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Prognostic effects of causative virus in hepatocellular carcinoma according to the Japan integrated staging (JIS) score

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Background. The Japan integrated staging (JIS) score is recognized to be useful in managing hepatocellular carcinoma (HCC). We evaluated the effects of the causative virus in patients stratified by this system. ***Methods.*** We compared clinicopathologic features, cumulative and tumor-free survival rates, and causes of death between 301 hepatitis C virus-positive patients (HCV group) and 60 hepatitis B virus-positive patients (HBV group). ***Results.*** Among patients with low JIS scores (0 or 1), the proportions of patients with high aspartate and alanine aminotranferase activities, moderate-to-severe active hepatitis, and with cirrhosis were significantly higher in the HCV than in the HBV group. Among patients with high JIS scores (2 to 4), the proportion with moderate-to-severe active hepatitis was also significantly higher in the HCV group. In patients with low JIS scores, those in the HCV group had significantly lower tumor-free and cumulative survival rates than those in the HBV group. Although no patient in the HBV group died of causes other than liver disease (HCC or hepatic failure), some patients in the HCV group died of causes other than liver disease. The proportion of patients who died because of HCC recurrence tended to be higher among patients with high JIS scores than among patients with a low JIS score. ***Conclusions.*** The effects of viral status on survival outcomes are greatest in patients with JIS scores of 0 or 1.

Key words: hepatocellular carcinoma, Japan integrated staging score, hepatitis virus, liver resection

Introduction

Various clinical staging systems for patients with hepatocellular carcinoma (HCC) have been proposed and evaluated for patient assessment and for guiding therapeutic decisions.[1–10] Recently, the Japan integrated staging (JIS) scores,[11] which includes both the grade of cancer spread (cancer stage) and grade of residual liver function (liver disease stage) according to the Liver Cancer Study Group of Japan criteria,[12] has been advocated because most HCC patients have chronic liver disease. The JIS score is recognized as an international standard scale since its effectiveness in stratifying patients and its prognostic predictive power have been demonstrated.[13]

Differences in clinicopathologic findings and outcomes after treatment between HCC patients infected with hepatitis B virus (HBV) and those infected with hepatitis C virus (HCV) have been reported by many investigators.[14–20] However, the effects of infection with these two hepatitis viruses in patients stratified by scoring systems such as the JIS have not been evaluated sufficiently in HCC patients undergoing surgical treatment.

Patients and methods

Between April 1990 and December 2002, 458 patients underwent liver resection for HCC. Of the 458 patients, sera from 301 were positive for anti-HCV antibody (enzyme-linked immunosorbent assay; International Reagents, Kobe, Japan), and negative for hepatitis B surface antigen (enzyme immunoassay; International Reagents). Sera from 60 of the 458 patients were positive for hepatitis B surface antigen, but negative for anti-HCV antibody. These 361 patients were divided into an HCV group (301 HCV-positive patients) and an HBV group (60 HBV-positive patients). We also

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divided these 361 patients into two stratification-based groups; one consisting of 200 patients assigned a JIS score of 0 or 1 (low JIS), and another consisting of 161 patients assigned a JIS score of 2 to 4 (high JIS). We compared clinicopathologic features, cumulative and tumor-free survival rates, and causes of death between the HCV and HBV groups as stratified by the JIS score. When patients died with HCC recurrence or hepatic failure, or hepatic failure with HCC recurrence, the cause of death was assumed to be liver disease. Trisegmentectomy, bisegmentectomy, and segmentectomy were designated as major hepatectomy. The absence of tumor cells along the parenchymal transaction line was confirmed histologically in all patients. No tumors were evident in the remaining liver parenchyma on computed tomography or ultrasonography 3 or 4 weeks after the operation.

