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Clinical Features and Outcome of Surgical Patients with Non-B Non-C Hepatocellular Carcinoma

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Abstract. *Aim: To investigate the clinical characteristics and prognosis of surgical patients with non-B non-C hepatocellular carcinoma (NBNC-HCC) compared to those of hepatitis B virus (HBV)- and hepatitis C virus (HCV)-HCC. Patients and Methods: Clinical data and outcomes were compared among the three groups. Prognostic factors of patients with NBNC-HCC were investigated. Results: Compared to HBV-HCC, patients with NBNC-HCC had higher chance of hypertension (HTN) ($p<0.01$), diabetes mellitus (DM) and body mass index (BMI) >25 kg/m^2. Compared to HCV-HCC, patients with NBNC-HCC had higher incidence of DM and higher BMI >25 kg/m^2 ($p<0.01$). There were no significant differences in overall survival (OS) rate among the three groups. In patients with NBNC-HCC, albumin (Alb; $p<0.05$) was an independent prognostic factor of OS, while Alb and α-fetoprotein (AFP) were independent prognostic factors of disease-free survival (DFS; $p<0.01$ each). Conclusion: Surgical patients with NBNC-HCC often have concomitant DM, HTN and high BMI, for whom factors related to prognosis were Alb and AFP.*

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world. HCC is gradually increasing and, at present, is the sixth most common cancer worldwide, being responsible for approximately 750,000 new cases globally every year (1). In Japan, HCC ranks third in men and fifth in women of cancer deaths (2).

To date, the etiology of HCC development has been reported to include various causative agents, such as hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, primary biliary cirrhosis, autoimmune hepatitis, hemochromatosis, and Budd-Chiari syndrome (2). Among the various causative agents, the majority of causes of HCC development in Japan have been infection with hepatitis viruses, such as HCV and HBV, and more than 70-80% of HCC are reported to be positive to HCV antibody, while 10-20% are positive to hepatitis B surface antigen (3).

In the carcinogenesis of HCV-related HCC, specific gene products of HCV are reported to be involved in malignant transformation (4), while in that of HBV-related HCC, HBV DNA is integrated into the hepatocyte DNA, resulting in genomic instability, and the gene product HBx promotes HCC carcinogenesis (5).

Recently, non-B non-C hepatocellular carcinomas (NBNC-HCCs), which are both HBs antigen (HBsAg)- and HCV antibody (HCVAb)-negative, have been gradually increasing in the United States and Japan (2) and suggested to be associated with metabolic syndromes, such as diabetes mellitus (DM) and hypertension (HTN) (6). Actually, with only few reports regarding the characteristics and prognosis in surgical patients with NBNC-HCC, the carcinogenesis and characteristics of the disease remain unclear. It is, therefore, important to clarify carcinogenesis pathway(s), characteristics and prognosis of NBNC-HCC. The aim of the present study was to investigate the clinical characteristics and prognosis of surgical patients with NBNC-HCC as compared with those of HBV- and HCV-related HCC.

Patients and Methods

Patients. From January 2000 through March 2010, 143 curative hepatic resections for primary HCC were performed at Jikei University Hospital, Tokyo, Japan. Curative hepatic resection was defined as complete macroscopic removal of the tumor with a pathologic negative margin. We could not record survival data of 7 patients who were excluded from the present study. In the preoperative examinations, all patients were tested for the presence of HBsAg and HCVAb; two patients who were positive for both HBsAg and HCVAb were also excluded from this study. Finally, the remaining 134 patients were included and classified into three

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groups according to viral status of hepatitis as follows: HBV group (HBV-HCC, n=36, 26.9%): positive for HBsAg only, HCV group (HCV-HCC, n=57, 42.5%): positive for HCVAb only and NBNC group (NBNC-HCC, n=41, 30.6%): negative for both HBsAg and HCVAb. A total of 134 HCC patients in the present study consisted of 115 (85.8%) men, while the median age was 62 years. The study protocol was approved by the Medical Ethics Committee of the Jikei University and the study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki. Written informed consent was obtained in each case.

The preoperative diagnosis of HCC was made by any one or a combination of the following studies: elevated serum tumor markers, such as α-fetoprotein (AFP) and protein induced by Vitamin K absence or antagonists-II (PIVKA-II), and findings of ultrasonography, computed tomography (CT), gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (EOB-MRI) or abdominal angiography. Pathological diagnosis was made in all patients based on liver tissue obtained from hepatectomy.

