

Retrospective Study

Prognostic roles of preoperative α -fetoprotein and des- γ -carboxy prothrombin in hepatocellular carcinoma patients

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Abstract

AIM: To clarify the utility of using des- γ -carboxy prothrombin (DCP) and α -fetoprotein (AFP) levels to predict the prognosis of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV) and the hepatitis C virus (HCV) infections.

METHODS: A total of 205 patients with HCC (105 patients with HBV infection 100 patients with HCV infection) who underwent primary hepatectomy between January 2004 and May 2012 were enrolled retrospectively. Preoperative AFP and DCP levels were used to create interactive dot diagrams to predict recurrence within 2 years after hepatectomy, and cutoff levels were calculated. Patients in the HBV and HCV groups were classified into three groups: a group with low AFP and DCP levels (LL group), a group in which one of the two parameters was high and the other was low (HL group), and a group with high AFP and DCP levels (HH group). Liver function parameters, the postoperative recurrence-free survival rate, and postoperative overall survival were compared between groups. The survival curves were compared by log-rank test using the Kaplan-Meier method. Multivariate analysis using a Cox forward stepwise logistic regression model was conducted for a prognosis.

RESULTS: The preoperative AFP cutoff levels for recurrence within 2 years after hepatectomy in the HBV and HCV groups were 529.8 ng/mL and 60 mAU/mL,

respectively; for preoperative DCP levels, the cutoff levels were 21.0 ng/mL in the HBV group and 67 mAU/mL in the HCV group. The HBV group was significantly different from the other groups in terms of vascular invasion, major hepatectomy, volume of intraoperative blood loss, and surgical duration. Significant differences were found between the LL group, the HL group, and the HH group in terms of both mean disease-free survival time (MDFST) and mean overall survival time (MOST): 64.81 ± 7.47 vs 36.63 ± 7.62 vs 18.98 ± 6.17 mo ($P = 0.001$) and 85.30 ± 6.55 vs 59.44 ± 7.87 vs 46.57 ± 11.20 mo ($P = 0.018$). In contrast, the HCV group exhibited a significant difference in tumor size, vascular invasion, volume of intraoperative blood loss, and surgical duration; however, no significant difference was observed between the three groups in liver function parameters except for albumin levels. In the LL group, the HL group, and the HH group, the MDFST was 50.09 ± 5.90 , 31.01 ± 7.21 , and 14.81 ± 3.08 mo (log-rank test, $P < 0.001$), respectively, and the MOST was 79.45 ± 8.30 , 58.82 ± 7.56 , and 32.87 ± 6.31 mo (log-rank test, $P < 0.001$), respectively.

CONCLUSION: In the HBV group, the prognosis was poor when either AFP or DCP levels were high. In the HCV group, the prognosis was good when either or both levels were low; however, the prognosis was poor when both levels were high. High levels of both AFP and DCP were an independent risk factor associated with tumor recurrence in the HBV and HCV groups. The relationship between tumor marker levels and prognosis was characteristic to the type of viral hepatitis.

Key words: Hepatocellular carcinoma; Hepatitis B; Hepatitis C; Des- γ -carboxy prothrombin; α -fetoprotein

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Core tip: There is no consensus regarding using cutoff levels of tumor markers to predict survival and recurrence after hepatectomy for hepatocellular carcinoma. Furthermore, the prognostic characteristics of these tumor markers according to hepatitis type remain unclear. The α -fetoprotein (AFP) cutoff level for recurrence within 2 years after surgery was 21.0 ng/mL in the hepatitis C virus (HCV) group compared with 529.8 ng/mL in the hepatitis B virus (HBV) group. Furthermore, patients in the HBV group with high levels of either AFP or des- γ -carboxy prothrombin (DCP) had poor prognoses, as did those patients with high levels of both tumor markers. In contrast, only those patients in the HCV group who had high levels of both AFP and DCP had poor prognoses. We believe that to predict prognosis, preoperative levels of tumor markers should be distinguished and assessed according to the type of viral hepatitis.

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INTRODUCTION

Chronic hepatitis caused by viral hepatitis often progresses to cirrhosis and hepatocellular carcinoma (HCC)^[1]. In Asia, HCC is mainly caused by infection with the hepatitis B virus (HBV), whereas in western countries, it is characteristically caused by infection with the hepatitis C virus (HCV)^[2]. The oncogenic mechanisms differ between the two virus types^[3,4], and these mechanisms should be taken into consideration when evaluating prognosis and establishing treatment regimens.

Various staging systems have been developed to predict the survival for HCC patients, such as the tumor-node-metastasis^[5], Okuda *et al*^[6], the Cancer of the Liver Italian Program (CLIP)^[7], Japan Integrated Staging (JIS)^[8], and the Barcelona Clinic Liver Cancer^[9] staging systems. These systems classify tumors according to tumor size, tumor number, vascular invasion, and metastatic regions (regardless of whether they are intrahepatic or extrahepatic metastases). Each of these parameters is closely associated with the overall prognosis of HCC patients^[5-9].

Liver function parameters are also important prognostic factors for HCC. In fact, the Okuda^[6], CLIP^[7], and JIS^[8] staging systems consider both tumor extension and liver function parameters in tumor classification. Accordingly, it has been reported that tumor-related factors and liver function parameters are also both closely associated with the prognosis of patients with HCC^[6-10].

In addition to these factors that impact tumorigenesis and liver function, α -fetoprotein (AFP) and des- γ -carboxy prothrombin (DCP) levels are tumor markers and known prognostic factors for HCC^[11,12]. Discovered by Abelev *et al*^[13] in 1963, AFP is a glycoprotein with an albumin-like structure produced by liver cells and in the yolk sac during the fetal stage with a half-life of 4-6 d and a molecular weight of 65 kDa. AFP production in the liver is increased in hepatocellular carcinoma as well as in chronic hepatitis and cirrhosis^[14]; therefore, AFP is considered to have low specificity for the diagnosis of cancer. In contrast, prothrombin is formed after the γ -carboxylation of vitamin K-dependent propeptides, and DCP is produced as a result of an acquired posttranslational defect in the vitamin K-dependent carboxylase system. According to a 1984 report by Liebman *et al*^[15], DCP has a molecular weight of 72 kDa and a half-life of 40-72 h. DCP production does not increase in chronic hepatitis or cirrhosis, and DCP is considered to have high specificity for the diagnosis of cancer. However, DCP has no prognostic value in cases with vitamin K deficiency or vitamin K

function inhibition.

Although the associations between these tumor markers and postoperative prognosis in HCC patients have been reported^[16-18], there is no consensus regarding the cutoff levels of these markers to predict survival and recurrence after hepatectomy. Furthermore, the prognostic characteristics of these tumor markers according to hepatitis type remain unclear. Therefore, the aim of the present study was both to compare preoperative tumor marker levels and prognosis after hepatectomy and to clarify the characteristics of these tumor marker levels according to hepatitis type. The prognostic findings associated with these tumor marker levels could inform the development of new selection criteria for living donor liver transplantation candidates with HCC, especially beyond the Milan criteria^[19].

MATERIALS AND METHODS

Patients and follow-up

We retrospectively reviewed the medical records of 256 consecutive HCC patients who underwent primary hepatectomy at the Sapporo Medical University Hospital (Sapporo, Japan) from January 2004 to May 2012. Using the Child-Pugh classification system^[20], the volume of resectable liver was determined, including the following items: prothrombin time (PT), serum total bilirubin (TBIL) levels, and serum albumin (ALB) levels, all of which are measured on both preoperative function tests and the indocyanine green retention rate at 15 min (ICGR₁₅)^[21] as measured by three-dimensional computed tomography. AFP and DCP levels were measured immediately before surgery. The present study excluded 40 patients with non-B/non-C hepatitis and six patients with concurrent HBV and HCV infections. In addition, two patients in the HBV group and three in the HCV group receiving warfarin were also excluded. The final sample included 105 patients with HBV infection and 100 with HCV infection (Figure 1).