The histologic grade of tumor differentiation was assigned using the Edmondson-Steiner classification, with certain modifications.[21,22] When clusters of cancer cells were present in the vessel(s), the disease was positive for vascular invasion. The histologic activity index (HAI) score[23] was used to evaluate the histologic severity of active hepatitis and the degree of fibrosis in noncancerous hepatic tissue. When scores for components 1 to 3 of the HAI totaled 0, no activity was indicated (histologic activity score, 0); scores of 1 to 3 indicated minimal activity (histologic activity score, 1); scores of 4 to 8 indicated mild activity (histologic activity score, 2); scores of 9 to 12 indicated moderate activity (histologic activity score, 3); and scores of 13 to greater indicated severe activity (histologic activity score, 4). Component 1 assessed the degree of periportal necrosis with or without bridging necrosis and piecemeal necrosis; component 2 assessed the degree of intralobular degeneration and focal necrosis; and component 3 assessed the degree of portal inflammation. Severity of fibrosis (histologic fibrosis score) was recorded separately as component 4 of the HAI. A histologic fibrosis score of 1 indicated portal fibrous expansion; a score of 2 indicated portal-to-portal septa without architectural distortion; a score of 3 indicated portocentral septa with architectural distortion; and a score of 4 indicated cirrhosis.

The serum concentrations of α-fetoprotein were measured every 3 moths after operation. Ultrasonography, computed tomography, magnetic resonance imaging, chest radiography, or some combination of these modalities was performed every 3 months. When tumor recurrence in the remnant liver was suspected on the basis of tumor marker levels or the results of imaging, we performed angiography, biopsy under ultrasonographic guidance, or both, to establish a definitive diagnosis. Computed tomography was also performed for the assessment of lung metastasis. Bone metastasis was assessed by scintigraphy. Although the indications for a second liver resection were almost the same as those for the first resection, we performed a second resection only when the following conditions were met.[24] First, the patients with recurrence had satisfactory liver function, similar to that prior to the first occurrence. Second, the recurrent tumors were localized lesions, enabling complete resection. For patients without satisfactory liver function for liver resection, percutaneous ablation therapy, including ethanol injection, microwave coagulation, or radiofrequency therapy, was mainly performed. For patients with recurrence who did not meet these conditions, transarterial treatment, including transcatheter arterial embolization or hepatic arterial infusion chemotherapy, was usually performed.

This study was conducted in accordance with the Helsinki Declaration and the guidelines of the Ethics Committee of our institution. Informed consent was obtained from each patient.

Statistical analysis

The Student's *t*-test was used to analyze differences in age. Categorical data were compared between groups by Fisher's exact analysis or the x^2 test. Survival rates were calculated by the Kaplan-Meier method, and significances of differences in rates between groups were compared by the log-rank test. The Cox proportional hazards model was used for multivariate analysis. A probability value of less than 0.05 was considered significant.

Results

The distribution of patients, classified by Child-Pugh classification and TNM stage according to the Liver Cancer Study Group of Japan, is shown in Table 1. In each Child-Pugh class, the distribution of patients according to cancer stage was not different between the HBV and HCV groups (Child-Pugh classification A; $P = 0.516$; Child-Pugh classification B; $P = 0.818$). The distribution of patients classified by JIS score was not different between the HBV and HCV groups ($P = 0.797$).

The cumulative survival rate was significantly lower in high-JIS patients than in low-JIS patients (Fig. 1; $P < 0.0001$). Thus, survival rates were clearly stratified by the JIS score.

Clinical findings, except for cancer stage and liver function, in the low- and high-JIS groups are shown in Tables 2 and 3, respectively. In both JIS-defined groups, the mean age as significantly higher in the HCV group than in the HBV group.

Table 1. Distribution of Child-Pugh classification, cancer stage, and JIS score in patients who underwent liver resection for hepatocellular carcinoma

Child-Pugh classification	TNM stage			
	I	II	III	IV
	No. of patients with HCV : HBV (JIS score 1)			
A	43:7 (0)	111:26 (1)	88:15 (2)	14:5 (3)
B	12:1 (1)	14:2 (2)	16:3 (3)	3:1 (4)

TNM stage classification by the Liver Cancer Study Group of Japan was used
HCV, hepatitis C virus; HBV, hepatitis B virus; JIS, Japan integrated staging

Table 2. Clinicopathologic findings in low-JIS patients (JIS score 0 or 1)

