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The Relationship Between Serum Interleukin-6 and the Recurrence of Hepatitis B Virus Related Hepatocellular Carcinoma after Curative Resection

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Abstract: The aim of this study is to assess whether preoperative serum interleukin-6 (IL-6) can predict recurrence of hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC).

The association between preoperative IL-6 levels and HCC recurrence following curative hepatectomy in 146 patients with chronic HBV infection was determined. Patients were divided into groups based on the presence or absence of HCC recurrence. Serum IL-6 levels were compared between groups, and the association between serum IL-6 level and greatest tumor dimension was also analyzed. Receiver operating characteristics (ROC) curve was used to define the optimal cutoff value for predicting recurrence-free survival (RFS) and overall survival (OS) rates. The OS and RFS rates were calculated using the Kaplan-Meier method.

Out of 146 patients, 80 (54.8%) patients were documented as having HCC recurrence during the follow-up period. After adjusting for potential confounders, serum IL-6 levels were significantly associated with HCC recurrence, and a saturation effect existed with serum IL-6 levels up to 3.7 pg/mL. In addition, patients with preoperative serum IL-6 levels over 3.1 pg/mL had lower RFS and OS rates ($P < 0.01$). There was no significant correlation between preoperative serum IL-6 levels and maximal tumor dimension ($r = 0.0003$, $P = 0.84$).

Elevated serum levels of IL-6 were significantly associated with an increased risk of HBV-associated HCC recurrence suggesting that preoperative IL-6 serum level is potential biomarker for early prediction of HBV-associated HCC recurrence.

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Abbreviations: AFP = alpha-fetoprotein, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, ICGR15 = indocyanine green retention rate at 15 minutes, IL-6 = interleukin-6, OS = overall

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survival, RFS = recurrence-free survival, ROC = receiver operating characteristics.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide.¹ With the exception of Japan, HCC in Asian countries most often occurs in patients with underlying chronic hepatitis B virus (HBV) infection through a multistep process of hepatocarcinogenesis.²⁻⁴ With the development of diagnostic and operative techniques, curative hepatic resection for this fatal disease is more accessible to patients. Nevertheless, the high recurrence rate following curative resection hampers the long-term benefits of surgical treatment.^{5,6} Therefore, identifying factors that contribute to HBV-associated HCC recurrence could provide potential targets for novel therapeutic strategies.

Recently, the expression profiling of fixed tissue HCC and nontumor tissue has been used to gain insight into HCC recurrence.⁷ The results indicated that most cases of HCC recurrence after curative therapy are not metastasis from the primary tumor, but rather de novo cancers arising within the cirrhotic liver. These findings prompted our investigation into the role of inflammation cytokines that are closely related to tumorigenesis in HCC recurrence.^{8,9}

Interleukin-6 (IL-6), produced by B-cells, T-cells, macrophages, and fibroblasts, regulates chronic inflammation and, thus, creates a cellular microenvironment beneficial to cancer growth.^{10,11} The potential association of IL-6 with the risk of HCC has been explored in previous studies.^{10,12} However, it is not clear whether this inflammatory cytokine is associated with HCC recurrence after curative resection in patients with chronic HBV infection.

Despite recommendations regarding periodic follow-up with imaging and tumor markers such as alpha-fetoprotein (AFP) and fibrosis markers, these strategies have not proven efficacious in the early prevention of HCC recurrence. The currently study analyzed the relationship between preoperative serum IL-6 and HBV-associated HCC recurrence after curative resection. In addition, the correlation between serum IL-6 levels and the original tumor characteristics was also explored to shed potential light on the underlying etiology of HBV-associated HCC recurrence.

METHODS

Study Population

This study was performed in accordance with National legislation and with the approval of the ethical committee of our hospital. This retrospective study utilized patient data that was

already collected. The processing and analysis of data were performed after anonymization.

