

Original Article

Preoperative levels of serum alanine aminotransferase conducive to predicting recurrence of HBV-related hepatocellular carcinoma after R0 resection

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Abstract: In the study, we aimed to investigate the relevance of preoperative serum alanine aminotransferase (ALT) levels to recurrence of hepatitis B virus-related hepatocellular carcinoma (HBV-HCC) after R0 resection. The medical histories of a cohort of HBV-HCC patients (663) having undergone R0 resection from 2000 to 2012 were retrospectively reviewed and analyzed. A receiver operating characteristic (ROC) curve was plotted to define the optimal cutoff values, and to identify the sensitivity and specificity of preoperative levels of serum ALT in predicting recurrence of HBV-HCC after R0 resection. The patients were subgrouped according to preoperative serum ALT levels. Subgroup analysis was conducted to investigate associations of preoperative ALT levels with serum HBV-DNA levels, cirrhosis occurrence or curative effect of postoperative antiviral therapy on HBV-HCC recurrence after R0 resection. ROC results showed that the optimum cutoff value for ALT was 37.5 U/L (AUC 0.698, 95% CI: 0.657-0.738, sensitivity 70.4%, specificity of 65.1%). Over a median follow-up period of 44.5 months after R0 resection, Kaplan-Meier analysis showed significantly high recurrence-free survival (RFS) rates for low preoperative ALT group compared to high ALT group over 15 year follow-ups. Multivariate analysis showed that an elevated preoperative ALT level and cirrhosis were independent risk factors affecting RFS. Subgroup analysis revealed that the patients with preoperative ALT levels ≤ 20 U/L had significantly less cirrhosis and their prognosis was much better with lower recurrence rates after R0 resection than those with higher ALT levels. Importantly, the subgroup analysis also revealed that postoperative antiviral therapy significantly improved RFS for the patients with high levels of preoperative ALT. Our analyses suggest that high levels of preoperative serum ALT in HBV-HCC patients may lead to poorer RFS after R0 resection and indicate a better prognostic effect of postoperative antiviral therapy on recurrence of HBV-HCC.

Keywords: Alanine aminotransferase, hepatocellular carcinoma, hepatitis B virus, recurrence, R0 resection, prognosis factors

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most frequent cause of cancer-related death and accounts for more than 90% of primary liver cancer [1]. Etiologically, HCC is largely associated with chronic hepatitis B virus (HBV) infection [2]. Since viral hepatitis is considerably prevalent in China, hepatitis virus-induced hepatocirrhosis and carcinogenesis occurs more frequently than other parts worldwide. Curative liver resection is the main treatment for HCC at present in our hospital as well as worldwide, but its overall curative effect remains unsatisfactory because of recurrence. It has been thought that the unsatisfactory effect is ascribed to the HBV-induced liver dam-

age and cirrhosis in HCC recurrence after curative resection, except for HCC potential intrahepatic metastasis.

Alanine aminotransferase (ALT) levels in serum have been considered as a measure of sensitive biochemical hepatitis activity and can reflect hepatocellular damage. The previous studies showed that elevated perioperative transaminase level could predict intrahepatic HBV-related HCC recurrence after curative hepatectomy [3]; high postoperative serum ALT level was closely associated with hepatitis C virus-HCC recurrence after curative resection [4]. However, the factors influencing preoperative ALT levels in patients with HBV-HCC have not been completely studied, and the association of preoperative ALT levels with HBV-HCC

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recurrence after R0 resection and efficiency of postoperative antiviral therapy remain elusive. Because serum ALT levels reflect the degree of both hepatitis B viral activity and liver damage which are known to be determinants of HCC recurrence, we assume that preoperative ALT ought to be relevant to HBV-HCC recurrence after surgical resection.

For this reason, the present retrospective analysis of the clinical and follow-up data of 663 cases of HBV-HCC who underwent R0 resection from January 2000 to December 2012 was performed to elucidate prognostic factors for RFS and to evaluate relationships of preoperative serum ALT levels with recurrence after R0 resection and curative effect of postoperative antiviral therapy on HCC recurrence. We found that the patients with low levels of preoperative serum ALT showed much better prognosis with lower recurrence rates after R0 resection than those with high ALT levels while postoperative antiviral therapy significantly improved RFS for the patients with high levels of preoperative ALT.