The operation type was classified as follows: partial hepatic resection including tumor enucleation (Hr0); subsegmentectomy (HrS); monosegmentectomy (Hr1); bisegmentectomy, including right hepatectomy, left hepatectomy, and central bisegmentectomy (Hr2); and trisegmentectomy (Hr3). Hr0, HrS, and Hr1 were defined as minor hepatectomy, whereas Hr2 and Hr3 resections were considered major hepatectomy. Red cell concentrate transfusion was administered at the discretion of the anesthetist on the basis of intraoperative factors, such as systemic hemodynamic factors, hemoglobin levels, and blood lactate levels on blood gas analysis. Following hepatectomy, the number of tumors, tumor size, presence or absence of vascular invasion, and condition of underlying liver tissue (normal liver, chronic hepatitis, and liver cirrhosis) were determined.

All patients were followed up every 3 mo until the

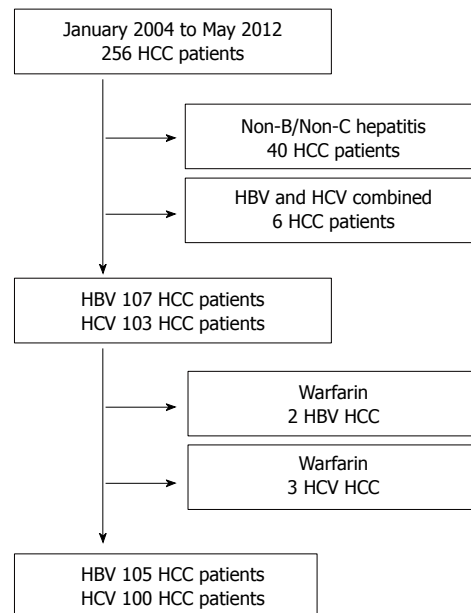


Figure 1 Flowchart of selection of hepatocellular carcinoma patients in this retrospective study. A total of 40 patients with non-B/non-C hepatitis, including those with obstructive jaundice with false-positive preoperative DCP levels, and patients with alcoholic hepatitis were excluded from the study. Six patients with combined HBV and HCV infections were also excluded. Finally, 107 HCC patients with HBV infection and 103 HCC patients with HCV infection were included for analysis. Two patients in the HBV group and three in the HCV group were receiving warfarin and subsequently excluded. Therefore, 105 patients in the HBV group and 100 patients in the HCV group were included in this retrospective study. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; DCP: Des- γ -carboxy prothrombin.

end of March 2013, until their last visit to our hospital, or until death. The study design conformed to the ethical guidelines of the Declaration of Helsinki, and informed consent was obtained from each subject before registration.

Surgical procedure

The surgery included total and pure laparoscopic procedures and laparoscopically assisted approaches. We used either five or six ports (5-12 mm in diameter) depending on the tumor location, and the first periumbilical port for the laparoscopic camera was inserted using the open technique. If the volume of blood loss exceeded 300 mL from any of these ports, the Pringle maneuver^[22] was performed for hepatectomy. The procedures were performed under carbon dioxide pneumoperitoneum, and intra-abdominal pressure was maintained at < 12 mmHg based on electronic readings. We used a variable view angle, high-definition endoscopic camera. Intraoperative ultrasonography (BK Medical, Herlev, Denmark) was performed routinely to examine the location and diameter of the hepatic tumor as well as the positional relationship of the tumor with the main hepatic vessels. Parenchymal transection and hemostasis were performed with a laparoscopic Cavitron ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, CO, United States), a

Table 1 Characteristics of hepatocellular carcinoma patients with hepatitis B virus infection

Variables	All patients (n = 105)	LL group (n = 55)	HL group (n = 34)	HH group (n = 16)	P value
Age (yr)	62 (57-68)	62 (59-66)	64 (56-70)	63 (56-70)	0.962
Sex, male/female	90/15	48/7	29/5	13/3	0.829
Body mass index (kg/m ²)	23.7 ± 3.1	24.0 ± 2.6	23.5 ± 3.3	23.1 ± 4.3	0.691
Open/pure lap/lap-assisted	83/8/14	43/6/6	29/1/4	11/1/4	0.390
Hr					
0/S/1/2/3	50/25/14/14/2	34/13/6/2/0	14/10/4/4/2	2/2/4/8/0	< 0.001
Preoperative laboratory values					
Aspartate transaminase (U/L)	31 (22-46)	31 (22-41)	30 (25-48)	43 (24-62)	0.153
Alanine transaminase (U/L)	29 (20-39)	32 (17-42)	27 (21-42)	27 (19-52)	0.978
Platelets (× 10 ⁴ /μL)	16.6 ± 13.3	16.4 ± 12.7	16.2 ± 16.2	18.0 ± 8.6	0.168
Serum ALB (g/dL)	3.95 ± 0.46	3.99 ± 0.46	3.87 ± 0.43	3.98 ± 0.53	0.334
PT (%)	93.3 ± 12.2	95.5 ± 11.1	90.3 ± 14.1	92.2 ± 10.6	0.062
Serum TBIL (mg/dL)	0.79 ± 0.44	0.80 ± 0.45	0.85 ± 0.49	0.65 ± 0.24	0.681
ICGR15	9.6 (5.7-14.9)	9.4 (5.9-14.0)	12.5 (5.7-22.5)	8.5 (5.0-14.6)	0.334
AFP (ng/mL)	24.2 (3.8-165.0)	5.2 (2.4-31.1)	45.0 (5.1-246.5)	1950 (753.5-2827.0)	< 0.001
DCP (mAU/mL)	38 (20-364)	22 (15-28)	399 (90-1,667)	4460 (223-34373)	< 0.001
Intraoperative data					
Blood loss (mL)	400 (130-660)	360 (110-560)	435 (100-1,040)	880 (130-1330)	0.042
Surgical duration (min)	332 (243-411)	313 (236-370)	361 (243-450)	432 (270-604)	0.020
Blood transfusion					
RCC: yes/no (%)	21/84 (20.0%)	4/51 (7.2%)	10/24 (29.4%)	7/9 (43.8%)	0.001
Pathological results					
Tumor size (cm)	4.27 ± 3.21	3.26 ± 2.56	4.97 ± 2.71	6.24 ± 4.77	< 0.001
Multiple tumors: yes/no (%)	39/66 (37.1%)	19/36 (34.5%)	15/19 (44.1%)	5/11 (31.3%)	0.575
Vascular invasion: yes/no (%)	34/71 (32.4%)	10/45 (18.2%)	14/20 (41.1%)	10/6 (62.5%)	0.002
Remnant liver: NL/CH/LC	13/47/41	6/23/26	3/17/14	4/7/5	0.464
Histological tumor differentiation					
Well/moderately/poorly	14/63/28	11/35/9	3/18/13	0/10/6	0.048
Recurrence within 2 yr after liver resection					
Yes/no (%)	50/55 (47.6%)				

Data are presented as medians (25th-75th percentile range) for skewed distribution and mean ± SD for normal distribution. LL group: AFP values < 529.8 ng/mL and DCP values < 60 mAU/mL; HL group: AFP values > 529.8 ng/mL or DCP values > 60 mAU/mL; HH group: AFP values > 529.8 ng/mL and DCP values > 60 mAU/mL; Open group: Open laparotomy hepatectomy group; Lap group: laparoscopic hepatectomy group; Pure Lap: Pure laparoscopic hepatectomy; Lap-assisted: Laparoscopy-assisted hepatectomy. Hr0: Partial hepatectomy; HrS: Subsegmentectomy; Hr1: Sectionectomy; Hr2: Bisegmentectomy; Hr3: Trisegmentectomy; ALB: Albumin; PT: Prothrombin; TBIL: Total bilirubin; ICGR15: Indocyanine green retention rate at 15 min; AFP: Alpha-fetoprotein; DCP: Des-γ-carboxy prothrombin.