Surgical procedures. The treatment for HCC was generally given according to the consensus-based treatment algorithm for HCC proposed by the Japanese Society of Hepatology (7) and hepatic resection was indicated on the basis of liver function results, the number, size and location of nodules, as well as general condition of patients. The surgical procedure for HCC was generally selected in accordance with " Indications for hepatectomy " advocated by Makuuchi *et al*. (8) and surgical procedures, such as anatomical and limited resection, were classified according to the Brisbane terminology proposed by Strasberg *et al*. (9).

Follow-up of surgical patients after hepatectomy for HCC. All surgical patients were followed up at least every 3 months after hepatectomy. Postoperative evaluation included physical examinations, liver function and tumor marker tests, as well as ultrasonography, CT or EOB-MRI to check for intrahepatic recurrence. Chest CT was performed once a year and bone scintigraphy was performed if necessary. When intrahepatic recurrence was detected during the follow-up evaluations, treatment for recurrence, such as repeat resection, ablation and transarterial chemoembolization (TACE), was selected according to remnant hepatic functional reserve, the number, size and location of hepatic recurrence, as well as patients' general condition. For extrahepatic recurrence, molecular-targeted therapy was introduced after 2009.

Annual trend in virus status in surgical patients with HCC. Annual trend in virus status was studied to examine the incidence of surgical patients with NBNC-HCC.

Comparisons of the clinical variables in surgical patients between NBNC- and HBV-HCC or HCV-HCC. The following clinical variables in surgical patients were compared to investigate the differences between NBNC-HCC and HBV- or HCV-HCC, respectively; age, gender, body mass index (BMI) >25 kg/m^2, presence or absence of DM and HTN, alcohol intake >20 gram per day, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-bil), albumin (Alb), alkaline phosphatase (Al-P) or γ-glutamyl transpeptidase (γ-GTP), peripheral white blood cell (WBC) count or platelet (Plt) count, C-reactive protein (CRP), indocyanine green retention test at 15 min (ICGR15), maximal tumor diameter (max TD), number of tumors (solitary or multiple), TNM stage, the serum tumor markers AFP and PIVKA-II at the time of diagnosis for HCC, operative time, intraoperative blood loss and the perioperative use of blood products, such as red cell concentrates (RCCs) and fresh frozen plasma (FFP). DM and HTN were diagnosed when patients were pharmacologically treated for those diseases or on the basis of medical records.

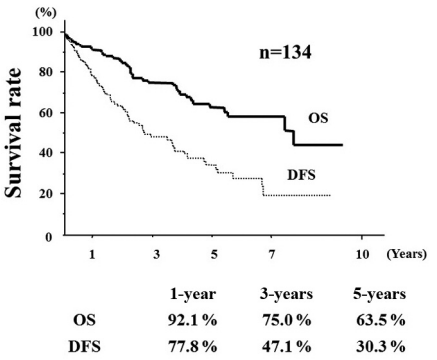


Figure 1. *Overall survival (OS) and disease-free survival (DFS) of all surgical patients with hepatocellular carcinoma (HCC) (January 2000-March 2010, n=134). The 3- and 5-year cumulative overall survival rates were 75.0% and 63.5%, respectively, while the 3- and 5-year cumulative disease-free survival rates were 47.1% and 30.3%, respectively.*

Survival and prognostic factor analyses in surgical patients with NBNC-HCC. Overall survival (OS) and disease-free survival (DFS) rates of the three groups after curative resection were compared using the Kaplan-Meier method and the log-rank test. In NBNC-HCC, factors related to OS and DFS were investigated using univariate and multivariate analyses.

Statistical analyses. All data are expressed as means±standard deviation (SD). Comparison of categorical variables were conducted using either the χ^2 test or the Fisher's exact test, as appropriate, and continuous variables were compared by the Mann-Whitney's *U*-test. The survival curves were analyzed by the Kaplan-Meier method and compared with the log-rank test. A Cox proportional hazards model was used for uni- and multivariate analyses for factors that influenced OS and DFS. In uni- and multivariate analyses, continuous variables were used to divide patients into 2 groups based on the median values. Only those variables showing a value of $p<0.10$ in univariate analyses were included in the overall multivariate Cox model. StatView for Windows software (version 5.0; SAS Institute Inc., Cary, NC, USA) was used for analyses in the present study. All p-values<0.05 were considered statistically significant.

