Prognostic profile of patients with non-viral hepatocellular carcinoma: A comparative study with hepatitis C virus-related hepatocellular carcinoma using data mining analysis

YU NODA[1], TAKUMI KAWAGUCHI[1], RYOKO KUROMATSU[1,2], SHO KOMUKAI[3], MASAHITO NAKANO[1], TAKASHI NIIZEKI[1], HIRONORI KOGA[1,4], ATSUSHI KAWAGUCHI[5] and TAKUJI TORIMURA[1,4]

[1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine; [2]Ultrasound Diagnostic Center, Kurume University Hospital, Kurume, Fukuoka 830-0011; [3]Division of Biomedical Statistics, Department of Integrated Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871; [4]Liver Cancer Research Division, Research Center for Innovative Cancer Therapy, Kurume University, Kurume, Fukuoka 830-0011; [5]Center for Comprehensive Community Medicine, Faculty of Medicine, Saga University, Saga 849-0937, Japan

Received December 20, 2018; Accepted April 4, 2019

DOI: 10.3892/ol.2019.10285

Abstract. Various factors are associated with the prognosis of patients with non-viral hepatocellular carcinoma (HCC). The present study aimed to investigate the prognosis of patients with non-viral HCC compared with that of patients with hepatitis C virus-related (HCV)-HCC and the features associated with prognosis of patients with non-viral HCC using data mining analyses. Patients with non-viral HCC (n=182, age 70.4±8.9 years) and HCV-HCC (n=612, age 70±8.4 years) were enrolled and the overall survival was compared between the non-viral HCC and HCV-HCC groups. The present study performed random forest and decision tree analyses to identify features that distinguish prognosis between the non-viral HCC and HCV-HCC groups. The median survival of the non-viral HCC group was significantly shorter than the HCV-HCC group (1,553 vs. 2,304 days, P<0.01). In the multivariate analysis, the non-viral HCC group was an independent risk factor for survival (HR 1.42, 95% CI 1.08-1.87, P=0.013). In the random forest analysis, the high-ranking distinguishable factors were 'number of tumors' and 'HCC stage' in the non-viral HCC group and 'albumin' and 'total bilirubin' in the HCV-HCC group. The decision tree analysis revealed that, in patients with HCC stage >I, the survival period in the non-viral HCC group was significantly shorter than the HCV-HCC group (HR 1.39, 95% CI 1.07-1.81, P=0.0132). The prognosis of patients with non-viral HCC was poorer than patients with HCV-HCC. In addition, data mining analysis revealed that tumor-related variables had the highest importance for survival in patients with non-viral HCC.

Correspondence to: Dr Takumi Kawaguchi, Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
E-mail: takumi@med.kurume-u.ac.jp

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCV-HCC, hepatitis C virus-related hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; CT, computed tomography; MRI, magnetic resonance imaging; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MVI, macrovascular invasion; TNM, tumor-node-metastasis; RFA, radiofrequency ablation; TACE, rans-arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; SVR, sustained virological response

Key words: hepatoma, prognosis, prognostic factors, non-hepatitis B and non-hepatitis C virus, artificial intelligence approach

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide (1) and it mostly develops in patients with chronic liver disease. Hepatitis C virus (HCV) is one of the major causes of HCC, and the prevalence of HCV-related HCC (HCV-HCC) has been decreasing worldwide owing to recent advances in prevention, surveillance, and treatment (2). Meanwhile, the prevalence of non-viral HCC is increasing worldwide (3). Non-viral HCC can have various causes, and alcoholic liver disease is a well-known risk factor (4). In addition, metabolic disorders, such as obesity, non-alcoholic fatty liver disease (NAFLD), and type 2 diabetes mellitus, are thought to be associated with the increased incidence of non-viral HCC (5,6) and growing evidence suggests that aging; lifestyle factors, such as smoking; hepatic fibrosis; and gamma-glutamyl transpeptidase levels are also risk factors (7,8). Accordingly, a surveillance strategy for non-viral HCC has been proposed (8).

Various factors are associated with HCC prognosis and have been reported elsewhere in patients with HCV-HCC. Lower serum albumin levels, presence of decompensated cirrhosis, higher serum levels of α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), and non-curative treatment have been associated with poor prognosis (9,10). In patients with non-viral HCC, the factors associated with disease-free survival have been investigated. For instance, Hashimoto *et al* (11), showed that sex has an impact on disease-free survival after surgery in patients with non-viral HCC and Hiwatashi *et al* (12), demonstrated that elevated serum bilirubin levels predict poor disease-free survival after surgery. However, limited information is available regarding prognosis and risk factors in patients with non-viral HCC, especially in the advanced stages of HCC. Moreover, no studies have investigated distinguishable differences in prognosis between patients with non-viral HCC and HCV-HCC.

In the present exploratory research investigating prognostic factors in non-viral HCC, we used an artificial intelligence technique called data mining analysis. Two popular approaches of data-mining analysis are random forest analysis and decision tree algorithms. Random forest analysis identifies hidden factors distinguishing between the case and control groups, with a high level of predictive accuracy, even if no a priori hypothesis has been imposed (13). Decision tree algorithms reveal a series of classification rules by identifying priorities, allowing clinicians to choose an option that maximizes benefit for the patient (8). Random forest analysis has been applied to reveal factors associated with survival in esophageal cancer patients treated using chemo-radiation therapy (14), and in patients with metastatic pancreatic adenocarcinoma (15). Decision tree analysis has been used to evaluate prognostic factors in patients with gastric cancer (16) and bile duct cancer (17). However, these techniques have never been applied to identify prognostic factors in patients with non-viral HCC.

