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Original Article

Clinical efficacy of laparoscopic hepatectomy and its effects on cellular immune function

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Abstract: Objective: To investigate the clinical efficacy of laparoscopic hepatectomy and its effects on organism cellular immune function. Methods: Two hundred liver cancer patients cured in our hospital from January 2013 to December 2016 were enrolled in this study and randomly divided into observation group and control group, with 100 cases in each group. The patients in the observation group were treated with laparoscopic hepatectomy, while patients in the control group were treated with open hepatectomy. Various intraoperative indexes, postoperative short-term and long-term efficacy, occurrence of complications, ratio of $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$) at different time points before and after operation, as well as expression levels of serum interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in two groups of patients were compared. Results: The operation time of the observation group was longer than that of the control group; total bleeding volume and blood occlusion rate were less than those of the control group; incision length was shorter than that of the control group. Compared with the control group, the indwelling time of the drainage tube, time to start eating and postoperative hospital stays of the patients in the observation group were significantly less than those in the control group. Compared with the control group, 24 h and 72 h after operation, the indexes of AST, ALT and TBIL of the patients in the observation group markedly reduced, while ALB level obviously increased ($P<0.05$), which was statistically significant. There were no statistical differences of postoperative metastasis rate, relapse rate and mortality between the two groups, but the incidence of complications in the observation group was significantly lower than that in the control group ($P<0.05$). At postoperative 72 h, the ratio of $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$) cell populations in the observation group was basically recovered to the preoperative level ($P>0.05$), while those in the control group were remarkably lower than the preoperative level ($P<0.05$). Compared with the preoperative condition, the levels of IL-6 and TNF-α in the control group increased 24 h and 72 h after operation ($P<0.05$); in the observation group, those two levels increased 24 h after operation ($P<0.05$), but there was no significant difference at 72 h and pre-operation ($P>0.05$). Conclusion: Laparoscopic hepatectomy for liver cancer had definite clinical efficacy, small trauma, high security, low incidence of complications, little impact on patients' cellular immune function and rapid postoperative recovery.

Keywords: Liver cancer, laparoscopic hepatectomy, open hepatectomy, clinical efficacy, cellular immune function

Introduction

Hepatectomy is regarded as the primary treatment for the radical resection of primary liver cancer. With complex liver structure and function, hepatectomy will result in different degrees of trauma to the body, cause a strong stress response, and lead to low cellular immune function. Studies have shown that the cellular immune function of patients with liver cancer surgery is negatively correlated with the degree of trauma [1, 2]. At present, on the basis of ensuring the clinical efficacy, minimizing the surgical trauma and utomostly preserving cellular immune function have become an important direction in the field of modern surgery. Compared with open hepatectomy, the trauma and postoperative stress response of laparoscopic hepatectomy significantly reduce [3-5], which plays an important role in maintaining the cellular immune function of the patients. Animal experimental studies have also shown that laparoscopic hepatectomy has a positive effect on maintaining normal immune function

Table 1. Comparison of general information of patients in two groups

Group	Case	Gender (case)		Age (year)	Height (cm)	Tumor diameter (cm)	Tumor position (Couinaud) (case)		
		Male	Female				II-III	IV	V-VI
Control group	100	57	43	47.8±15.4	162.1±4.6	5.42±3.18	55	10	35
Observation group	100	56	44	48.4±16.5	164.5±4.2	5.35±3.22	50	12	38
T/χ^2		0.513		0.899	0.530	0.580	0.630		
P value		0.736		0.426	0.157	0.575	0.430		

[6, 7], but the clinical changes in cellular immune function are still unclear. In recent years, laparoscopic hepatectomy has gradually replaced open hepatectomy and been widely used in the treatment of liver cancer, with widely recognized clinical efficacy, but the adequacy of laparoscopic hepatectomy for resection of malignant liver tumor remains controversial [8], which lacks a large sample of clinical data to confirm and some of data needs long-term accumulation and exploration. In this regard, this study aims to observe the short-term and long-term efficacy of patients with laparoscopic hepatectomy and changes of T lymphocyte subsets and cytokines to evaluate the effects of laparoscopic hepatectomy, cellular immunity and cytokine levels.

