

PROGNOSTIC VALUE OF SERUM HUMAN CARTILAGE GLYCOPROTEIN 39 AND GOLGI PROTEIN 73 IN LIVER CANCER PATIENTS TREATED WITH INTERVENTIONAL THERAPY

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ABSTRACT

Introduction: The aim of the present study was to evaluate the prognostic value of serum human cartilage glycoprotein 39 (YKL-40) and golgi protein 73 (GP73) levels in liver cancer patients treated with interventional therapy.

Materials and method: One hundred and one patients with liver cancer received interventional therapy and were followed up for three years. According to the follow-up results, all patients were divided into a survival group and a death group. Serum YKL-40 and GP73 levels were measured. Prognosis value of serum YKL-40 and GP73 for patients before interventional therapy was evaluated by calculating the area under the receiver operating characteristic (ROC) curve (AUC).

Results: One week after the first interventional therapy, levels of serum YKL-40 and GP73 in patients were lower than those before interventional therapy (both $P < 0.001$). Pearson correlation analysis revealed that there was a positive correlation between serum YKL-40 and GP73 levels in patients before interventional therapy ($r = 0.686$, $P < 0.001$). Before interventional therapy, serum YKL-40 and GP73 levels in death group were higher than those in the survival group ($P < 0.001$ and $P = 0.002$, respectively). The AUC of serum YKL-40 before interventional therapy was 0.882 (95% CI: 0.819-0.946), higher than AUC of serum GP73 before interventional therapy, which was 0.733 (95% CI: 0.629-0.836) ($P < 0.001$).

Conclusion: Serum YKL-40 and GP73 are closely related to the prognosis of liver cancer patients treated with interventional therapy. Compared with serum GP73 before interventional therapy, serum YKL-40 before interventional therapy may have a higher predictive value for the prognosis of this patient treated with interventional therapy.

Keywords: Liver cancer, Interventional therapy, prognosis, human cartilage glycoprotein 39 (YKL-40), golgi protein 73 (GP73).

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Introduction

Liver cancer is one of the most common malignant tumors worldwide. Interventional therapy is a common method in the treatment of liver cancer in clinic⁽¹⁾. However, there is a risk of recurrence after interventional therapy, and the prognosis and survival status of recurrent patients are poor. How to effectively assess the prognosis of patients after interventional therapy is of great significance to prevent postoperative recurrence and improve the quality of life of patients. Traditionally, the tumour-nodes-metastases (TNM) staging based on tumor clinicopathological features is used to evaluate the

postoperative prognosis of patients with liver cancer, but it has an obvious shortcoming, i.e., there is a lag in the evaluation time⁽²⁾. At present, barcelona clinical liver cancer (BCLC) staging is usually used to evaluate the prognosis of liver cancer,⁽³⁾ but it needs to refer to many indicators (such as patients' health status, tumor characteristics and liver function indicators) to judge the prognosis of patients with liver cancer. Moreover, it requires doctors to have certain clinical experience and their accuracy still needs to be improved. Related studies have shown that serum markers are expected to be used as an independent index to evaluate the prognosis of patients with tumors, and the measurement of serum

markers is relatively simple and easy to operate⁽⁴⁾. Human cartilage glycoprotein 39 (YKL-40) is an inflammatory factor associated with malignant tumors based on chronic inflammation⁽⁵⁻⁶⁾. There are studies indicating that YKL-40 is related to the occurrence and development of liver cancer⁽⁷⁾. It has also been found that the level of serum YKL-40 in patients with liver cancer increase, so it has certain diagnostic value for liver cancer⁽⁸⁾. However, there are few reports on the prognostic value of serum YKL-40 in liver cancer patients treated with interventional therapy.

Golgi protein 73 (GP73) is an important transmembrane glycoprotein, which is mainly expressed in bile duct epithelial cells. The level of GP73 is low in healthy people, but increases in patients with liver diseases⁽⁹⁻¹⁰⁾ and significantly increases in patients with liver cancer⁽¹¹⁾. At present, many studies have reported the good sensitivity of serum GP73 in the diagnosis of liver cancer⁽¹²⁻¹³⁾. However, there are few reports on the prognostic value of serum GP73 in liver cancer patients treated with interventional therapy. The objective of this study was to evaluate the prognostic value of serum YKL-40 and GP73 levels in liver cancer patients treated with interventional therapy.

