ORIGINAL ARTICLE

Characteristics of hepatocellular carcinoma in patients with hepatitis C virus who received direct-acting antiviral therapy and achieved sustained virological response: The impact of a hepatologist on surveillance

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Abstract

Background and Aim: The relationship between the characteristics of hepatocellular carcinoma (HCC) diagnosed after sustained virological response (SVR) with direct-acting antiviral (DAA) therapy and surveillance status has not been sufficiently investigated. This study investigated the clinical risk factors for HCC development and HCC characteristics according to which type of physician performed follow-up after SVR.

Methods: A total of 1070 patients in whom hepatitis C virus (HCV) was eradicated with DAA therapy were evaluated.

Results: There were 458 patients followed by hepatologists (specialist group) and 612 followed by non-hepatologists (non-specialist group) after SVR. During the follow-up period, 54 patients developed HCC. The 1-, 2-, 3-, 4-, and 5-year cumulative incidence rates of HCC were 1.8, 4.1, 6.9, 10.5, and 17.2%, respectively. Multivariate Cox proportional hazards analysis showed that male sex (hazard ratio [HR], 3.139; 95% confidence interval [CI], 1.732–5.690), α-fetoprotein level (HR, 1.056; 95% CI, 1.035–1.077), and fibrosis-4 (FIB-4) index (HR, 1.051; 95% CI, 1.017–1.085) were significantly associated with HCC development, while the follow-up physician type after SVR was not. There were 25 patients with stage I HCC, 17 with stage II, 9 with stage III, and 3 with stage IV. Multivariate ordinal logistic regression showed that follow-up physician type (non-specialist) (HR, 39.100; 95% CI, 9.350–224.00) was independently associated with HCC stage, while α-fetoprotein level and FIB-4 index were not.

Conclusion: When patients have more risk factors for HCC development after SVR (i.e., male sex, elevated α-fetoprotein, or elevated FIB-4 index), they should be followed by a hepatologist for HCC surveillance.

Introduction

In 2019, there were 58 million people with hepatitis C virus (HCV) infection worldwide.[1] Chronic HCV infection remains one of the main causes of chronic liver diseases such as cirrhosis and hepatocellular carcinoma (HCC).[2] In Japan, 1–1.5 million people are chronically infected with HCV, and approximately 55% of HCCs are associated with HCV infection.[3]

The primary goal of HCV treatment is to cure the infection, that is, to achieve a sustained virological response (SVR), defined as undetectable HCV RNA after the completion of treatment. Achievement of SVR is generally associated with normalization of hepatic enzyme levels, regression of hepatic necroinflammation and fibrosis, and improvement in hepatic function.[4–6] Several studies have confirmed that patients with HCV who achieve SVR with interferon-based therapy generally have good clinical outcomes.[7–9] However, although the development of HCC is uncommon in this population, sometimes it still occurs.[10–14] Risk factors for HCC development in patients with HCV who achieve SVR include advanced age, male sex, advanced liver fibrosis, high α-fetoprotein level, low albumin level, and type 2 diabetes mellitus.[15–19] Direct-acting antivirals (DAAs) have recently been developed to treat chronic HCV infection. They have higher SVR rates, shorter and simpler therapeutic regimens, and minimal treatment-related side effects relative to interferon-based therapy.[20] The emergence of DAAs to treat HCV will dramatically increase the number of patients who achieve SVR. Given the remarkable increase expected in the number of patients with HCV who will achieve SVR with DAA therapy, the number of patients who develop HCC despite SVR will increase in the near future.

Surveillance for HCC has been recommended for patients with chronic hepatitis B or HCV infection, especially patients with cirrhosis.[21] However, the efficacy and effectiveness of HCC surveillance after SVR with DAA therapy have not been sufficiently investigated. In addition, which type of physician (i.e., hepatologist or non-hepatologist) is appropriate for performing follow-up, including HCC surveillance, in patients after SVR has also not been sufficiently investigated. Several studies have confirmed that patients with HCV who achieve SVR with DAA therapy have a lower incidence of HCC.[22–24] However, there are insufficient investigations on the relationship between the characteristics of HCC diagnosed after SVR and surveillance status in patients with HCV who achieve SVR with DAA therapy.