The aims of this study are to investigate prognosis of patients with non-viral HCC compared to that of patients with HCV-HCC. We also performed an exploratory analysis to ascertain distinguishable factors associated with prognosis between patients with non-viral HCC and HCV-HCC.

Patients and methods

Study design and ethics. This was a retrospective study to compare prognosis between patients with non-viral HCC and those with HCV-HCC. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was granted prior approval by the institutional review board of Kurume University. An opt-out approach was used to obtain informed consent from the patients, and personal information was protected during data collection.

Patients. We enrolled 794 consecutive adult patients with either non-viral HCC (n=182) or HCV-HCC (n=612) who had been treated at Kurume University Hospital between January 2005 and December 2015. HCC was diagnosed on the basis of either histological examination or a combination of serum tumor makers, such as AFP and DCP, and imaging modalities, such as dynamic computed tomography (CT) and dynamic magnetic resonance imaging (MRI), as detailed in the Japanese Clinical Practice Guidelines for HCC, published by The Japan Society of Hepatology (18). Non-viral HCC was defined as primary HCC accompanied by negative results for serum hepatitis B surface antigen and anti-HCV antibody. HCV-HCC was defined as primary HCC accompanied by a positive result for serum anti-HCV antibody and a negative result for hepatitis B surface antigen. The exclusion criteria were as follows: i) age less than 20 years; ii) history of treatment for HCC; iii) observational period less than 90 days, and iv) positive result for hepatitis B surface antigen or history of anti-viral treatment for chronic hepatitis B.

In the 182 patients with non-viral HCC, the etiologies were as follows: alcoholic liver disease (n=84), non-alcoholic steatohepatitis (n=9), normal liver (n=9), autoimmune hepatitis (n=9), primary biliary cholangitis (n=4), and cryptogenic liver disease (n=67).

Data collection. The following three items of categorical data were collected at the time of HCC diagnosis: i) host factors, namely age, sex, body mass index, alcohol intake of ≥60 g/day, <60 g/day, >20 g/day, or ≤20 g/day' in ethanol amount), history of diabetes mellitus, Child - Pughscore/class, platelet count, and prothrombin activity, as well as serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and hepatitis B core antibody; ii) tumor factors, namely size and number of HCCs, presence or absence of macrovascular invasion (MVI), clinical staging (tumor-node-metastasis [TNM] classification) based on the criteria of the Liver Cancer Study Group of Japan, and serum levels of AFP, AFP-L3, and DCP (19), and iii) treatment factors, namely treatment modality (hepatic resection, radiofrequency ablation [RFA], trans-arterial chemoembolization [TACE], and hepatic arterial infusion chemotherapy [HAIC]). The treatment strategies were based on the Japan Society of Hepatology's clinical practice guidelines for HCC (18). For patients with advanced HCC, beneficial effects of HAIC has been reported (20-23). In our institution, HAIC was employed as a treatment option for advanced HCC, and therapeutic strategy for HCC including the indication of HAIC was determined by 10 hepatologists, all of whom were board certified by the Japan Society of Hepatology.

Observational period. All the enrolled patients were followed up until March 2016. The observational period was defined as the time span from the first date of treatment for HCC to death or the end date.

Comparison of survival. Overall survival in patients with non-viral HCC was compared to that in patients with HCV-HCC. In addition, we performed stratification analyses of survival according to HCC treatment (hepatic resection/RFA/TACE/HAIC) and Child - PughClass (A-C).

Statistical analysis. Data were expressed as a number, percentage, or mean ± SD (standard deviation). Differences between the two groups were analyzed using the Mann-Whitney U-test and chi-squared test, as appropriate. A Kaplan-Meier curve and log-rank test were used to compare

Table I. Patients' characteristics.

Variables	Non-viral HCC	HCV-HCC	P-value
N	182	612	
Host factors			
Age, years	70.4 ± 8.93	70 ± 8.41	0.459
Sex, female/male, n (%)	44 (24.2)/138 (75.8)	238 (38.9)/374 (61.1)	<0.001
Ethanol consumption			<0.001
<20 g/day, n (%)	69 (37.9)	439 (71.7)	
20 - 60 g/day, n (%)	32 (17.6)	37 (6)	
≥60 g/day, n (%)	81 (44.5)	136 (22.2)	
Diabetes mellitus, n (%)	90 (49.5)	176 (28.8)	<0.001
Child - Pugh class			0.922
A, n (%)	144 (79.1)	487 (79.6)	
B, n (%)	35 (19.2)	112 (18.3)	
C, n (%)	3 (1.6)	13 (2.1)	
Platelet count (10^4/mm^3)	14 ± 8.11	11.6 ± 6.74	<0.001
AST (IU/l)	45.2 ± 26.45	59.8 ± 28.79	<0.001
ALT (IU/l)	39.1 ± 25.57	51.7 ± 30.78	<0.001
Albumin (g/dl)	3.66 ± 0.499	3.59 ± 0.498	0.103
Total bilirubin (mg/dl)	1.04 ± 0.57	0.98 ± 0.482	0.57
PT activity (%)	84.7 ± 15.87	83.9 ± 14.12	0.596
Tumor factors			
AFP (ng/ml)	5,169 ± 26,608	1,408 ± 12,953	0.15
DCP (mAU/ml)	6,247 ± 16,513	960 ± 4,912	<0.001
Tumor diameter (mm)	45.1 ± 33.1	26.8 ± 18.65	<0.001
No. of tumors	2.7 ± 2.93	1.9 ± 1.78	0.021
MVI, n (%)	27 (14.8)	29 (4.7)	<0.001
HCC stage			<0.001
I, n (%)	16 (8.8)	199 (32.5)	
II, n (%)	91 (50)	244 (39.9)	
III, n (%)	45 (24.7)	134 (21.9)	
IVA, n (%)	22 (12.1)	22 (3.6)	
IVB, n (%)	8 (4.4)	13 (2.1)	
Treatment for HCC			<0.001
Hepatic resection, n (%)	42 (23.1)	139 (22.7)	
RFA, n (%)	53 (29.1)	339 (55.4)	
TACE, n (%)	50 (27.5)	95 (15.5)	
HAIC, n (%)	37 (20.3)	39 (6.4)	