Materials and methods

General information

Two hundred liver cancer patients cured in our hospital from January 2013 to December 2016 were enrolled in this study. Inclusion criteria: Superficial lesions located in the II-VI; the size of tumor <10 cm; no intrahepatic metastasis and metastasis of lung, brain, gastrointestinal and other visceral organs; no history of abdominal surgery; no portal vein tumor thrombus; Child Pugh Class A or B. Exclusion criteria: Associated with cardiopulmonary dysfunction and other important organ dysfunction; surgical contraindications; abdominal adhesions, portal hypertension and severe cirrhosis. All patients underwent preoperative routine examinations such as CT, MRI, echocardiograms, etc. This study was approved by the Ethics Committee and every patient signed an informed consent.

Liver cancer patients were randomly divided into observation group and control group by the random number table, with 100 cases in each group. The general information (gender, age, height, weight, etc.) of patients in two groups had no statistical significance (P>0.05) and was comparable, see **Table 1**.

Surgical methods

Laparoscopic hepatectomy was applied in observation group. A 10 mm longitudinal incision was conducted under general anesthesia in the lower edge of the annulus umbilicalis, a Veress needle was inserted into the incision with conventional CO_2, pressure was maintained at about 12 mmHg. The 4-hole method was adopted to select the corresponding poke holes of different anatomical sites of the liver tumor for the local or regular hepatectomy, according to the operational needs. Local hepatectomy: Ata distance of 2 cm from the separated liver lesion, the liver parenchyma was directly mutilated from the liver by using the ultrasound knife; the resected portion of the liver was placed in the laparoscopic specimen bag, followed by rapidly removed from the extended epidermal incision. Regular hepatectomy: After the ligaments around the lesion were separated and mutilated, liver lobes exposed. We pre-controlled and dealt with portal blood flow, marking in the liver segment and anatomical structures of liver lobes; tumor specimens were directly resected and removed by using the ultrasound knife according to signs. After electric coagulation hemostasis and placing a drainage tube, the incision was sewed layer by layer. The control group was treated with open hepatectomy, according to the separated perihepatic ligament, the local or regular hepatectomy was performed on the basis of the operation steps. The postoperative specimens of two groups were used for pathological examination.

Observation index

The operation time, total blood loss, incision length and blood flow occlusion of two groups

Table 2. Comparison of the various indexes of patients in two groups

Group	Case	Operation time (min)	Total bleeding volume (ml)	Incision length (cm)	Blood occlusion rate (%)
Control group	100	158.3±24.62	451.5±167.12	25.1±0.14	46
Observation group	100	192.7±22.55*	323.3±158.33*	4.56±0.17*	11*
T/χ^2		5.698	2.597	41.233	30.058
P value		0.000	0.012	0.000	0.000

Note: Compared with the control group, *P<0.05.

Table 3. Comparison of short-term efficacy indexes of patients in two groups

Group	Case	Indwelling time of the drainage tube (d)	Timeto start eating (d)	Postoperative hospital stay (d)
Control group	100	6.68±0.73	3.48±0.82	12.47±1.49
Observation group	100	3.57±0.63*	1.57±0.78*	7.02±1.12*
T value		10.571	6.394	8,921
P value		0.000	0.000	0.000

Note: Compared with the control group, *P<0.05.

were compared; the postoperative short-term efficacy indicators: indwelling time of drainage tube, time to start eating and postoperative hospital stays were analyzed and compared; the postoperative long-term efficacy index (metastasis rate, relapse rate, mortality) and complications (perihepatic effusions, ascites, infection, bile leakage, etc.) were compared.

Venous blood was extracted at different time points of before operation, 24 h and 72 h after operation respectively. FACS flow cytometry (BD Co. USA) was applied to detect $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$); Thermo thermoelectric FC microplate reader was adopted to detect the levels of serum interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) via enzyme-linked immunosorbent assay (ELISA).

Follow-up visit

All patients were followed up after surgery once per month by means of outpatient appointment and telephone follow-up for one year to observe the long-term efficacy index of them.

Statistical processing

SPSS17.0 software was used to process the experimental data, measurement data was expressed as $\bar{x} \pm s$, and T test was adopted to compare the data between groups. Enumeration data was represented as percentage, and χ^2 test was used to compare the data between groups. P<0.05 was considered statistically significant.

Results

Comparison of intraoperative indexes between two groups of patients

The operation time of the observation group was longer than that of the control group; total bleeding volume and blood occlusion rate were less than those of the control group; incision length was shorter than that of the control group. According to the statistical analysis, various intraoperative differences of patients in the two groups were statistically significant, see **Table 2**.

