

Impact of Total Splenectomy on Peripheral Lymphocytes and Their Subsets in Patients with Hypersplenism Associated with Cirrhotic Portal Hypertension

Yunfu Lv (✉ yunfu_lv@126.com)

Hainan General Hospital (Hainan Medical College Affiliated People's Hospital)

Hongfei Wu

Hainan General Hospital (Hainan Medical College Affiliated People's Hospital)

Wan Yee Lau

Chinese University of Hong Kong

Jinfang Zheng

Hainan General Hospital (Hainan Medical College Affiliated People's Hospital)

Jincai Wu

Hainan General Hospital (Hainan Medical College Affiliated People's Hospital)

Min Zeng

Hainan General Hospital (Hainan Medical College Affiliated People's Hospital)

Research Article

Keywords: total splenectomy, cirrhosis, portal hypertension, hypersplenism, immune function

Posted Date: June 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-620360/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objective

To study the impact of total splenectomy (TS) on peripheral lymphocytes and their subsets in patients with hypersplenism associated with cirrhotic portal hypertension (CPH).

Methods

Consecutive patients who underwent TS for hypersplenism associated with CPH from January 2008 to January 2020 were studied. A group of a similar number of healthy individuals was used as healthy controls (HCs).

Results

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 ($P > 0.05$).

Conclusions

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.

1. Introduction

Hypersplenism associated with cirrhotic portal hypertension is a common condition that is often complicated by peripheral cytopenias ^[1], and it can even be life-threatening ^[2] The more lineages that are affected in peripheral cytopenias, the worse is the prognosis. Peripheral cytopenias can be caused by hypersplenism, non-hypersplenism, and a combination of other factors, though hypersplenism is still the major contributing factor ^[3].

The definition of hypersplenism was controversial until in 1955, Dameshek ^[4] 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. However, as one of the clinical manifestations of portal hypertension is splenomegaly, hypersplenism in patients with portal hypertension should be defined using only 3 of the 4 criteria by Dameshek. Furthermore, non-hypersplenism factors that cause peripheral cytopenias such as toxic effects of hepatitis viruses on bone marrow ^[5-7], gastrointestinal bleeding ^[8], immunocompromised status ^[9-10], drug toxicity ^[11-13], platelet destruction in peripheral circulation ^[14], and hematopoiesis disorders caused by deficiency of vitamins and nutrients ^[15-16] should be excluded. The remaining two criteria that should be satisfied are presence of mono-lineage or multi-lineage peripheral cytopenias, and correction of cytopenias after splenectomy ^[17].

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 blood ^[18]. 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 response ^[19], 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 ^[20-21].

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 immunity ^[22]. CD8⁺ cells exert cytotoxicity to inhibit T lymphocytes ^[19] and are the main effectors of the immune system to eliminate virus-infected cells ^[18]. Appropriate immune functions are maintained through the interaction of the T-lymphocyte subsets ^[1]. The CD4⁺:CD8⁺ ratio is an important indicator that reflects directly a balanced immune function of host T cells.

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 research.

2. 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 $\leq 5 \times 10^9$ /L (n = 31) and splenomegaly (n = 17). In addition, 91 of these 102 patient 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 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) (Table 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) (Table 2). The CD4⁺:CD8⁺ ratio showed no significant difference before or 1 month after surgery (P > 0.05).

3. Discussion

Chu and colleagues [23] 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 [24-26] 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 destruction [27]. 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 coworkers [28]. 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 subsets [29], 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 system [30]. There are approximately 94 genes involved in the activation of T lymphocytes [31]. 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 balance [19]. After 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 cells [22]. In health, the CD4⁺:CD8⁺ ratio is relatively balanced, and the normal range is approximately 1.4–2.5 [32–33]. 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 controversial [34]. Total splenectomy can reduce symptoms caused by splenomegaly, including abdominal distension, pain, and a feeling of fullness [35]. It corrects hypersplenism, promotes recovery of WBCs, platelets and RBCs, reduces liver fibrosis, and improves liver function [36–38]. However, some researchers believe that splenectomy causes surgical trauma [39]. 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 [40–41], and additional risks of cardiovascular complications [42]. 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 colleagues [43] to treat hypersplenism. It has also been used to treat portal hypertension and esophagogastric variceal bleeding [44–45]. PSE not only can increase [46–49] the counts of platelets and WBCs, but can also reduce splenic volume and improve immune function [50]. Li and collaborators [51] 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 Seror ^[52] 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.