Materials and methods

Patients

Consecutive R0 hepatic resection for HCC was performed for 827 patients with HCC in the Affiliated Hospital of Qingdao University from January 2000 to December 2012. All the cases were confirmed by pathological examination. Among them, 725 patients were identified positive for hepatitis B surface antigen. Patients with the following situations were excluded: concurrent infection with HCV, bile duct tumor thrombus, tumor rupture, postoperative extrahepatic metastases within 2 months of follow-up and if patients died from liver disease-related but non HCC-related causes within 2 years after operation (without evidence of HCC recurrence). Ultimately, 663 patients were included for this study, among whom were 559 men and 104 women (ratio 5.4:1) and the age ranged 14-82 years old with an average of 54.3.

Surgical methods

All 663 cases underwent liver resection in accordance with the Couinaud segmentation method to implement hepatic segmentectomy or combined resection for adjacent liver seg-

ments (anatomical resection) or partial hepatectomy containing tumor (nonanatomical resection). R0 hepatic resection means that there were no residual cancer cells present or tumor nodules visible in the surgical margin when checked microscopically and macroscopically.

Test methods

The serum ALT of the targeted patients was assessed with help of ALT Modified UV (IFCC), Kinetic Assay (Span Diagnostics Ltd.) following the instructions of the manufacturer. The normal values range 10-40 U/L at 37°C.

Serum HBV-DNA was measured by way of PCR (ABI Prism 7000 fluorescence quantitative PCR instrument, ABI, USA); HBV DNA levels of $<10^3$ copies/mL was considered to be a low viral load.

Antiviral therapy and follow-up

In the present study, patients with HBV-HCC took nucleoside analogues as antiviral drugs, starting either before or after surgery. Adjuvant antiviral therapy with lamivudine 100 mg, adefovir dipivoxil 10 mg, or entecavir 0.5 mg orally daily was commenced within a week after operation or after discharge for some patients with the high viral load. For patients with renal function insufficiency, the daily lamivudine or adefovir dipivoxil dose was adjusted according to creatinine clearance.

Serum alpha-fetoprotein (AFP), liver function tests, liver ultrasonography or computed tomography (CT) image, and lung CT were performed monthly for 3 months after surgical resection, then trimonthly. The time of recurrence after resection was adjudged by the presence of clear masses on imaging examination. Patients with confirmed recurrence were subject to further treatment. If the recurrent tumor was located, a second liver resection, radiofrequency ablation (RFA) or percutaneous ethanol injection was suggested; if the recurrent tumor was multiple or diffused, transcatheter arterial chemoembolization (TACE) was the choice. Treatment decision was made based on the pattern of recurrence and liver function reserve. The follow-up ended on 31 January 2015 or when patients died. The median follow-up time was 44.5 months (range 3.3-180.8 months).

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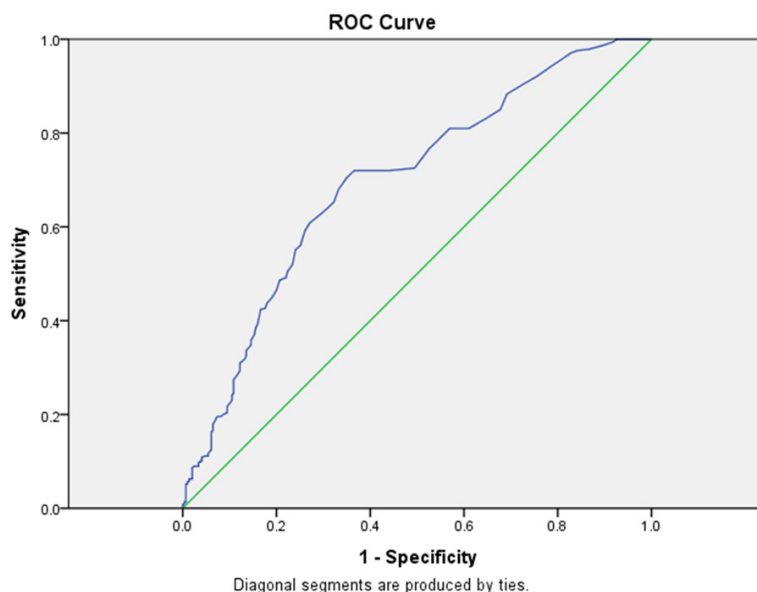


Figure 1. ROC curves of preoperative levels of serum ALT and HBV-HCC recurrence.