harmonic scalpel (UltraCision; Ethicon Endo-Surgery, Inc., Blue Ash, OH, United States), saline-associated monopolar electrocautery, and a thermofusion device (BiClamp; ERBE, Marietta, GA, United States). The resected specimen was placed in a plastic bag and extracted through a slightly enlarged periumbilical port site or additional minilaparotomy. For open laparotomy, right subcostal, upper middle, or inverted L-shaped or T-shaped incisions were made depending on tumor location. Intraoperative ultrasonography (Hitachi-Aloka Medical, Ltd., Tokyo, Japan) was performed routinely. Parenchymal transection and hemostasis were performed primarily using a CUSA, saline-associated monopolar electrocautery, and an absorbable fibrin sealant patch (Tachosil, Baxter Healthcare Corporation, Irvine, CA, United States) as necessary.

Statistical analysis

Data are presented as medians (25th-75th percentile range) for skewed distributions and as mean ± SD for normal distributions. The Pearson χ^2 analysis or Fisher exact test was used to compare categorical variables, whereas the Kruskal-Wallis, Mann-Whitney *U* test,

or analysis of variance was used for comparisons of continuous variables. Recurrence-free survival or overall survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. A *P* value < 0.05 was considered statistically significant. Variables with statistical significance (*P* < 0.05) in the univariate analysis were subjected to multivariate analysis using a Cox forward stepwise logistic regression model. Statistical analysis was performed using StatView[®] software (version 5.0; SAS Institute Inc., Cary, NC, United States) and SPSS version 21.0 for Windows (IBM-SPSS Inc., Chicago, IL, United States). Interactive dot diagrams were created using MedCalc[®] software (version 10.2.0.0; Mariakerke, Ostend, Belgium).

RESULTS

HBV group

The clinical characteristics of all patients in the HBV group (*n* = 105) are shown in Table 1. The median age was 62 years, and there were more males than females. Major hepatectomy was performed in 16 patients (15.2%), and anatomical resection was

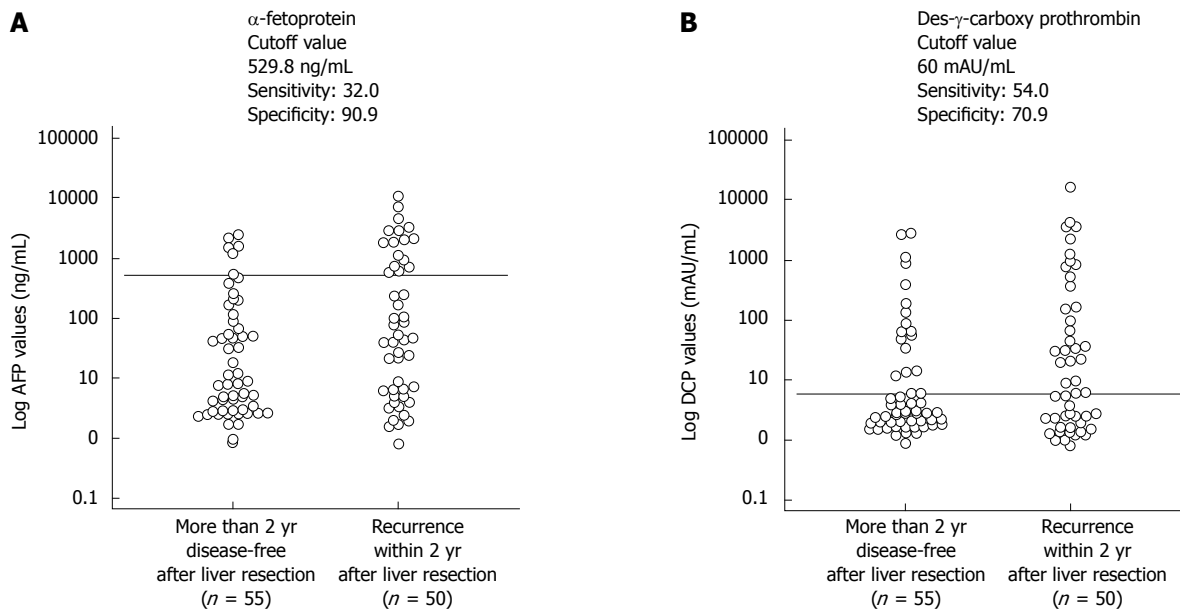


Figure 2 Interactive dot diagrams. A: Interactive dot diagrams showing α -fetoprotein levels were used to predict recurrence within 2 years after hepatectomy among hepatocellular carcinoma patients with hepatitis B infection; B: Interactive dot diagrams showing des- γ -carboxy prothrombin levels were used to predict recurrence within 2 years after hepatectomy among hepatocellular carcinoma patients with hepatitis B infection. The horizontal line indicates the cutoff point with the best separation (minimal false-negative and false-positive results) between the two subgroups.

performed in 55 patients (52.4%). Preoperative liver function was good in most patients, with a median ICGR₁₅ level of 9.6%. The median preoperative levels of AFP and DCP were 24.2 ng/mL and 38 mAU/mL, respectively. The median volume of intraoperative blood loss was 400 mL and median surgical duration was 332 min. The mean tumor size was 4.27 ± 3.21 cm; 39 patients (37.1%) had multiple tumors, and vascular invasion was observed in 34 patients (32.4%). Sixty patients (61.0%) presented with either normal liver function or chronic hepatitis. Fifty patients (47.6%) developed recurrence within 2 years after surgery.

The preoperative AFP and DCP cutoff levels for recurrence within 2 years of hepatectomy calculated using an interactive dot diagram were 529.8 ng/mL (sensitivity, 32.0%; specificity, 90.0%) and 60 mAU/mL (sensitivity, 54.0%; specificity, 70.9%), respectively (Figure 2). Table 1 depicts the characteristics of patients in three groups when these cutoff levels were used as the reference levels: a group with low AFP and DCP levels (LL group, $n = 55$), a group in which one of the two parameters was high and the other was low [high and low (HL) group, $n = 34$], and a group with high AFP and DCP levels (HH group, $n = 16$). The rates of anatomical resection in the LL, HL, and HH groups were significantly different (38.2%, 58.8%, and 87.5%; $P = 0.002$). There were no significant differences observed between groups in any preoperative liver function parameter, including aspartate transaminase levels, alanine transaminase levels, platelet count, serum ALB, serum TBIL, PT, and ICGR₁₅ levels. However, there were significant differences in AFP levels ($P < 0.001$), DCP levels ($P <$

0.001), volume of intraoperative blood loss ($P = 0.042$), surgical duration ($P = 0.020$), rate of intraoperative transfusion ($P = 0.001$), tumor size ($P < 0.001$), vascular invasion ($P = 0.002$), and histological tumor differentiation ($P = 0.048$). The mean disease-free survival time (MDFST) in the LL, HL, and HH groups was 64.81 ± 7.47 , 36.63 ± 7.62 , and 18.98 ± 6.17 mo, respectively (log-rank test, $P = 0.001$); the mean overall survival time (MOST) in the LL, HL, and HH groups was 85.30 ± 6.55 , 59.44 ± 7.87 , and 46.57 ± 11.20 mo, respectively (log-rank test, $P = 0.018$). Significant differences were observed between all groups on both measures (Figure 3).