Findings	HCV (n = 166)	HBV (n = 34)	P
Age, years (mean ± SD)	63.1 ± 7.4	53.0 ± 9.3	<0.0001
Sex (male:female)	129:37	27:7	>0.999
Alcohol abuse	38	8	>0.999
Blood transfusion	45	2	0.0069
AST (IU/l)	62 (25, 100)	37 (24, 68)	<0.0001
ALT (IU/l)	73 (31, 124)	48 (17, 115)	0.0076
ICGR15 (%)	16.0 (8.9, 26.7)	10.8 (7.5, 23.4)	0.0004
Platelet count ($\times 10^4/mm^3$)	13.0 (7.0, 21.0)	13.0 (8.4, 26.8)	0.149
α-Fetoprotein (>20 ng/ml)	86	17	0.853
Tumor size (cm ± SD)	3.0 ± 1.7	3.3 ± 2.2	0.440
Tumor number (single:multiple)	160:6	33:1	>0.999
Differentiation of main tumor (good:moderate:poor)	22:108:36	0:27:7	0.0678
Microscopic vascular invasion	32	7	0.816
Major hepatectomy	44	18	0.0040
Histologic activity score			
0, 1	39	21	<0.0001
2–4	127	13	
Histologic fibrosis score			
0–3	83	24	0.0373
4 (Cirrhosis)	83	10	

AST, aspartate aminotransferase; ALT, alanine aminotrasferase; ICGR15, indocyanine green retention test at 15 min
Results of laboratory tests are given as medians, with 10th and 90th percentiles

Table 3. Clinicopathologic findings in high-JIS patients (JIS score 2, 3 or 4)

Findings	HCV (n = 135)	HBV (n = 26)	P
Age, years (mean ± SD)	64.4 ± 5.6	50.8 ± 8.3	<0.0001
Sex (male:female)	115:20	19:7	0.152
Alcohol abuse	40	4	0.157
Blood transfusion	42	4	0.154
AST (IU/l)	62 (37, 111)	61 (38, 251)	0.884
ALT (IU/l)	63 (30, 121)	63 (31, 126)	0.964
ICGR15 (%)	18.2 (8.4, 31.2)	13.7 (5.2, 28.0)	0.0381
Platelet count ($\times 10^4/mm^3$)	13.3 (7.1, 22.0)	14.4 (7.5, 25.4)	0.432
α-Fetoprotein (>20 ng/ml)	78	20	0.0807
Tumor size (cm ± SD)	4.0 ± 2.7	6.7 ± 5.1	0.0002
Tumor number (single:multiple)	16:119	7:19	0.0629
Differentiation of main tumor (good:moderate:poor)	15:83:37	1:11:14	0.0255
Microscopic vascular invasion	44	15	0.152
Major hepatectomy	43	12	0.179
Histologic activity score			
0, 1	28	13	0.0031
2–4	107	13	
Histologic fibrosis score			
0–3	61	9	0.390
4 (Cirrhosis)	74	17	

AST, aspartate aminotransferase; ALT, alanine aminotrasferase; ICGR15, indocyanine green retention test at 15 min
Results of laboratory tests are given as medians, with 10th and 90th percentiles

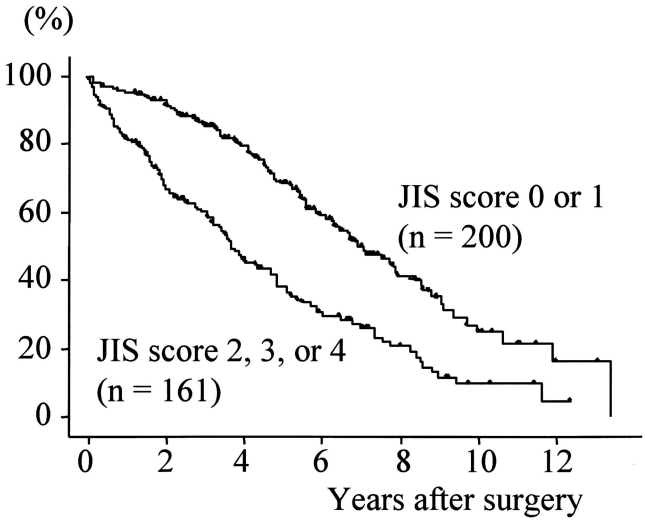


Fig. 1. Cumulative survival rates after liver resection for hepatocellular carcinoma patients with high and low Japan integrated staging (*JIS*) scores. The 200 low-JIS patients were scored as 0 or 1 and the 161 high-JIS patients were scored as 2, 3, or 4. $P < 0.0001$

