune system. However, if they are not activated, they cannot initiate signal transduction as mediated by cytokine receptors, nor can they activate the immune system²⁹. There are approximately 94 genes involved in the activation of T lymphocytes³⁰. Activated T lymphocytes produce various functional subsets, with $CD4^+$ and $CD8^+$ cells being the main subsets produced in the thymus. The $CD4^+ : CD8^+$ ratio reflects cellular immune function and is an important measure of immune balance¹⁸. After

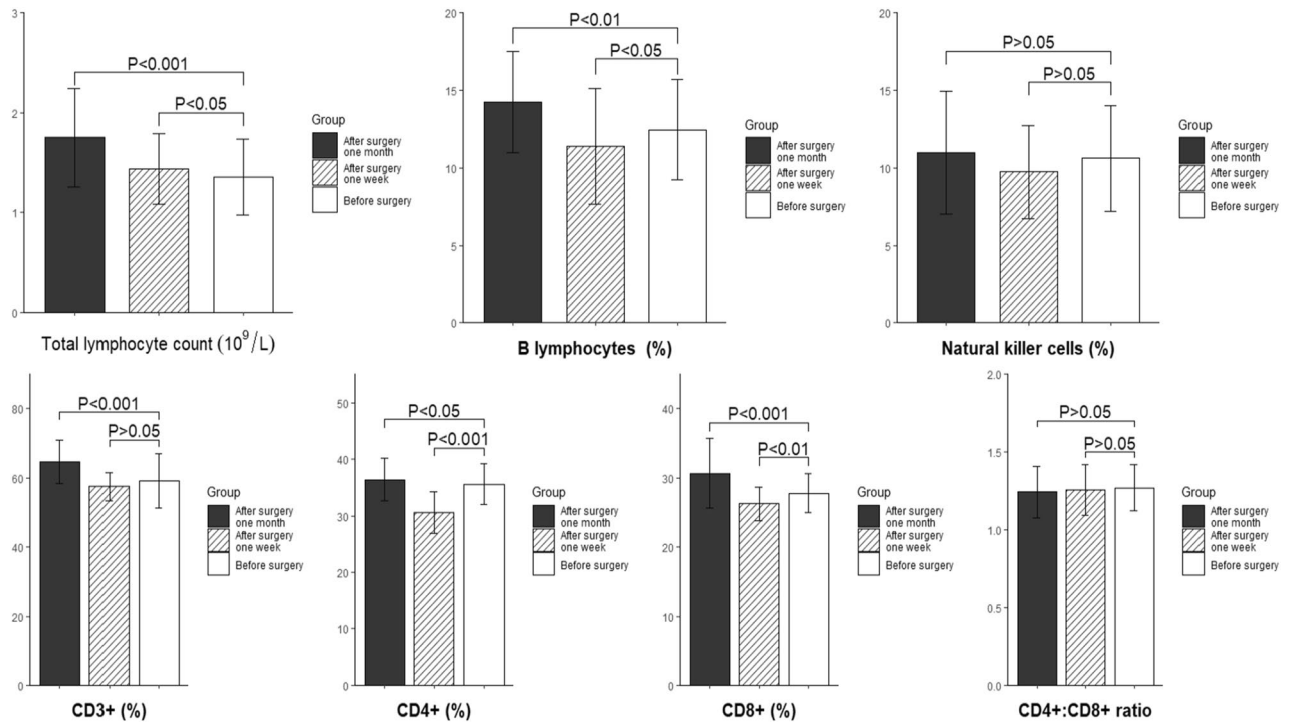


Figure 2. Changes in peripheral lymphocytes and their subsets in patients with hypersplenism before and after surgery.

CD4⁺ cells enter into peripheral immune organs, they are activated by a complex of antigen peptides and major histocompatibility complex (MHC) class-II molecules and they are called Th cells. After activation by a complex of antigen peptides and MHC class-I molecules, CD8⁺ cells can kill infected or otherwise harmed cells and they are called cytotoxic T cells²¹. In health, the CD4⁺:CD8⁺ ratio is relatively balanced, and the normal range is approximately 1.4–2.5^{31,32}. In fact, there are no adverse effects if the ratio is > 1, or otherwise immune dysfunction occurs. In the present study, although the percentages of CD4⁺ and CD8⁺ cells increased significantly after splenectomy, the ratio remained > 1.2, and this did not result in any diseases caused by immune dysfunction.

Whether splenectomy is indicated for hypersplenism is controversial³³. Total splenectomy can reduce symptoms caused by splenomegaly, including abdominal distension, pain, and a feeling of fullness³⁴. It corrects hypersplenism, promotes recovery of WBCs, platelets and RBCs, reduces liver fibrosis, and improves liver function^{35–37}. However, some researchers believe that splenectomy was a surgical trauma³⁸. In addition, as the spleen is considered to be the center for regulating the immune system, splenectomy can lead to immune imbalance, with possible resultant consequences of overwhelming post-splenectomy infection, thrombosis in portal venous system, intra-abdominal abscesses/ascites, pancreatic fistulae^{39,40}, and additional risks of cardiovascular complications⁴¹. However, the results of this study demonstrated that total splenectomy provided benefits for the immune system, and did not lead to any immune imbalance, overwhelming post-splenectomy infection, or cardiovascular complications.

Partial splenic arterial embolization (PSE) was first described by Spigos and colleagues⁴² to treat hypersplenism. It has also been used to treat portal hypertension and esophagogastric variceal bleeding^{43,44}. PSE not only can increase the counts of platelets and WBCs^{45–48}, but can also reduce splenic volume and improve immune function⁴⁹. Li and collaborators⁵⁰ reported that by maintaining the volume of PSE to 60–80% in patients with cirrhosis and hypersplenism, improved peripheral cytopenias reduced portal blood flow pressure, and less bleeding from esophagogastric varices could result. However, Kontchou and Seror⁵¹ argued that although PSE could be used to treat splenomegaly and hypersplenism, its indications were limited because of the possible serious complications of splenic infarction and abscesses formation which can be fatal.

Partial splenectomy is theoretically better than total splenectomy, which can preserve part of the spleen function, but there is no significant difference between the two from the actual analysis. Moreover, partial splenectomy is more difficult, longer operation time, and more bleeding after surgery. Splenectomy remains an important treatment modality in Asian countries including China and Japan⁵². Previously published studies showed that total splenectomy did not reduce humoral and cellular immunity⁵³, but increased the number of blood cells and improved liver and immune functions⁵⁴. However, not all patients with hypersplenism associated with cirrhotic portal hypertension are good candidates for total splenectomy. The indications for total splenectomy should be considered carefully for an individual patient⁵⁵.

Summary

The controversial issue of how total splenectomy impacts on the immune function of patients with cirrhotic portal hypertension is addressed. The results of the study showed for the first time that patients who were significantly immunocompromised before TS had their total lymphocyte counts, percentages of B lymphocytes and total T lymphocytes and their subsets to increase significantly after total splenectomy, with resultant improvements in immune function. The causes of immunocompromised status, which is of clinical importance, was discussed in this article to illustrate the indications for splenectomy in patients associated with liver cirrhosis and portal hypertension, as not all such patients should be subjected to splenectomy.

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Author contributions

These authors Y.L., H.W., W.Y.L. and J.Z. contributed equally to this work. Specifically, Y.L. is responsible for class design and essay writing, H.W. and J.Z. are responsible for implementation and statistics, and W.Y.L. is responsible for project guidance and paper revision. All authors have read this article and agreed to publish it.

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Competing interests

The authors declare no competing interests.

Additional information

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