Splenectomy remains an important treatment modality in Asian countries including China and Japan ^[53]. Previously published studies showed that total splenectomy did not reduce humoral and cellular immunity ^[54], but increased the number of blood cells and improved liver and immune functions ^[55]. 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 patient ^[56].

4. 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.

5. Patients And Methods

5.1. The Study cohort

Ethical approval for this research project was obtained from the Ethics Committee of Hainan General Hospital (Hainan, China). And the patient's informed consent was obtained. 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.

5.2. 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.

5.3. 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.

5.4. 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.

5.5 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 \pm standard deviation. Count data were expressed as percentages. A $P < 0.05$ was considered significant.

Declarations

Acknowledgments

None.

Funding

This study was financed by the Science and Technology Department of Hainan Province (Qiongke [2020] 256).

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

These authors Yunfu Lv, Hongfei Wu, Wan Yee Lau and Jinfang Zheng contributed equally to this work. Specifically, Yunfu Lv is responsible for class design and essay writing, Hongfei Wu and Jinfang Zheng are responsible for implementation and statistics, and Wan Yee Lau is responsible for project guidance and paper revision.

All authors have read this article and agreed to publish it.

References

1. Bashour, F. N., Carlos, J., Kevin, T. & Mullen, D. M. Prevalence of Peripheral Blood Cytopenias (Hypersplenism) in Patients With Nonalcoholic Liver Disease. *Am Coll of Gastroeterology*, **95** (10), 2937–2939 (2000).
2. Lv, Y., Gong, X., Xie, X. & Wang, B. Yijun Yang & Yejuan Li.. Clinical Study on the Relationship Between Hematocytopenia and Splenomegaly Caused by Cirrhotic Portal Hypertension. *Cell Biochem Biophys*, **70** (1), 355–360 <https://doi.org/10.1007/s12013-014-9920-9> (2014).
3. Yunfu Lv¹. Wan Yee Lau^{1, 2}, Hongfei Wu¹, Xiaoyu Han¹, Xiaoguang Gong¹, Ning Liu¹, Jie Yue¹, Qingqing Li ¹, Yejuan Li¹, Jie Deng¹. Causes of peripheral cytopenia in hepatic cirrhosis and portal hypertensive splenomegaly. *Experimental Biology and Medicine*, **242** (7), 744–749 (2017 Apr).
4. Dameshek, W. & Hypersplenism, W. *Bull N Y Acad Med*, **31** (2), 113–136 (1955).
5. Cudillo, L. Aplastica anemia and viral hepatitis. *Mediterranean Journal of Hematology and Infectious Diseases*, **1** (3), 026 (2009).
6. Djordjevic, J., Svorcan, P., Vrinic, D. & Dapcevic, B. Splenomegaly and thrombocytopenia in patients with liver cirrhosis. *Vojnosanitetski Pregled Military-medical and Pharmaceutical Review*, **67** (2), 166–169 (2010).
7. Jelena Djordjević, P., Svorcan, D. Å. & Vrinic Branka Dapčević. Splenomegaly and thrombocytopenia in patients with liver cirrhosis. *Vojnosanit Pregl*, **67** (2), 166–169 (2010).
8. Srichaikul, T. *et al.* Hemophagocytic syndrome in Dengue hemorrhagic fever with severe multiorgan complications. *Journal of the Medical Association of Thailand Chotmaihet Thangphaet*, **91** (1), 104–109 (2008).
9. Barzaghi, F., Passerini, L. & Bacchetta, R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. *Frontiers in Immunology*, **3**, 211 (2012).
10. Zheng, P., Chang, X., Lu, Q. & Liu, Y. Cytopenia and autoimmune diseases: a vicious cycle fueled by mTOR dysregulation in hematopoietic stem cells. *Journal of Autoimmunity*, **41**, 182–187 (2013).
11. Singh, N., Yu, V. L., Mieles, L. A. & Wagener, M. M. Beta-Lactam antibiotic-induced leukopenia in severe hepatic dysfunction: risk factors and implications for dosing in patients with liver disease. *Am J Med*, **94** (3), 251–256 (1993 Mar).
12. Cobo, F. *et al.* Oxaliplatin-induced immune hemolytic anemia: a case report and review of the literature. *Anti-cancer Drugs*, **18** (8), 973–976 (2007).
13. Saif, M. W. *et al.* A dpyd variant (Y186C) specific to individuals of African descent in a patient with life-threatening 5-FU toxic effects: potential for an individualized medicine approach. *Mayo Clinic Proceedings*. 2014; 89(1):131–136.
14. Cho, Y. G., Lee, J. H., Kim, D. S., Lee, H. S. & Choi, S. I. Clinical usefulness of the simple technique to diagnose thrombocytopenia using immature platelet fraction. *The Korean Journal of Laboratory Medicine*, **27** (1), 1–6 (2007).