Results

Patients. Figure 1 shows OS and DFS rates of 134 patients with HCC, with their backgrounds being summarized in Table I.

Table I. *Clinical characteristics of all surgical patients with HCC.*

Variable	All patients (n=134)
Age (years)	62±11*
Gender (male:female)	115:19
Virus type	
HBV-HCC	36
HCV-HCC	57
NBNC-HCC	41
DM (yes)	30 (22.4%)
HTN (yes)	50 (37.3%)
BMI (kg/m^2)	23.6±3.2
Alcohol intake >20g/day	54 (40.3%)
Serum AST (IU/l)	45±28
Serum ALT (IU/l)	47±36
Serum total bilirubin (mg/dl)	0.9±0.4
Serum albumin (g/dl)	3.9±0.5
Serum Al-P (IU/l)	302±138
Serum γ-GTP (IU/l)	47±36
White blood cell (/μl)	5,061±1,856
Platelet (×10^3/μl)	151±62
Serum CRP (mg/dl)	0.33±0.97
ICG R15 (%)	14.4±8.8
Serum AFP (ng/ml)	6,475±42,055
Serum PIVKA-II (mAU/ml)	1,079.3±3,446.5
Max TD (cm)	4.5±3.4
Number of tumors (solitary/multiple)	107/27
Stage (I+II/III+IV)	121/13
Operative time (min)	364.1±156.0
Intraoperative blood loss (ml)	1,533±2,811
Intraoperative use of blood products	
RCC (yes/no)	40/94
FFP (yes/no)	44/90

*means±SD; NBNC-HCC, Non-B non-C- hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICGR15, indocyanine green retention test at 15 min; γ-GTP, γ-glutamyl transpeptidase; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; CRP, C-reactive protein; Al-P, alkaline phosphatase; DM, diabetes mellitus; HTN, hypertension; Max TD, maximal tumor diameter; RCC, red cell concentrates; FFP, fresh-frozen plasma.

Annual number of NBNC-HCC in surgical patients with HCC. Figure 2 depicts the annual distribution of NBNC-HCC in all surgical patients with HCC.

Comparison of clinical characteristics between NBNC- and HBV-HCC. As shown in Table II, patients with NBNC-HCC as compared with HBV-HCC had a significantly higher incidence of HTN ($p<0.01$), while DM and BMI >25 kg/m^2 were more frequent. Patients with NBNC-HCC were significantly older and their max TD was larger than those in HBV-HCC ($p<0.05$), respectively. Patients with NBNC-HCC had significantly more intraoperative blood loss ($p<0.05$) and more blood transfusion of RCC ($p<0.01$) than those with HBV-HCC.

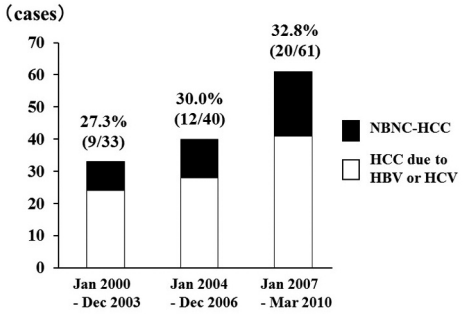


Figure 2. *The incidence of non-B non-C hepatocellular carcinoma (NBNC-HCC) in relation to overall surgical patients with hepatocellular carcinoma (HCC) (January 2000-March 2010, n=134). NBNC-HCC accounted for 27.3% between January 2000 to December 2003, 30.0% between January 2004 to December 2006 and 32.8% between January 2007 to March 2010.*

Comparison of clinical characteristics between NBNC- and HCV-HCC. As shown in Table III, patients with NBNC-HCC as compared with HCV-HCC had a significantly higher incidence of BMI >25 kg/m^2 ($p<0.01$), while DM was more frequent. Also, the values of serum AST, ALT, γ-GTP and ICG R15 were significantly lower ($p<0.01$), respectively. Both peripheral white blood cell and platelet counts were significantly higher ($p<0.01$), respectively. Maximal TD and the value of serum AFP were also significantly increased ($p<0.01$), respectively. Operative time in patients with NBNC-HCC was significantly longer than that with HCV-HCC ($p<0.05$). Patients with NBNC-HCC had significantly more intraoperative blood loss ($p<0.05$) and more blood transfusion of RCC ($p<0.01$) and FFP ($p<0.05$) than those with HCV-HCC.

