

## EFFECT OF LAMIVUDINE COMBINED WITH THYMOSIN ON POSTOPERATIVE RECURRENCE OF ALCOHOLIC HEPATITIS COMPLICATED WITH LIVER CANCER

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### ABSTRACT

**Introduction:** The purpose of this study was to investigate the effect of lamivudine combined with thymosin on postoperative recurrence of alcoholic hepatitis complicated with liver cancer.

**Materials and method:** According to the method of random digital table, 160 patients were divided into control group (n = 80) and study group (n = 80). Control group was given lamivudine once a day for 100 mg for 1 year (withdrawal of lamivudine after operation) at the first week after operation. Study group were treated with lamivudine combined with thymosin after operation. Serum total bilirubin, albumin, AST and ALT, immune function indexes, recurrence of patients were compared.

**Results:** After postoperative treatment for 6 months, the indexes of serum total bilirubin, AST and ALT in the study group were lower than those in the control group (all  $p < 0.001$ ), and the serum albumin in the study group was higher than that in the control group ( $p < 0.001$ ); serum CD3+, CD4+, CD8+ and CD4+/CD8+ in the study group were better than those in the control group ( $P = 0.030$ ,  $P = 0.001$ ,  $P = 0.042$ ,  $P = 0.038$ ). The recurrence rate of cancer in the study group was lower than that in the control group ( $P = 0.029$ ,  $0.035$ ) after 6-month and 1-year follow-up.

**Conclusion:** Combined treatment of lamivudine and thymosin after operation can improve both liver function and immune function of patients with alcoholic hepatitis complicated with liver cancer and reduce postoperative recurrence.

**Keywords:** Alcoholic hepatitis, liver cancer, lamivudine, thymosin, postoperative recurrence.

DOI: 10.19193/0393-6384\_2022\_3\_262

Received March 15, 2021; Accepted January 20, 2022

### Introduction

Alcoholic hepatitis is mainly caused by chronic and great alcohol consumption<sup>(1)</sup>. The clinical symptoms of these patients including vomiting, nausea, jaundice, fatigue and so on. Hepatic function will be seriously damaged if not treated timely, and liver cancer may occur eventually, thus threatening the lives and health of these patients<sup>(2)</sup>. Surgical resection is still a main method for the treatment of alcoholic hepatitis complicated with liver cancer, but the postoperative recurrence rate is high. At present, the mechanism of postoperative cancer recurrence is not clear.

The biological characteristics of liver cancer, low systemic immune function, radical operation and other factors may be related to postoperative recurrence of alcoholic hepatitis complicated with liver cancer<sup>(3-4)</sup>. Generally speaking, it is difficult to prevent postoperative recurrence of alcoholic hepatitis complicated with liver cancer from the point of view of multicenter origin of liver cancer. However, it may be an effective way to prevent postoperative recurrence of alcoholic hepatitis complicated with liver cancer from the point of view of radical resection combined with postoperative chemotherapy and improved immune function therapy<sup>(51)</sup>.

Lamivudine is an antiviral drug of nucleosides, which can effectively inhibit the replication of chronic hepatitis B virus (HBV), help patients alleviate liver necrosis and improve the liver function of patients<sup>(6-7)</sup>. Thymosin is a polypeptide composed of 28 amino-terminal acetylated amino acids and belongs to an immunomodulator, which can induce the immune effect in cells, improve the function of T cells, induce the hepatocytes infected by virus to produce endogenous interferon, and effectively eliminate the infected hepatocytes<sup>(8-9)</sup>. Most of the patients with alcoholic hepatitis complicated with liver cancer were treated with lamivudine. Although lamivudine can effectively inhibit the condition of patients, it cannot effectively eliminate the virus in hepatocytes and the patients may recur after drug withdrawal<sup>(10)</sup>. Thymosin is an immunomodulator that can inhibit the virus and promote the immune function of immune and specific cells<sup>(11)</sup>. Some studies suggest that lamivudine combined with thymic therapy can reduce the recurrence rate of patients with liver cancer after operation<sup>(12)</sup>. However, there are few reports on the postoperative recurrence of patients with alcoholic hepatitis complicated with liver cancer treated with lamivudine and thymosin.

The purpose of this study was to investigate the effect of lamivudine combined with thymosin on postoperative recurrence of alcoholic hepatitis complicated with liver cancer.

## Materials and methods

### Clinical materials

With the approval of the Research Ethical Committee of the Second Affiliated Hospital of Kunming Medical University, China. The 160 cases of alcoholic hepatitis complicated with liver cancer diagnosed and treated in our hospital from February 2017 to March 2020 were selected as the subjects of this study. Inclusion criteria: patients diagnosed as alcoholic hepatitis complicated with liver cancer; treated with radical resection of liver cancer, surgical margin  $\geq 1.0$  cm and with negative margin; and signed informed consent.