We retrospectively collected patients' data from original medical records and the cancer patients' follow-up database at our hospital. Serum IL-6 was measured using ECLIA, Modular-System (Roche, Mannheim, Germany). In the current study laboratory test results obtained immediately prior to the date of surgery were selected to exclude interference from other preoperative invasive examinations.

During 2008 to 2009 at our hospital, 183 consecutive patients with chronic HBV infection underwent liver resection for primary HCC. All patients in this study had a histologic diagnosis of HCC. Out of the 183 patients, 37 patients were excluded from this study for the following reasons: 12 patients received noncurative resection, 3 patients died in the perioperative period, 15 patients received preoperative transarterial chemoembolization, and 7 patients had malignancy other than HCC. The remaining 146 patients were included in the analysis.

Preoperative Assessment and Surgical Procedures

All patients received laboratory assessment of liver function, preoperative viral serologic testing, and diagnostic imaging [including computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography-computed tomography (PET-CT)] to evaluate tumor location and tumor characteristics. Patients who had neither hilar nodal involvement nor extrahepatic metastases were treated with liver resection as the initial treatment for their primary HCC.

The selection criteria and type of operative procedures were determined according to preoperative indocyanine green retention rate at 15 minutes (ICGR15), as previous described. In general, patients with an ICGR15 less than 35% were selected for anatomic resection. An ICGR15 of 35% or more indicated limited liver resection. Liver resections were performed by the same medical team using previously described procedures.^{13,14}

Postoperative Follow-Up

After the operation, patients received routine follow-up with physical examination, serum AFP level, and ultrasonography at 3-month intervals for the first year and then every 6 months. The patients also received contrast-enhanced CT scans at 6-month intervals. Suspected HCC recurrence was confirmed using MRI, hepatic angiography, and percutaneous biopsy in some cases. Additional examinations, such as chest CT, bone scan, or PET-CT, were also performed if there was any sign of extrahepatic recurrence. The end of follow-up was determined as either the time of last follow-up (January 2013) or death.

Statistical Analysis

Case-controlled differences were assessed using Student *t*-test, Pearson Chi-square test, and the Fisher exact test, where appropriate (Table 1). Serum IL-6 levels were compared between groups by unpaired Student *t*-test. The association between serum IL-6 level and greatest tumor dimension and HBsAg amount were analyzed by the Pearson correlation test (Figures 1 and 2). Exploratory stratified analysis was performed and *P* for interaction was calculated from the log likelihood ratio test comparing 2 nested models (Table 2). The relationship between serum IL-6 and the risk of HCC recurrence was explored using a smoothing plot (Figure 3). A 2-piecewise linear regression model was used to examine the saturation effect of serum IL-6 on the risk of HCC recurrence, according to

the smoothing plot (Table 3). An inflection of serum IL-6 level, at which the relationship between serum IL-6 levels and the risk of HCC recurrence began to diminish was determined using a trial method. The latter involved moving the trial inflection point along a predefined interval and detecting the inflection point that gave the maximum likelihood. Receiver operating characteristics (ROC) curve was used to define the optimal cutoff value, sensitivity, and specificity (Figure 4). The overall survival (OS) and recurrence-free survival (RFS) rates were calculated using the Kaplan-Meier method. The difference between the 2 groups was determined using the log rank test (Figure 5).

All data were double entered and then exported to tab-delimited text files. A *P*-value less than 0.05 (2-tailed) was considered statistically significant. Statistical analyses were performed with R (<http://www.R-project.org>).

RESULTS

Patients' clinicopathological characteristics are summarized in Table 1. Out of 146 patients, 80 (54.8%) patients were documented as having HCC recurrence during the follow-up period (group 1). For patients with HCC recurrence compared with those patients without tumor recurrence (controls, group 2), serum IL-6 levels were significantly higher (3.7 vs 2.8 pg/mL, respectively, $P < 0.01$) and the maximal tumor dimensions were significantly larger (6.2 vs 5.3 cm, respectively, $P < 0.01$). Moreover, multiple tumors and portal vein invasion were more common in HCC recurrence patients. There were no significant differences, however, regarding Child-Pugh score, alcohol consumption, AFP concentration, liver function tests, intraoperative factors, HCC stages, or degree of tumor differentiation ($P > 0.05$).