Survival and prognostic factor analyses in surgical patients with NBNC-HCC. Figures 3 and 4 show OS and DFS rates of 134 patients with HCC in relation to viral type. There were no significant differences in OS rate among the three groups, while NBNC-HCC tended to have a better DFS, which, however, did not achieve statistical significance.

Tables IV and V show the relationship between the clinical variables and OS or DFS in NBNC-HCC. In univariate analysis, as shown in Table IV, OS rate was significantly worse in patients with lower serum Alb ($p<0.01$), whereas DM tended to be associated with worse OS ($p=0.076$). In multivariate analysis of OS shown in Table V, serum Alb ($p<0.05$) was an independent prognostic factor of OS. On the other hand, in univariate analysis as shown in Table IV, DFS was significantly worse in older patients ($p<0.05$), while patients showed higher serum AST ($p<0.05$), lower serum Alb ($p<0.01$) and higher value of serum AFP

Table II. *Comparison of clinical variables between NBNC- and HBV-HCC.*

Variable	NBNC-HCC (n=41)	HBV-HCC (n=36)	*p*-Value
Age (years)	63±12 *	52±9	<0.0001
Gender (male:female)	36:5	33:3	0.579
BMI >25kg/m^2	48.8%	31.4%	0.103
DM	34.1%	16.7%	0.080
HTN	51.2%	14.3%	0.0005
Alcohol intake >20g/day	43.9%	30.6%	0.306
Serum AST (IU/l)	38±25	39±14	0.052
Serum ALT (IU/l)	36±22	42±19	0.045
Serum total bilirubin (mg/dl)	0.9±0.4	1.0±0.5	0.274
Serum albumin (g/dl)	3.9±0.5	4.0±0.4	0.660
Serum Al-P (IU/l)	316±153	323±185	0.831
Serum γ-GTP (IU/l)	36±22	42±19	0.045
White blood cell (/μl)	5,635±1,845	5,239±1,929	0.365
Platelet (×10^3/μl)	177±70	151±55	0.059
Serum CRP	0.62±1.60	0.57±1.74	0.063
ICG R15 (%)	11.5±6.9	11.7±5.8	0.669
Serum AFP (ng/ml)	8,741±46,243	11,499±64,148	0.151
Serum PIVKA-II (mAU/ml)	2,249±5,546	861±2,179	0.285
Max TD (cm)	6.3±4.2	4.4±3.5	0.0175
Number of tumors (solitary/multiple)	34/7	27/9	0.392
TNM stage (I+II/III+IV)	35/6	32/4	0.646
Operation time (min)	413.0±174.8	353.7±162.4	0.133
Intraoperative blood loss (ml)	2,254±4,067	1,465±2,886	0.044
Intraoperative use of blood products			
RCC (yes/no)	21/20	7/29	0.003
FFP (yes/no)	19/22	12/24	0.245

*means±SD; DM, Diabetes mellitus; HTN, hypertension; Max TD, maximal tumor diameter; RCC, red cell concentrates; FFP, fresh-frozen plasma; NBNC-HCC, non-B non-C- hepatocellular carcinoma; HBV, hepatitis B virus; AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICGR15, indocyanine green retention test at 15 min; γ-GTP, γ-glutamyl transpeptidase; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; CRP, C-reactive protein; Al-P, alkaline phosphatase.

Table III. *Comparison of clinical variables between NBNC- and HCV-HCC.*

Variable	NBNC-HCC (n=41)	HCV-HCC (n=57)	*p*-Value
Age (years)	63±12 *	67±7	0.403
Gender (male:female)	36:5	46:11	0.348
BMI >25kg/m^2	48.8%	19.3%	0.002
DM	34.1%	17.5%	0.059
HTN	51.2%	42.1%	0.371
Alcohol intake >20g/day	43.9%	28.1%	0.118
Serum AST (IU/l)	38±25	52±34	0.0006
Serum ALT (IU/l)	36±22	58±47	0.0028
Serum total bilirubin (mg/dl)	0.9±0.4	0.9±0.3	0.405
Serum albumin (g/dl)	3.9±0.5	3.8±0.4	0.068
Serum Al-P (IU/l)	316±153	279±82	0.296
Serum γ-GTP (IU/l)	36±22	58±47	0.0028
White blood cell (/μl)	5,635±1,845	4,546±1,702	0.0003
Platelet (×10^3/μl)	177±70	132±53	0.0003
Serum CRP	0.62±1.60	0.27±0.53	0.326
ICG R15 (%)	11.5±6.9	18.1±10.1	0.0002
Serum AFP (ng/ml)	8,741±46,243	1,583±4,493	0.0091
Serum PIVKA-II (mAU/ml)	2,249±5,546	289±556	0.096
Max TD (cm)	6.3±4.2	3.3±1.7	<0.0001
Number of tumors (solitary/multiple)	34/7	46/11	0.779
Stage (I+II/III+IV)	35/6	54/3	0.113
Operation time (min)	413.0±174.8	335.3±129.8	0.036
Intraoperative blood loss	2,254±4,067	1,056±1,063	0.048
Intraoperative use of blood products			
RCC (yes/no)	21/20	12/45	0.0018
FFP (yes/no)	19/22	13/44	0.014

