

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

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**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.

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**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, trans-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  $\alpha$ -fetoprotein (AFP) and des- $\gamma$ -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  $\geq 60$  g/day,  $<60$  g/day,  $>20$  g/day, or  $\leq 20$  g/day' in ethanol amount), history of diabetes mellitus, Child - Pugh score/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, radio-frequency 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 - Pugh Class (A-C).

**Statistical analysis.** Data were expressed as a number, percentage, or mean  $\pm$  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 <sup>4</sup> /mm <sup>3</sup> ) | 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, trans-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.<sup>8</sup> 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.<sup>8</sup> 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 <sup>4</sup> /mm <sup>3</sup> | 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, deci-

sion 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 <sup>4</sup> /mm <sup>3</sup> | 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  $\geq$ 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  $\geq$ 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-

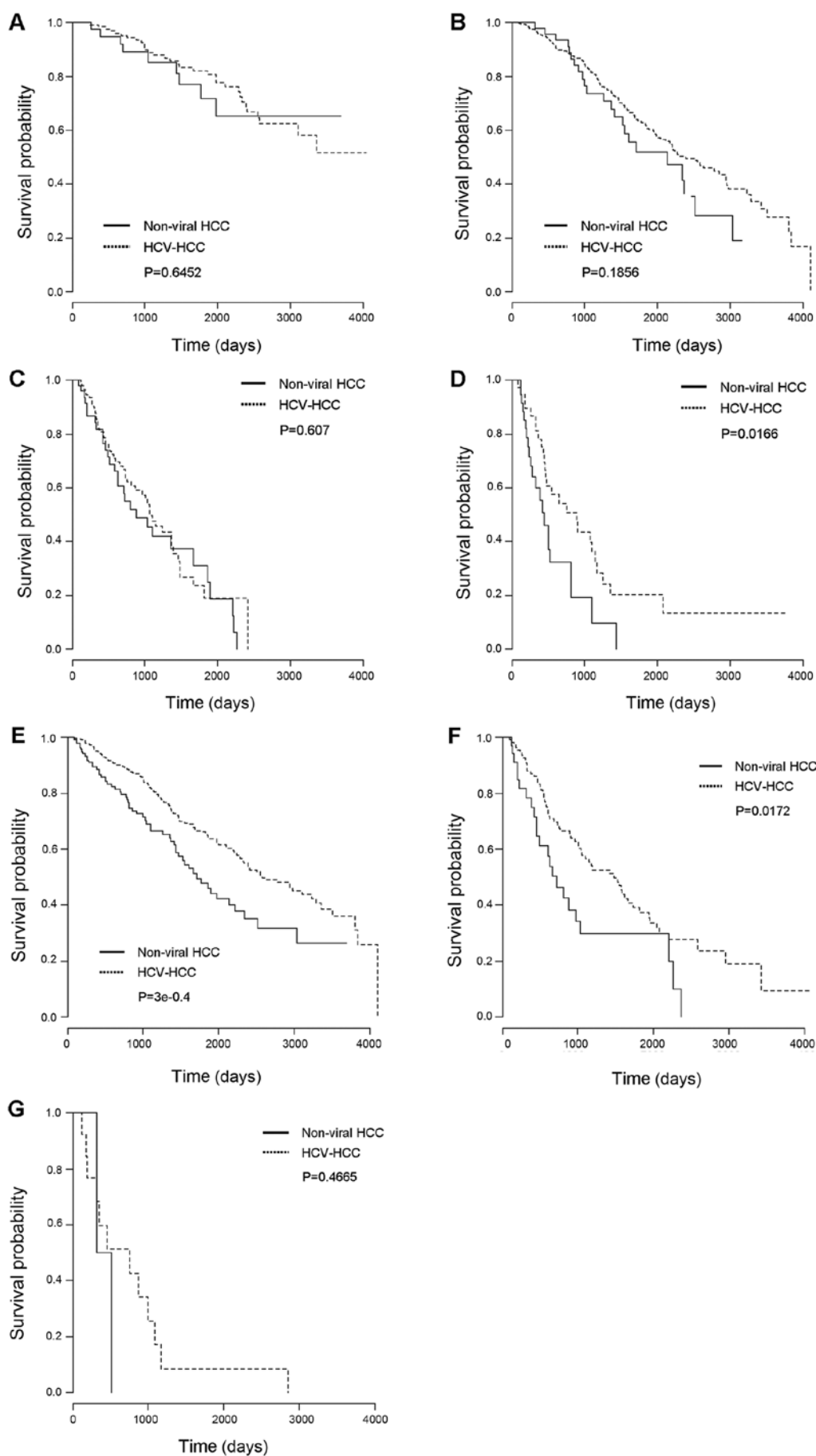


Figure 1. Stratification analysis of survival according to treatment for HCC and Child - Pugh class. (A) Hepatic resection, (B) radiofrequency ablation, (C) transarterial chemoembolization, (D) hepatic arterial infusion chemotherapy, (E) Child - Pugh class A, (F) Child - Pughclass B, and (G) Child - 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<br>(Variable importance)   | Non-viral HCC<br>(Variable importance) | HCV-HCC<br>(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.

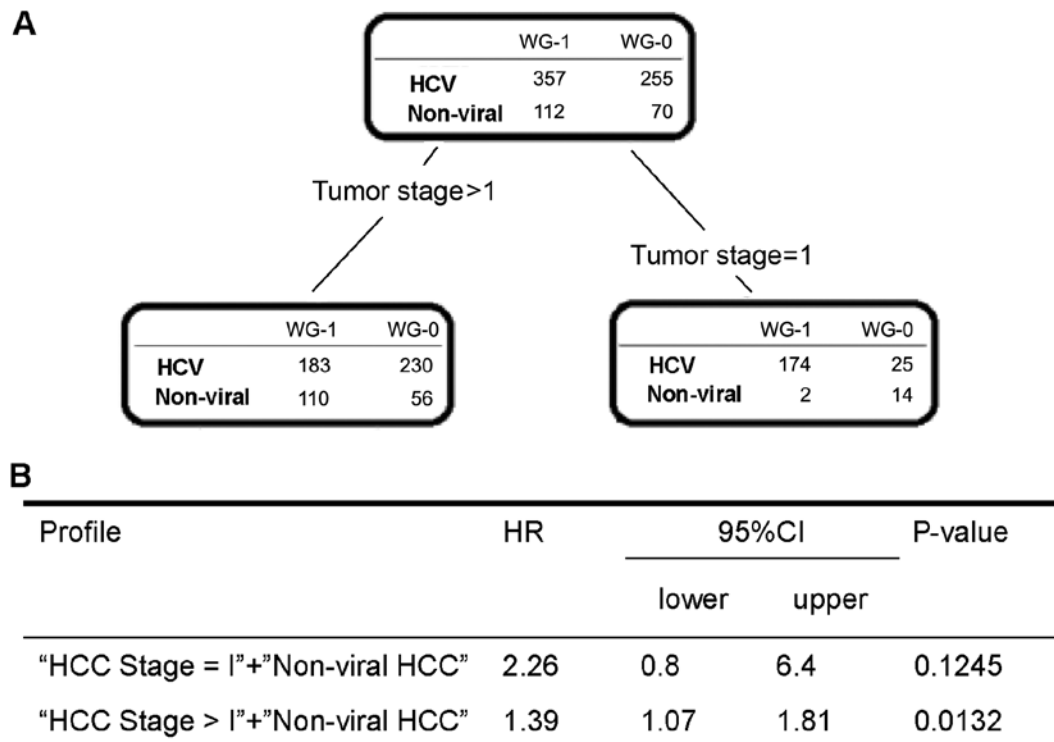


Figure 2. Decision tree analysis for characteristic difference in survival term between hepatitis C virus-related HCC and non-viral HCC. (A) Decision tree for survival term. (B) Hazard ratios for profile based on the decision tree. HCC, hepatocellular carcinoma.

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 - Pugh class C, HCC stage  $\geq$ 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 - Pugh class 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 - Pugh class 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.



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## 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.

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