Data are expressed as mean ± SD or (%), or numbers. SD, standard deviation; HCC, hepatocellular carcinoma; HCV-HCC, hepatitis C virus-related hepatocellular carcinoma; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; MVI, macrovascular invasion; RFA, radio-frequency ablation; TACE, rans-arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

overall survival between the groups. P<0.05 was considered to indicate a statistically significant difference. Variables or profiles associated with the survival of patients with HCC were analyzed using data mining techniques using the software environment for statistical computing R (http://www.rproject.org/index.html). The statistical methods are described in detail below.

Multivariate stepwise analysis. A Cox proportional hazards regression model was used in a multivariate stepwise analysis to identify any independent variables associated with the survival of patients with HCC. Data were expressed as hazard ratio and 95% confidence intervals, as previously described.8 Explanatory variables were selected in a stepwise manner from factors listed in Table I.

Random forest analysis. Random forest analysis was used to identify factors that distinguished prognosis between the non-viral HCC and HCV-HCC groups, as previously described.8 The procedure employed for building the random

Table II. Univariate analysis of survival in patients with HCC.

Variables	Group/Unit	HR	95% CI		P-value
			Lower	Upper	
Group	Non-viral	1.7	1.32	2.19	<0.0001
Sex	Male	1.1	0.87	1.38	0.4406
Ethanol consumption	20-60 g/day	1.13	0.76	1.69	0.5489
	≥60 g/day	1.37	1.08	1.74	0.0104
Diabetes mellitus	Presence	1.05	0.83	1.32	0.6922
Tumor diameter, mm	10	1.21	1.17	1.25	<0.0001
No. of tumors	1	1.3	1.24	1.35	<0.0001
MVI	Presence	2.84	1.98	4.08	<0.0001
HCC Stage	II	1.75	1.27	2.42	0.0007
	III	3.49	2.48	4.92	<0.0001
	IVA	5.96	3.79	9.36	<0.0001
	IVB	7.49	4.2	13.35	<0.0001
Child - Pugh class	B	2.32	1.81	2.98	<0.0001
	C	6.14	3.56	10.58	<0.0001
Treatment of HCC	RFA	1.99	1.41	2.8	0.0004
	TACE	6.48	4.39	9.55	<0.0001
	HAIC	10.33	6.75	15.81	<0.0001
Platelet count, $10^4/mm^3$	1	0.98	0.96	1	0.0716
AST, IU/L	10	1.06	1.02	1.09	0.0015
ALT, IU/L	10	1	0.96	1.03	0.8491
Albumin, g/dL	0,1	0.9	0.88	0.92	<0.0001
Total bilirubin, mg/dL	0,1	1.08	1.06	1.1	<0.0001
PT activity, %	10	0.83	0.76	0.9	<0.0001
AFP, ng/mL	10	1	1	1	<0.0001
DCP, mAU/mL	10	1	1	1	<0.0001

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin.

forest was as follows: Firstly, n tree models were created using bootstrap samples that were randomly chosen from the original dataset; Secondly, each classification or regression tree model was grown with no pruning. Instead of determining the best split among all potential predictors, we chose a random sample of these variables (one-third of the variables) to consider as potential splitting variables. Thus, the best split variable was chosen from among these variables; Thirdly, new data were predicted by aggregating the predictions of the n trees; Finally, the error rate was estimated by predicting the data not in the bootstrap sample (out-of-bag) using the tree grown with the bootstrap sample. The variable importance, which reflects the relative contribution of each variable to the model, was estimated by random permutation of its value and subsequent recalculation of the predictive accuracy of the model. Random forest analysis was conducted using the R package.

Decision tree analysis using prognostic score. To evaluate distinguishable prognostic factors of survival period between patients with HCV-HCC and those with non-viral HCC, decision tree analysis was performed using a prognostic score that was based on the Cox regression model. Firstly, all patients were classified into short survival or long survival group based on median prognostic score. Next, the short survival group of patients with HCV-HCC and the long survival group of patients with non-viral HCC were defined as working group 1. Conversely, the long survival group of HCV-HCC and the short survival group of non-viral HCC were defined as working group 2 (Fig. S1).

We then performed a decision tree analysis to ascertain distinguishable prognostic factors between working groups 1 and 2, which provided profiles of subgroups with different prognosis among the HCV-HCC and non-viral HCC groups. Decision tree analysis was conducted using the R package.

Results

Patients' characteristics. Patients' characteristics were summarized in Table I. There was no significant difference in age between the non-viral HCC and HCV-HCC groups;

Table III. Multivariate analysis of survival in patients with HCC.