Statistical analysis

Receiver operating characteristic (ROC) curve was utilized to evaluate the accuracy of preoperative serum ALT levels to predict HBV-HCC recurrence. Area under the curve (AUC) was calculated as measurements of the accuracy of the test. The Kaplan-Meier survival analysis (log-rank test) was used to analyze RFS time. The factors with $P < 0.05$ from the Kaplan-Meier analysis were enrolled in the Cox regression hazard model. Categorical variables were compared using the chi-square test or Fisher's exact test, where appropriate. Spearman correlation analysis method was used in correlation analysis. P values were two tailed. Statistical significance was accepted for P values of < 0.05 . All the data were statistically analyzed with the software, SPSS Statistics for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

ROC curves of preoperative levels of serum ALT and HBV-HCC recurrence

A ROC curve was utilized to define the optimal cutoff values, and to identify the sensitivity and specificity of preoperative levels of serum ALT in predicting recurrence of HBV-HCC after R0 resection. Based on the ROC curve, the optimal cutoff value of preoperative serum ALT levels

as an indicator for predicting recurrence of HBV-HCC was projected to be 37.5 U/L, which yielded a sensitivity of 70.4% and a specificity of 65.1%, with the area under the curve at 0.698 (95% CI, 0.657-0.738) (**Figure 1**). As the sensitivity and specificity were similar to those for the recommended clinical cutoff of 40 U/L, we chose 40 U/L as the cutoff value for ALT in this study.

Then, on the basis of the ROC results, patients were subgrouped into the high ALT group (ALT > 40 U/L, 48.3%) and the low ALT group (ALT ≤ 40 U/L, 51.7%). To further analyze the data in the low ALT group, the preoperative ALT levels in the group were sub-categorized in two subgroups: ≤ 20 U/L ($n=56$) and > 20 U/L ($n=287$).

Patients with different preoperative ALT levels showed different clinical characteristics

As shown in **Table 1**, we found that the following clinical characteristics happened more frequently in the high ALT group than in the low ALT group: male, age of ≤ 60 , positive history of alcohol abuse (heavy alcohol consumption of > 80 g/d ethanol for at least 5 years [5]), GGT > 64 U/L, surgical margin < 0.5 cm, hepatic inflow occlusion, intraoperative blood transfusion and liver capsule invasion ($P < 0.05$).

Prognostic factors for RFS

The patients with HBV-HCC were followed up after R0 resection. The median follow-up time was 44.5 months (ranging 3.3-180.8 months). Over their follow-up periods, 419 patients (63.2%) were diagnosed with HCC recurrence. Kaplan-Meier analysis showed that the following factors significantly decreased RFS: preoperative levels of ALT > 40 U/L and GGT (gamma glutamyltransferase) > 64 U/L, liver cirrhosis, liver resection range > 2 hepatic segments, surgical margin < 0.5 cm, intraoperative blood loss ≥ 1000 ml, intraoperative blood transfusion, preoperative levels of AFP > 20 ng/ml, multiple tumors, major tumor size > 5 cm, naked eye

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Table 1. Baseline characteristics compared between the high ALT group and the low ALT group

Characteristic	High ALT group (n=320)	Low ALT group (n=343)	χ^2 -value	P-value
Sex			11.980	0.001
Male	286 (89.4)	273 (79.6)		
Female	34 (10.6)	70 (20.4)		
Age (years)			14.618	0.000
≤ 60	255 (79.7)	228 (66.5)		
> 60	65 (20.3)	115 (33.5)		
History of alcohol abuse positive			6.436	0.011
No	209 (67.9)	261 (76.8)		
Yes	99 (32.1)	79 (23.2)		
Preoperative TACE			1.304	0.253
No	269 (84.1)	299 (87.2)		
Yes	51 (15.9)	44 (12.8)		
Cirrhosis			0.333	0.564
No	18 (5.6)	23 (6.7)		
Yes	302 (94.4)	320 (93.3)		
Portal hypertension			0.856	0.355
No	257 (80.3)	285 (83.1)		
Yes	63 (19.7)	58 (16.9)		
GGT (U/L)			85.912	0.000
≤ 64	164 (51.3)	289 (84.8)		
> 64	156 (48.8)	52 (15.2)		
Child-Pugh classification			0.030	0.862
A	308 (96.3)	331 (96.5)		
B	12 (3.8)	12 (3.5)		
Liver resection range (segments)			0.422	0.516
≤ 1	188 (58.8)	210 (61.2)		
> 1	132 (41.3)	133 (38.8)		
Surgical margin (cm)			4.052	0.044
< 0.5	121 (37.9)	104 (30.5)		
≥ 0.5	198 (62.1)	237 (69.5)		
Hepatic inflow occlusion			10.236	0.001
No	131 (40.9)	183 (53.4)		
Yes	189 (59.1)	160 (46.6)		
Intraoperative blood transfusion			4.260	0.039
No	237 (74.1)	277 (80.8)		
Yes	83 (25.9)	66 (19.2)		
Intraoperative blood loss (mL)			0.862	0.353
< 1000	278 (86.9)	306 (89.2)		
≥ 1000	42 (13.1)	37 (10.8)		
AFP (ng/mL)			2.216	0.137
≤ 20	148 (46.5)	179 (52.3)		
> 20	170 (53.5)	163 (47.7)		
Multiple tumors			0.546	0.460
No	252 (78.8)	278 (81.0)		
Yes	68 (21.3)	65 (19.0)		
Major tumor size (cm)			1.358	0.244
≤ 5.0	193 (60.7)	220 (65.1)		
> 5.0	125 (39.3)	118 (34.9)		