The relationship between serum IL-6 levels and primary tumor characteristics is shown in Figures 1 and 2. Serum IL-6 levels were associated with multiple tumors. Serum IL-6 levels were significantly higher in patients with multiple tumors compared with patients with a solitary tumor (3.5 vs 3.0 pg/mL, respectively, $P = 0.04$, Figure 1A). In addition, serum IL-6 level has some relevance with HBsAg amount ($r = 0.504$, $P < 0.001$, Figure 1B). However, no significant difference in serum IL-6 levels were found between portal vein invasion versus no portal vein invasion (3.6 vs 3.2 pg/mL, $P = 0.20$, Figure 2A), and between microvascular invasion versus no microvascular invasion (3.5 vs 3.2 pg/mL, $P = 0.25$, Figure 2B). Furthermore, there was no significant correlation between preoperative serum IL-6 levels and maximal tumor dimension ($r = 0.0003$, $P = 0.84$, Figure 2C).

The effect of different clinicopathological features on the association between preoperative serum IL-6 levels and HCC recurrence is shown in Table 2. The predictive capability of preoperative serum IL-6 levels was not significantly influenced by the number of tumors. The preoperative serum IL-6 was not associated with HCC recurrence in either the solitary or multiple tumor groups (P for interaction > 0.05). In addition, there was no evidence for an interaction between preoperative serum IL-6 and maximal tumor dimension, microvascular invasion, or portal vein invasion (all $P > 0.05$).

A multivariate regression analysis was performed to estimate the independent relationship between serum IL-6 level and HCC recurrence, while adjusting for potential confounders. Adjusted smoothed plots suggested a nonlinear relationship between serum IL-6 levels and risk of HCC recurrence (Figure 3). The risk of HCC recurrence increased with increasing serum IL-6 level up to the turning point of 3.7 pg/mL

TABLE 1. Baseline Characteristics of 146 Patients With Chronic HBV Infection Who Underwent Curative Hepatectomy for Hepatocellular Carcinoma

Variable	Nonrecurrence	Recurrence	P Value
	N = 66	N = 80	
IL-6, pg/mL	2.8 ± 1.5	3.7 ± 1.5	<0.001*
Age, years	50 ± 7	51 ± 7	0.36
Gender (male:female)	54:12	64:16	0.78
Smoking (yes:no)	44:22	55:25	0.79
Child-Pugh grade (A:B)	46:20	50:30	0.29
HBsAg amount, IU/mL	5.6 ± 2.8	6.1 ± 2.5	0.19
AFP			0.42
≤20 ng/mL	16 (24.2)	15 (18.8)	
>20 ng/mL	50 (75.8)	65 (81.2)	
Antiviral treatment (yes:no)	51:15	63:17	0.83
Alcohol intake	15.3 ± 23.7	18.8 ± 23.4	0.38
Cirrhosis (present:absent)	58:8	72:8	0.68
ALT, IU/L	78 ± 30	75 ± 27	0.48
AST, IU/L	66 ± 27	65 ± 26	0.81
Total bilirubin, mg/dL	1.0 ± 0.4	1.0 ± 0.3	0.36
Albumin, g/dL	4.0 ± 0.3	3.9 ± 0.2	0.55
Platelet count, 10 ⁴ /mm ³	14.7 ± 4.2	15.5 ± 4.3	0.22
Tumor number (multiple:solitary)	32:34	59:21	<0.002*
Maximal tumor dimension, cm	5.3 ± 2.0	6.2 ± 1.9	0.006*
MVI (present:absent)	30:36	36:44	0.96
PVI (present:absent)	9:57	24:56	0.02*
Anatomic resection (yes:no)	46:20	50:30	0.36
Blood loss, mL	419 ± 219	428 ± 272	0.83
AJCC stage, n, %			0.12
I	30 (45.5)	24 (30.0)	
II	21 (31.8)	28 (35.0)	
III	15 (22.7)	28 (35.0)	
Histology, n, %			0.30
Well differentiated	21 (31.8)	20(25.0)	
Moderately differentiated	22 (33.3)	22 (27.5)	
Poorly differentiated	23 (34.9)	38 (47.5)	
Complications (present:absent)	20:46	25:55	0.90