Variables	Group/Unit	HR	95% CI		P-value
			Lower	Upper	
Group	Non-viral	1.42	1.08	1.87	0.0131
Tumor diameter, mm	10	1.08	1.01	1.15	0.0349
No. of tumors	1	1.15	1.09	1.22	<0.0001
MVI	None	0.27	0.13	0.57	0.0006
HCC stage	II	1.39	0.98	1.96	0.0618
	III	1.68	1.1	2.55	0.0154
	IVA	6.64	2.98	14.76	<0.0001
	IVB	4.4	1.92	10.1	0.0005
Child - Pugh class	C	2.03	1.1	3.74	0.0241
Treatment of HCC	RFA	1.73	1.17	2.54	0.0057
	TACE	2.45	1.56	3.84	0.0001
	HAIC	2.28	1.19	4.36	0.0128
Platelet count, $10^4/mm^3$	1	0.97	0.95	0.99	0.0074
Albumin, g/dl	0.1	0.95	0.92	0.97	0.0001
Total bilirubin, mg/dl	0.1	1.03	1	1.05	0.0233
AFP, ng/ml	10	1	1	1	0.0040

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; AFP, alpha-fetoprotein.

however, the male ratio, alcohol consumption, and diabetes mellitus rate were significantly higher in the non-viral HCC group than in the HCV-HCC group (Table I). Although Child - Pughclass did not differ significantly between the two groups, there was a significant difference in HCC stage and HCC treatment (Table I).

Overall survival. Overall survival rates were presented in Fig. S2. Overall survival of patients with non-viral HCC was significantly shorter than that of patients with HCV-HCC. Specifically, the median survival terms of patients with non-viral HCC and HCV-HCC were 1,553 days and 2,304 days, respectively. The 1-, 3-, and 5-year survival rates were 86.8%, 59.4%, and 43.8%, respectively, in patients with non-viral HCC and 93.3%, 76%, and 59.3%, respectively, in patients with HCV-HCC.

Univariate and multivariate analysis of survival in patients with HCC. Univariate analysis for survival was summarized in Table II. Non-viral HCC group, HCC stage ≥II, Child - Pughclass B or C, and treatment for HCC were independent risk factors for reduced survival (Table II). Multivariate analysis revealed that, in the non-viral HCC group, HCC stage ≥III, Child - Pughclass C, and treatment for HCC were independent risk factors for reduced survival (Table III).

Stratification analysis of survival according to HCC treatment. Stratification analysis for survival according to treatment for HCC was shown in Fig. 1A-D. Although there was no significant difference in survival rate after hepatic resection, RFA and TACE between the non-viral HCC and HCV-HCC groups (Fig. 1A-C), survival rate after HAIC in the non-viral HCC group was significantly lower than in the HCV-HCC group. In patients with non-viral HCC treated using HAIC, the 1-, 3-, and 5-year survival rates were 60%, 9.7%, and 0%, respectively, while the equivalent rates were 78.1%, 39.9%, and 20.2%, respectively, in patients with HCV-HCC (Fig. 1D).

Stratification analysis for survival according to Child - Pughclass. Stratification analysis for survival according to Child-Pugh class was shown in Fig. 1E-G. In Child - Pughclasses A and B, survival rate was significantly lower in the non-viral HCC group than in the HCV-HCC group (Fig. 1E and F). Specifically, in patients with Child - Pughclass A, the 1-, 3-, and 5-year survival rates were 89.4%, 67.9%, and 47.9%, respectively, in the non-viral HCC group, and 95.5%, 81.8%, and 65.9%, respectively, in the HCV-HCC group (Fig. 1E). In patients with Child - Pughclass B, the 1-, 3-, and 5-year survival rates were 78.4%, 29.8%, and 29.8%, respectively, in the non-viral HCC group, and 88%, 58%, and 37.4%, respectively, in the HCV-HCC group (Fig. 1F).

Random forest analysis for survival in patients with HCC. Factors distinguishing between life and death in patients with HCC were evaluated by a random forest analysis (Table IV). In all patients, the distinguishable factors, from the top, were number of tumors, treatment for HCC, albumin, total bilirubin, and AFP (Table IV, left column). In the non-viral HCC group, distinguishable factors, from the top, were number of tumors, HCC stage, treatment for HCC, tumor diameter, and albumin (Table IV, middle column). In the HCV-HCC group, distin-