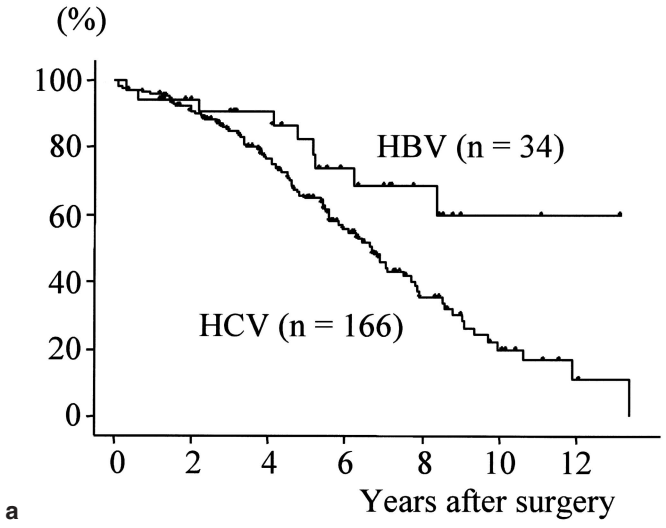
In low-JIS patients, there was no difference in the sex distribution or in the proportion of alcohol abusers (86 g of ethanol per day for at least 10 years, according to the definition by the Liver Cancer Study Group of Japan[25]), between the virally defined groups. The proportion of patients with a history of blood transfusion was significantly higher in the HCV group than in the HBV group ($P = 0.0069$). The activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and the indocyanine green retention rate at 15 min (ICGR15) were significantly higher in the HCV group than in the HBV group. The proportion of patients with well-differentiated HCC was significantly higher in the HCV group (22 of 166 patients) than in the HBV group (none of 34 patients; $P = 0.0297$). The tumor size, tumor number, and the proportion of patients with microscopic vascular invasion were not different between the groups. The proportion of patients who underwent major hepatectomy was significantly lower in the HCV group than in the HBV group. The proportion of patients with moderate-to-severe active hepatitis (histologic activity score, 2 to 4) and the proportion of patients with cirrhosis (histologic fibrosis score 4) were significantly higher in the HCV group than in the HBV group ($P < 0.0001$; $P = 0.0373$, respectively).

In the high-JIS patients, there was no difference in the sex distribution, the proportion of alcohol abusers, or the history of blood transfusion between the HCV and HBV groups. The ICGR15 was significantly higher in the HCV group than in the HBV group. The tumor size was significantly higher in the HBV group than in the HCV group. The proportion of patients with poorly differentiated HCC was significantly higher in the HBV group (14 of 26 patients) than in the HCV group (37 of 135 patients; $P = 0.0112$). The tumor number, the proportion of patients with microscopic vascular invasion, and type of operation were not different between the groups. Although the proportion of high-JIS patients with cirrhosis was not different between the virally defined groups, the proportion of patients with moderate-to-severe active hepatitis was significantly higher in the HCV group than in the HBV group ($P = 0.0031$).