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Differentiation			1.569	0.456
High	37 (11.6)	50 (14.6)		
Middle and low	271 (84.7)	278 (81.0)		
Necrosis	12 (3.8)	15 (4.4)		
Naked eye vascular invasion			0.990	0.320
No	293 (91.6)	321 (93.6)		
Yes	27 (8.4)	22 (6.4)		
Liver capsule invasion			3.895	0.048
No	96 (30.2)	126 (37.5)		
Yes	222 (69.8)	210 (62.5)		
Regional lymph node metastasis			6.626	0.062
No	320 (100)	338 (98.5)		
Yes	0 (0)	5 (1.5)		

AFP: alpha-fetoprotein, ALT: alanine aminotransferase, CI: confidence interval, GGT: gamma glutamyltransferase, HR: hazard ratio, TACE: transcatheter hepatic arterial chemoembolization.

Table 2. Univariate and multivariate analyses of the factors related to recurrence-free survival

Characteristic	Kaplan-Meier analysis		Cox regression hazard model	
	Median (mo)	P-value	HR (95% CI)	P-value
Sex (male/female)	31.4/50.0	0.123		
Age (≤ 60 / >60 years)	36.8/27.7	0.284		
History of alcohol abuse positive (no/yes)*	36.0/26.0	0.247		
Preoperative TACE (no/yes)	32.0/34.0	0.950		
Cirrhosis (no/yes)	71.6/31.0	0.011	1.864 (1.158-3.002)	0.010
Portal hypertension (no/yes)	35.8/30.0	0.123		
Child-Pugh Classification (A/B)	34.0/24.0	0.105		
ALT (≤ 40 / >40 U/L)	50.8/24.1	0.000	1.471 (1.189-1.821)	0.000
GGT (≤ 64 / >64 U/L)	45.0/21.0	0.000		
Liver resection range (≤ 1 / >1 segments)	43.0/23.7	0.003		
Surgical margin (≥ 0.5 / <0.5 cm)*	43.0/23.0	0.000	1.270 (1.035-1.558)	0.022
Hepatic inflow occlusion (no/yes)	36.9/27.0	0.109		
Intraoperative blood loss (<1000 / ≥ 1000 mL)	35.0/23.0	0.041		
Intraoperative blood transfusion (no/yes)	38.0/26.0	0.011		
AFP (≤ 20 / >20 ng/mL)	45.0/25.0	0.000	1.263 (1.035-1.543)	0.022
Multiple tumors (no/yes)	43.1/16.7	0.000	1.669 (1.323-2.106)	0.000
Major tumor size (≤ 5.0 / >5.0 cm)	51.0/19.2	0.000		
Differentiation (high/middle and low/necrosis)	39.8/31.0/57.8	0.308		
Naked eye vascular invasion (no/yes)	39.0/6.5	0.000	2.497 (1.790-3.482)	0.000
Liver capsule invasion (no/yes)*	42.9/27.0	0.279		
Regional lymph node metastasis (no/yes)	33.9/3.5	0.042	5.810 (1.943-17.372)	0.002

AFP: alpha-fetoprotein, ALT: alanine aminotransferase, CI: confidence interval; GGT: gamma glutamyltransferase, HR: hazard ratio, TACE: transcatheter hepatic arterial chemoembolization, *some patients lacked data.

vascular invasion, and regional lymph node metastasis (**Table 2**). By Cox regression analysis, we found that the recurrence of HBV-HCC after RO resection was independently influenced by the following factors: preoperative levels of ALT >40 U/L, liver cirrhosis, surgical margin <0.5 cm, preoperative levels of AFP >20

ng/ml, multiple tumors, naked eye vascular invasion and regional lymph node metastasis (**Table 2**).