*means±SD; DM, Diabetes mellitus; HTN, hypertension; Max TD, maximal tumor diameter; RCC, red cell concentrates; FFP, fresh-frozen plasma; NBNC-HCC, non-B non-C- hepatocellular carcinoma; HCV, hepatitis C virus; AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICGR15, indocyanine green retention test at 15 min; γ-GTP, γ-glutamyl transpeptidase; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; CRP, C-reactive protein; Al-P, alkaline phosphatase.

($p<0.05$). In multivariate analysis, as shown in Table V, serum Alb ($p<0.01$) and AFP ($p<0.01$) were independent prognostic factors of DFS.

Discussion

In the present study, we found that the incidence of surgical patients with NBNC-HCC is gradually increasing. The study's findings are in agreement with previous reports demonstrating an increased number and rate of patients with NBNC-HCC accounting for 20% of all HCC patients (2). Therefore, it was important to clarify the characteristics of surgical patients with NBNC-HCC for optimal pre- and post-operative management. It is suggested that NBNC-HCC might be associated with obesity, DM and metabolic syndromes, which are at an increased risk for developing HCC (6).

The current study demonstrated the clinical characteristics of surgical patients with NBNC-HCC in comparison to those of surgical patients with HBV-HCC or HCV-HCC; the results were consistent with previous reports (10). We, herein, showed that NBNC-HCC and HBV-HCC patients seem to share similar factors in their background characteristics. Shiraishi *et al.* (11) have reported that HBV-DNA is found frequently in the non-cancerous region of liver tissue in NBNC-HCC patients, while Hatanaka *et al.* (10) also speculated the possible association of HBV with hepatocarcinogenesis to some extent in NBNC-HCC

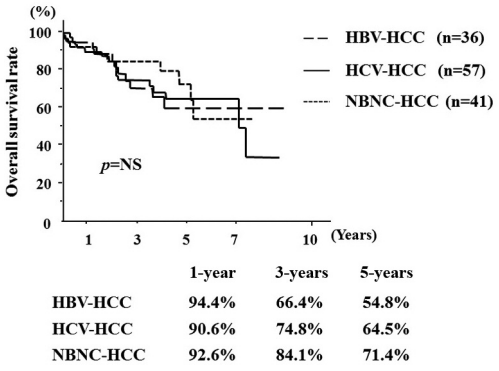
Table IV. *Univariate analysis of the prognostic factors for OS and DFS in NBNC-HCC.*