AFP = α-fetoprotein, AJCC = American Joint Committee on Cancer, ALT = alanine aminotransferase, AST = aspartate aminotransferase, HBV = hepatitis B virus, IL-6 = interleukin-6, MVI = microvascular invasion, PVI = portal vein invasion. Values shown are expressed as mean ± standard deviation.

*Statistically significant difference.

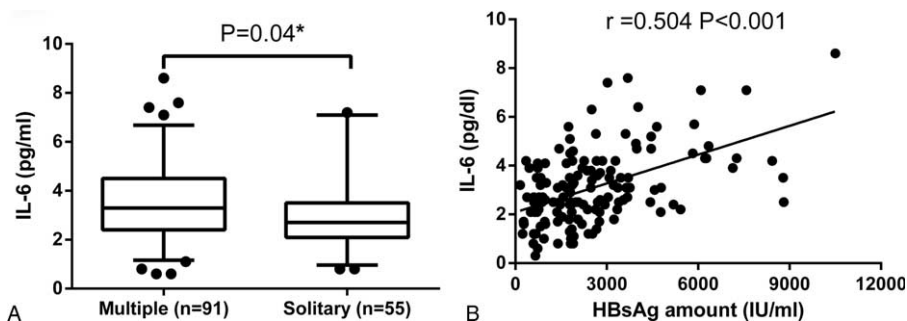


FIGURE 1. Characteristics significantly associated with serum IL-6 levels. (A) Serum IL-6 is significantly higher in patients with multiple hepatic tumors compared with patients with only solitary tumor recurrence (3.5 vs 3.0 pg/mL, $P=0.04$). (B) Serum IL-6 level has some relevance with HBsAg amount ($r=0.504$, $P<0.001$).

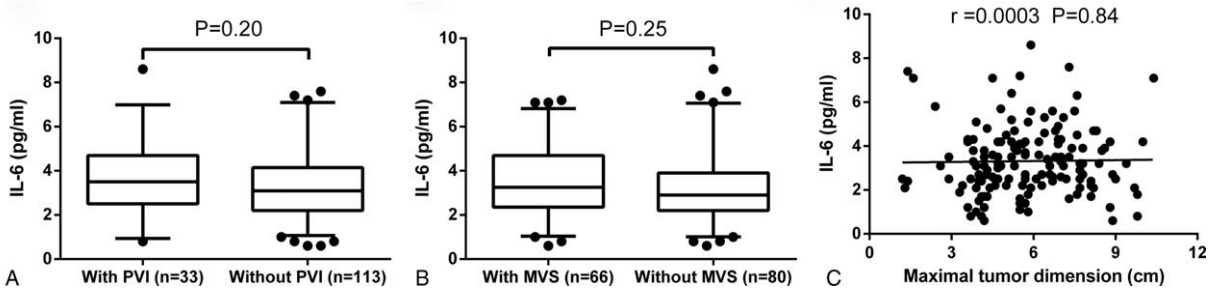


FIGURE 2. Tumor characteristics do not associated with IL-6 levels. There is no significant difference in serum IL-6 levels (A) between portal vein invasion versus no portal vein invasion (3.6 vs 3.2 pg/mL, $P=0.20$), and (B) between microvascular invasion versus no microvascular invasion (3.5 vs 3.2 pg/mL, $P=0.25$). (C) Serum IL-6 levels are not significantly associated with the maximal tumor dimension ($r=0.0003$, $P=0.84$).