Relevance of preoperative ALT levels to RFS

The RFS curves between the high ALT group and low ALT group are shown in **Figure 2**, dem-

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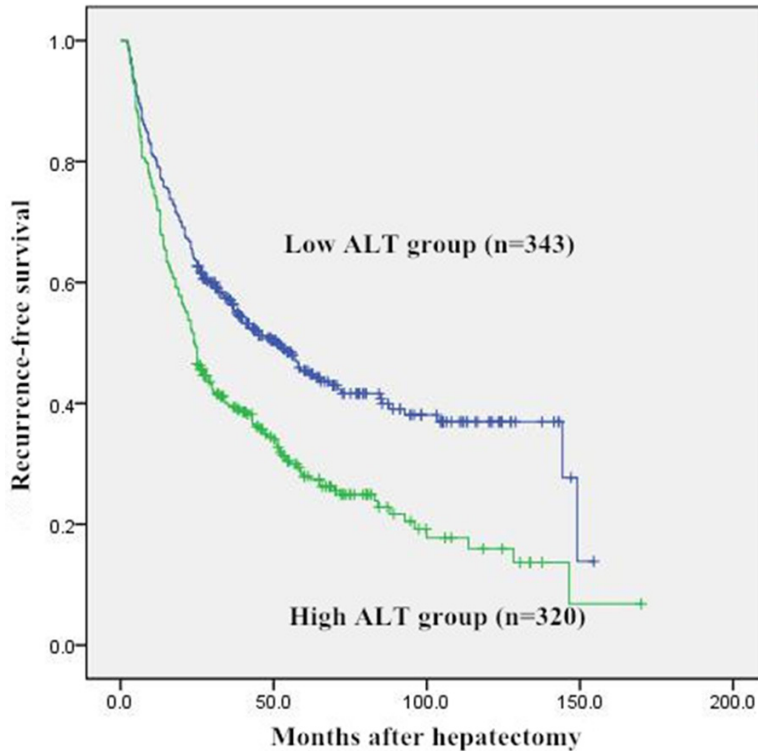


Figure 2. Cumulative RFS rate in the two groups after R0 resection ($P=0.000$).

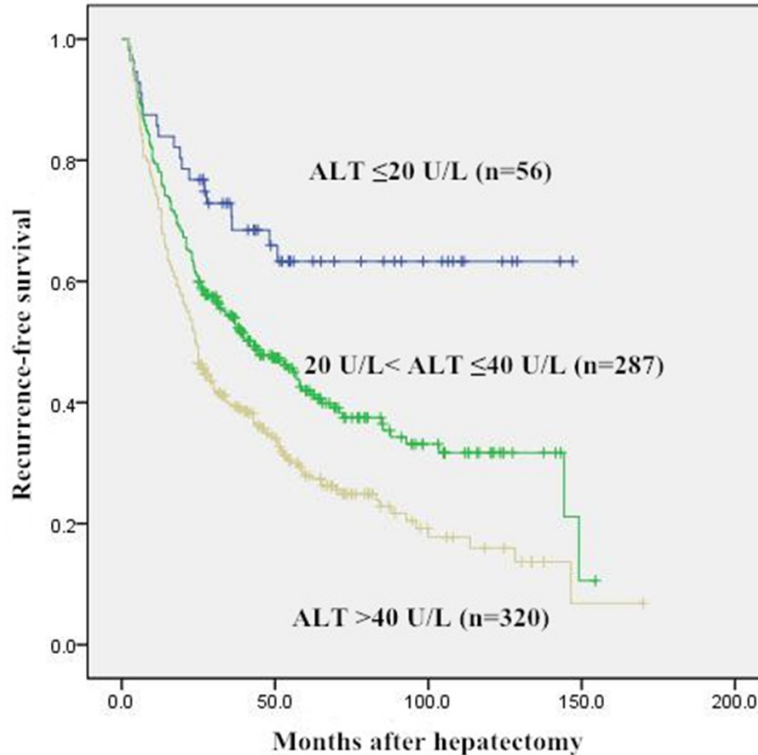


Figure 3. Cumulative RFS rate in different preoperative ALT levels after R0 resection ($P=0.000$).

onstrating a significant difference between the two groups. Patients in the high ALT group had lower RFS rates (1-, 2-, 5- and 10-years: 72.2%, 50.3%, 27.9% and 16.0%, respectively) compared to those in the low ALT group (1-, 2-, 5- and 10-years: 79.3%, 63.8%, 45.4% and 36.9%, respectively) ($P<0.001$). The comparison indicates that low levels of preoperative serum ALT are highly relevant to high RFS rates after R0 resection of HBV-HCC.