Materials and methods

Clinical materials

A total of 101 patients with liver cancer diagnosed in Daqing Oil Field General Hospital, China, from August 2018 to August 2019 were selected as research subjects.

The inclusion criteria were:

- Patients with primary liver cancer diagnosed by ultrasound guided liver biopsies and postoperative pathology;

- With single focus;
- Stage B or C according to BCLC staging;
- Cartesian functional status (KPS) score >60;
- Willing to receive interventional therapy;
- No other treatments before the interventional therapy;

- Willing to receive the measurement of serum YKL-40 and GP73 levels;

- Patients who signed the informed consent and had complete follow-up data.

The exclusion criteria were:

- Patients complicated with other malignant tumors;

- History of infection or operation;

- Severe coagulation dysfunction;
- Massive or intractable celiac effusion;
- Autoimmune diseases and systemic diseases;
- Distant metastasis involving organs other than the liver;

- Diffused primary liver cancer;
- Severe insufficiency or dysfunction of heart, lung, kidney and other important organs;

- Unable to tolerate interventional therapy;
- Peri-operative death;
- Survival time less than 3 months.

Interventional therapy method

All patients received the following interventional therapy. Femoral artery puncture was conducted with Seldinger method. Then, hepatic arteriography was performed after insertion of the catheter. Chemotherapeutic drugs oxaliplatin and fluorouracil were mixed evenly with 10-20 mL embolic agent ultra-fluid lipiodol, and the mixture was slowly injected into the hepatic artery.

The hepatic artery was embolized with embolic microspheres. All patients were treated with transcatheter arterial chemoembolization (TACE) at intervals of 30 days and 60 days, respectively. And routine symptomatic treatments such as antiemetic, liver protection, anti-infection, and acid inhibition were also implemented.

Determination of serum markers

Before the interventional therapy and one week after the first interventional therapy, 5 mL fasting venous blood was collected, and serum was collected by centrifugation for further measurement. Serum YKL-40 and GP73 levels were measured by enzyme-linked immunosorbent assay. After the interventional therapy, all patients were followed up for three years (once every six months). The follow-up was carried out through telephone, outpatient, or visit. The deadline for follow-up was August 2022. The survival of all patients was recorded, and there was no loss of follow-up. According to the follow-up results, all patients with liver cancer were divided into a survival group and a death group.

The levels of serum YKL-40 and GP73 were compared between the survival group and the death group before operation. The value of preoperative serum YKL-40 and GP73 in evaluating the prognosis of patients with liver cancer were analyzed.

Statistic analysis

SPSS 26.0 software was used for data analysis.

Measurement data were calculated by mean \pm standard deviation, independent sample t test was used for comparison between groups, and the paired t test was used for comparison before and after treatment. Enumeration data were calculated by n (%), and chi-square test was adopted.

Pearson correlation was used to analyze the correlation between serum YKL-40 and GP73. Prognosis value of serum YKL-40 and GP73 for this patients before interventional therapy was evaluated by calculating the area under the receiver operating characteristic (ROC) curve (AUC). $P < 0.05$ was considered statistically significant.

Results

Among the 101 patients with liver cancer, there were 60 (59.41%) males and 41 (40.59%) females, and they were aged 39-72 years with an average of 55.30 ± 7.81 years. One week after the first interventional therapy, the levels of serum YKL-40 and GP73 in the patients with liver cancer were lower than those before interventional therapy (both $P < 0.001$), as shown in Table 1.

Parameter	Before interventional therapy (n=101)	One week after the first interventional therapy (n=101)	p-value
Serum YKL-40 (ng/mL)	201.17 \pm 30.84	160.32 \pm 24.58	<0.001
Serum GP73 (μ g/L)	68.05 \pm 9.90	52.44 \pm 7.63	<0.001

Table 1: Comparison of serum YKL-40 and GP73 levels in patients before and after treatment.