Our univariate and multivariate analyses to determine the risk factors associated with tumor recurrence after hepatectomy in the patients with HBV infection ($n = 105$) are shown in Table 2. The multivariate analysis revealed that high levels of TBIL ($P = 0.004$), HH group ($P = 0.031$), large tumor size ($P = 0.003$), and the presence of vascular invasion ($P = 0.002$) were associated with significantly higher incidences of tumor recurrence after liver resection.

Our univariate and multivariate analyses to determine the risk factors associated with poor overall survival after hepatectomy in patients with HBV infection ($n = 105$) are shown in Table 3. The multivariate analysis revealed that the presence of vascular invasion ($P = 0.008$) was associated with significantly higher incidences of poor overall survival after liver resection.

HCV group

The clinical characteristics of all patients in the HCV group ($n = 100$) are shown in Table 4. The median

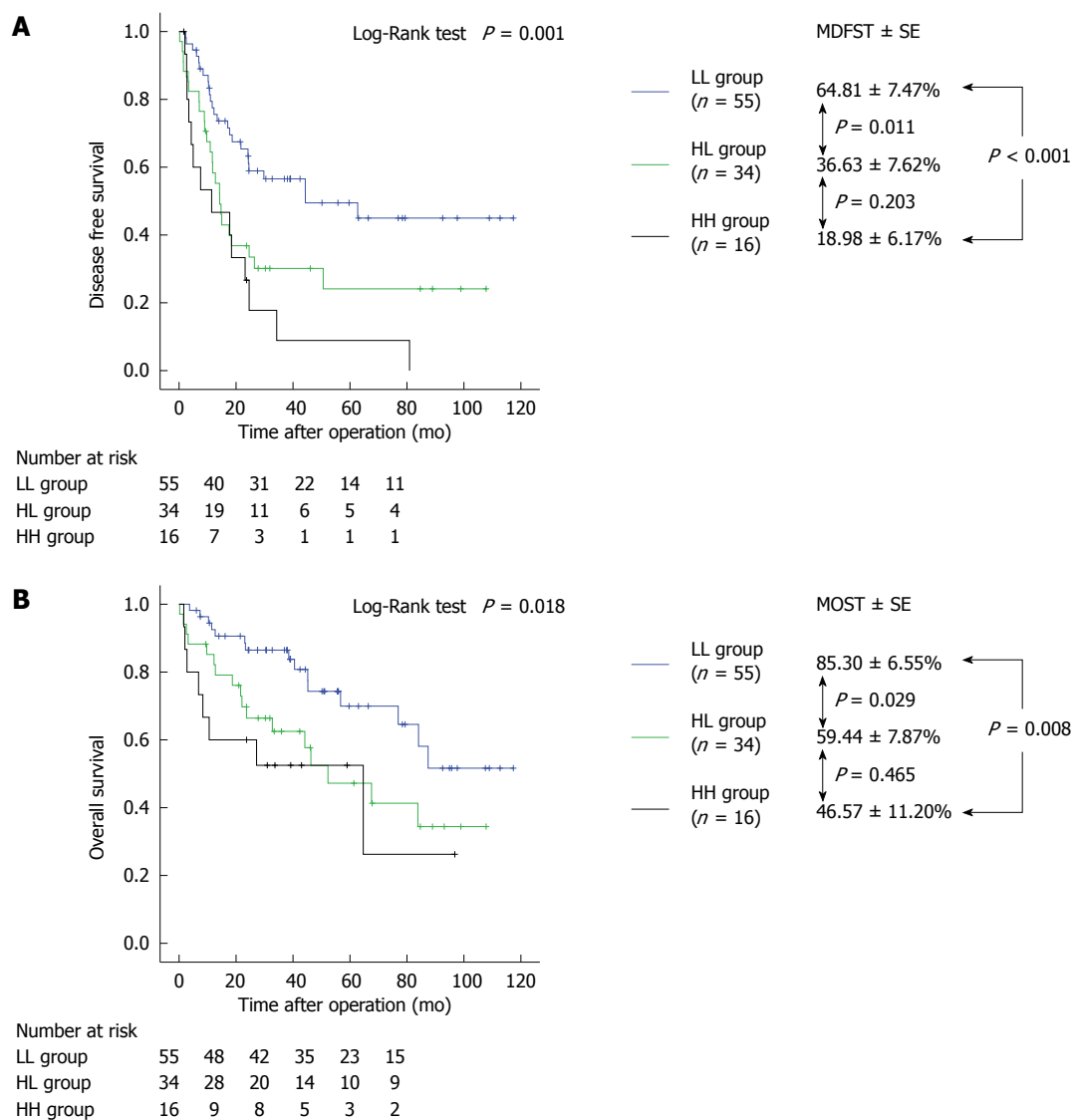


Figure 3 Disease-free survival and overall survival of hepatocellular carcinoma patients with hepatitis B viral infection. A: In the disease-free survival analysis, there were significant differences between the three groups; B: In the analysis of overall survival, there were significant differences between the three groups.

age was 71 years, and there were more males than females. Major hepatectomy of type Hr2 or higher was performed in five patients (5.0%), and anatomical resection combining subsegmentectomy of the liver, segmentectomy of the liver, and hepatic lobe resection was performed in 43 patients (43.0%). Many patients had poor preoperative liver function, and 58 patients (58.0%) had liver cirrhosis with a median ICGR₁₅ level of 14.2%. The median preoperative levels of AFP and DCP were 18.6 ng/mL and 45 mAU/mL, respectively. The median volume of intraoperative blood loss was 330 mL, and the median surgical duration was 304 min. The mean tumor size was 3.51 ± 2.48 cm, and multiple tumors were observed in 36 patients (36.0%). Furthermore, vascular invasion was observed in 30 patients (30.0%), and 51 patients (51.0%) developed recurrence within 2 years after hepatectomy.

The preoperative cutoff levels for recurrence within 2 years after hepatectomy, as calculated using an

interactive dot diagram, were 21.0 ng/mL for AFP (sensitivity, 58.8%; specificity, 67.3%) and 67 mAU/mL for DCP (sensitivity, 60.8%; specificity, 75.5%) (Figure 4). Table 4 summarizes the characteristics of HCC patients with HCV infection in the LL group ($n = 34$), HL group ($n = 39$), and HH group ($n = 27$) with these cutoff levels as baselines. There were no significant differences observed in pathological background ($P = 0.161$), type of operation ($P = 0.784$), or histological differentiation ($P = 0.213$). There were significant differences in preoperative ALB levels ($P = 0.006$); however, no significant difference was observed for other laboratory variables. There were also significant differences between groups in AFP levels ($P < 0.001$), DCP levels ($P < 0.001$), volume of intraoperative blood loss ($P = 0.006$), surgical duration ($P = 0.040$), intraoperative transfusion rate ($P = 0.030$), tumor size ($P = 0.008$), and vascular invasion ($P = 0.018$). MDFST and MOST for the LL, HL, and HH

Table 2 Univariate and multivariate analyses of factors associated with tumor recurrence in patients with hepatitis B virus infection