Comparison of the short-term efficacy indexes between the two groups of patients

Compared with the control group, the indwelling time of the drainage tube, time to start eating and postoperative hospital stays of patients in the observation group were significantly less than those in the control group. According to the statistical analysis, the differences were statistically significant, see **Table 3**.

Comparison of liver function indexes between the two groups of patients

Compared with the control group, the indexes of AST (158.68±96.45 U/L vs 241.85±98.32 U/L), ALT (236.67±102.37 U/L vs 376.25±104.46 U/L) and TBIL (13.22±4.73 μmol/L vs 17.25±4.31 μmol/L) significantly decreased 24 h after operation, while the ALB level in the observation group was apparently higher than that in the control group (33.85±4.67 g/L vs

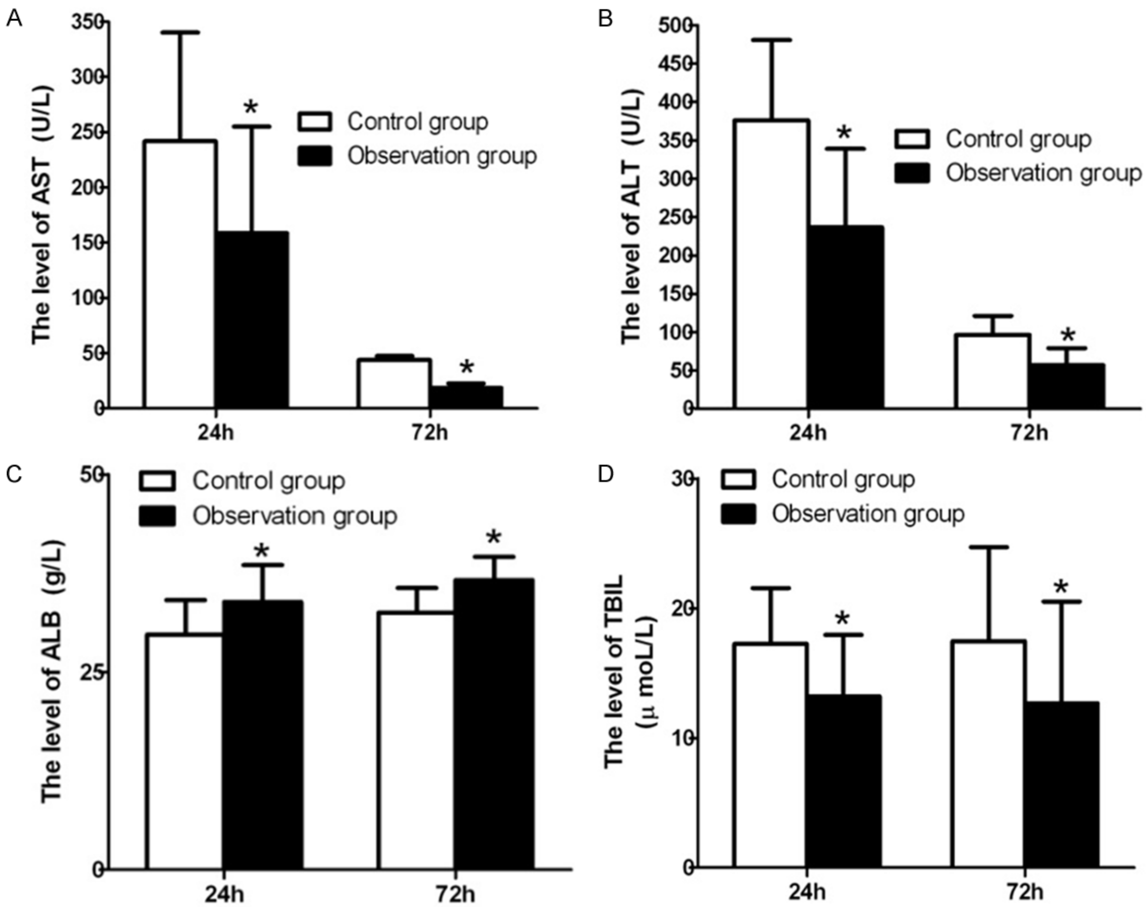

Figure 1. Comparison of postoperative liver function indexes of patients in two groups. A: AST index; B: ALT index; C: ALB index; D: TBIL index. Compared with the control group, *P<0.05.