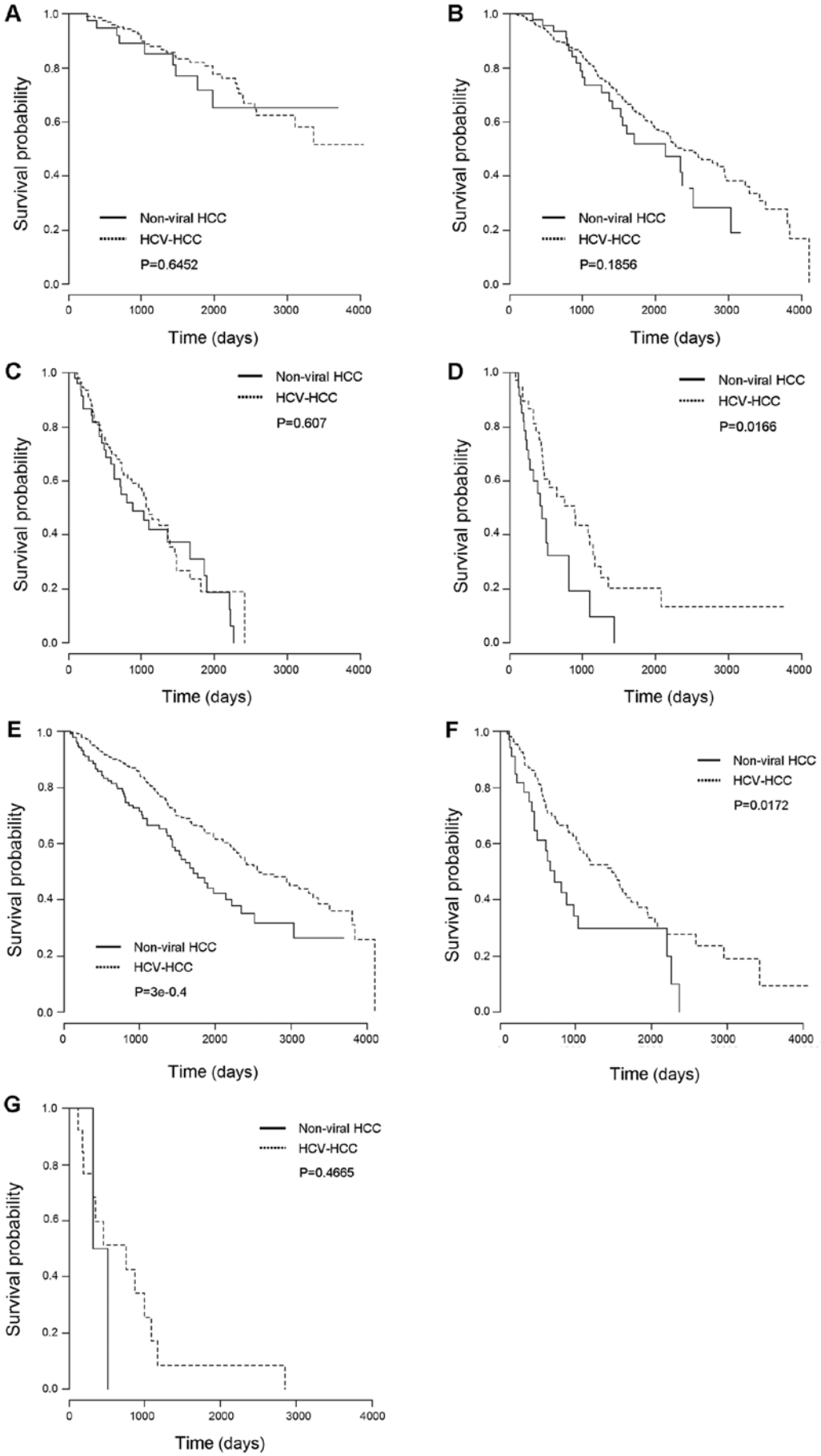
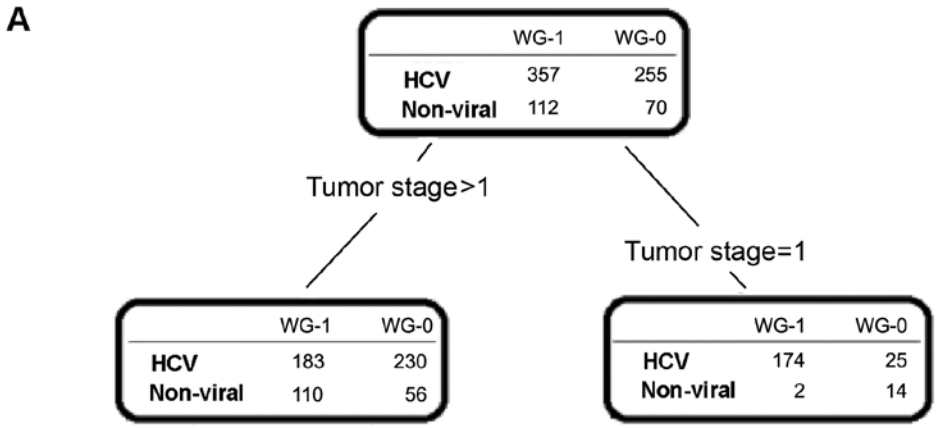


Figure 1. Stratification analysis of survival according to treatment for HCC and Child - Pugh class. (A) Hepatic resection, (B) radiofrequency ablation, (C) transarterial chemoembolization, (D) hepatic arterial infusion chemotherapy, (E) Child - Pugh class A, (F) Child - Pughclass B, and (G) Child - Pugh class C. Solid line indicates non-viral HCC and dotted line indicates hepatitis C virus-related HCC. HCC, hepatocellular carcinoma.

Table IV. Random forest analysis of life and death in patients with HCC.

	ALL (Variable importance)	Non-viral HCC (Variable importance)	HCV-HCC (Variable importance)
1	No. of tumors (1.000)	No. of tumors (1.000)	Albumin (1.000)
2	Treatment for HCC (0.938)	HCC stage (0.694)	Total bilirubin (0.956)
3	Albumin (0.704)	Treatment for HCC (0.385)	AFP (0.913)
4	Total bilirubin (0.615)	Tumor diameter (0.246)	Treatment for HCC (0.881)
5	AFP (0.549)	Albumin (0.223)	DCP (0.719)
6	Tumor diameter (0.513)	Platelet count (0.218)	No. of tumors (0.681)
7	DCP (0.504)	AFP (0.167)	Platelet count (0.438)
8	Platelet count (0.412)	Child - Pughclass (0.118)	Age (0.413)
9	Child - Pughclass (0.363)	AST (0.113)	Child - Pughclass (0.344)
10	HCC stage (0.363)	DCP (0.096)	Tumor diameter (0.338)
11	Age (0.186)	Total bilirubin (0.066)	HCC stage (0.288)
12	ALT (0.133)	PT activity (0.062)	AST (0.163)
13	AST (0.115)	Male (0.015)	PT activity (0.119)
14	PT activity (0.080)	Diabetes mellitus (0.006)	ALT (0.019)
15	Non-viral HCC Group (0.035)	Macrovascular invasion (0.004)	Diabetes mellitus (0.006)
16	Diabetes mellitus (0.009)	Ethanol consumption (0.000)	Macrovascular invasion (0.000)

HCC, hepatocellular carcinoma; HCV-HCC, hepatitis C virus-related hepatocellular carcinoma; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.