### Exclusion criteria:

patients confirmed with distant metastasis before operation; patients with other liver diseases such as autoimmune liver disease and hepatolenticular degeneration; patients infected with human immunodeficiency virus, type A, C, and other hepatitis viruses; and unable to be followed after operation.

## Methods

According to the method of random digital table, 160 patients were divided into control group ( $n = 80$ ) and study group ( $n = 80$ ). All patients were treated with routine clinical examination, symptomatic treatment and radical resection of liver cancer. Among them, the control group was given lamivudine once a day for 100 mg for 1 year (withdrawal of lamivudine after operation) at the first week after operation. The patients in the study group were treated with lamivudine combined with thymosin, that is, the usage and dosage of lamivudine were consistent with those in the control group. The patients in the study group were given subcutaneous injection of thymosin twice a week for 6 months (withdrawal of lamivudine for 6 months).

### Observation indexes

Before and 6 months after operation, serum total bilirubin, albumin, AST and ALT were measured and compared by automatic biochemical analyzer, and immune function indexes such as serum CD3+, CD4+, CD8+ and CD4+/CD8+ were measured and compared by flow cytometry.

The recurrence of patients in the two groups was compared between the two groups after 6 months and 1 year (the deadline for follow-up was March 2021). The diagnostic criteria for recurrence of liver cancer after operation were diagnosed by imaging evidence (B-ultrasound or CT of liver) after follow-up.

### Statistic analysis

SPSS 25 software was used to analyze data. Measurement data were expressed by mean  $\pm$  standard deviation, and tested by independent sample t-test. Counting data were expressed by  $n$  (%), and tested by Chi-square test.  $P < 0.05$  indicates that difference is significant.

## Results

### Demographic data

In the control group (80 cases), there were 45 males (56.25%) and 35 females (43.75%). The age was 40-71 years old, with an average age of ( $56.40 \pm 8.32$ ) years old. In the study group, there were 80 patients, 46 males (57.50%) and 34 females (42.50%). The age was 41-72 years old, with an average age of ( $51.75 \pm 13.10$ ) years old. There was no significant difference in sex and age between the two groups ( $X^2 = 0.025$ ,  $P = 0.873$ ;  $t = 1.896$ ,  $p = 0.062$ ).

**Comparison of liver function indexes between the two groups**

Before operation, there was no significant difference in serum total bilirubin, albumin, AST and ALT between the two groups (P=0.882, 0.128, 0.853, 0.674). After postoperative treatment for 6 months, the indexes of serum total bilirubin, AST and ALT in the study group were lower than those in the control group (all p<0.001), and the serum albumin in the study group was higher than that in the control group (p<0.001), as shown in Table 1.

Parameter	Time	Study group(n=80)	Control group(n=80)	t	P-value
Serum total bilirubin( $\mu$ mol/L)	Before operation	43.23 $\pm$ 5.97	43.01 $\pm$ 7.10	0.149	0.882
	After post-operative treatment for 6 months	22.74 $\pm$ 3.38	27.17 $\pm$ 5.34	-4.436	<0.001
Serum albumin(U/L)	Before operation	21.76 $\pm$ 1.55	22.39 $\pm$ 2.04	-1.538	0.128
	After post-operative treatment for 6 months	35.64 $\pm$ 3.58	30.90 $\pm$ 2.97	6.450	<0.001
Serum AST(U/L)	Before operation	135.05 $\pm$ 13.73	134.50 $\pm$ 12.51	0.186	0.853
	After post-operative treatment for 6 months	81.52 $\pm$ 7.61	106.98 $\pm$ 10.03	-12.790	<0.001
Serum ALT(U/L)	Before operation	85.66 $\pm$ 8.95	84.78 $\pm$ 9.62	0.422	0.674
	After post-operative treatment for 6 months	30.71 $\pm$ 3.63	41.25 $\pm$ 4.99	-10.793	<0.001