Pearson correlation analysis revealed that there was a positive correlation between serum YKL-40 and GP73 levels in patients with liver cancer before interventional therapy ($r = 0.686$, $p < 0.001$).

All the 101 patients with liver cancer were followed up, including 33 cases of death (included in death group) and 68 cases of survival (included in survival group). There was no significant difference in male proportion, female proportion and age between the death group and the survival group ($P = 0.488$, $P = 0.488$ and $P = 0.682$, respectively), as shown in Table 2. There were significant differences in the proportion of tumor tissue high differentiation, moderately and poorly differentiation and portal vein tumor thrombus between the death group and the survival group (all $P < 0.001$), as shown in Table 2. Before interventional therapy, levels of serum YKL-40 and GP73 in the death group were higher than those in the survival group ($P < 0.001$ and $P = 0.002$, respectively), as shown in Table 2.

Parameter	Survival group (n=68)	Death group (n=33)	p-value
Male [n (%)]	42 (61.76)	18 (54.55)	0.488
Female [n (%)]	26 (38.24)	15 (45.45)	0.488
Age (years)	55.07 \pm 7.92	55.76 \pm 7.67	0.682
Tumor tissue high differentiation [n (%)]	50 (73.53)	9 (27.27)	<0.001
Tumor tissue moderately and poorly differentiation [n (%)]	18 (26.47)	24 (72.73)	<0.001
Portal vein tumor thrombus [n (%)]	11 (16.18)	27 (81.82)	<0.001
Serum YKL-40 before interventional therapy (ng/mL)	191.71 \pm 30.03	220.67 \pm 22.41	<0.001
Serum GP73 before interventional therapy (μ g/L)	65.94 \pm 10.32	72.40 \pm 7.36	0.002

Table 2: Comparison of parameters between survival group and death group.

The results of ROC curve analysis indicated that the AUC of serum YKL-40 before interventional therapy was 0.882 (95% CI: 0.819-0.946), higher than the AUC of serum GP73 before interventional therapy, which was 0.733 (95% CI: 0.629-0.836) ($P < 0.001$). The cut-off values of serum YKL-40 and GP73 before interventional therapy were 211.74 ng/mL and 69.46 μ g/L, respectively, as shown in Figure 1 and Table 3.

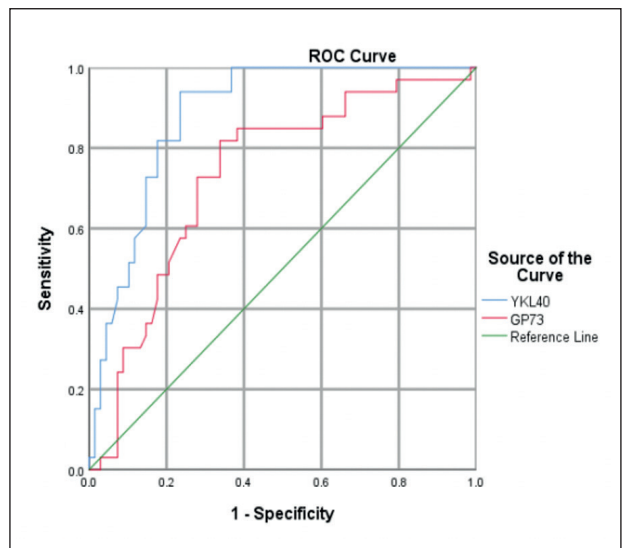


Figure 1: ROC curve of serum YKL-40 and GP73 levels in predicting prognosis of patients before interventional therapy.

Parameter	AUC (95% CI)	Std. Error	Sensitivity (%)	Specificity (%)	P value	Cut-off value
Serum YKL-40	0.882 (0.819-0.946)	0.033	81.80	82.40	<0.001	211.74 ng/mL
Serum GP73	0.733 (0.629-0.836)	0.053	72.7	72.1	<0.001	69.46 μ g/L

Table 3: Prognostic value of serum YKL-40 and GP73 in patients before treatment.