Table 4. Comparison of the long-term efficacy indexes and the incidence of complications of patients in two groups

Group	Case	Long-term efficacy (case)			Complications (case)
		Metastasis	Relapse	Mortality	
Control group	100	4	5	8	30 (30%)
Observation group	100	10	8	7	18 (18%)
χ^2 value		1.920	0.740	0.072	3.947
P value		0.166	0.390	0.788	0.047

29.72±4.38 g/L). The difference was statistically significant (P<0.05), see **Figure 1**.

The levels of AST (18.62±3.95 U/L vs 43.88 ±3.56 U/L), ALT (56.74±22.39 U/L vs 96.52± 24.63 U/L) and TBIL (12.68±7.83 μmol/L vs 17.47±7.23 μmol/L) were significantly lower than those of the control group, while the level of ALB in the observation group was significantly higher than that in the control group (36.62±2.95 g/L vs 32.48±3.15 g/L) 72 h after operation. The difference was statistically significant, see **Figure 1**.

Comparison of the long-term efficacy and incidence of complications in patients between the two groups

There were no significant differences in tumor metastasis rate, relapse rate and mortality both in the observation group and the control group. Compared with the observation group, the incidence of postoperative complications was significantly lower in the control group, reaching statistical significance (P<0.05), see **Table 4**.

Comparison of the proportion of T lymphocytes between the two groups of patients

The ratio of $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$) in two groups significantly