In Figure 3, we noted that the patients with preoperative ALT levels ≤ 20 U/L ($n=56$) had the longest median RFS (144.0 months) while those with preoperative ALT levels $>20-40$ U/L ($n=287$) and >40 U/L ($n=320$) had median RFS (43.0 months and 24.1 months, respectively; $P<0.001$). The analytic results show large differences among three subgroups.

Analysis of related factors also showed that the significantly fewer patients with preoperative ALT levels ≤ 20 U/L had liver cirrhosis ($P=0.005$) than the numbers of patients in other subgroups. However, preoperative AFP levels and BCLC (Barcelona Clinic Liver Cancer) stage 0-A did not significantly differ between three different preoperative ALT levels (Table 3).

Relevance of HBV viral load or preoperative ALT levels to the antiviral effect on HBV-HCC recurrence

One hundred and forty-two patients were identified having clear results of serum HBV DNA test. Using 10^3 copies/

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Table 3. The relationship between different preoperative ALT levels and other tumor-pathologic parameters

	ALT ≤20 U/L	20 U/L < ALT ≤40 U/L	ALT >40 U/L	P-value
Cirrhosis	47 (83.9)	273 (95.1)	302 (94.4)	0.005
AFP >20 ng/mL	32 (58.2)	131 (45.6)	170 (53.5)	0.077
BCLC stage 0-A	48 (85.7)	234 (81.6)	249 (77.8)	0.636

AFP: alpha-fetoprotein, ALT: alanine aminotransferase, BCLC: Barcelona Clinic Liver Cancer.

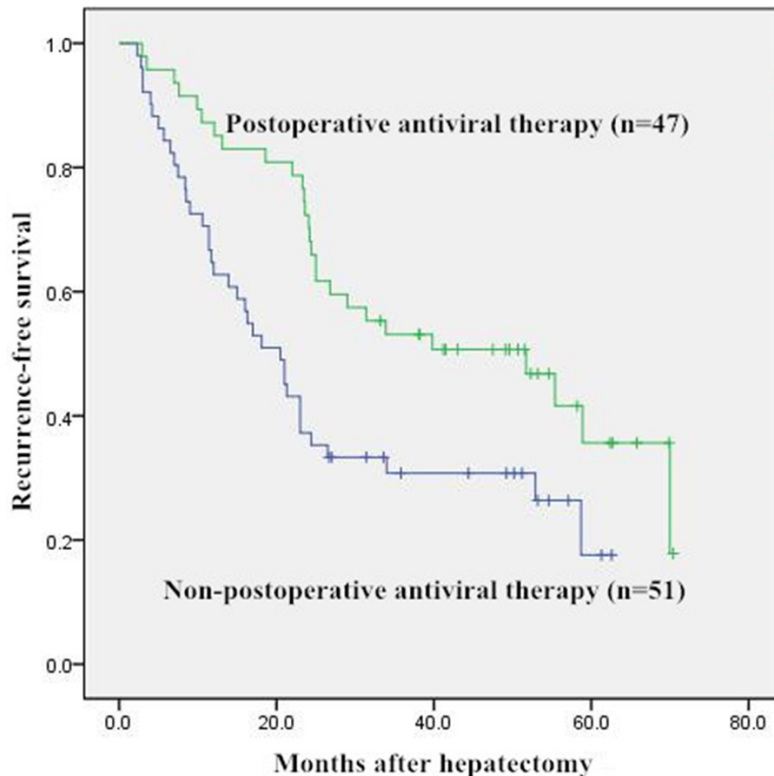


Figure 4. Cumulative RFS rate in patients with and without postoperative antiviral therapy in the high viral load group after R0 resection ($P=0.006$).

mL of HBV-DNA as our cut-off value, the patients were divided into high viral load group ($\geq 10^3$ copies/mL, $n=98$) and low viral load group ($< 10^3$ copies/mL, $n=44$). In our retrospective study, patients with HBV-HCC started to take nucleoside analogues as antiviral drugs either before or after surgery.

In the low viral load group, the median RFS for patients who received antiviral therapy was 35.1 months ($n=19$) while it was 39.4 months for those who did not receive antiviral therapy ($n=25$) ($P>0.05$), showing no significant difference between two groups. Among the 19 patients who received antiviral therapy, 14 patients received it both before and after surgery and their preoperative serum ALT levels

were normal. However, in contrast to the low viral load group, in the high viral load group, the median RFS was 51.7 months ($n=47$) for the patients who received postoperative antiviral therapy but only 20.5 months ($n=51$) for those without receiving antiviral therapy ($P=0.006$) (**Figure 4**), suggesting that the patients with high viral load could obtain better curative effect on RFS from postoperative antiviral therapy.