B

Profile	HR	95%CI		P-value
		lower	upper	
"HCC Stage = I"+"Non-viral HCC"	2.26	0.8	6.4	0.1245
"HCC Stage > I"+"Non-viral HCC"	1.39	1.07	1.81	0.0132

Figure 2. Decision tree analysis for characteristic difference in survival term between hepatitis C virus-related HCC and non-viral HCC. (A) Decision tree for survival term. (B) Hazard ratios for profile based on the decision tree. HCC, hepatocellular carcinoma.

guishable factors, from the top, were albumin, total bilirubin, AFP, treatment for HCC, and DCP (Table IV, right column).

Decision tree analysis of the characteristic differences in survival terms between HCV-HCC and non-viral HCC. To evaluate distinguishable factors for survival period between patients with HCV-HCC and those with non-viral HCC, we performed a decision tree analysis using the linear-prediction method. HCC stage I was identified as the most distinguishable factor for survival period (Fig. 2A). In patients with

HCC stage I, there was no significant difference in survival period between patients with non-viral HCC and those with HCV-HCC. Meanwhile, in patients with HCC stage >I, the survival period of patients with non-viral HCC was significantly shorter than that of patients with HCV-HCC (HR 1.39, 95% CI: 1.07-1.81, P= 0.0132; Fig. 2B).

Discussion

In the present study, we demonstrated that patients with non-viral HCC have poorer prognosis than patients with HCV-HCC. Random forest analysis for survival showed that 'number of tumors' and 'HCC stage' were high-ranking factors in the non-viral HCC group, while 'serum albumin level' and 'serum total bilirubin level' were high-ranking factors in the HCV-HCC group. In addition, decision tree analysis demonstrated that 'HCC stage >I' was a distinguishable factor associated with prognosis between patients with non-viral HCC and HCV-HCC. These data suggest that the survival of patients with non-viral HCC may be shorter than that of patients with HCV-HCC because it is difficult to detect non-viral HCC at early stages.

In the present study, Child - Pughclass C, HCC stage ≥III, presence of tumor MVI, and treatment for HCC were independent risk factors for prognosis of patients. Cabibbo *et al* (24), performed a meta-analysis of survival rates in 30 randomized clinical trials of HCC and reported that impaired performance status and Child - Pughclass B or C were independently associated with shorter survival of patients with HCC. In addition, MVI is observed in up to 44% of patients with advanced HCC (25), and MVI of the hepatic and/or portal vein branches in particular is associated with poorer prognosis than HCC without MVI (26). Moreover, treatment strategy for HCC is a well-known independent prognostic factor (27-29). These findings corroborate our results and suggest that the patients enrolled in our study had similar characteristics to those of previous studies. The results of the multivariate analysis were supported by results of random forest analysis and decision-tree analysis. However, there were high intercorrelations among independent variables such as Child-Pugh score and serum levels of albumin and bilirubin in a multiple regression model and we have to be aware that multicollinearity may exist in the multivariate analysis.

We demonstrated that the non-viral HCC is an independent factor associated with survival. Overall survival of patients with non-viral HCV was significantly shorter than that of patients with HCV-HCC. In contrast, Wakiyama et al. reported no significant differences in overall survival after hepatic resection between patients with HCV-HCC and those with non-viral HCC (30). Piscaglia *et al* (31), performed a propensity score analysis and also showed no significant difference in overall survival between patients with nonalcoholic fatty liver disease-related HCC and those with HCV-HCC. In the present study, we performed a stratification analysis and revealed no significant difference in overall survival between HCV-HCC and non-viral HCC in patients treated with hepatic resection, RFA, and TACE. However, in patients treated with HAIC, overall survival was significantly shorter in the non-viral HCC group than in the HCV-HCC group. Moreover, among patients with Child - Pughclass A and B, overall survival was significantly shorter in the non-viral HCC group than in the HCV-HCC group. These data suggest that prognostic factors may differ between patients with non-viral HCC and those with HCV-HCC. To further evaluate this difference, we performed exploratory analyses, namely random forest analysis and decision tree analysis.

To investigate factors that distinguish prognosis between non-viral HCC and HCV-HCC groups, we performed a random forest analysis and a decision tree analysis. Random forest analysis for survival showed that 'number of tumors' and 'HCC stage' were high-ranking factors in the non-viral HCC group, while 'serum albumin level' and 'serum total bilirubin level' were high-ranking factors in the HCV-HCC group. Decision tree analysis with consideration of survival period showed that 'HCC stage >I' was a distinguishing factor associated with the survival period between patients with non-viral HCC and those with HCV-HCC. Thus, both exploratory methods revealed that tumor factors were important for prognosis of patients with non-viral HCC. Followings are 2 possible reasons for the importance of tumor factors in survival of patients with non-viral HCC. First, non-viral HCC is diagnosed at a more advanced stage (32-34). Second, a GALNT14 single nucleotide polymorphism, rs9679162, has been reported to predict chemotherapy response in HCC (35). Specifically, the TT genotype of rs9679162 is less represented among patients with viral HCC than among those with non-viral HCC. Moreover, the TT genotype is significantly more prevalent among Japanese individuals (35). Based on this prognostic factor, early detection of non-viral HCC may prolong survival of patients.

There are several limitations on this study. First, this is not a multicenter prospective study. Second, BMI was not measured in all patients and, therefore, we could not evaluate the impact of BMI on prognosis of patients with non-viral HCC and HCV-HCC. Third, there is a possibility that non-viral HCC patients may include those with positive for hepatitis B core antibody. Fourth, the non-viral HCC group was consisted of several etiologies of liver diseases including alcoholic liver disease and non-alcoholic steatohepatitis. Fifth, for patients with advanced HCC, molecular targeted agents are first line treatment option for advanced cancer. However, in our institution, HAIC was employed as a treatment option for advanced HCC, since beneficial effects of HAIC has been reported (20-23). Thus, a large-scale, long-term, prospective study is required to improve prognosis of patients with non-viral HCC. In addition, the natural course of liver diseases differs depending on the etiology of liver disease. Moreover, sustained virological response (SVR) can be achieved by direct acting antivirals even in HCC patients nowadays. Accordingly, prognostic profile should be analyzed according to each etiology of liver disease including the SVR or non-SVR in the future studies.