15. Lavigne, C. *et al.* Role of vitamin deficiency in pancytopenia in Djibouti. Findings in a series of 81 consecutive patients. *Medecine Tropicale: Revue Du Corps De Sante Coloniale*, **65** (1), 59–63 (2005).
16. Abrishami, F. & Golshan, A. Frequency of iron deficiency anemia in girls studying in mashhad high schools. *Iranian Journal of Pediatric Hematology and Oncology*, **3** (4), 143–148 (2013).
17. Lv, Y., Gong, X., Xie, X. & Wang, B. Yijun Yang & Yejuan Li. Clinical Study on the Relationship Between Hematocytopenia and Splenomegaly Caused by Cirrhotic Portal Hypertension. *Cell Biochem Biophys*, **70** (1), 355–360 <https://doi.org/10.1007/s12013-014-9920-9> (2014).
18. Cao Xuetao. *Medical Immunology*. Beijing: People's Medical Publishing House. 2013, Sixth Edition, 15–17.
19. Bashour, F. N., Teran, J. C. & Mullen, K. D. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease[J]. *Am J Gastroentero*, **95** (10), 2936–2939 (2000).
20. Terai, S. *et al.* Status and prospects of liver cirrhosis treatment by using bone marrow-derived cells and mesenchymal cells[J]. *Tissue Engineering, Part B. Reviews*, **20** (3), 206–210 (2014).
21. Owman, T. *et al.* Embolization of the spleen for treatment of splenomegaly and hypersplenism in patients with portal hypertension[J]. *Invest Radiol*, **14** (6), 457–464 (1979).
22. Pearce, E. J., Caspar, P., Grzych, J. M., Lewis, F. A. & Sher, A. Downregulation of Th1 cytokine production accompanies induction of Th2 responses by a parasitic helminth, *Schistosoma mansoni*[J]. *J Exp Med*, **173** (1), 159–166 (1991).
23. Chu, H. B. *et al.* Tang JY⁸, Sun HJ⁹, Li K¹⁰, Guo WJ¹¹, Zhu XJ¹². Assessment of immune cells and function of the residual spleen after subtotal splenectomy due to splenomegaly in cirrhotic patients. *BMC Immunol*. 2014, 8(15):42–45. doi: 10.1186/s12865-014-0042-3.
24. Eissa, L. A., Gad, L. S., Rabie, A. M. & El-Gayar, A. M. Thrombopoietin level in patients with chronic liver diseases. *Ann Hepatol*. 2008 Jul-Sep; 7(3):235–244.
25. Wolber, E. M., Ganschow, R., Burdelski, M. & Jelkmann, W. Hepatic thrombopoietin mRNA levels in acute and chronic liver failure of childhood., **29** (6), 1739–1742 (1999).
26. Ichikawa, N. *et al.* Changes in serum thrombopoietin levels after splenectomy. *Acta Haematol*, **100** (3), 137–141 (1998 Dec).
27. Garibaldi, B., King, K. E., Jaffe, J. M. & Moliterno, A. R. Hypersplenism induced by splenic vein ligation[J]. *Am J Hematol*, **83** (3), 242–244 (2008).
28. Graffner, H., Gullstrand, P. & Hallberg, T. Immunocompetence after incidental aplenectomy[J]. *Scand J Hemat*, **28** (5), 369–375 (1982).
29. LV, Y. F., LI, X. Q., GONG, X. G., XIE, X. H. & HAN, X. Y. B. C. WANG. Effect of surgery treatment on hypersplenism caused by cirrhotic portal hypertension. *MINERVA CHIR*, **68**, 409–413 (2013).
30. Yunfu Lv^{1,3}, Wan Yee Lau^{1,2*}, Yejuan Li^{1,3}, Jie Deng^{1,3}, and Yonghong Dong¹, Xiaoyu Han¹ Xiaoguang Gong¹, Ning Liu¹, Hongfe Wu¹. Hypersplenism: History and current status(Review). *Experimental and Therapeutic Medicine*, 2016, 12:2377–2382.

