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ORIGINAL ARTICLE

Direct-acting antiviral agents do not increase the incidence of hepatocellular carcinoma development: a prospective, multicenter study

Tatsuya Ide[1] · Hironori Koga[1] · Masahito Nakano[1] · Satoru Hashimoto[2] · Hiroshi Yatsuhashi[2] · Nobito Higuchi[3] · Makoto Nakamuta[3] · Satoshi Oeda[4] · Yuichiro Eguchi[4] · Satoshi Shakado[5] · Shotaro Sakisaka[5] · Yoko Yoshimaru[6] · Yutaka Sasaki[6] · Yuichi Honma[7] · Masaru Harada[7] · Masataka Seike[8] · Tatsuji Maeshiro[9] · Satoshi Miuma[10] · Kazuhiko Nakao[10] · Seiichi Mawatari[11] · Akio Ido[11] · Kenji Nagata[12] · Shuichi Matsumoto[13] · Yuko Takami[14] · Tetsuo Sohda[15] · Tatsuyuki Kakuma[16] · Takuji Torimura[1]

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Abstract

Background While achieving sustained virological response (SVR) following interferon-based or direct-acting antiviral agent (DAA) treatments reduces the incidence of hepatocellular carcinoma (HCC), an increase in unexpected early occurrence or recurrence of HCC after hepatitis C virus elimination by DAA treatments has been reported. We prospectively investigated the incidence and risk factors of HCC after DAA treatment in a large multicenter cohort in Japan.

Methods Patients with chronic hepatitis C with or without cirrhosis who were treated with DAAs and obtained SVR were enrolled. DAAs were administered for 3 or 6 months. A total of 2552 patients were enrolled.

Results Of these, 70 patients (2.7%) developed HCC. The 12-, 24-, and 36-month cumulative HCC incidences were 1.3%, 2.9%, and 4.9% in all patients; 2.5%, 5.2%, and 10.0% in those with cirrhosis; and 0.9%, 2.1%, and 2.9% in those without cirrhosis, respectively. Multivariate analysis revealed age, sex, gamma-glutamyl transpeptidase level, and fibrosis-4 index to be independent factors associated with HCC. Patients with these four factors had an approximately six-to-sevenfold increased risk for HCC development. Five patients with large and early tumor occurrence did not receive contrast imaging examinations before treatment.

Conclusion Although the results of our prospective study suggested that achieving SVR by DAA treatment reduces the incidence of HCC, HCC development still occurs. Careful follow-up is important in patients with risk factors.

Keywords Hepatitis C virus · Sustained virological response · Fibrosis-4 (FIB-4) index · Hepatocarcinogenesis

Abbreviations

HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
DAA	Direct-acting antiviral
SVR	Sustained virological response
IFN	Interferon
AFP	Alpha-fetoprotein
ASV	Asunaprevir
DCV	Daclatasvir
SOF	Sofosbuvir
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGTP	Gamma-glutamyl transpeptidase
FIB-4	Fibrosis-4
APRI	AST to platelet count ratio index
AUC	Area under the curve
ROC	Receiver-operating characteristics
US	Ultrasonography
CT	Computed tomography
MRI	Magnetic resonance imaging
Vp	Tumor thrombus of the portal vein

✉ Hironori Koga
hirokoga@med.kurume-u.ac.jp

Extended author information available on the last page of the article

Introduction

Chronic hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) [1]. Interferon (IFN)-based regimens have been standard care for HCV treatment for over two decades, and offer a reduced risk of contracting HCC [2]. Recently, IFN-free direct-acting antiviral agents (DAAs) have been developed, resulting in high rates of sustained virological response (SVR) in patients with HCV-associated chronic liver diseases with fewer adverse effects [3–5]. Thus, these agents have brought about significant benefits for patients.

Risk factors for HCC development include older age, advanced liver fibrosis, male sex, high levels of post-IFN alpha-fetoprotein (AFP), glucose metabolism disorders, lipid metabolism disorders, and excessive alcohol intake. [2] Japan has become an aging society, in which older HCV-infected patients could be candidates for DAA treatments.

The risk of HCC is expected to decrease in the near future. Indeed, it has recently been reported that the HCV SVR induced by DAA treatment reduced the incidence of HCC [6]; however, increases in unexpected early occurrence or recurrence of HCC after HCV elimination by DAAs have also been reported [7–9]. Therefore, it is important to clarify whether DAAs have a favorable effect on suppressing the development of HCC. We prospectively investigated the incidence and risk factors for HCC development after DAA therapy in a large multicenter cohort in the Kyushu area of Japan using a Cox proportional hazard model.