In this study, we investigated the clinical risk factors for HCC development in patients with HCV who received DAA therapy and achieved SVR. In addition, we investigated the characteristics of HCC diagnosed after SVR based on which type of physician performed follow-up.

Materials and methods

Patients. A total of 1347 patients with HCV received DAA therapy at the Japanese Red Cross Society Himeji Hospital and the Himeji St. Mary's Hospital between October 2014 and March 2020. Of these, 1070 met the following eligibility criteria and were enrolled in this study: (i) achieved SVR; (ii) no history of HCC at the start of DAA therapy; (iii) no evidence of HCC development at least 6 months after SVR; (iv) no co-infection with human immunodeficiency virus or hepatitis B virus; (v) no other cause of chronic liver disease (alcohol consumption more than 80 g/day,[25] hepatotoxic drugs, autoimmune hepatitis, primary biliary cholangitis, hemochromatosis, and Wilson's disease); and (vi) no missing clinical data (Fig. 1).

The date of SVR (baseline) was defined as the start of follow-up. The end of follow-up was defined as the date of the final visit for patients who had not developed HCC and as the date of HCC diagnosis for patients who developed HCC during follow-up.

Located in the Naka-Harima area (population 580 000), the Japanese Red Cross Society Himeji Hospital and the Himeji St. Mary's Hospital are major hospitals for liver diseases in Hyogo Prefecture and treat 85% of patients with HCC in the Naka-Harima area and employ approximately 10 hepatologists.[26]
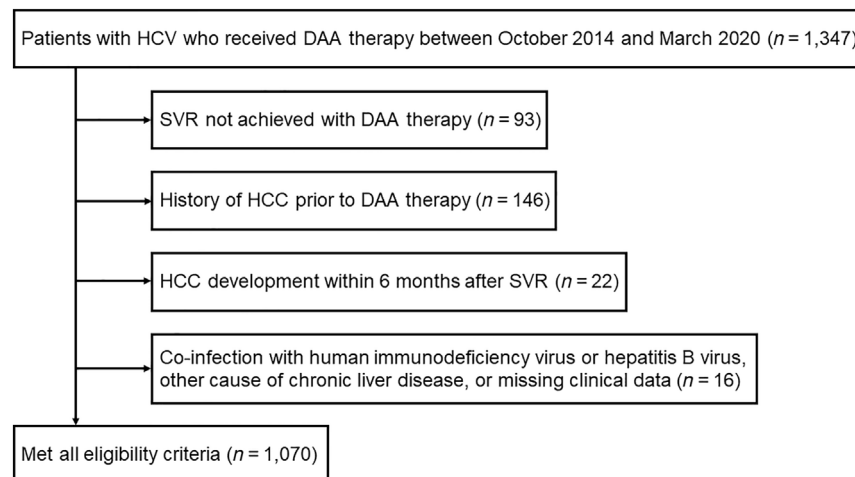

Figure 1 Flowchart of the patient selection process. DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response.

Therefore, many patients with liver diseases including chronic HCV infection and HCC receive outpatient care at these hospitals. In addition, there is also close contact, including consultation of the patient when HCC develops, between general outpatient clinics and our hospitals.

The study protocol complied with the Helsinki Declaration and was approved by the institutional review board (#2021-02) of the Japanese Red Cross Society Himeji Hospital. Before the start of the study, written informed consent was obtained from all patients for use of their laboratory data.

Clinical and laboratory data. Patients' age, sex, height, weight, recumbent blood pressure at rest, smoking status, and daily alcohol consumption at baseline were recorded. Fasting blood counts and biochemistry tests were conducted using standard methods.