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age	0.977	0.952-1.003	0.086			
Sex, male	1.077	0.512-2.264	0.843			
Preoperative laboratory values						
Aspartate transaminase	1.008	1.003-1.013	0.001 ¹	1.001	0.993-1.010	0.778
Alanine transaminase	0.999	0.989-1.009	0.811			
Platelets	1.001	0.979-1.024	0.929			
Serum ALB	0.648	0.367-1.142	0.134			
PT	0.974	0.953-0.996	0.021 ¹	0.976	0.946-1.007	0.124
Serum TBIL	2.305	1.346-3.947	0.002 ¹	4.068	1.586-10.436	0.004 ¹
ICGR ₁₅	1.033	1.008-1.059	0.011 ¹	0.967	0.919-1.018	0.967
Tumor markers						
HH group	3.235	1.673-6.257	< 0.001 ¹	2.464	1.086-5.587	0.031 ¹
HL group	2.042	1.164-3.583	0.013 ¹	1.083	0.497-2.360	0.841
Intraoperative data						
Blood loss	1.001	1.000-1.001	0.002 ¹	1.000	1.000-1.001	0.416
Surgical duration	1.002	1.000-1.004	0.003 ¹	1.000	0.997-1.003	0.868
Pathologic results						
Tumor size	1.148	1.068-1.234	< 0.001 ¹	1.182	1.059-1.318	0.003 ¹
Multiple tumors	1.363	1.152-1.612	< 0.001 ¹	1.336	0.955-1.869	0.091
Vascular invasion	2.088	1.261-3.458	0.004 ¹	2.624	1.408-4.892	0.002 ¹

¹Represents statistical significance. HH group: Alpha-fetoprotein values > 529.8 ng/mL and des-gamma-carboxy prothrombin values > 60 mAU/mL; HL group: Alpha-fetoprotein values > 529.8 ng/mL or des-gamma-carboxy prothrombin values > 60 mAU/mL. ALB: Albumin; PT: Prothrombin; TBIL: Total bilirubin; ICGR₁₅: Indocyanine green retention rate at 15 min.

Table 3 Univariate and multivariate analyses of factors associated with poor overall survival in patients with hepatitis B virus infection

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age	0.996	0.964-1.028	0.797			
Sex, male	1.440	0.511-4.056	0.490			
Preoperative laboratory values						
Aspartate transaminase	1.008	1.002-1.014	0.012 ¹	1.004	0.992-1.016	0.518
Alanine transaminase	0.992	0.976-1.007	0.296			
Platelets	1.015	0.994-1.035	0.158			
Serum ALB	0.469	0.234-0.939	0.033			
PT	0.975	0.950-1.000	0.051			
Serum TBIL	2.249	1.125-4.495	0.022 ¹	1.584	0.447-5.613	0.476
ICGR ₁₅	1.056	1.025-1.087	< 0.001 ¹	1.040	0.976-1.108	0.229
Tumor markers						
HH group	2.985	1.259-7.075	0.013 ¹	2.274	0.698-7.403	0.173
HL group	2.112	1.054-4.232	0.035 ¹	1.025	0.390-2.693	0.960
Intraoperative data						
Blood loss	1.001	1.001-1.001	< 0.001 ¹	1.000	1.000-1.001	0.391
Surgical duration	1.004	1.001-1.008	0.005 ¹	1.002	0.996-1.007	0.534
Pathologic results						
Tumor size	1.239	1.133-1.356	< 0.001 ¹	1.127	0.969-1.310	0.122
Multiple tumors	1.385	1.121-1.711	0.002 ¹	1.200	0.813-1.772	0.358
Vascular invasion	2.491	1.335-4.647	0.004 ¹	3.173	1.352-7.447	0.008 ¹

¹Represents statistical significance. HH group: Alpha-fetoprotein values > 529.8 ng/mL and des-gamma-carboxy prothrombin values > 60 mAU/mL; HL group: Alpha-fetoprotein values > 529.8 ng/mL or des-gamma-carboxy prothrombin values > 60 mAU/mL. ALB: Albumin; PT: Prothrombin; TBIL: Total bilirubin; ICGR₁₅: Indocyanine green retention rate at 15 min.

groups were 50.09 ± 5.90 , 31.01 ± 7.21 , and 14.81 ± 3.08 mo (log-rank test, $P < 0.001$), respectively, and 79.45 ± 8.30 , 58.82 ± 7.56 , and 32.87 ± 6.31 mo (log-rank test, $P < 0.001$), respectively, with a significant difference observed between all groups (Figure 5).

Our univariate and multivariate analyses to determine the risk factors associated with tumor recurrence after hepatectomy in the patients with HCV infection ($n = 100$) are shown in Table 5. The multivariate analysis revealed that high levels of ICGR₁₅ ($P < 0.001$), HH group ($P < 0.001$), HL group

Table 4 Characteristics of hepatocellular carcinoma patients with hepatitis C virus infection

Variables	All patients (n = 100)	LL group (n = 34)	HL group (n = 39)	HH group (n = 27)	P value
Age (yr)	71 (62-77)	72 (64-77)	70 (62-75)	70 (65-77)	0.766
Sex, male/female	82/18	22/12	29/10	16/11	0.413
Body mass index	23.6 ± 3.6	23.6 ± 2.9	23.8 ± 3.8	23.4 ± 4.1	0.737
Open/Pure Lap/Lap-assisted	77/12/11	26/3/5	27/8/4	24/1/2	0.218
Hr					
0/S/1/2/3	57/27/11/2/3	23/8/3/0/0	21/10/5/1/2	13/9/3/1/1	0.784
Preoperative laboratory values					
Aspartate transaminase (U/L)	47 (30-64)	41 (23-56)	48 (35-67)	53 (47-71)	0.101
Alanine transaminase (U/L)	38 (26-57)	33 (21-53)	41 (28-57)	42 (29-62)	0.496
Platelets (× 10 ⁴ /μL)	13.5 ± 6.8	13.9 ± 4.7	13.9 ± 9.2	12.5 ± 4.4	0.804
Serum ALB (g/dL)	3.76 ± 0.39	3.94 ± 0.40	3.67 ± 0.35	3.67 ± 0.38	0.006 ¹
PT (%)	89.8 ± 13.4	92.5 ± 11.4	87.8 ± 15.0	89.2 ± 13.5	0.254
Serum TBIL (mg/dL)	0.78 ± 0.34	0.74 ± 0.32	0.79 ± 0.33	0.81 ± 0.39	0.777
ICGR15	14.2 (8.4-18.5)	12.1 (8.1-15.4)	14.7 (8.4-21.5)	15.6 (13.0-24.6)	0.163
AFP (ng/mL)	18.6 (5.6-134.0)	5.3 (3.8-11.0)	21.1 (6.9-99.2)	299.7 (68.1-1046.0)	< 0.001 ¹
DCP (mAU/mL)	45 (21-244)	22 (15-35)	37 (23-134)	429 (124-1902)	< 0.001 ¹
Intraoperative data					
Blood loss (mL)	330 (20-650)	263 (70-500)	230 (20-500)	535 (300-1270)	0.006 ¹
Surgical duration (min)	304 (230-377)	303 (175-377)	296 (230-352)	345 (282-475)	0.040 ¹
Blood transfusion					
RCC: yes/no (%)	12/88 (12.0%)	3/31 (8.8%)	2/37 (5.1%)	7/20 (25.9%)	0.030 ¹
Pathologic results					
Tumor size (cm)	3.51 ± 2.48	2.84 ± 1.23	3.26 ± 2.31	4.72 ± 3.39	0.008 ¹
Multiple tumor: yes/no (%)	36/64 (36.0%)	8/26 (23.5%)	17/22 (43.6%)	11/16 (40.7%)	0.171
Vascular invasion: yes/no (%)	30/70 (30.0%)	5/29 (14.7%)	12/27 (30.8%)	13/14 (48.1%)	0.018 ¹
Remnant liver: NL/CH/LC	5/37/58	2/18/14	2027/10/2	2017/9/1	0.161
Histological tumor differentiation					
Well/Moderately/Poorly	17/63/20	7/23/4	8/24/7	2/16/9	0.213
Recurrence within 2 yr after hepatectomy					
Yes/no (%)	51/49 (51.0%)				

¹Represents statistically significance. Data are presented as medians (25th-75th percentile range) for skewed distribution and mean ± SD for normal distribution. LL group: AFP values < 21.0 ng/mL and DCP values < 67 mAU/mL; HL group: AFP values < 21.0 ng/mL or DCP values < 67 mAU/mL; HH group: AFP values < 21.0 ng/mL and DCP values < 67 mAU/mL; Open group: Open laparotomy group; Lap group: Laparoscopic hepatectomy group; Pure Lap: Pure laparoscopic hepatectomy; Lap-assisted, laparoscopy-assisted hepatectomy; Hr0: Partial hepatectomy; Hr3: Sub-segmentectomy; Hr1: Sectionectomy; Hr2: Bisegmentectomy; Hr3: Trisegmentectomy. ALB: albumin; PT: prothrombin; TBIL: total bilirubin; ICGR15: indocyanine green retention rate at 15 min; AFP: Alpha-fetoprotein; DCP: Des-γ-carboxy prothrombin.