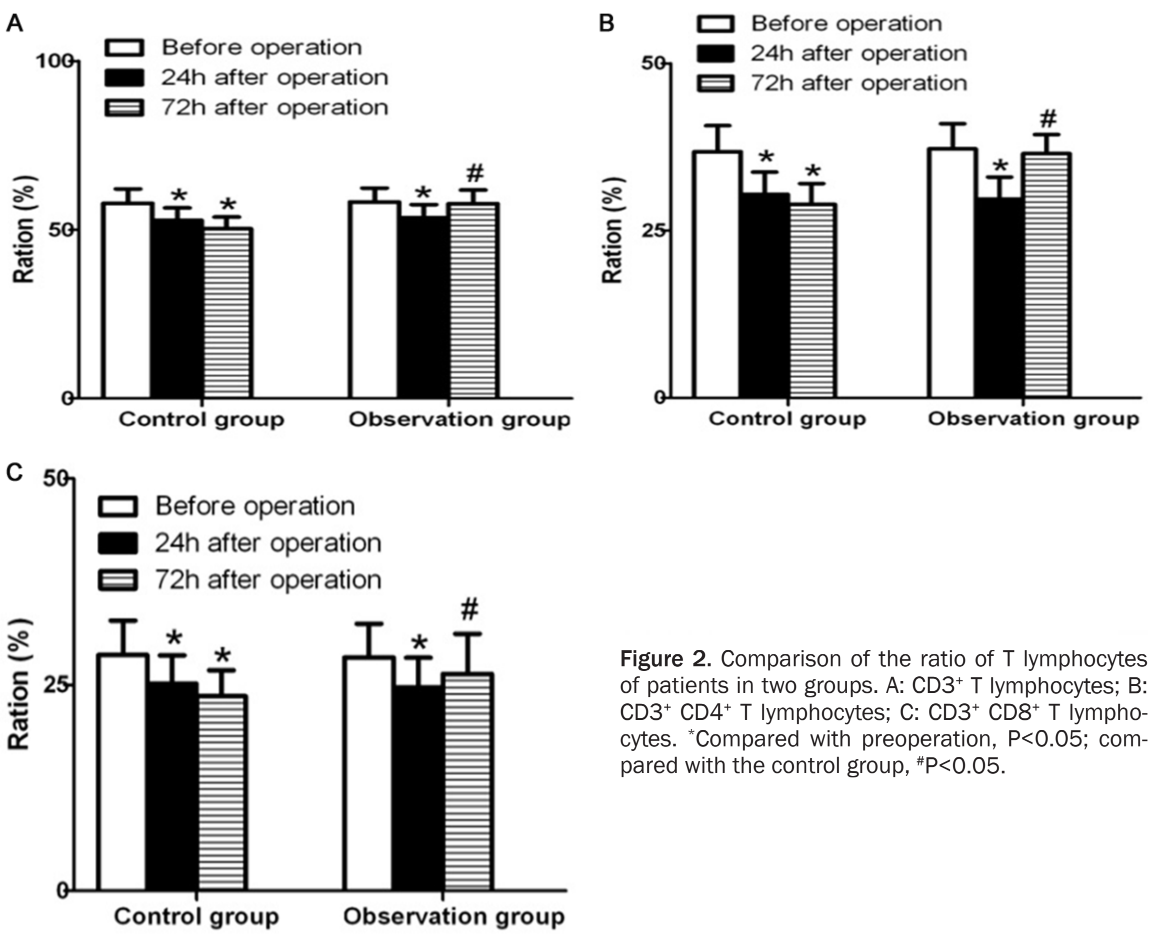

Figure 2. Comparison of the ratio of T lymphocytes of patients in two groups. A: CD3+ T lymphocytes; B: CD3+ CD4+ T lymphocytes; C: CD3+ CD8+ T lymphocytes. *Compared with preoperation, P<0.05; compared with the control group, #P<0.05.

reduced compared to the preoperation 24 h after operation. The difference was statistically significant. However, the quantity differences of $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$) in two groups were not statistical significant. Compared with the preoperative condition, there was no statistical difference in the ratio of $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$) in the observation group 72 h after operation, but the ratio in the control group was still lower ($P<0.05$). The ratio of $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$) in the observation group was significantly higher than that in the control group ($P<0.05$), which had statistical significance. See **Figure 2**.

Comparison of the expression levels of IL-6 and TNF-α between the two groups of patients

Compared with the preoperative condition, the postoperative expression levels of IL-6 and TNF-α in the control group significantly increased with statistical significance (all P=0.000); those expression levels in observation group 24 h after operation were also obviously increased with statistical significance (all P=0.000); however, those expression levels in the observation group 72 h after operation and the preoperative condition showed no statistical significance (P=0.905, P=0.897). Compared with the control group, those expression levels in the observation group significantly decreased 72 h after operation (all P=0.000), and the difference was of statistical significance, see **Table 5**.

Discussion

Hepatectomy is the first choice for the treatment of liver cancer. Compared with open hepatectomy, laparoscopic hepatectomy has obvious advantages for liver cancer [9, 10]. For example, in the process of laparoscopic hepa-

Table 5. Comparison of expression levels of cytokines of patientsin two groups

Index	Group	Preoperation	Postoperative 24 h	Postoperative 72 h
IL-6 (ng/L)	Control group	8.36±3.47	33.24±10.04*	45.81±18.35*
	Observation group	8.21±3.58	28.62±12.17*	9.25±4.72$^{\Delta}$
TNF-a (ng/L)	Control group	32.23±7.48	63.82±13.7*	73.13±10.72*
	Observation group	33.41±8.27	54.27±12.49*	35.46±9.59$^{\Delta}$

Note: Compared with the preoperative, *P<0.05; compared with the control group, $^{\Delta}$P<0.05.

tectomy, a set of operation procedures can be completed under the direct vision, bleeding in the liver section can be reduced by the combined usage of ultrasonic knife cutting, and it has clear vision, high operational accuracy, as well as significantly reduced damage of the surrounding tissues and organs. The key to laparoscopic hepatectomy for the treatment of liver cancer lies in the following aspects: whether the liver cancer tissues can be fully resected, whether bile leakage, bleeding and other complications can be avoided, and it must ensure that the resected liver cancer tissues can be removed completely and successfully. With the development and progress of laparoscopic technology, the scope of indications of laparoscopic hepatectomy is further expanded, which can be used to treat liver surface tumors, apical tumors and multiple liver cancer, with less and less surgical contraindications [11-13]. The total bleeding volume and blood occlusion rate of the observation group were less than those of the control group; incision length was shorter than that of the control group. All of these suggested that laparoscopic hepatectomy was significantly less traumatic than open laparotomy, its safety can be assured, and it had a good prospect, which was consistent with the previous studies [14, 15]. Laparoscopic hepatectomy, with the ultrasound knife as an intraoperative instrument, has the characteristics of the exact location of cutting and less damage on normal tissues. In addition, the surgery becomes more difficult due to its small incision and surgeons must keep good vision and avoid blood occlusion at the same time. Therefore, normative refined operation is needed, leading to prolonged operation time, which is, in this study, one of the reasons why the observation group spends more operative time than the control group.