Since we noticed that among the patients who received postoperative antiviral therapy, 58.0% of them showed high levels of serum ALT while 37.5% low level ($P=0.042$), we assumed a correlation may exist between HBV viral load and serum ALT levels. For this reason, we applied Spearman correlation analysis and found that preoperative serum ALT level was closely and positively correlated with serum HBV-DNA levels ($r=0.424$; $P<0.001$).

Since 2005 we had established clear records for 193 patients in the high preoperative ALT group on whether or not they had received postoperative antiviral therapy. Out of 193 patients, 73 (37.8%) received the therapy. By Kaplan-Meier analysis, these 73 patients showed a significantly longer median RFS of 39.8 months than that of 17.0 months of other 120 patients who did not receive postoperative antiviral therapy ($P=0.029$) (**Figure 5**). In line with the above, the analytic result indicates that the patients with high level of preoperative ALT benefited from postoperative antiviral therapy.

In summary, HCC patients with high HBV viral load or high preoperative ALT level may acquire high RFS rates after R0 resection by postoperative antiviral therapy.

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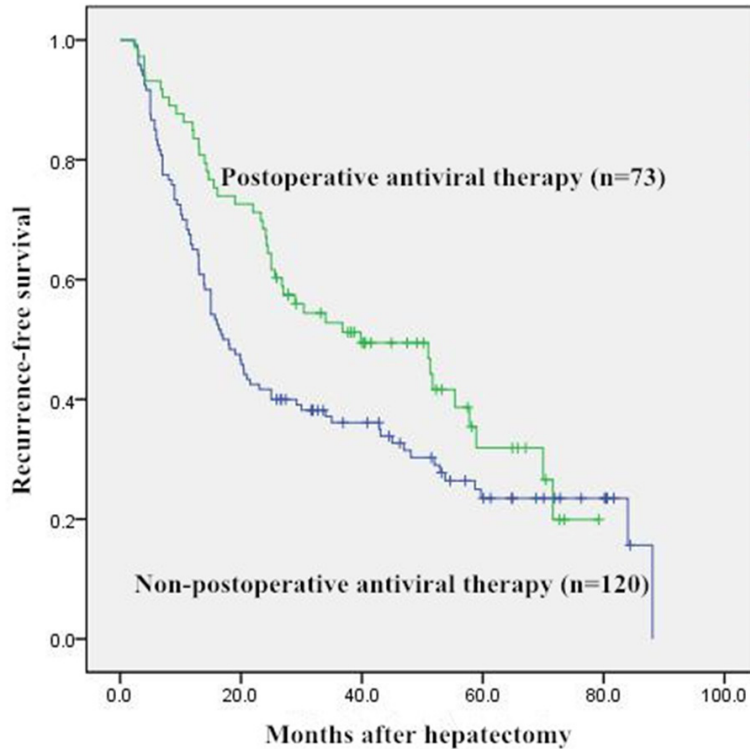


Figure 5. Cumulative RFS rate in patients with and without postoperative antiviral therapy in the high ALT group after RO resection ($P=0.029$).

Serum ALT is the most extensively investigated serum enzyme. Elevated ALT level was associated with mortality of various liver diseases [13]. Cheung et al. [3] found that high perioperative ALT level could predict intrahepatic recurrence in patients with HBV-HCC after curative hepatectomy, and patients with high serum ALT level had higher incidence of tumor recurrence and worse prognosis after curative resection compared to those with low serum ALT levels. A community-based cohort study showed high serum ALT level is independently associated with a higher risk for HBV-HCC [14]. Moreover, Lin et al. [15] also revealed that preoperative ALT and AFP levels could significantly affect HCC incidence in patients with chronic hepatitis B infection.

Discussion

As the level of medical treatment has improved, the overall survival rate after liver resection among patients with HCC has increased. RO hepatic resection is the primary effective treatment for HCC and can prolong overall survival of patients although their prognosis is still unsatisfactory [6]. Previous studies identified that various factors, such as tumor factors and serum AFP levels, were associated with higher incidences of tumor recurrence [7-12].

In our study, we found two independent risk factors: preoperative ALT level and cirrhosis which evidently influenced recurrence of HBV-HCC patients after RO resection. Moreover, subgroup analysis showed that patients with preoperative levels of ALT ≤ 20 U/L suffered much less liver cirrhosis and their prognosis was much better than those with higher preoperative ALT levels. Additionally, we also found preoperative ALT level was correlated with serum HBV-DNA levels, and postoperative antiviral therapy significantly decreased tumor recurrence rates after RO resection if the preoperative ALT levels were high in the HBV-HCC patients.