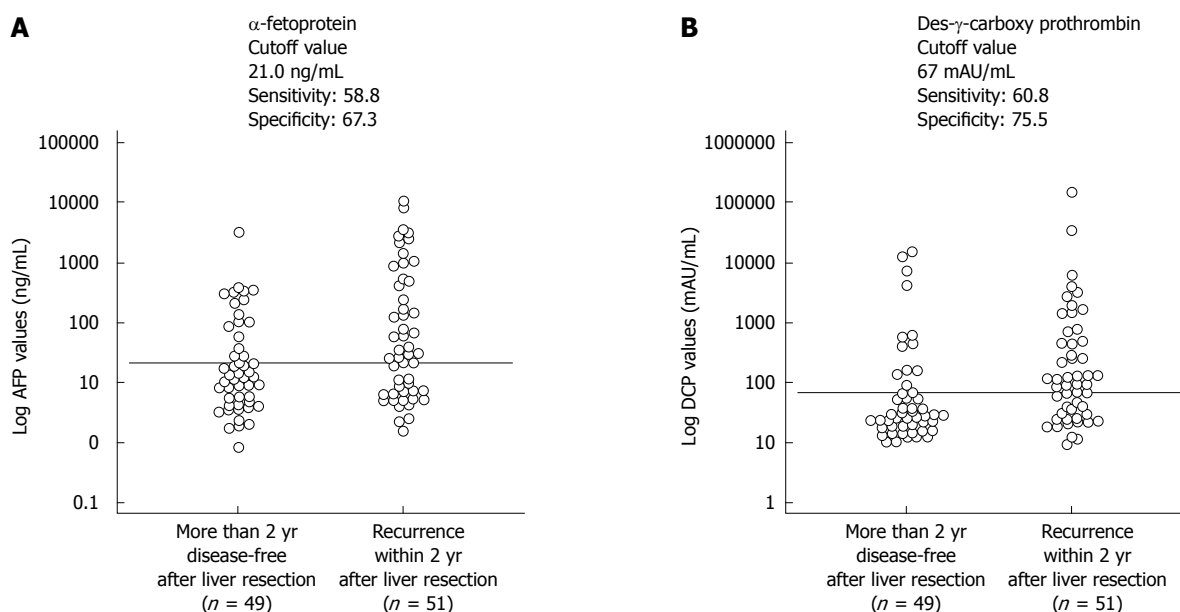


Figure 4 Interactive dot diagrams. A: Interactive dot diagrams showing α -fetoprotein levels were used to predict recurrence within 2 years after hepatectomy among hepatocellular carcinoma patients with hepatitis C infection; B: Interactive dot diagrams showing des-γ-carboxy prothrombin levels were used to predict recurrence within 2 years after hepatectomy among hepatocellular carcinoma patients with hepatitis C infection. The horizontal line indicates the cutoff point with the best separation (minimal false-negative and false-positive results) between the two subgroups.

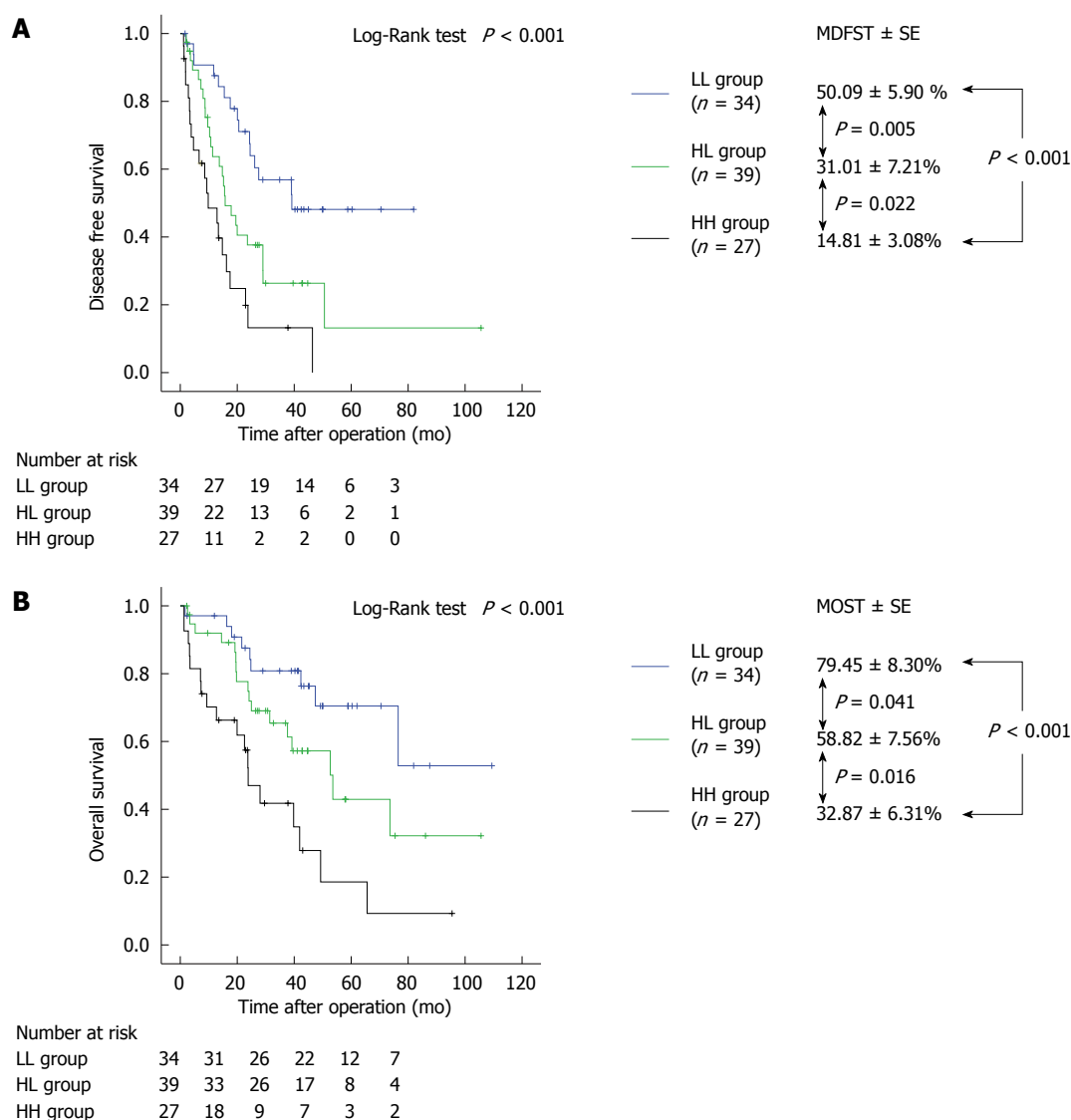


Figure 5 Disease-free survival and overall survival in hepatocellular carcinoma patients with hepatitis C viral infection. A: In the disease-free survival analysis, there were significant differences between the three groups; B: In the analysis of overall survival, there were significant differences between the three groups.