Patients and methods

Patient eligibility

In this cohort study, we analyzed data from chronic hepatitis C patients with or without cirrhosis who were treated with DAAs and achieved a SVR at 12 weeks (SVR12) between January 1, 2015, and January 31, 2017. SVR12 was confirmed by the absence of serum HCV-RNA 12 weeks after the end of treatment. Once SVR12 was achieved, the patients were followed up prospectively. Patients were excluded if they had HCC prior to DAA treatment, hepatitis B virus surface antigen, or other forms of liver diseases. Among abdominal imaging tests such as ultrasonography (US), contrast computed tomography (CT), and contrast magnetic resonance imaging (MRI), at least US was required as an instrumental test to assess HCC development at the time of patient enrollment. Contrast CT or contrast MRI was not mandatory for patients before DAA therapy, because our primary goal was to obtain "real-world" data from reliable core hospitals reflecting typical clinical practice in hepatology. Diagnosis of liver cirrhosis was comprehensively made based on not only high FIB-4 index but also other factors, including biochemical test results, imaging findings, and physical findings of the patients on a case-by-case basis.

DAA therapy

DAA therapy was administered at 15 institutions. The attending physicians in all institutions were Board Certified Hepatologists of the Japan Society of Hepatology. The DAA regimens included asunaprevir (ASV) plus daclatasvir (DCV) for 24 weeks, sofosbuvir (SOF)/ledipasvir for 12 weeks, SOF plus ribavirin for 12 weeks, or paritaprevir/ombitasvir/ritonavir for 12 weeks. The main outcome was HCC occurrence. The endpoint was the date when HCC was diagnosed in patients who developed HCC, or the date when the lack of HCC was confirmed at the last follow-up. The period of observation was defined as the time from the DAA treatment initiation to the endpoint.

Laboratory

The results of routine tests for platelet count, liver biochemical parameters [aspartate aminotransferase (AST); alanine aminotransferase (ALT); gamma-glutamyl transpeptidase (GGTP)] and AFP before DAA treatment were collected. The fibrosis-4 (FIB-4) index [10] was calculated as the AST [IU/L] × age [years]/platelet count [10^9/L] × ALT [IU/L]$^{1/2}$, while the AST to platelet count ratio index (APRI) [11] was calculated as AST [IU/L] (/upper limit of normal AST [IU/L]) × 100/platelet count (10^9/L). If a patient had idiopathic thrombocytopenic purpura or other forms of hematological disorder, the platelet count, FIB-4 index, and APRI score were excluded from the data. All patients had HCV genotype (serotype) 1 or 2 infections. The attending physician clinically diagnosed the presence of cirrhosis. Habitual alcohol intake was defined as an average daily consumption of >75 g of ethanol. Patients with a bright liver, deep attenuation, and hepatorenal contrast on abdominal US were diagnosed with fatty liver. A diagnosis of diabetes mellitus was made in accordance with the diagnostic criteria established by the Japan Diabetes Society [12].

Registration of the study

This study has been registered in the UMIN Clinical Trials Registry (Trial ID: UMIN000027988).

Statistical analysis

A Cox proportional hazard regression model was used to estimate the hazard ratios for risk factors. The cumulative incidence curve was determined using the Kaplan–Meier method and differences between groups were assessed by log-rank tests. The area under the curve (AUC) was calculated using receiver–operating characteristics (ROC) analysis and an attempt was made to derive a suitable clinical cut-off that would best predict the risk of HCC. For all methods, the level of significance was set at $p < 0.05$. All statistical analyzes were performed using JMP pro 13 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 2553 patients were enrolled. However, one patient was excluded because the patient had undergone a living donor liver transplantation before DAA treatment. Thus, 2552 patients were included in this study. A summary of the baseline characteristics of the cohort is provided in Table 1. The mean follow-up period was 22.6 ± 8.3 months.