We used the fibrosis-4 (FIB-4) index as a marker of liver fibrosis. This index was calculated as aspartate aminotransferase (IU/L) $\times$ age (years)/platelet count ($\times 10^9$/L) $\times$ alanine aminotransferase (IU/L) $^{1/2}$. As previously reported, it has utility in diagnosing liver fibrosis in patients with HCV.[27]

Treatment. At baseline, HCV infection was confirmed by both positive serum HCV antibody titers (ARCHITECT Anti-HCV; Abbott Laboratories, Abbott Park, IL, USA) and serum HCV RNA using a real-time PCR–based method (COBAS AmpliPrep or COBAS TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, USA; lower limit of detection, 1.2 $\log_{10}$IU/mL). At our hospitals, DAA therapy indications and regimens for each patient were determined by hepatologists according to the guidelines of the Japan Society of Hepatology.[28]

All patients in this study were treated with DAAs prescribed by hepatologists. Patients were asked to visit the outpatient clinic of hepatologists in our hospitals for treatment and adverse effect monitoring every 2–4 weeks throughout the treatment period. Laboratory data were collected before the start of therapy, every 2–4 weeks thereafter, at the end of treatment, and 12 weeks after treatment cessation. Serum HCV RNA levels were measured at baseline, end of treatment, and 12 weeks after treatment cessation using a real-time PCR–based method. SVR was confirmed by the absence of serum HCV RNA at 12 weeks after the end of treatment.

HCC surveillance and diagnosis. HCC surveillance was conducted every 3–6 months via imaging examinations and blood tests, including measurement of the tumor marker α-fetoprotein, according to the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan.[21] The diagnosis of HCC was based on imaging characteristics specified in the American Association for the Study of Liver Diseases guidelines.[29] Tumor node metastasis (TNM) staging according to the sixth edition of TNM staging for HCC by the Liver Cancer Study Group of Japan (LCSGJ) (TNM-LCSGJ) was used to evaluate tumor progression.[30]

Definition of hepatologist and non-hepatologist. We defined hepatologists as physicians certified by the Japan Society of Hepatology.[31] In this study, there were hepatologists in our hospitals as well as several hepatologists who work in general outpatient clinics who performed HCC surveillance for patients with HCV who achieved SVR with DAA therapy. Conversely, in this study, there were many non-hepatologists who worked in general outpatient clinics who were requested by hepatologists at our hospitals to continue medical care for chronic diseases such as hypertension and diabetes and perform HCC surveillance after SVR for patients who achieved HCV elimination with DAA therapy. The decision on whether or not to request continued medical care by family doctors (non-hepatologists) was made with discussions between the hepatologists at our hospitals and the patients. If patients who achieved SVR opted for continued care with their family doctor (non-hepatologists), the hospital hepatologist provided the family doctor with medical information, including information on HCC surveillance after SVR. If patients who achieved SVR opted to continue care with hepatologists at our hospitals, those hepatologists provided HCC surveillance for their patients. The hepatologist who had been the main provider of DAA treatment for the patients under study had already retired.

Statistical analysis. Continuous variables are expressed as medians (interquartile range). The Mann–Whitney U test was used to compare continuous variables. The chi-square test or Fisher's exact test was used for categorical variables.

Actuarial analysis of cumulative HCC incidence was performed using the Kaplan–Meier method. A multivariate Cox proportional hazards model was used to analyze the incidence of HCC. In addition, multivariate ordinal logistic regression was used to analyze the factors associated with HCC stage at the time of initial HCC diagnosis. The variance inflation factor (VIF) was used to assess for multicollinearity in multivariate ordinal logistic regression models. VIF > 10 was defined as serious multicollinearity. VIF > 4 was considered a cause for concern.[32]

Statistical significance was defined as P <0.05. Statistical analyses were performed with EZR, version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[33] More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics. The baseline characteristics of the 1070 patients are shown in Table 1. The patients included 635 (59.3%) females and 435 (40.7%) males, with a median age of 69.5 (60.7–76.4) years. The median α-fetoprotein level and FIB-4 index were 3.6 (2.2–5.8) ng/mL and 2.37 (1.64–3.46), respectively. Median follow-up was 15.9 (3.5–41.9) months. During the follow-up period, 54 (5.0%) patients developed HCC. After SVR, 458 (42.8%) and 612 (57.2%) patients were followed by hepatologists (specialist group) and non-hepatologists (non-specialist group), respectively. There were 397, 297, 178, 88, 51, 50, and 9 patients who received ledipasvir–sofosbuvir, daclatasvir + asunaprevir, sofosbuvir + ribavirin, glecaprevir–pibrentasvir, elbasvir + grazoprevir, ombitasvir–paritaprevir–ritonavir, and daclatasvir–asunaprevir–beclabuvir as DAA therapy.