(OR = 3.8, 95% CI 2.1–6.8, $P < 0.001$). A serum IL-6 level over 3.7 pg/mL was not associated with a higher risk of HCC recurrence (OR = 0.89, 95% CI 0.47–1.7, $P = 0.71$) (Table 3).

Receiver operating characteristic (ROC) analysis was used to further verify the discriminating capacity of serum IL-6 level to predict HCC recurrence (Figure 4). The results demonstrated that the preoperative serum IL-6 level was able to distinguish HCC recurrence patients from controls with an area under the curve of 0.70 (95% CI 0.62–0.78). The optimal cutoff point for preoperative serum IL-6 level in predicting HCC recurrence was 3.1 pg/mL, with a sensitivity of 66.2% and a specificity of 74.2%.

According to the optimal cutoff value, patients with preoperative serum IL-6 levels ≤ 3.1 pg/mL were defined as low IL-6 ($n=76$), while patients with preoperative serum IL-6 levels >3.1 pg/mL were defined as high IL-6 ($n=70$). The RFS rate in the high IL-6 group was significantly lower compared with the rate in the low IL-6 group (Figure 5A) ($P < 0.01$). The 1, 3, and 5-year RFS rates were 87.1%, 31.4%, and 21.4%, respectively, in the high IL-6 group and 86.8%, 71.1%, and 61.8%, respectively, in the low IL-6 group. The OS rate in the high IL-6 group was also significantly lower compared with the OS rate in the low IL-6 group (Figure 5B) ($P < 0.01$). The 1, 3, and 5-year OS rates were 98.6%, 34.3%,

and 22.9%, respectively, in the high IL-6 group and 98.7%, 73.7%, and 65.8%, respectively, in the low IL-6 group.

DISCUSSION

In patients with HBV-associated HCC, we determined that the preoperative serum IL-6 level may serve as an independent and significant prognostic indicator of HCC recurrence after curative hepatic resection. Both RFS and OS in the high IL-6 group were significantly lower compared with the rates in the low IL-6 group. Different from previous study,¹⁵ we also found a saturation effect when using serum IL-6 to predict HCC recurrence.

Inflammation is recognized as an important factor in the development and progression of malignancy.^{8,9} As an inflammatory cytokine, IL-6 is one of the best characterized protumorigenic cytokines.¹⁶ IL-6 could activate the nuclear factor- κ B and the signal transducer and activator of transcription 3, thereby contributing to HCC development.^{17,18} Recent clinical researches have also demonstrated that IL-6 is elevated in HCC patients.^{19–23} Our current data demonstrated that serum IL-6 levels significantly correlated with tumor recurrence in patients with HBV-associated HCC, even after they received curative resection.

TABLE 2. Stratified Analysis of Factors Affecting the Correlation Between Preoperative Serum IL-6 and HCC Recurrence

	N (%)	OR (95% CI)	P^*
Tumor number			0.92
Solitary	55 (37.7)	2.3 (1.2, 4.4)	
Multiple	91 (62.3)	2.4 (1.6, 3.7)	
Maximal tumor dimension			0.23
≤ 5 cm	57 (39)	1.9 (1.1, 3.1)	
>5 cm	89 (61)	3.0 (1.7, 5.0)	
MVI			0.18
Absent	80 (54.8)	2.0 (1.3, 3.1)	
Present	66 (45.2)	3.2 (1.8, 5.7)	
PVI			0.32
Absent	113 (77.4)	2.2 (1.5, 3.3)	
Present	33 (22.6)	3.8 (1.3, 10.9)	

CI = confidence interval, HCC = hepatocellular carcinoma, MVI = microvascular invasion, OR = odds ratio, PVI = portal vein invasion. $*P$ for interaction.