As for postoperative short-term efficacy, through the study we can see that the indwelling time of drainage tube, time to start eating, postoperative hospital stays of the observation group were shorter than those of the control group, which also showed that the short-term efficacy of laparoscopic hepatectomy of the observation group was significantly better than that of the control group. This was probably because that laparoscopic hepatectomy kept the patients' abdominal cavity a relative closed state, which effectively reduced the exposure and water evaporation of the internal organs, alleviating the stimulation of the gastrointestinal tract, and the less intraoperative bleeding volume reduced the postoperative infusion quantity. With respect to the postoperative recovery of liver function, the results of this study showed that the indexes of AST, ALT, TBIL of patients in the observation group were significantly lower than those in the control group at 24 h and 72 h after operation, while the ALB level was apparently higher than that in the control group, with statistical differences. It demonstrated that the patients with laparoscopic hepatectomy had a better recovery of liver function than those with open hepatectomy, which may result from lighter degree of hepatic section trauma and liver crush injury of laparoscopic surgery.

The long-term efficacy of laparoscopic hepatectomy for liver cancer is always attracting the concern and attention of scholars. In the early stage, the inaccurate identification of liver tumor boundary combined with intra-abdominal hypertension, ineffective lymph node dissection and tumor spread, resulted in limiting the extensive application of laparoscopic hepatectomy. This study indicated that the complications of laparoscopic hepatectomy for liver cancer were relatively few; it reached statistically significance, compared with open hepatectomy. By one year of postoperative follow-up, we found there was no significant difference in tumor metastasis rate, relapse rate and mortality rate in the two groups of patients, which further illustrated that the long-term clinical efficacy of laparoscopic hepatectomy for the treatment of liver cancer was the same as that of open laparotomy.

Previous studies have suggested that laparoscopic hepatectomy cannot completely remove hepatoma carcinoma cells and still remained in the treatment phase of reducing tumor load [16, 17]. At present, it is believed that the tumor metastasis or relapse depends entirely on the cellular immune function. If the patients have normal cellular immune function after hepatectomy, it had a certain role in inhibiting or killing tumor cells; on the contrary, tumor cells free of immune surveillance can be quickly metastasized or relapsed [18]. T lymphocytes were a multifunctional cell population that plays an important role in humoral immunity and cellular immunity. $CD3^+$ T lymphocytes can help T lymphocyte antigen receptor to identify the major histocompatibility complex on antigen presenting cells. $CD4^+$ and $CD8^+$ are two important cell subsets of $CD3^+$ T lymphocytes, which can reflect the immunoregulation ability of living organisms. This study aims to detect the changes of cellular immune function after hepatectomy by measuring the ratio of $CD3^+$ T lymphocytes and their subsets ($CD4^+$ and $CD8^+$). The results show that the ratio in the observation group is restored to the preoperative level 72 hours after operation, while that in the control group is still lower than the preoperative level, indicating that laparoscopic surgery has little effect on the postoperative cellular immune function and has a quick recovery. This is probably because that laparoscopic hepatectomy has fewer traumas, small operation incision, and relatively complete skin and mucosal barrier, which can exhibit exogenous pathogens into living organisms, and has lighter stress reactions [19]. Although living organisms are subjected to a certain degree of immunosuppression, laparoscopic hepatectomy can promote the rapid recovery of cellular immune function [20, 21].

IL-6 and TNF-α are cytokines produced by macrophages and monocytes. In the acute inflammatory phage of trauma, IL-6 can regulate proliferation and differentiation of T lymphocytes, and induce cytotoxic T lymphocytes. And TNF-α, an effector of cell-mediated and tissue damaged immune inflammatory response, can enhance the proliferation of T lymphocytes to the antigens. It can be seen that IL-6 and TNF-α can complete the immune response and inflammation-mediated response in acute inflammatory phage of trauma. In this study, the results showed that the expression levels of IL-6 and TNF-α significantly increased at 24 h after liver resection. However, They in the observation group were basically back to the preoperative level at 72 h after operation, while in the control group, the levels still remained at a high level, suggesting laparoscopic surgery had few impacts on the living organism's immune function damage and inflammation response, further reflecting the minimal invasion of laparoscopic hepatectomy.

In summary, laparoscopic hepatectomy for liver cancer has definite clinical efficacy and the advantages such as little trauma, high safety, low incidence of complications, small impact on cellular immune function and rapid postoperative recovery. However, there are still some limitations in this study, such as small sample size, single-center research and so on. The result still needs to be further confirmed by broad scholars' continuous exploration and practice through a large sample size, and multicenter randomized trial. It is believed that with the constant improvement of technology, laparoscopic hepatectomy will have a broader application prospect.

Disclosure of conflict of interest

None.

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