($P = 0.032$), long surgical duration ($P = 0.031$), large tumor size ($P = 0.012$), and the presence of multiple tumors ($P = 0.018$) were associated with significantly higher incidences of tumor recurrence after liver resection.

Our univariate and multivariate analyses to determine the risk factors associated with poor overall survival after hepatectomy in patients with HCV infection ($n = 100$) are shown in Table 6. The multivariate analysis revealed that high levels of ICGR₁₅ ($P = 0.047$), HH group ($P = 0.009$), and the presence of multiple tumors ($P = 0.028$) were associated with significantly higher incidences of poor overall survival after liver resection.

DISCUSSION

We investigated the clinical correlations between prognosis in HCC patients who underwent initial

hepatectomy and levels of the tumor markers AFP and DCP. There was a significant difference between the HBV and HCV groups in the AFP and DCP cutoff levels to predict recurrence within 2 years after hepatectomy. In the HBV group, high AFP or DCP levels were sufficient to predict poor prognosis. In contrast, a low level of either or both tumor markers was correlated with a good prognosis in the HCV group. However, when levels of both markers were high, prognosis was poor in both the HBV and HCV groups. Furthermore, HH group membership was an independent risk factor associated with tumor recurrence in both the HBV and HCV group.

It has been reported that among HCC patients who acquired HBV infection at a relatively young age (approximately 60 years), many do not have liver cirrhosis and have normal liver function^[23-25]. In the HBV group in the present study (Table 1), the median patient age was 62 years, the median ICGR₁₅ was

Table 5 Univariate and multivariate analyses of factors associated with tumor recurrence in patients with hepatitis C virus infection

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age	1.001	0.972-1.031	0.950			
Sex, male	1.455	0.823-2.570	0.197			
Preoperative laboratory values						
Aspartate transaminase	1.005	0.999-1.011	0.134			
Alanine transaminase	1.003	0.966-1.010	0.412			
Platelets	1.015	0.983-1.049	0.363			
Serum ALB	0.569	0.297-1.092	0.090			
PT	0.999	0.980-1.019	0.943			
Serum TBIL	1.281	0.610-2.692	0.513			
ICGR15	1.049	1.017-1.081	0.002 ¹	1.069	1.032-1.108	< 0.001 ¹
Tumor markers						
HH group	4.427	2.238-8.760	< 0.001 ¹	5.098	2.165-12.005	< 0.001 ¹
HL group	2.210	1.166-4.189	0.015 ¹	2.325	1.077-5.018	0.032 ¹
Intraoperative data						
Blood loss	1.001	1.000-1.001	< 0.001 ¹	1.000	0.999-1.000	0.292
Surgical duration	1.003	1.002-1.004	< 0.001 ¹	1.002	0.998-1.006	0.129
Pathologic results						
Tumor size	1.290	1.178-1.413	< 0.001 ¹	1.160	1.033-1.302	0.012 ¹
Multiple tumors	1.264	1.073-1.487	0.005 ¹	1.264	1.041-1.534	0.018 ¹
Vascular invasion	2.454	1.479-4.071	0.001 ¹	1.597	0.890-2.867	0.117

¹Represents statistical significance. HH group: Alpha-fetoprotein values > 21.0 ng/mL and des-gamma-carboxy prothrombin values > 67 mAU/mL; HL group: Alpha-fetoprotein values > 21.0 ng/mL or des-gamma-carboxy prothrombin values > 67 mAU/mL. ALB: Albumin; PT: Prothrombin; TBIL: Total bilirubin; ICGR15: Indocyanine green retention rate at 15 min.

Table 6 Univariate and multivariate analyses of factors associated with poor overall survival in patients with hepatitis C virus infection

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age	1.025	0.987-1.065	0.195			
Sex, male	1.328	0.668-2.642	0.418			
Preoperative laboratory values						
Aspartate transaminase	1.006	0.999-1.013	0.106			
Alanine transaminase	1.001	0.992-1.009	0.849			
Platelets	1.036	0.995-1.077	0.084			
Serum ALB	0.246	0.114-0.531	< 0.001 ¹	0.611	0.219-1.706	0.347
PT	0.994	0.971-1.018	0.643			
Serum TBIL	1.206	0.523-2.780	0.660			
ICGR15	1.054	1.021-1.087	0.001 ¹	1.042	1.001-1.084	0.047 ¹
Tumor markers						
HH group	4.562	2.031-10.248	< 0.001 ¹	4.018	1.424-11.337	0.009 ¹
HL group	2.049	0.911-4.609	0.083	2.209	0.829-5.885	0.113
Intraoperative data						
Blood loss	1.001	1.000-1.001	< 0.001 ¹	1.000	0.999-1.001	0.727
Surgical duration	1.003	1.002-1.004	< 0.001 ¹	1.002	0.998-1.005	0.414
Pathologic results						
Tumor size	1.285	1.162-1.421	< 0.001 ¹	1.081	0.946-1.235	0.255
Multiple tumors	1.204	1.021-1.420	0.027 ¹	1.257	1.025-1.542	0.028 ¹
Vascular invasion	2.223	1.221-4.045	0.009 ¹	1.089	0.490-2.421	0.835

¹Represents statistical significance. HH group: Alpha-fetoprotein values > 21.0 ng/mL and des-gamma-carboxy prothrombin values > 67 mAU/mL; HL group: Alpha-fetoprotein values > 21.0 ng/mL or des-gamma-carboxy prothrombin values > 67 mAU/mL. ALB: Albumin; PT: Prothrombin; TBIL: Total bilirubin; ICGR15: Indocyanine green retention rate at 15 min.

9.6%, and liver function parameters were good, with median ALB levels, PTs, and TBIL levels of 3.95 ± 0.46 g/dL, $93.3\% \pm 12.2\%$, and 0.79 ± 0.44 mg/dL, respectively. The literature finds that few HCC patients with HBV infection present with liver cirrhosis^[23-25]. Similarly, in this study, relatively few patients in the

HBV group had liver cirrhosis [41 patients (39.0%)], and the platelet count, which is decreased in cirrhosis, was maintained at $16.6 \times 10^4/\mu\text{L}$ (Table 1). In the present study, the subjects in the HBV group were comparable to subjects in other reports to date; thus, we believe that this sample was not biased.

A study evaluating the relationship between prognosis and levels of AFP and DCP in 1447 HCC patients used AFP and DCP cutoff levels randomly set at 400 ng/mL and 100 mAU/mL, respectively. The patients with high levels of both AFP and DCP had poor prognoses, which is similar to the findings of our study. These cutoff levels were similar to the levels in our HBV group. In addition, of the 1447 patients in the abovementioned report, 1048 had HBV-induced HCC^[26]. The cutoff levels commonly used to diagnose HCC are 20 ng/mL to 200 ng/mL for AFP and 40 mAU/mL to 100 mAU/mL for DCP^[27-30]. The cutoff levels to predict cancer prognosis are almost twice the levels used for cancer diagnosis. Therefore, once cancer develops, treatment should be administered before the tumor marker levels increase to levels indicative of poor prognosis.