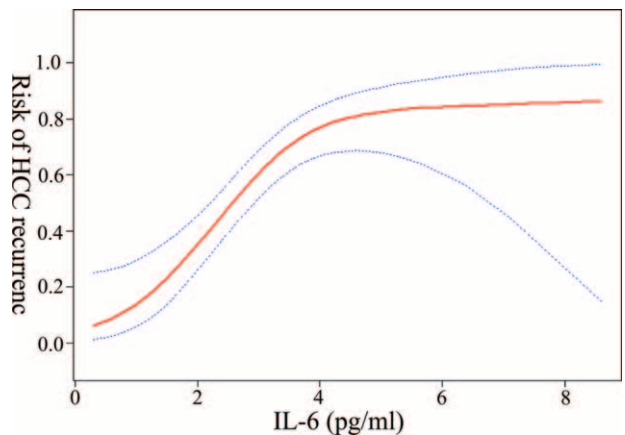


FIGURE 3. The adjusted relationship between serum IL-6 level and the risk of HCC recurrence. A nonlinear relationship between serum IL-6 level and risk of HCC recurrence is observed after adjusting for age, tumor number, portal vein invasion, and microvascular invasion.

TABLE 3. Threshold Effect Analysis of Serum IL-6 Level on Hepatocellular Carcinoma Recurrence Using Piecewise Linear Regression

Infection Point of IL-6	Hepatocellular Carcinoma Recurrence	
	Adjusted Odds Ratio (95% CI)*	P
≤3.7(pg/mL)	3.8 (2.1, 6.8)	<0.001†
>3.7(pg/mL)	0.89 (0.47, 1.7)	0.71

* Adjusted for age, HBsAg amount, tumor number, portal vein invasion, and microvascular invasion.
 † Statistically significant difference.

Previous studies have demonstrated a significant correlation between HCC recurrence and unfavorable tumor factors, such as tumor size, multiple tumors, and the presence of microvascular invasion.^{24–26} Some researchers have explained the elevation in inflammatory cytokines as 1 aspect of a paraneoplastic syndrome, and as such, may predict HCC recurrence.^{27,28}

In the current study, we found that tumor size, multiple tumors, and portal vein invasion were associated with HCC recurrence. However, serum IL-6 levels were not significantly associated with tumor size or portal vein invasion. Subsequent subgroup analysis suggested that serum IL-6 levels could effectively predict HCC recurrence, whether in a solitary tumor or in multiple tumors. In addition, although preoperative serum IL-6 levels had some relevance with HBV amount, the association between serum IL-6 levels and HCC recurrence was not significantly changed, after adjusting the HBV amount in the multivariate regression analysis. These suggest that IL-6 can serve as an independent factor for HCC recurrence and not just the reflection of unfavorable primary tumor factors or HBV infection status. Since our study population involved patients with chronic HBV infection, this difference may be explained as follows:

Serum IL-6 levels are primarily affected by chronic HBV infection, liver fibrosis, and coexistent cirrhosis. Previous studies have shown that HBV X protein can regulate the expression of IL-6 via protein phosphatase type 2 Cα.²⁹

A portion of HCC recurrences after curative therapy might be de novo cancers arising in cirrhotic livers, as proposed by some researchers.^{7,30} Serum IL-6 levels could be a comprehensive reflection of systemic metabolism, inflammation, and immune status.