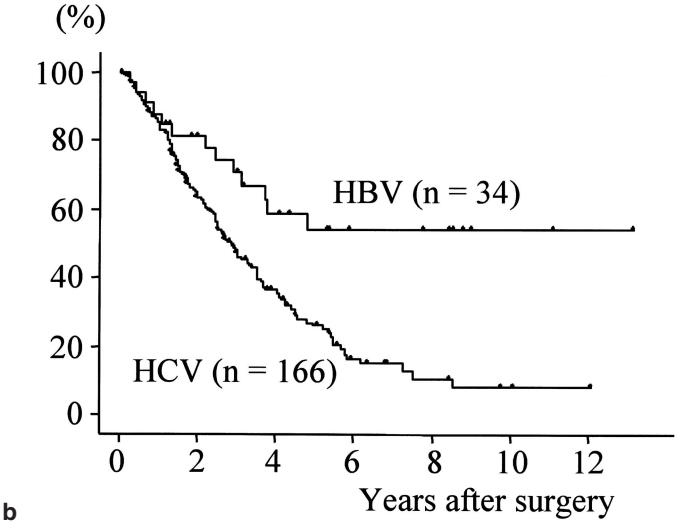
Among the low-JIS patients, tumor-free survival rates (Fig. 2a; $P = 0.0201$) and cumulative survival rates (Fig. 2b; $P = 0.0006$) were significantly lower in the HCV group than in the HBV group. In the high-JIS patients, although tumor-free survival was significantly lower in the HBV group than in the HCV group (Fig. 3a; $P = 0.0305$), the cumulative survival rate was not different between the virally defined groups (Fig. 3b; $P = 0.238$). In low-JIS patients, tumor-free survival decreased gradually; HCC recurrences were seen even later than 3 years after surgery, especially in the HCV group. In the HBV group, HCC did not recur later than 5 years after surgery in low-JIS patients. On the other hand, among high-JIS patients, tumor-free survival decreased rapidly after surgery; HCC recurred within 3 years in 91 of 111 HCV patients with HCC recurrence (82%) and in 21 of 23 HBV patients with HCC recurrence (91%).

In the low-JIS group, a histologic fibrosis score of 4 (cirrhosis; $P = 0.0065$), and minor hepatectomy ($P = 0.0247$) were significant factors for a short tumor-free survival time by univariate analysis. By univariate analysis, HCV infection (risk ratio [RR], 2.462; 95% confidence interval [CI], 1.373–4.414) and cirrhosis (RR, 1.472; 95% CI, 1.037–2.008) were significant independent risk factors for a short tumor-free survival time. A histologic activity score of 2–4 (mild to severe active hepatitis; $P = 0.0182$) was also a significant risk factor for a short cumulative survival by univariate analysis. By multivariate analysis, HCV infection alone (RR, 2.194; 95% CI, 1.113–4.405) was a significant independent risk factor for a short cumulative survival time.

In the low-JIS patients, HCC recurred in 12 HBV patients and in 115 HCV patients. For the first recurrent tumor(s) in the 12 HBV patients, a second liver resection was performed in 5 patients, percutaneous ablation therapy in 1 patient, and transarterial therapy in 6 patients. In the 115 HCV patients, a second liver resection was performed in 22 patients, with percutaneous ablation therapy done in 18 patients, transarterial therapy in 69 patients, radiation therapy in 1 patient, and systemic chemotherapy in 2 patients. In the other 3 patients, supportive care therapy alone was performed. In the high-JIS patients, HCC recurred in 23 HBV patients and in 112 HCV patients. In the 23 HBV patients, a

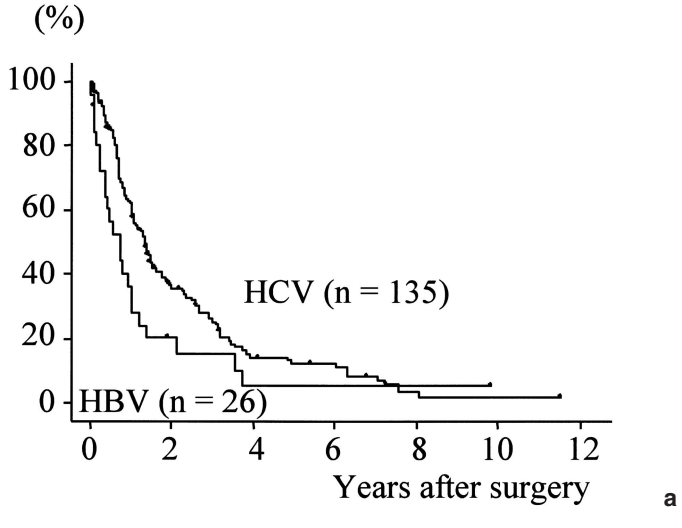


a



b

Fig. 2. **a** Tumor-free survival after liver resection for hepatocellular carcinoma in low-JIS patients. $P = 0.0201$. **b** Cumulative survival after liver resection for hepatocellular carcinoma among low-JIS patients. $P = 0.0006$