The baseline characteristics of the study patients stratified by type of physician who followed them after SVR are summarized in Table 1. Age, HCV genotype, and FIB-4 index were

Table 1 Patient characteristics (*N* = 1070)

	Overall (*N* = 1070)	Specialist group (*N* = 458)	Non-specialist group (*N* = 612)	*P*-value
Institution (Japanese Red Cross Society Himeji Hospital/ Himeji St. Mary's Hospital)	965/105	368/90	597/15	<0.001
Age (years)[†]	69.5 (60.7–76.4)	68.5 (59.2–75.2)	70.3 (61.7–66.0)	0.003
Sex (female/male)	635/435	270/188	365/247	0.850
Drinking alcohol (yes/no)	31/1039	23/435	8/604	0.001
Fatty liver by imaging (yes/no)	80/990	34/424	46/566	1.000
Aspartate aminotransferase (IU/L)[†]	23 (19–30)	23 (19–30)	23 (19–30)	0.183
Alanine aminotransferase (IU/L)[†]	17 (12–25)	16 (12–24)	17 (13–25)	0.220
Albumin (g/dL)[†]	4.1 (3.9–4.4)	4.1 (3.9–4.4)	4.1 (3.9–4.4)	0.855
Total bilirubin (mg/dL)[†]	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.311
Platelet count ($\times 10^4$/mm^3)[†]	17.0 (13.2–21.4)	17.0 (13.7–21.7)	17.0 (13.0–21.2)	0.242
α-Fetoprotein (ng/mL)[†]	3.6 (2.2–5.8)	3.7 (2.3–5.7)	3.6 (2.2–6.0)	0.960
FIB-4 index[†]	2.37 (1.64–3.46)	2.25 (1.54–3.32)	2.43 (1.77–3.54)	0.037
HCV genotype (1/2/other)	788/269/13	341/107/10	447/162/3	0.028
Development of HCC	54	30	24	0.066
Follow-up duration (months)[†]	15.9 (3.5–41.9)	29.1 (3.7–47.4)	7.0 (3.5–35.9)	<0.001

[†]Values are expressed as medians (interquartile range).
FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

significantly different between the specialist and non-specialist groups.

Cumulative incidence of HCC. Figure 2 shows the Kaplan–Meier curve for the cumulative incidence of HCC in all study patients. The 1-, 2-, 3-, 4-, and 5-year cumulative incidence rates of HCC were 1.8, 4.1, 6.9, 10.5, and 17.2%, respectively.

Multivariate analysis of HCC incidence. Multivariate Cox proportional hazards models, which included the covariates of sex, α-fetoprotein level, FIB-4 index, and follow-up physician type, showed that male sex (hazard ratio [HR], 3.139; 95% confidence interval [CI], 1.732–5.690), α-fetoprotein (per 1 ng/mL) (HR, 1.056; 95% CI, 1.035–1.077), and FIB-4 index (per 1 unit) (HR, 1.051; 95% CI, 1.017–1.085) were independently associated with HCC incidence (Table 2).
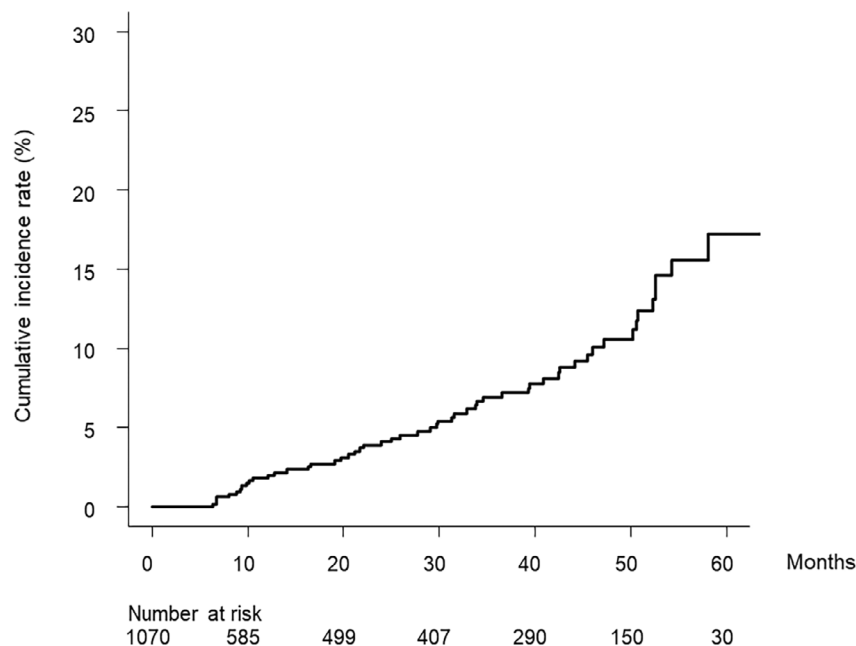