Discussion

Interventional therapy is the first choice for patients with liver cancer who are not suitable for surgical resection. Although interventional therapy has made great progress in the treatment of liver cancer, the therapeutic effect is not good because some patients still suffer tumor recurrence after operation. Clinically, there is no effective marker for predicting the prognosis of patients with liver cancer after interventional therapy.

YKL-40 is a kind of glycoprotein belonging to the chitinase protein family and consists of one polypeptide chain⁽¹⁴⁾. It is expressed and secreted by synovial cells, monocytes, and neutrophils, while in malignant tumors it is expressed and secreted by tumor cells⁽¹⁵⁻¹⁶⁾. Research suggests that YKL-40 is highly expressed at the molecular, cellular and tissue levels in hepatocellular carcinoma (HCC), but it may not be possible to distinguish HCC from liver cirrhosis by measuring serum YKL-40 levels⁽¹⁷⁾. Some studies find that the level of serum YKL-40 in patients with breast cancer is higher than that in healthy controls, and high serum YKL-40 level indicates a shorter overall survival rate in patients with breast cancer⁽¹⁸⁾. It is also found that serum YKL-40 is an independent prognostic factor for the overall and recurrence-free survival rate of HCC patients after radical resection, and continuous monitoring of serum YKL-40 after radical resection can provide prognostic information for patients⁽¹⁹⁾.

GP73 is a transmembrane protein existing in the Golgi apparatus. GP73 is rarely expressed in healthy human hepatocytes, but the expression of GP73 is significantly increased in the liver with acute chronic inflammatory reaction or hepatic fibrosis and reaches the peak when it develops to liver cancer⁽²⁰⁾. Some studies have also shown that the survival time of patients with a high concentration of serum GP73 is shorter than that of patients with a low concentration of HCC. The expression of serum GP73 may affect the prognosis of patients with liver cancer⁽²¹⁾.

The results of this study indicated that the levels of serum YKL-40 and GP73 in the patients with liver cancer one week after the first interventional therapy were lower than those before treatment, suggesting that interventional therapy can effectively clear the micrometastases and reduce the levels of serum YKL-40 and GP73 in patients with liver cancer. Pearson correlation analysis showed that there was a positive correlation between serum YKL-40 and GP73 levels in the patients before interventional

therapy. The author discovered that levels of serum YKL-40 and GP73 in the death group were higher than those in the survival group, indicating that the levels of serum YKL-40 and GP73 may reflect the changes of liver cancer. Thus, it is inferred that they may be used to evaluate the prognosis of liver cancer patients treated with interventional therapy.

It was also found in this study that there were significant differences in the proportion of high differentiation of tumor tissue, the proportion of low differentiation of tumor tissue and the occurrence of portal vein tumor thrombus between the death group and the survival group. The reason may be that the formation of portal vein tumor thrombus is closely related to hepatic portal vein countercurrent, and then affects the prognosis. The higher the degree of tumor differentiation, the more similar with the normal tissue, the lower the malignant degree, the better the prognosis⁽²²⁾.

The results of ROC curve analysis displayed that the AUC of serum YKL-40 before interventional therapy in evaluating the prognosis of patients with liver cancer was higher than that of serum GP73, suggesting that serum YKL-40 and GP73 have certain value in predicting the prognosis of patients treated with interventional therapy, and serum YKL-40 has a higher predictive value than serum GP73 in predicting the prognosis of patients receiving interventional therapy. It should be noted that the effect of interventional therapy in patients may vary according to individual differences. The sample size included in this study is relatively small. Therefore, multicenter prospective studies with large samples are needed to further confirm the value of serum YKL-40 and GP73 levels in evaluating the prognosis of patients treated with interventional therapy.

Conclusions

Serum YKL-40 and GP73 are closely related to the prognosis of liver cancer patients treated with interventional therapy. Serum YKL-40 and GP73 before interventional therapy have certain value in evaluating the prognosis of these patients.

Compared with serum GP73 before interventional therapy, serum YKL-40 before interventional therapy may have a higher predictive value for the prognosis of this patient treated with interventional therapy.

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