In keeping with these findings, we found that high preoperative ALT level was a significant independent non-tumor risk factor for RFS. Moreover, survival analysis showed that respective RFS rates significantly differed between the high ALT and low ALT groups (**Figure 2**).

Many studies have shown that chronic active hepatitis and cirrhosis were the most significant risk factors for intrahepatic tumor recurrence, which probably develops through multicentric hepatocarcinogenesis [9, 10, 16, 17]. This is the apparent result of repeated inflammation and cellular necrosis in patients with chronic hepatitis and cirrhosis which enhance proliferation and accelerate development of new HCC foci via an elevated rate of spontaneous mutations and promotion due to gene instability, eventually leading to tumor recurrence [18]. Adachi et al. [8] considered active inflammation a basic cause of recurrence. Heathcote et al. [19] also thought that active inflammation and worsening fibrosis were significant risk factors for developing HCC in chronic hepatitis-C virus infection. Moreover, Tarao et al. [20] also suggested serum ALT level was an index of inflammatory activity that

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reflects hepatocyte necrosis followed by cirrhosis occurrence.

Our study also suggested that liver cirrhosis is an independent risk factor for recurrence of HBV-HCC after R0 resection. Related factor analysis also showed that liver cirrhosis was significantly less severe and RFS was significantly longer for the patients with preoperative levels of ALT ≤ 20 U/L than those with higher preoperative ALT levels. Higher serum ALT level is widely considered to indicate inflammatory necrosis of hepatocytes. Indeed, one study found a close correlation between high transaminase levels and histologic necroinflammation in biopsied specimens from patients with chronic cirrhosis [21]. Subsequently, one study also mentioned that histologic findings of necroinflammation coincided with high transaminase levels in 53 of 64 patients (83%) with cirrhosis [4].

In this study, we think that there was much less inflammation in the liver tissue of the patients with preoperative levels of ALT ≤ 20 U/L. They were inclined to suffer less from cirrhosis, and the degree of cirrhosis in the patients might also be much lighter than that in the patients with higher preoperative ALT levels. However, information on pathological assessment of the fibrosis stage caused by inflammation was not fully collected. The fibrosis stage may be associated with long-term prognosis after curative resection.

High levels of serum HBV-DNA have been demonstrated to be a major risk factor for HCC development in patients with chronic HBV infection [22-24]; some researchers have suggested that HBV-DNA levels of $\geq 10^4$ copies/mL are the strongest predictor of future HCC risk [22, 23]. Similarly, studies have also reported that the necroinflammatory process resulting from high viral load may induce hepatocarcinogenesis [25]. Necrosis, regeneration and increased spontaneous mutation rate caused by HBV replication in liver cells may also increase the chances of HCC occurrence [26]. We think that the above process would damage liver cells and cause serum ALT level to increase.

In our study, the preoperative ALT levels for some patients receiving preoperative antiviral

therapy were found to be normal. We assumed that this was possibly because the antiviral drugs suppressed HBV replication, which decreased serum ALT level to the normal range. Kim et al. [27] also reported that preoperative ALT level was correlated with serum HBV-DNA levels in patients with HBV-HCC. Subsequently, Ishikawa et al. [28] showed that the serum ALT was higher in patients with high HBV-DNA load than that in those with low HBV-DNA load. Additionally, Yang et al. [29] showed that postoperative antiviral therapy independently improved RFS for patients with high viral load in accord with our findings. We, therefore, thought that high viral load is often accompanied with increased serum ALT level in patients with HBV-HCC and could increase the chance of tumor recurrence. Since the high level of serum ALT is due to high viral load, our study strongly suggests that postoperative antiviral therapy should be applied to the patients with high levels of ALT.

The current study was limited by the small sample size, regional area and use of data from a single institution, which may not be representative of other HBV-HCC populations. Our retrospective analysis showed that a high preoperative ALT level, which reflects increased hepatitis activity, is an independent risk factor for HBV-HCC recurrence after R0 resection, and is correlated with serum HBV-DNA levels. Therefore, we suggest that antiviral management should be considered as soon as possible for HBV-HCC patients who have undergone R0 resection, especially those with a high preoperative ALT level. We also recommend that regular liver function and imaging examination be performed after R0 resection, especially for those with high preoperative serum ALT levels in order to detect and treat recurrence early and ultimately improve prognosis.

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Disclosure of interest of conflict

None.

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