MDFST and MOST in the HBV group were significantly different from the other groups in all analyses; however, there was no significant difference in MDFST and MOST between the HH and HL groups ($P = 0.203$ and $P = 0.465$, respectively) (Figure 3). The HH group had a relatively large median tumor size of 6.24 ± 4.77 cm, and there was a high frequency of patients with vascular invasion (10/16 patients, 62.5%). Tumor size was smaller in the HL group than in the HH group, and there was less vascular invasion. However, the prevalence of poorly differentiated HCC on histological examination in the HL group was comparable to that in the HH group. Moreover, the liver function parameters, including the ICGR₁₅ level, ALB level, PT, and TBIL level, were worse in the HL group than in the HH group. Although the underlying mechanisms of poor liver function in the HL group remain unclear, poor liver function may explain the similar long-term prognoses found in the HH and HL groups. It is assumed that when the HBV group had high levels of either AFP or DCP, liver function parameters strongly affected prognosis.

Studies suggest that liver function decreases and liver cirrhosis progresses with age in many HCC patients with HCV infection^[31,32]. In the present study, the median age in the HCV group was 71 years, and many patients had decreased liver function parameters (Table 4). Furthermore, the majority of patients (58/100, 58.0%) had liver cirrhosis (Table 4), and the characteristics of subjects in the HCV group were similar to the characteristics of subjects in other studies; thus, we believe that there was no selection bias.

In the HCV group, the AFP and DCP cutoff levels for recurrence within 2 years after hepatectomy were 21.0 ng/mL and 67 mAU/mL, respectively (Figure 4). The specificity of AFP levels to predict recurrence within 2 years after hepatectomy was relatively low (67.3%), which is similar to the results of other studies^[33]. Furthermore, the DCP cutoff level was approximately the same as that for the HBV group. The lack of association between DCP cutoff level and

the underlying virus may be because unlike the AFP level, the DCP level is typically not elevated in chronic hepatitis or liver cirrhosis^[14]; thus, it is not affected by liver function parameters, but rather fluctuates specifically in response to tumor marker levels. The AFP cutoff level varied between the HCV and HBV groups. However, the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) has been shown to have a high specificity for a cancer diagnosis^[34]. We believe that the AFP-L3 cutoff level would have been similar in the HCV and HBV groups.

MDFST and MOST in the HCV group varied by subgroup (Figure 5). This difference demonstrates that high levels of either AFP or DCP were clinically significant^[31]. The analysis of the clinical characteristics (Table 4) revealed no significant differences in liver function parameters; however, tumor-related factors, including tumor size and incidence of vascular invasion, were different between the groups. This difference suggests that tumor-related characteristics strongly affected prognosis with HCV infection; therefore, we believe that prognosis can be predicted by AFP and DCP levels together with tumor-related factors.

In our study, various clinical factors were associated with tumor recurrence and overall survival; therefore, we conducted a multivariate analysis for prognosis using a Cox forward stepwise logistic regression model. In the HBV group, the independent prognostic factors associated with tumor recurrence were tumor size, vascular invasion, and TBIL (Table 2). Significant differences in tumor size and vascular invasion were found between the three groups (Table 1). Tumor recurrence prognosis among the three groups was affected by these two factors, and a significant difference in disease-free survival was found (Figure 3A). However, membership in the HH group was an independent prognostic factor associated with tumor recurrence. Therefore, high levels of both AFP and DCP may be a prognostic predictor of tumor recurrence in the HBV group. The only independent prognostic factor associated with poor overall survival was vascular invasion (Table 3), which differed significantly between the three groups (Table 1). Therefore, a significant difference in overall survival rates was found between groups (Figure 3B). The identification of AFP and DCP levels was not always useful for predicting the prognosis associated with poor overall survival in the HBV group because neither HH group membership nor HL group membership was an independent prognostic factor associated with poor overall survival (Table 3). In the HCV group, the independent prognostic factors associated with tumor recurrence were ICGR₁₅, surgical duration, tumor size, vascular invasion, and multiple tumors (Table 5). Surgical duration and tumor size differed significantly between the three groups (Table 4). Tumor recurrence prognosis in all three groups was affected by these two factors, yielding a significant difference between groups in disease-free survival (Figure 5A). However, membership in the HH group

and membership in the HL group were independent prognostic factors associated with tumor recurrence (Table 5), suggesting that high levels of AFP and/or DCP are prognostic predictors of tumor recurrence in the HCV group. The independent prognostic factors associated with poor overall survival were ICGR₁₅ and multiple tumors (Table 6), neither of which differed significantly between the three groups (Table 4). A prognosis of poor overall survival in all three groups was not affected by ICGR₁₅ or multiple tumors. Membership in the HH group was an independent prognostic factor associated with poor overall survival (Table 6), indicating that high levels of both AFP and DCP are a prognostic predictor of poor overall survival in the HCV group.

In conclusion, among HCC patients treated in our department, the AFP cutoff level for recurrence within 2 years after surgery was 21.0 ng/mL in the HCV group and 529.8 ng/mL in the HBV group. Furthermore, patients in the HBV group with high levels of either AFP or DCP had poor prognoses, as did patients with high levels of both AFP and DCP. In contrast, poor prognoses were found in patients in the HCV group only when both levels were high. High AFP and DCP levels were an independent risk factor for tumor recurrence in both the HBV and HCV groups. We believe that to predict prognosis, preoperative levels of tumor markers should be distinguished and assessed according to the type of viral hepatitis.

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COMMENTS

Background

There is no consensus regarding preoperative α -fetoprotein (AFP) and des- γ -carboxy prothrombin (DCP) cutoff levels to predict survival and recurrence after hepatectomy. Furthermore, the prognostic characteristics of these tumor markers according to hepatitis type remain unclear. Therefore, the aim of the present study was to compare these preoperative tumor marker levels and prognosis after hepatectomy as well as to clarify the characteristics of these tumor marker levels according to hepatitis type.

Research frontiers

Chronic hepatitis caused by viral hepatitis often progresses to cirrhosis and hepatocellular carcinoma. The oncogenic mechanisms differ between hepatitis B and C viral infections, and these mechanisms should be taken into consideration when evaluating prognosis and establishing treatment regimens. In this study, the authors demonstrate that the relationship between preoperative tumor marker levels and prognosis varied by the type of viral hepatitis.

Innovations and breakthroughs

Although associations between preoperative tumor markers and postoperative hepatocellular carcinoma prognosis have been reported, this is the first study to report that the AFP cutoff level for recurrence within 2 years after surgery was 21.0 ng/mL in hepatitis C virus (HCV) patients compared with a higher level of 529.8 ng/mL in hepatitis B virus (HBV) patients. Furthermore, patients in the HBV group with high levels of either AFP or DCP had poor prognoses, as did those patients with high levels of both tumor markers. In contrast, in patients in the HCV group, poor prognoses were found only when levels of both AFP and

DCP were high.

Applications

In the HBV group, prognosis was poor when either AFP or DCP levels were high. In the HCV group, prognosis was good when either or both levels were low; however, prognosis was poor when both levels were high.

Terminology

AFP is a glycoprotein produced by liver cells and in the yolk sac during the fetal stage with an albumin-like structure, a half-life of 4-6 d and a molecular weight of 65 kDa. AFP production in the liver is increased in hepatocellular cancer as well as in chronic hepatitis and cirrhosis; therefore, AFP is considered to have low specificity for the diagnosis of cancer. Prothrombin is formed after the γ -carboxylation of vitamin K-dependent propeptides, and DCP is produced as a result of an acquired posttranslational defect in the vitamin K-dependent carboxylase system. DCP has a molecular weight of 72 kDa and a half-life of 40-72 h. DCP production does not increase in chronic hepatitis or cirrhosis, and it is considered to have high specificity for the diagnosis of cancer. However, DCP has no prognostic value in cases with vitamin K deficiency or vitamin K function inhibition.

Peer-review

Nice paper. Many patients included but a regression model is needed to confirm data. If they would do these statistical analysis, paper is interesting enough to be published.

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