31. Yan, F. *et al.* cDNA microarray-based screening of differentially expressed genes in macrophages in the spleen of patients with portal hypertension and hypersplenism. *Nan Fang Yi Ke Da Xue Xue Bao*, **26** (11), 1548–1551 (2006 Nov).
32. Pham 1, B. N. CD4+/CD8 + ratio of liver-derived lymphocytes is related to viraemia and not to hepatitis C virus genotypes in chronic hepatitis C. *Clin Exp Immunol*, **102** (2), 320–327 <https://doi.org/10.1111/j.1365-2249.1995.tb03784.x> (1995 Nov).
33. Hidenori Sato ¹, Eisuke Adachi ², Lay Ahyoung Lim ¹, Michiko Koga ¹, Tomohiko Koibuchi ¹, Takeya Tsutsumi ¹, Hiroshi Yotsuyanagi ¹ CD4/CD8 ratio predicts the cellular immune response to acute hepatitis C in HIV-coinfected adults. *J Infect Chemother*, 2019 Aug; 25(8):646–648. doi: 10.1016/j.jiac.2019.04.001. Epub 2019 Apr 17
34. Hayashi, H. *et al.* Recent role of Hassab's operation for cirrhotic patients: combination with endoscopic procedure for varices [J]. *Asian J Surg*, **35** (2), 57–61 (2012).
35. Pei, Y. *et al.* Benefits of Splenectomy and Curative Treatments for Patients with Hepatocellular Carcinoma and Portal Hypertension: a Retrospective Study[J]. *Gastrointest Surg*, **23** (11), 2151–2162 (2019).
36. Toshimi Kaido, H. *et al.* Expressions of molecules associated with hepatocyte growth factor activation after hepatectomy in liver cirrhosis[J]. *Hepatogastroenterology*, **51** (56), 547–551 (2004).
37. Li, L. *et al.* The Spleen Promotes the Secretion of CCL2 and Supports an M1 Dominant Phenotype in Hepatic Macrophages During Liver Fibrosis[J]. *Cell Physiol Biochem*, **51** (2), 557–574 (2018).
38. Yada, A. *et al.* Splenectomy attenuates murine liver fibrosis with hypersplenism stimulating hepatic accumulation of Ly-6C(lo) macrophages[J]. *Journal of Hepatology*, **63** (4), 905–916 (2015).
39. Hosea, S. W. *et al.* Opsonic requirements for intravascular clearance after splenectomy[J]. *The New England Journal of Medicine*, **304** (5), 245–250 (1981).
40. Tsutsumi, N. *et al.* Pancreatic fistula after laparoscopic splenectomy in patients with hypersplenism due to liver cirrhosis: effect of fibrin glue and polyglycolic acid felt on prophylaxis of postoperative complications[J]. *American Journal Surgery*, **212** (5), 882–888 (2016).
41. Cheng, Z. *et al.* Therapeutic effects of laparoscopic splenectomy and esophagogastric devascularization on liver cirrhosis and portal hypertension in 204 cases[J]. *Laparoendoscopic & Advanced Surgical Techniques*, **24** (9), 612–616 (2014).
42. Weledji, E. P. Benefits and risks of splenectomy[J]. *International journal of surgery*, **12** (2), 113–119 (2014).
43. Spigos, D. G. *et al.* Partial splenic embolization in the treatment of hypersplenism [J]. *Am J Roentgenol*, **132** (5), 777–782 (1979).
44. Sankararaman, S., Velayuthan, S., Veal, R. & Herbst, J. Severe gastric variceal bleeding successfully treated by emergency splenic artery embolization. *Pediatr Int*, **55** (3), 42–45 <https://doi.org/10.1111/ped.12014> (2013 Jun).