**Table 1:** Comparison of liver function indexes between the two groups.

Parameter	Time	Study group (n=80)	Control group (n=80)	t	P-value
Serum CD <sub>3</sub> <sup>+</sup> (%)	Before operation	52.98 $\pm$ 3.45	53.49 $\pm$ 3.89	-0.619	0.537
	After post-operative treatment for 6 months	57.86 $\pm$ 3.51	55.30 $\pm$ 6.44	2.211	0.030
Serum CD <sub>4</sub> <sup>+</sup> (%)	Before operation	30.93 $\pm$ 1.56	31.17 $\pm$ 2.01	-0.602	0.549
	After post-operative treatment for 6 months	35.81 $\pm$ 3.47	33.30 $\pm$ 3.31	3.310	0.001
Serum CD <sub>8</sub> <sup>+</sup> (%)	Before operation	29.03 $\pm$ 2.49	29.17 $\pm$ 1.57	-0.323	0.748
	After post-operative treatment for 6 months	28.24 $\pm$ 2.22	29.56 $\pm$ 3.35	-2.065	0.042
Serum CD <sub>4</sub> <sup>+</sup> /CD <sub>8</sub> <sup>+</sup>	Before operation	1.08 $\pm$ 0.29	1.09 $\pm$ 0.24	-0.101	0.920
	After post-operative treatment for 6 months	1.32 $\pm$ 0.47	1.11 $\pm$ 0.59	2.114	0.038

**Table 2:** Comparison of immune function indexes between the two groups.

**Comparison of immune function indexes between the two groups**

Before operation, there was no significant difference in serum CD3+, CD4+, CD8+ and CD4+/CD8+ between the two groups (P = 0.537, 0.549, 0.748, 0.920). After postoperative treatment for 6 months, the indexes of serum CD3+, CD4+, CD8+ and CD4+/CD8+ in the study group were better than those in the control group (P=0.030, P=0.001, P=0.042, P=0.038), as shown in Table 2.

**Comparison of recurrence between the two groups**

The recurrence rate of cancer in the study group was lower than that in the control group (P =0.029, 0.035) after 6-month and 1-year follow-up, as shown in Table 3.

Group	After 6-month follow-up	After 1-year follow-up
Study group (n=80)	2(2.50)	4(5.00)
Control group (n=80)	9(11.25)	12(15.00)
X <sup>2</sup>	4.783	4.444
P value	0.029	0.035

**Table 3:** Recurrence of patients in the two groups during the postoperative follow-up.

**Discussion**

Liver is the most important metabolic organ for human body to synthesize a variety of egg quality and enzymes. Total bilirubin, albumin, AST and ALT are commonly used serological indexes to reflect hepatocyte injury<sup>(13)</sup>. The activity of serum total bilirubin, albumin, AST and glutamic pyruvic transaminase can reflect the damage of hepatocytes and the degree of injury<sup>(14-15)</sup>.

The results showed that the indexes of serum total bilirubin, albumin, AST and glutamic pyruvic transaminase in the study group were better than those in the control group after postoperative treatment for 6 months. The results showed that lamivudine combined with thymosin was effective in the treatment of liver cancer complicated with alcoholic hepatitis and could effectively improve the liver function indexes of patients. The reason may be that lamivudine combined with thymosin can play a more effective role in anti-HBV replication, effectively eliminate the virus, and help patients to restore liver function<sup>(16)</sup>.

Tumor metastasis and tumor recurrence are closely related to immune dysfunction or decline<sup>(17)</sup>. CD3+ and CD4+ play an important role in cellular immunity and auxiliary humoral immunity, and have

an auxiliary killing effect on tumor cells<sup>(18)</sup>. In order to maintain the immune function of the body, CD4+ and CD8+ were in relative balance in T lymphocyte subpopulation under the normal condition of the human body. For patients with liver cancer, due to the disorder of immune function, it is difficult to clear tumor cells in the immune system, and the levels of CD4+ and CD8+ in the body will be out of balance<sup>(19)</sup>. The results of this study showed that the indexes of serum CD3+, CD4+, CD8+ and CD4+/CD8+ in the study group were better than those in the control group after postoperative treatment for 6 months. Thus it can be seen that lamivudine combined with thymosin can improve the immune function of patients compared with lamivudine alone.

Postoperative recurrence of liver cancer is an important factor affecting the curative effect of liver cancer<sup>(20)</sup>. This study found that the recurrence rate of cancer in the study group was lower than that in the control group after 6-month and 1-year follow-up, suggesting that lamivudine combined with thymosin can reduce the recurrence and metastasis rate after operation, and it is speculated that the reason may be related to the improvement of liver function and immune status of the patients. The limitation of this study was that the sample size was small and the follow-up time was short. In the future, a prospective study of multicenter cooperation and larger sample size can be carried out to further explore the effect of lamivudine combined with thymosin therapy on postoperative recurrence of alcoholic hepatitis complicated with liver cancer.

## Conclusion

The combined treatment of lamivudine and thymosin after operation can improve both liver function and immune function of patients with alcoholic hepatitis complicated with liver cancer and reduce postoperative recurrence.

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#### Acknowledgement

This work was supported by the Basic Research Program of Yunnan Province in 2019 (Grant No.2019FE001-180); Thailand's Education Hub for ASEAN Countries (Grant No. THE-AC 053/2017).

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