Figure 2 Cumulative incidence of HCC. The 1-, 2-, 3-, 4-, and 5-year cumulative incidence rates of HCC were 1.8, 4.1, 6.9, 10.5, and 17.2%, respectively. HCC, hepatocellular carcinoma.

Table 2 Multivariate analysis of HCC incidence

	HR	95% CI	*P*-value
Sex (male)	3.139	1.732–5.690	<0.001
α-fetoprotein (per 1 ng/mL)	1.056	1.035–1.077	<0.001
FIB-4 index (per 1 unit)	1.051	1.017–1.085	0.003
Follow-up physician type (non-specialist)	1.044	0.591–1.843	0.882

CI, confidence interval; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HR, hazard ratio.

Table 3 Baseline characteristics of patients who developed HCC (*N* = 54)

	Overall (*N* = 54)	Specialist group (*N* = 30)	Non-specialist group (*N* = 24)	*P*-value
Institution (Japanese Red Cross Society Himeji Hospital/ Himeji St. Mary's Hospital)	49/5	25/5	24/0	0.059
Age (years)[†]	72.9 (67.2–79.0)	74.4 (71.3–79.1)	70.3 (61.7–66.0)	0.280
Sex (female/male)	21/33	11/19	10/14	0.783
Aspartate aminotransferase (IU/L)[†]	30 (25–45)	31 (25–50)	29 (25–44)	0.629
Alanine aminotransferase (IU/L)[†]	20 (15–29)	19 (15–30)	20 (17–28)	0.775
Albumin (g/dL)[†]	3.9 (3.5–4.1)	3.7 (3.5–4.0)	4.0 (3.7–4.3)	0.107
Total bilirubin (mg/dL)[†]	0.9 (0.7–1.2)	0.9 (0.7–1.4)	0.9 (0.7–1.2)	0.990
Platelet count ($\times 10^4$/mm^3)[†]	13.5 (11.2–16.1)	13.0 (11.3–15.6)	14.1 (9.4–17.2)	0.844
α-Fetoprotein (ng/mL)[†]	7.1 (4.2–11.0)	7.6 (3.7–9.5)	6.2 (4.6–12.3)	0.646
FIB-4 index[†]	3.86 (2.79–5.20)	4.23 (3.25–5.20)	3.55 (2.49–5.32)	0.421
HCV genotype (1/2)	41/13	22/8	19/5	0.753
Modalities or triggers at the time of HCC diagnosis				0.001
Ultrasonography	36	25	11	
Computed tomography	6	2	4	
Magnetic resonance imaging	2	2	0	
Tumor marker	10	1	9	

[†]Values are expressed as medians (interquartile range).

FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

Characteristics of patients who developed HCC. The baseline characteristics of the 54 patients who developed HCC during follow-up are shown in Table 3. The patients included 21 (38.9%) females and 33 (61.1%) males, with a median age of 72.9 (67.2–79.0) years. The median α-fetoprotein level and FIB-4 index were 7.1 (4.2–11.0) ng/mL and 3.86 (2.79–5.20), respectively. After SVR, 30 (55.6%) and 24 (44.4%) patients were followed by hepatologists (specialist group) and non-hepatologists (non-specialist group), respectively.