45. Huang, J. H. *et al.* Study on primary hepatocellular carcinoma associated with hypersplenism treated by partial splenic embolization combined with hepatic arterial chemoembolization. *Ai Zheng*, **25** (8), 1003–1006 (2006 Aug).
46. Chikamori, F. *et al.* Hemodynamic effects of combined therapy using partial splenic embolization and transjugular retrograde obliteration for gastric varices with gastrosplenic shunt. *World J Surg*, **34** (5), 1046–1051 <https://doi.org/10.1007/s00268-010-0451-2> (2010 May).
47. Noguchi, H., Hirai, K., Aoki, Y., Sakata, K. & Tanikawa, K. Changes in platelet kinetics after a partial splenic arterial embolization in cirrhotic patients with hypersplenism., **22** (6), 1682–1188 (1995 Dec).
48. He, X. H. *et al.* Total embolization of the main splenic artery as a supplemental treatment modality for hypersplenism. *World J Gastroenterol*, **28** (24), 2953–2957 <https://doi.org/10.3748/wjg.v17.i24.2953> (2011 Jun).
49. Harao, M. *et al.* [The significance of combined treatment for hepatocellular carcinoma with partial splenic embolization and transcatheter arterial chemoembolization using IA call/lipiodol]. *Gan to Kagaku Ryoho Cancer & Chemotherapy*, **35** (12), 2027–2029 (2008).
50. Krishnan, S. K. *et al.* Improving cytopenia with splenic artery embolization in a patient with paroxysmal nocturnal hemoglobinuria on eculizumab. *International Journal of Hematology*, **98** (6), 716–718 (2013).
51. Zhengran, L., Hong, S. & Kangshun, Z. Clinical quantitative study of therapeutic effect of partial splenic embolization (PSE) on portal vein hemodynamis. *Chinese Journal of Radiology*, **36** (10), 913–917 (2002).
52. N'Kontchou, G. *et al.* Partial splenic embolization in patients with cirrhosis: efficacy, tolerance and long-term outcome in 32 patients. *Eur J Gastroenterol Hepatol*, **17** (2), 179–184 (2005 Feb).
53. Liang, Y., Wenjing, Y. & Zhansheng, J. Zhang Ying. Research progress in the treatment of hypersplenism in patients with liver cirrhosis[J]. *Journal of Clinical Hepatobiliary Diseases*, **31** (11), 1924–1927 (2015).
54. Li, Z. The effect of splenectomy on the immune function of patients with portal hypertension complicated with hypersplenism[J]. *China Current General Surgery Progress Experience Forum*, **15** (10), 834–835 (2012).
55. Yang Hongzhi. The effect of splenectomy on the immune function, liver function and blood routine of patients with hepatitis B liver cirrhosis and portal hypertension combined with hypersplenism[J]. *Guangxi Medicine*, **11** (37), 1591–1594 (2015).
56. Han, X. & Ning, L. Li Qingqing. Summary of Hainan Provincial Liver Cirrhosis and Portal Hypertension Summit Seminar. *Chinese Abdominal Surgery*, **30** (1), 77 (2017).

Tables

Table 1. Comparison of peripheral lymphocytes and their subsets between the hypersplenism group and control group (mean ± SD)

Item	Hypersplenism group	Control group	T	P
Total lymphocyte count ($10^9/L$)	1.357±0.3815	1.761±0.4642	-6.683	0.0001
B lymphocytes (%)	12.45±3.216	13.85±2.942	-2.289	0.02300
Natural killer cells (%)	10.59±3.427	11.66±3.148	-3.208	0.002000
CD3 ⁺ (%)	59.26±7.827	64.88±9.254	-4.613	0.0001
CD4 ⁺ (%)	35.59±3.650	37.28±5.117	-2.672	0.008000
CD8 ⁺ (%)	27.81±2.859	35.58±3.742	-16.41	0.0001
CD4 ⁺ :CD8 ⁺ ratio	1.270±0.1473	1.265±0.2620	0.1420	0.8870

Note: n = 102 in both groups

Table 2. Changes in peripheral lymphocytes and their subsets in patients with hypersplenism before and after surgery (mean ± SD)

Item	Before surgery	After surgery	
		One week	One month
Total lymphocyte count ($10^9/L$)	1.357±0.3815	1.435±0.350*	1.748±0.4906***
B lymphocytes (%)	12.45±3.216	11.36±3.726*	14.23±3.277**
Natural killer cells (%)	10.59±3.427	9.718±3.014 Δ	10.95±3.961 Δ
CD3 ⁺ (%)	59.26±7.827	57.53±4.131 Δ	64.65±6.186***
CD4 ⁺ (%)	35.59±3.650	30.53±3.674***	36.38±3.717*
CD8 ⁺ (%)	27.81±2.859	26.26±2.469**	30.70±5.100***
CD4 ⁺ /CD8 ⁺	1.270±0.1473	1.256±0.1646 Δ	1.244±0.1652 Δ

Note: *p < 0.05, **p < 0.01, ***p < 0.001, and Δ p > 0.05, respectively, compared with before surgery.