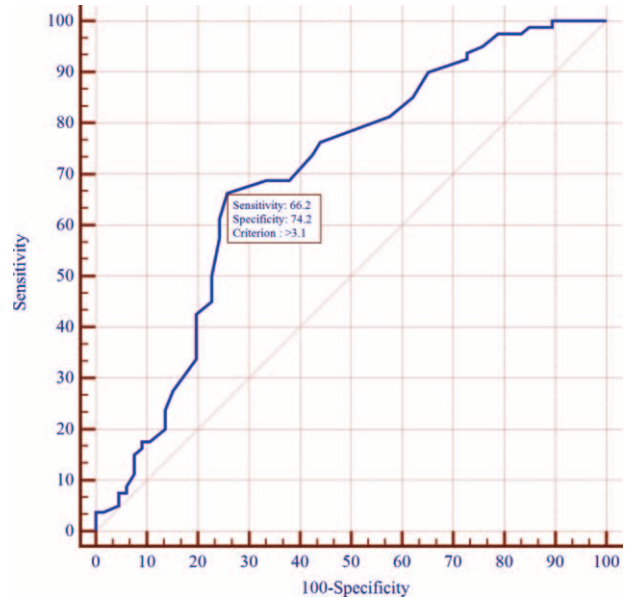


FIGURE 4. Receiver operating characteristics (ROC) curve analysis using serum IL-6 level for predicting HCC recurrence. The serum IL-6 level predicts HCC recurrence using the area under the curve (AUC) of 0.70 (95% CI: 0.62–0.78). The optimal cutoff point for preoperative serum IL-6 level in predicting HCC recurrence is 3.1 pg/mL, with a sensitivity of 66.2% and a specificity of 74.2%.

The finding of a preoperative serum IL-6 saturation effect when predicting HBV-related HCC recurrence after curative resection suggests a complex link between IL-6 and tumor recurrence, that is, IL-6 could have strong protumorigenic activity due to its multiple effects on tumor cell proliferation and survival, angiogenesis, tumor metabolism, and inflammation.^{16,31} In addition, IL-6, alone or in combination with other cytokines, is an architect for shaping and generating immune responses which can exert a profound influence on HCC development. In hepatoma cell lines and in rodents injected with hepatoma cells, IL-6 actually inhibits instead of enhances tumor growth.^{32–35} Only after IL-6 reaches a certain concentration can assume the multifaceted role needed to reach a balance and not increase the risk of tumor recurrence. To date, few studies have obtained such a quantitative finding, although the mechanisms underlying this result need to be further studied.

In addition, we also found that both RFS and OS were significantly lower if preoperative serum IL-6 levels exceeded 3.1 pg/mL. Since few studies have defined a cutoff value for IL-6 when predicting HCC recurrence, measurements of preoperative IL-6 level may help in selecting patients who

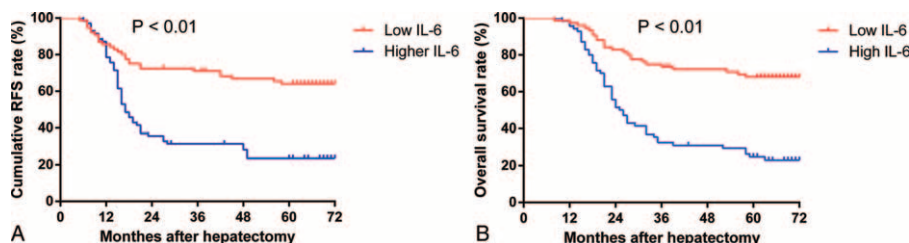


FIGURE 5. The recurrence-free survival curves and the overall survival curves in patients with low versus high serum IL-6 level. (A) The recurrence-free survival rates in the high serum IL-6 group are significantly higher than those in the low serum IL-6 group ($P < 0.01$). (B) The overall survival rates in the high serum IL-6 group are significantly higher than those in the low serum IL-6 group ($P < 0.01$).

would benefit from additional therapy following surgery, even after curative resection.

Our study had several limitations including its retrospective nature, which limited our ability to detect IL-6 in the tissues surrounding HCC. This reduced our ability to further explore the mechanisms underlying this phenomenon. In addition, not all studies have supported this notion.³⁶

In conclusion, a complex interaction exists between tumor–host immunity and inflammatory response, but the key mechanisms underlying this response are not fully understood. However, elevated serum levels of IL-6 were significantly associated with an increased risk of HBV-associated HCC recurrence, even after adjusting for unfavorable primary. The causal role of IL-6 in HCC recurrence can provide valuable information when selecting additional therapy following surgery. Targeting the IL-6 system may also prove beneficial in the early prevention of this disease, and this area may prove fertile ground for future research.

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