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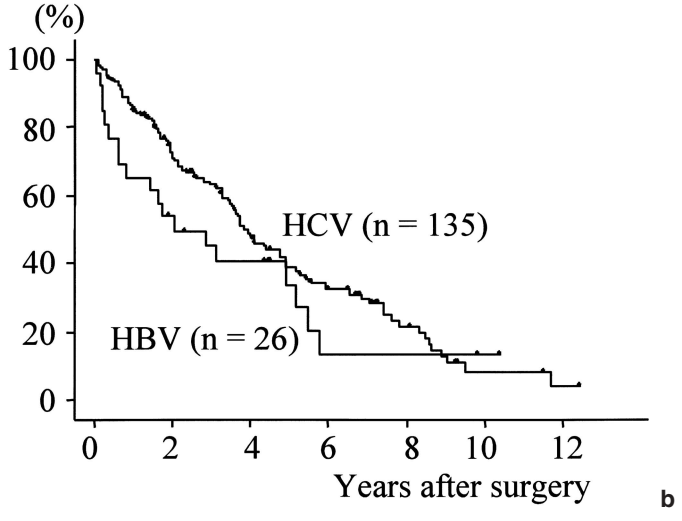

b

Fig. 3. **a** Tumor-free survival after liver resection for hepatocellular carcinoma among high-JIS patients. $P = 0.0305$. **b** Cumulative survival after liver resection for hepatocellular carcinoma among high-JIS patients. $P = 0.238$

second liver resection was performed in 4 patients, with percutaneous ablation therapy done in 2 patients, transarterial therapy in 13 patients, and supportive care therapy given in 4 patients. In the 112 HCV patients, a second liver resection was performed in 6 patients, with percutaneous ablation therapy done in 17 patients, transarterial therapy in 77 patients, systemic chemotherapy in 3 patients, and supportive care therapy given in 9 patients. The treatments for the recurrent tumor(s) were not different between the HCV and the HBV groups in each low- and high-JIS group.

Among the low-JIS patients, 86 HCV patients and 9 HBV patients died before the end of the study period (Table 4). Of these 86 HCV patients, 73 patients died of liver disease (69 of the 73 patients had HCC recurrence), 4 died during the hospital stay after the operation, and 9 died of other disorders, including heart disease and other malignancies. In the 9 HBV patients, the causes of death were liver disease (7 of the 9 patients had HCC recurrence).

Among the high-JIS patients, 92 HCV patients and 19 HBV patients died. In the HCV group, deaths were liver disease-related in 81 patients (all had HCC recurrence), perioperative in 2, and unrelated (including heart disease, pulmonary disease, and other malignant diseases) in 9. In the HBV group, 18 patients died of liver disease (all had HCC recurrence) and 1 died of postoperative hepatic failure. When patients who died during the hospital stay were excluded, none of the 27 deaths in the HBV group were due to causes other than liver disease, whereas 18 of the 176 deaths in the HCV

Table 4. Causes of death in patients who underwent liver resection for hepatocellular carcinoma

JIS score	Cause of death	HCV	HBV	Total
0 or 1	Liver disease	73	9	82
	Heart disease	3	0	3
	Respiratory disease	2	0	2
	Renal failure	1	0	1
	Other malignant disease	2	0	2
	Traffic accident	1	0	1
	Operative death	4	0	4
2, 3, or 4	Liver disease	82	18	100
	Respiratory disease	5	0	5
	Other malignant disease	3	0	3
	Operative death	2	1	3

group were due to causes other than liver disease. The proportion of patients who died with HCC recurrence tended to be higher in the high-JIS patients (99 of 108 fatalities) than in the low-JIS patients (76 of 91 fatalities; $P = 0.0854$).

Discussion

The JIS score combines the Child-Pugh grade and TNM staging by the Liver Cancer Study Group of Japan. The JIS scoring system has proven more effective in stratification than the Cancer of the Liver Italian Program (CLIP) scoring system.[11,13] However, the differential effects of causative viruses have not been clarified according to the JIS scoring system. In this study, survival was significantly lower in the HCV group than in the HBV group among low-JIS patients, which indicates that viral status affects the results as classified by the JIS scoring system. We found a similar outcome pattern when survival rates were compared between HCV and HBV groups in patients assigned a CLIP score of 1 or 2 (data not shown).