The baseline characteristics of patients who developed HCC stratified by follow-up physician type after SVR are summarized in Table 3. No clinical factors were significantly different between the specialist and non-specialist groups.

HCC characteristics and treatment. The characteristics and treatment of initial HCC are shown in Table 4. The median tumor size was 19.5 (14.0–31.8) mm. Forty-five (83.3%) patients had a single tumor, while 9 (16.7%) patients had multiple tumors. There were 25 (46.3%) patients with stage I HCC, 17 (31.5%) patients with stage II, 9 (16.7%) patients with stage

III, and 3 (5.6%) patients with stage IV. Regarding initial treatment for HCC, 19 (35.2%) patients underwent surgical resection, 26 patients (48.1%) underwent local ablation therapy, 7 (13.0%) patients underwent transarterial chemoembolization, 1 (1.9%) patient underwent radiation therapy, and 1 (1.9%) patient received best supportive care.

The characteristics and treatment of these HCCs stratified by follow-up physician type after SVR are summarized in Table 4. Tumor size, macroscopic vascular invasion, HCC stage, and initial treatment were significantly different between the specialist and non-specialist groups.

Multivariate ordinal logistic regression analysis for HCC stage. Multivariate ordinal logistic regression, which included the covariates of α-fetoprotein level, FIB-4 index, and follow-up physician type, showed that physician type (non-specialist group) (HR, 39.100) was independently associated with HCC stage (Table 5). VIF for α-fetoprotein, FIB-4 index, and follow-up physician type were 1.642, 3.942, and 1.964, respectively.

Table 4 HCC characteristics (N = 54)

	Overall (N = 54)	Specialist group (N = 30)	Non-specialist group (N = 24)	P-value
Tumor size (mm)[†]	19.5 (14.0–31.8)	16.0 (11.3–18.8)	36.5 (26.8–50.0)	<0.001
Number of tumors (single/multiple)	45/9	27/3	18/6	0.165
Macroscopic vascular invasion (yes/no)	9/45	1/29	8/16	0.007
Extrahepatic spread (yes/no)	1/53	1/29	0/24	1.000
TNM LCSGJ 6th edition (I/II/III/IV)	25/17/9/3	22/8/0/0	3/9/9/3	<0.001
HCC treatment				<0.001
Surgical resection	19	6	13	
Local ablation therapy	26	22	4	
Transarterial chemoembolization	7	2	5	
Radiation therapy	1	0	1	
Best supportive care	1	0	1	

[†]Values are expressed as medians (interquartile range).
HCC, hepatocellular carcinoma; TNM LCSGJ 6th edition: tumor node metastasis stage according to the sixth edition of the Liver Cancer Study Group of Japan guidelines.

Table 5 Multivariate analysis of HCC stage

	HR	95% CI	P value
α-fetoprotein (per 1 ng/mL)	1.000	0.948–1.070	0.944
FIB-4 index (per 1 unit)	0.974	0.903–1.050	0.458
Follow-up physician type (non-specialist)	39.100	9.350–224.00	<0.001

CI, confidence interval; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HR, hazard ratio.

Discussion

In this study, the incidence of HCC was approximately 7% at 3 years and 17% at 5 years after SVR in patients with HCV who received DAA therapy. In multivariate analysis, male sex, α-fetoprotein level, and FIB-4 index were associated with a higher incidence of HCC in patients with HCV who achieved SVR with DAA therapy. Conversely, follow-up physician type, that is, hepatologist (specialist group) or non-hepatologist (non-specialist group), was not associated with incident HCC. In the analysis of the characteristics of HCCs diagnosed after SVR, tumor size, macroscopic vascular invasion, HCC stage, and initial treatment were significantly different between the specialist and non-specialist groups. In other words, patients followed by non-specialists had larger tumors, more macroscopic vascular invasion, and more advanced tumor stage at the time of HCC diagnosis than patients followed for by specialists. Furthermore, multivariate ordinal logistic regression analysis for HCC stage showed that follow-up physician type was significantly associated with HCC stage. Namely, patients followed by non-specialists had significantly more advanced HCC stage at diagnosis than those followed by specialists after SVR. These results suggest that follow-up that includes HCC surveillance after SVR by a hepatologist might be better for early diagnosis of HCC than follow-up by a non-hepatologist.