In conclusion, we demonstrated that patients with non-viral HCC have poorer prognosis than those with HCV-HCC. Data mining analysis revealed that tumor-related variables were high-ranking prognostic factors in the non-viral HCC group. These data suggest that the prognosis of patients with non-viral HCC may be improved by the early detection of HCC through the identification of high-risk factors.

Acknowledgements

Not applicable.

Funding

The present study was supported by AMED (grant no. JP18fk0210040).

Availability of data and materials

The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YN and TK participated in study conception and design, acquisition of data, interpretation of data, and drafting of manuscript. RK, MN, and NT participated in acquisition of data. SK and AK participated in analysis and interpretation of data. HK and TT participated in study conception and design, and critical revision.

Ethics approval and consent to participate

The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was granted prior approval by the institutional review board of Kurume University. An opt-out approach was used to obtain informed consent from the patients, and personal information was protected during data collection.

Patient consent for publication

Not applicable.

Conflicts of interest

Takumi Kawaguchi received lecture fees from Mitsubishi Tanabe Pharma Corporation, MSD K.K., and Otsuka Pharmaceutical Co., Ltd. The other authors have no conflicts of interest.

References

1. Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M and Negri E: Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol 67: 302-309, 2017.
2. Cazzagon N, Trevisani F, Maddalo G, Giacomin A, Vanin V, Pozzan C, Poggio PD, Rapaccini G, Nolfo AM, Benvegnù L, *et al*; Italian Liver Cancer (ITA.LI.CA) Group: Rise and fall of HCV-related hepatocellular carcinoma in Italy: A long-term survey from the ITA.LI.CA centres. Liver Int 33: 1420-1427, 2013.
3. Taura N, Fukushima N, Yastuhashi H, Takami Y, Seike M, Watanabe H, Mizuta T, Sasaki Y, Nagata K, Tabara A, *et al*: The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased in Kyushu area. Med Sci Monit 17: PH7-PH11, 2011.
4. Marot A, Henrion J, Knebel JF, Moreno C and Deltenre P: Alcoholic liver disease confers a worse prognosis than HCV infection and non-alcoholic fatty liver disease among patients with cirrhosis: An observational study. PLoS One 12: e0186715, 2017.
5. Hamed MA and Ali SA: Non-viral factors contributing to hepatocellular carcinoma. World J Hepatol 5: 311-322, 2013.
6. Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW and Sawicki PT: Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: A cohort study. Diabetologia 52: 1732-1744, 2009.
7. Oda K, Uto H, Mawatari S and Ido A: Clinical features of hepatocellular carcinoma associated with nonalcoholic fatty liver disease: A review of human studies. Clin J Gastroenterol 8: 1-9, 2015.
8. Yamada S, Kawaguchi A, Kawaguchi T, Fukushima N, Kuromatsu R, Sumie S, Takata A, Nakano M, Satani M, Tonan T, *et al*: Serum albumin level is a notable profiling factor for non-B, non-C hepatitis virus-related hepatocellular carcinoma: A data-mining analysis. Hepatol Res 44: 837-845, 2014.
9. Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M and Chevret S: Hepatitis C virus related cirrhosis: Time to occurrence of hepatocellular carcinoma and death. Gut 47: 131-136, 2000.
10. Minami T, Tateishi R, Shiina S, Nakagomi R, Kondo M, Fujiwara N, Mikami S, Sato M, Uchino K, Enooku K, *et al*: Comparison of improved prognosis between hepatitis B- and hepatitis C-related hepatocellular carcinoma. Hepatol Res 45: E99-E107, 2015.
11. Hashimoto M, Tashiro H, Kobayashi T, Kuroda S, Hamaoka M and Ohdan H: Clinical characteristics and prognosis of non-B, non-C hepatocellular carcinoma: The impact of patient sex on disease-free survival - A retrospective cohort study. Int J Surg 39: 206-213, 2017.
12. Hiwatashi K, Ueno S, Sakoda M, Iino S, Minami K, Yamasaki Y, Okubo K, Noda M, Kurahara H, Mataki Y, *et al*: Problems of long survival following surgery in patients with nonBNonC-HCC: Comparison with HBV and HCV related-HCC. J Cancer 6: 438-447, 2015.
13. Radice R, Ramsahai R, Grieve R, Kreif N, Sadique Z and Sekhon JS: Evaluating treatment effectiveness in patient subgroups: A comparison of propensity score methods with an automated matching approach. Int J Biostat 8: 25, 2012.
14. Desbordes P, Ruan S, Modzelewski R, Pineau P, Vauclin S, Gouel P, Michel P, Di Fiore F, Vera P and Gardin I: Predictive value of initial FDG-PET features for treatment response and survival in esophageal cancer patients treated with chemo-radiation therapy using a random forest classifier. PLoS One 12: e0173208, 2017.
15. Diouf M, Filleron T, Pointet AL, Dupont-Gossard AC, Malka D, Artru P, Gauthier M, Lecomte T, Aparicio T, Thirot-Bidault A, *et al*: Prognostic value of health-related quality of life in patients with metastatic pancreatic adenocarcinoma: A random forest methodology. Qual Life Res 25: 1713-1723, 2016.
16. Mohammadzadeh F, Noorkojuri H, Pourhoseingholi MA, Saadat S and Baghestani AR: Predicting the probability of mortality of gastric cancer patients using decision tree. Ir J Med Sci 184: 277-284, 2015.
17. Min KW, Kim DH, Son BK, Kim EK, Ahn SB, Kim SH, Jo YJ, Park YS, Seo J, Oh YH, *et al*: Invasion depth measured in millimeters is a predictor of survival in patients with distal bile duct cancer: Decision tree approach. World J Surg 41: 232-240, 2017.
18. Kokudo N, Hasegawa K, Akahane M, Igaki H, Izumi N, Ichida T, Uemoto S, Kaneko S, Kawasaki S, Ku Y, *et al*: Evidence-based clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res 45: 45, 2015.
19. Liver Cancer Study Group of Japan: The general rules for the clinical and pathological study of primary liver cancer. Jpn J Surg 19: 98-129, 1989.
20. Kawaoka T, Aikata H, Kobayashi T, Uchikawa S, Ohya K, Kodama K, Nishida Y, Daijo K, Osawa M, Teraoka Y, *et al*: Comparison of hepatic arterial infusion chemotherapy between 5-fluorouracil-based continuous infusion chemotherapy and low-dose cisplatin monotherapy for advanced hepatocellular carcinoma. Hepatol Res 48: 1118-1130, 2018.
21. Saeki I, Yamasaki T, Maeda M, Hisanaga T, Iwamoto T, Matsumoto T, Hidaka I, Ishikawa T, Takami T and Sakaida I: Evaluation of the 'assessment for continuous treatment with hepatic arterial infusion chemotherapy' scoring system in patients with advanced hepatocellular carcinoma. Hepatol Res 48: E87-E97, 2018.
22. Tsunematsu S, Suda G, Yamasaki K, Kimura M, Takaaki I, Umemura M, Ito J, Sato F, Nakai M, Sho T, *et al*: Combination of neutrophil-to-lymphocyte ratio and early des-γ-carboxyprothrombin change ratio as a useful predictor of treatment response for hepatic arterial infusion chemotherapy against advanced hepatocellular carcinoma. Hepatol Res 47: 533-541, 2017.