	OS (years)		DFS (years)	
Variables	median	*p*-Value	median	*p*-Value
Age (years)		0.596		0.040
≥66 (n=21)	0.879		0.778	
<66 (n=20)	3.323		3.097	
Gender		0.933		0.821
male (n=36)	2.492		1.564	
female (n=5)	0.778		0.573	
BMI (kg/m^2)		0.165		0.896
≥24.9 (n=21)	1.367		1.170	
<24.9 (n=20)	2.886		1.347	
DM		0.076		0.345
yes (n=14)	1.375		1.042	
no (n=27)	3.162		1.386	
HTN		0.552		0.533
yes (n=21)	3.162		1.386	
no (n=20)	0.877		0.867	
Serum AST (IU/l)		0.174		0.031
≥1 (n=21)	1.123		0.888	
<31 (n=19)	3.162		2.611	
Serum ALT (IU/l)		0.734		0.659
≥29 (n=21)	2.092		1.870	
<29 (n=19)	1.384		0.874	
Serum total bilirubin (mg/dl)		0.652		0.782
≥0.8 (n=25)	2.611		1.386	
<0.8 (n=16)	1.096		1.090	
Serum albumin (g/dl)		0.001		<
0.0001				
≥4.0 (n=22)	3.048		2.492	
<4.0 (n=19)	1.307		0.915	
Serum Al-P (IU/l)		0.436		0.121
≥291.5 (n=21)	1.307		1.170	
<291.5 (n=20)	2.886		2.492	
Serum γ-GTP (IU/l)		0.734		0.659
≥29 (n=21)	2.092		1.870	
<29 (n=19)	1.384		0.874	
White blood cell (/μl)		0.720		0.962
≥5,400 (n=21)	1.384		1.170	
<5,400 (n=19)	2.886		1.377	
Platelet (×10^3/μl)		0.435		0.681
≥171 (n=21)	1.384		1.307	
<171 (n=20)	2.211		1.268	
Serum CRP (mg/dl)		0.173		0.066
≥0.10 (n=21)	1.811		1.170	
<0.10 (n=18)	1.870		1.870	
ICG R15 (%)		0.711		0.879
≥10 (n=23)	1.384		1.170	
<10 (n=18)	2.492		1.347	
Serum AFP (ng/ml)		0.286		0.021
≥20 (n=13)	1.134		0.645	
<20 (n=26)	2.611		1.742	
Serum PIVKA-II (mAU/ml)		0.243		0.377
≥400 (n=16)	1.997		1.555	
<400 (n=21)	1.811		1.170	
Max TD (cm)		0.614		0.701
≥4.5 (n=23)	0.885		0.860	
<4.5 (n=18)	3.942		2.097	
Number of tumors		0.088		0.111
solitary (n=34)	2.886		2.058	
multiple (n=7)	0.874		0.860	
TNM stage		0.263		0.453
I + II (n=35)	2.611		1.386	
III + IV (n=6)	0.873		0.645	
Operative time (min)		0.623		0.075
≥410 (n=21)	1.307		0.778	
<410 (n=20)	3.489		2.452	
Intraoperative blood loss (ml)		0.775		0.404
≥1,280 (n=21)	3.162		1.386	
<1,280 (n=20)	1.375		1.042	
Intraoperative use of RCC		0.444		0.058
yes (n=21)	2.611		1.307	
no (n=20)	1.597		1.268	
Intraoperative use of FFP		0.342		0.922
yes (n=19)	1.367		1.307	
no (n=22)	2.092		1.456	

*means±SD; OS, Overall survival; DFS, disease-free survival; NBNC-HCC, non-B non-C- hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICGR15, indocyanine green retention test at 15 min; γ-GTP, γ-glutamyl transpeptidase; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; CRP, C-reactive protein; Al-P, alkaline phosphatase; DM, diabetes mellitus; HTN, hypertension; Max TD, maximal tumor diameter; RCC, red cell concentrates; FFP, fresh-frozen plasma; TNM, tumor-node-metastasis.

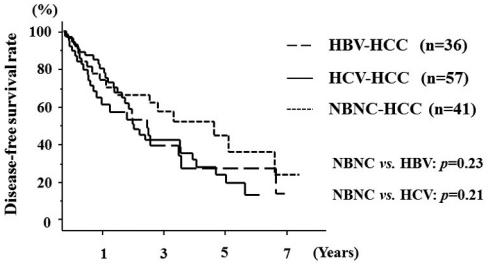
patients. Therefore, carcinogenesis of NBNC-HCC might be associated with HBV carcinogenesis.

The relationship between OS or DFS and viral status has been controversial. Kondo *et al*. (12) have showed that OS and DFS rates in NBNC-HCC patients are significantly better than those in HBV- and HCV-HCC patients, respectively. Also, several other reports (13, 14) have shown that OS rate in NBNC- or non-alcoholic fatty liver disease (NAFLD)-HCC patients are significantly better than that in HCV-HCC patients. On the other hand, some reports (15, 16) have shown no difference in OS in relation to viral status. Kaibori *et al*. (17) have found significant differences in DFS rate, but not in OS rate among the three groups, and demonstrated that both OS and DFS of patients with NBNC-HCC after hepatic resection are significantly better in cases with a maximal tumor diameter of 5 cm or less. Subgroup



	1-year	3-years	5-years
HBV-HCC	94.4%	66.4%	54.8%
HCV-HCC	90.6%	74.8%	64.5%
NBNC-HCC	92.6%	84.1%	71.4%