In the high-JIS group, tumor-free survival rates in both the HCV and HBV groups decreased rapidly after the operation, and HCC recurred within 3 years in most patients with HCC recurrence. The proportion of patients who died with HCC recurrence tended to be higher in high-JIS than in low-JIS patients. Recurrence of HCC includes intrahepatic metastasis from the original tumor and newly developed HCC (metachronous multicentric carcinogenesis). Usually, recurrent tumors detected within 3 years after surgery are intrahepatic metastases that eluded detection before or during the operation.[26,27] The high-JIS patients included many with advanced HCC in both the HBV and HCV groups, resulting in a high incidence of early HCC recurrence caused by intrahepatic metastasis and a high proportion of patients who died with HCC recurrence. In high-JIS patients, the advanced state of HCC may obscure differences between the HCV and HBV groups.

In low-JIS patients, tumor-free survival was significantly lower in the HCV group than in the HBV group although the proportion of patients with well-differentiated HCC, which usually does not form intrahepatic metastases, was significantly higher in the HCV group than in the HBV group. In the HCV group, tumor-free survival decreased gradually, often with tumor recurrence being even later than 3 years after the operation. Late HCC recurrence is thought to be caused by new development of HCC.[26,27] In contrast, most HCC recurrences in low-JIS patients in the HBV group occurred within 3 years. The incidences of HCC development and multicentric carcinogenesis are higher in patients with chronic hepatitis C than in patients with chronic hepatitis B, and the potential for HCC development continues in patients with chronic hepatitis C, even after surgery.[28–32] In patients with chronic hepatitis B, HCC recurrence, including multicentric carcinogenesis, decreased after the operation according to the natural history of chronic hepatitis B.[33,34] Such different characteristics may affect survival rates. The proportions of patients with high AST and ALT activities, histologically active hepatitis, and cirrhosis were significantly higher in the HCV group than in the HBV group, even though the JIS scores were similar. Active hepatitis and cirrhosis are well-known risk factors for recurrence and for multicentric carcinogenesis.[35–43] Thus, the difference in tumor-free survival rates between the HCV and HBV groups is related to differences in the potential for carcinogenesis and in the natural history of infection between the HCV and HBV groups. In the low-JIS group, multivariate analyses showed that HCV infection and cirrhosis were independent risk factors for a short tumor-free survival time and HCV infection alone was an independent risk factor for short survival time. In patients with fair liver function and nonadvanced HCC, i.e., low-JIS patients, the specific characteristics of

chronic hepatitis C and chronic hepatitis B infection affect the results after treatment.

In the high-JIS group, the tumor-free survival rate was significantly lower in the HBV group than in the HCV group. The high proportion of patients with poorly differentiated HCC and large tumor size may have decreased the survival rate in the HBV group.

Although no patients in the HBV group died of causes other than liver disease, some patients in the HCV group died of causes other than liver disease, including heart disease, respiratory disease, and other malignant diseases. This difference may be partially related to the higher age of the HCV group. Among the low-JIS patients, the presence of individuals who died of nonhepatic disease decreased the cumulative survival rate in the HCV group, contributing to the difference in cumulative survival rates. Among the high-JIS patients, although tumor-free survival was significantly lower in the HBV group than in the HCV group, the presence of individuals who died of nonhepatic disease also decreased the cumulative survival rate in the HCV group, resulting in similar survival curves in the HCV group and the HBV group.

Treatments of HCC include microwave coagulation, radiofrequency ablation, and transcatheter arterial embolization. Subjects in the present study underwent only liver resection as the initial treatment. In addition, this study did not include patients classified as Child-Pugh classification C; the results in this study were mainly affected by the TNM classification rather than the Child-Pugh classification. The effect of viral status on treatment outcomes should be investigated in patients who are treated by additional methods and in patients with severe liver dysfunction.

In conclusion, although the JIS score is prognostically useful in HCC patients, the effects of viral status should be considered, particularly in low-JIS patients.

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