23. Nakano M, Niizeki T, Nagamatsu H, Tanaka M, Kuromatsu R, Satani M, Okamura S, Iwamoto H, Shimose S, Shirono T, *et al*; Kurume Liver Cancer Study Group of Japan: Clinical effects and safety of intra-arterial infusion therapy of cisplatin suspension in lipiodol combined with 5-fluorouracil versus sorafenib, for advanced hepatocellular carcinoma with macroscopic vascular invasion without extra-hepatic spread: A prospective cohort study. Mol Clin Oncol 7: 1013-1020, 2017.
24. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A and Cammà C: A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 51: 1274-1283, 2010.
25. Pirisi M, Avellini C, Fabris C, Scott C, Bardus P, Soardo G, Beltrami CA and Bartoli E: Portal vein thrombosis in hepatocellular carcinoma: Age and sex distribution in an autopsy study. J Cancer Res Clin Oncol 124: 397-400, 1998.
26. Costentin CE, Ferrone CR, Arellano RS, Ganguli S, Hong TS and Zhu AX: Hepatocellular carcinoma with macrovascular invasion: Defining the optimal treatment strategy. Liver Cancer 6: 360-374, 2017.
27. Hasegawa K, Kokudo N, Makuuchi M, Izumi N, Ichida T, Kudo M, Ku Y, Sakamoto M, Nakashima O, Matsui O, *et al*: Comparison of resection and ablation for hepatocellular carcinoma: A cohort study based on a Japanese nationwide survey. J Hepatol 58: 724-729, 2013.
28. Murakami T, Ishimaru H, Sakamoto I, Uetani M, Matsuoka Y, Daikoku M, Honda S, Koshiishi T and Fujimoto T: Percutaneous radiofrequency ablation and transcatheter arterial chemoembolization for hypervascular hepatocellular carcinoma: Rate and risk factors for local recurrence. Cardiovasc Intervent Radiol 30: 696-704, 2007.
29. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, *et al*; Barcelona Liver Cancer Group: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet 359: 1734-1739, 2002.
30. Wakiyama S, Matsumoto M, Haruki K, Gocho T, Sakamoto T, Shiba H, Futagawa Y, Ishida Y and Yanaga K: Clinical features and outcome of surgical patients with non-B non-C hepatocellular carcinoma. Anticancer Res 37: 3207-3213, 2017.
31. Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C and Bellentani S; HCC-NAFLD Italian Study Group: Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. Hepatology 63: 827-838, 2016.
32. Jun TW, Yeh ML, Yang JD, Chen VL, Nguyen P, Giama NH, Huang CF, Hsing AW, Dai CY, Huang JF, *et al*: More advanced disease and worse survival in cryptogenic compared to viral hepatocellular carcinoma. Liver Int 38: 895-902, 2018.
33. Mohsen W, Rodov M, Prakoso E, Charlton B, Bowen DG, Koorey DJ, Shackel NA, McCaughan GW and Strasser SI: Patients with non-viral liver disease have a greater tumor burden and less curative treatment options when diagnosed with hepatocellular carcinoma. World J Gastroenterol 23: 2763-2770, 2017.
34. Kimura T, Kobayashi A, Tanaka N, Sano K, Komatsu M, Fujimori N, Yamazaki T, Shibata S, Ichikawa Y, Joshita S, *et al*: Clinicopathological characteristics of non-B non-C hepatocellular carcinoma without past hepatitis B virus infection. Hepatol Res 47: 405-418, 2017.
35. Liang KH, Yang PC and Yeh CT: Genotyping the GALNT14 gene by joint analysis of two linked single nucleotide polymorphisms using liver tissues for clinical and geographical comparisons. Oncol Lett 8: 2215-2220, 2014.