Clinical factors such as age, sex, platelet count, type 2 diabetes mellitus status, as well as levels of total bilirubin, albumin, α-fetoprotein, and mac2 binding protein glycosylation isomer have been confirmed as indicators of HCC development in patients with HCV who have achieved SVR with DAA therapy.[28]

In addition, ultrasound elastography and FIB-4 index, which are validated as indicators of liver fibrosis in many studies of patients with chronic liver disease, have been reported as indicators of HCC development in patients with HCV who had achieved SVR with DAA therapy.[28,34,35] Watanabe *et al.*[36] investigated the predictors of HCC development in 1174 patients with HCV who had achieved SVR with DAA therapy. They found that male sex (HR, 2.46), post-treatment α-fetoprotein (per 1 ng/mL) (HR, 1.11), and post-treatment FIB-4 index (per 1 unit) (HR, 1.09) are independent predictors of HCC development after DAA therapy in a multivariate analysis.[36] Hiraoka *et al.*[37] developed the after-DAA recommendation for surveillance (ADRES) score as a composite model using clinical factors in 1069 patients with HCV who had received DAA therapy and achieved SVR. The ADRES score can be used to predict the risk of HCC in patients after SVR with DAA therapy. In addition, this score was validated as being useful in predicting HCC development in a larger number of patients after SVR with DAA therapy.[38] The ADRES score is based on sex, FIB-4 index, and α-fetoprotein level upon achieving SVR.[37,38] In this study, we also found that male sex, elevated AFP level, and elevated FIB-4 index are risk factors for HCC development in patients after SVR with DAA therapy. Therefore, patients with such risk factors should receive closer surveillance for HCC even after SVR.

Toyoda *et al.*[39] investigated the characteristics of HCC diagnosed after SVR with interferon-based antiviral therapy for chronic HCV infection, namely the eradication of HCV, according to surveillance status after SVR. They found that in patients who did not undergo surveillance after SVR, HCC was significantly more advanced at diagnosis, with tumors that were

larger and of higher stage than in patients who underwent surveillance after SVR.[39] In this study, we clarified that HCC was diagnosed at an earlier stage in patients followed by hepatologists than in those followed by non-hepatologists after SVR. The strength of our study is that we clarified that the stage at the time of HCC diagnosis was significantly different according to follow-up physician type, in patients who achieved SVR with DAA, which is the mainstay of HCV treatment in recent years. Another strength of our study is that our hospitals treat approximately 85% of patients with HCC in communities with populations of 500 000 or more, which means that this investigation was conducted in a community-based setting.

The most important points in this study are the differences in both the knowledge of the specialists and the quality of imaging examinations in the follow-up after SVR. Specialists are often located in liver disease centers, where they are more likely to perform a close examination using high-quality modalities such as high-performance ultrasonic equipment, dynamic computed tomography, or magnetic resonance imaging based on their advanced knowledge of HCC development after SVR.

The main limitations of this study include its retrospective nature and the relatively small number of patients. Further prospective studies with a larger number of patients are warranted. In addition, the median follow-up duration in this study was only approximately 16 months. This may be due to the fact that the follow-up period of patients followed by the non-specialist group depended only on whether HCC developed. Studies with longer term follow-up for all study patients should be performed in the future. Further, choice of the physician type was not random. It could be that patients who chose non-specialist follow-up after SVR were different in some other ways that affected the results. Finally, we have not been able to show overall survival rates for this study patients, especially divided into specialist and non-specialist follow-up. Further studies that include the analysis of overall survival in similar cohorts of this study are warranted.

In conclusion, even in patients with HCV who achieved SVR with DAA therapy, those with particularly high risk of HCC development (i.e., male sex, elevated α-fetoprotein level, or elevated FIB-4 index) should be followed by a hepatologist for HCC surveillance. Further studies should be conducted to confirm these findings in other populations.

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