Figure 3. *Overall survival (OS) of 134 patients with hepatocellular carcinoma (HCC) at our Institute in relation to status of viral hepatitis: hepatitis B virus (HBV), hepatitis C virus (HCV) and non-B non-C hepatocellular carcinoma (NBNC). There were no significant differences in OS rate among the three groups. NS, Not significant.*



	1-year	3-years	5-years
HBV-HCC	67.8%	39.1%	26.8%
HCV-HCC	84.8%	42.1%	23.4%
NBNC-HCC	77.8%	62.0%	44.9%

Figure 4. *Disease-free survival (DFS) of 134 patients with hepatocellular carcinoma (HCC) at our Institute in relation to status of viral hepatitis: hepatitis B virus (HBV), hepatitis C virus (HCV) and non-B non-C hepatocellular carcinoma (NBNC). There was a tendency for better DFS rate in patients with NBNC-HCC as compared to those with the other groups, which did not, however, achieve statistical significance.*

analysis of patients with NBNC-HCC will be needed as the NBNC-HCC group is composed of patients affected by various etiologies, including non-alcoholic steatohepatitis (NASH), NAFLD, alcohol abuse and others, still unknown.

In the present study, we demonstrated that serum Alb is a prognostic factor for OS and serum Alb and AFP for DFS using uni- and multivariate analyses. Until now, reported prognostic factors in patients with NBNC-HCC after hepatic resection include tumor diameter, multiple tumors, portal invasion and curative resection with an adequate surgical margin (13, 18), which, however, remain controversial.

Kaibori *et al.* (17) reported serum Alb and PIVKA-II levels to be independent predictors of OS and DFS in patients with NBNC-HCC after hepatectomy. On the other hand, some authors report that AFP could be an independent prognostic factor in patients with NBNC-HCC or NAFLD. Wakai *et al.* (15) have demonstrated that serum AFP could be an independent prognostic factor after hepatectomy in patients with HCC in NAFLD, whereas Babali *et al.* (19) have shown that AFP levels could rise in accordance with the grade of liver steatosis in NAFLD. Also, Witjes *et al.* (20) have reported significant association between increased serum AFP levels and clinical outcome of non-cirrhotic patients with HCC without well-established risk factors, such as hepatitis B or C infection, alcohol abuse and hemochromatosis. Therefore, we believe that serum AFP level could be an independent prognostic factor of DFS in NBNC-HCC patients.

We also demonstrated that serum Alb level is an independent prognostic factor for OS and DFS and we, therefore, suggest that nutritional therapy might be beneficial to improve OS in patients with NBNC-HCC. Further prospective studies are required to validate the significance of serum Alb and AFP as prognostic factor of NBNC-HCC.

There are several limitations associated with the present study. First, this single-center study's design was retrospective and, therefore, there may be potential selection bias for the patients with HCC after hepatectomy. Second, pathological findings from all three groups were not

Table V. *Multivariate analyses of the prognostic factors for OS and DFS in NBNC-HCC.*

OS or DFS	*p*-Value	Relative risk
OS		
DM (yes)	0.360	2.048
Serum albumin <4.0 g/dl	0.021	12.642
Number of tumors (multiple)	0.275	2.616
DFS		
Age ≥66 years	0.109	3.389
Serum AST ≥31 IU/l	0.860	1.160
Serum albumin <4.0 g/dl	0.0002	152.558
Serum CRP ≥0.10 mg/dl	0.165	4.198
Serum AFP ≥20 ng/ml	0.0072	9.121
Operative time ≥410 min	0.137	4.275
Intraoperative use of RCC (yes)	0.478	0.507

OS, Overall survival; DFS, disease-free survival; NBNC-HCC, non-B non-C- hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; AST, aspartate aminotransferase; CRP, C-reactive protein; DM, diabetes mellitus; RCC, red cell concentrates.

available. Finally, we were unable to properly evaluate the subgroup of patients with NBNC-HCC and, therefore, analysis of subgroup of patients with NBNC-HCC would be needed in the future, although it would be complicated to divide NBNC-HCC group into subgroups according to the etiology of NBNC-HCC, such as occult HBV, NAFLD, NASH, alcohol abuse and unknown (21, 22).

In conclusion, surgical patients with NBNC-HCC have been gradually increasing. The present study elucidated that surgical patients with NBNC-HCC have a high incidence of DM, HTN and BMI >25 kg/m^2 and clinical factors related to prognosis seem to be serum Alb and AFP.

Conflicts of Interest

All Authors disclose no conflicts.

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