Incidence of HCC

Among 2552 patients, 70 patients (2.7%) developed HCC. The 12-, 24-, and 36-month cumulative HCC incidence was 1.3%, 2.9%, and 4.9%, respectively (Fig. 1). Table 2 shows

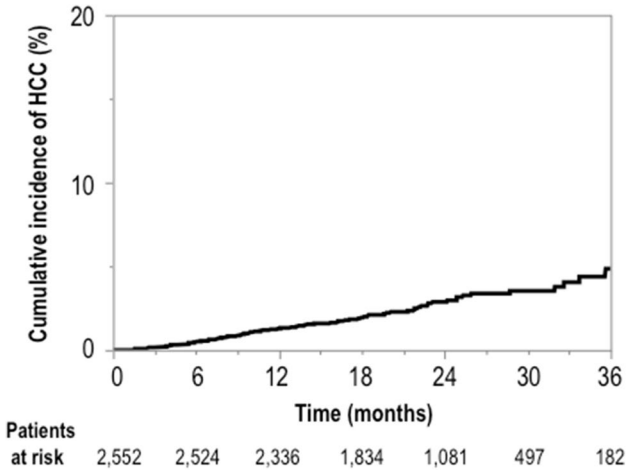

Fig. 1 Cumulative incidence of HCC in all patients

Table 1 Baseline characteristics of all patients

Number of patients	255	
Age years (range)	64.6 ± 11.9 (20–92)	
Sex, male/female	1003/1549	
AST (IU/L)	51.0 ± 35.6	(n = 2552)
ALT (IU/L)	51.8 ± 45.5	(n = 2552)
GGTP (IU/L)	46.9 ± 61.6	(n = 2537)
Platelet count (×10^4/μL)	15.7 ± 6.2	(n = 2545)
AFP (ng/mL)	10.0 ± 23.1	(n = 2448)
APRI	1.44 ± 1.55	(n = 2544)
FIB-4 index	3.86 ± 3.22	(n = 2544)
Geno (sero) type (1/2/1+2)	1992/556/4	
Habitual alcohol intake (presence/absence/unknown)	304/1961/287	
Diabetes mellitus (presence/absence/unknown)	508/2035/9	
Fatty liver (presence/absence/unknown)	531/1809/212	
Cirrhosis (presence/absence)	648/1904	

Results are expressed as the mean standard deviation

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *GGTP* gamma-glutamyl transpeptidase, *AFP* a-fetoprotein, *APRI* aspartate aminotransferase to platelet count ratio index, *FIB-4 index* Fibrosis-4 index

Table 2 Baseline characteristics of patients who developed HCC

Number of patients	70	
Age (years) (range)	69.7 ± 8.5 (48–85)	
Sex, male / female	41/29	
AST (IU/L)	73.6 ± 52.9	(n = 70)
ALT (IU/L)	68.2 ± 55.3	(n = 70)
GGTP (IU/L)	86.0 ± 153.5	(n = 68)
Platelet count (×10^4/μL)	11.8 ± 6.0	(n = 70)
AFP (ng/mL)	20.6 ± 26.3	(n = 67)
APRI	2.89 ± 2.7	(n = 70)
FIB-4 index	7.11 ± 5.3	(n = 70)
Geno (sero) type (1 / 2 / 1 + 2)	61/9/0	
Habitual alcohol intake (presence / absence / unknown)	13/57/0	
Diabetes mellitus (presence / absence / unknown)	23/47/0	
Fatty liver (presence / absence / unknown)	11/53/6	
Cirrhosis (presence / absence)	35/35	

Results are expressed as the mean ± standard deviation

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *GGTP* gamma-glutamyl transpeptidase, *AFP* a-fetoprotein, *APRI* aspartate aminotransferase to platelet count ratio index, *FIB-4 index* Fibrosis-4 index

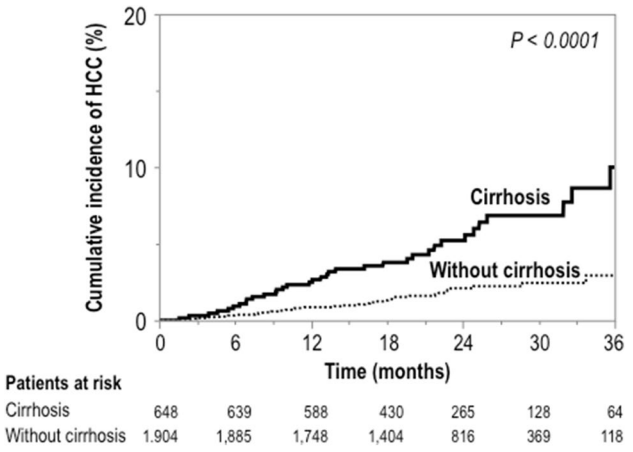

Fig. 2 Cumulative incidence of HCC stratified according to cirrhosis status

the baseline characteristics of the patients who developed HCC. The interval between starting DAA treatment and the diagnosis of HCC was 13.9 ± 8.5 months. Half of the patients had cirrhosis. Figure 2 shows the cumulative HCC incidence stratified by cirrhosis status. The 12-, 24-, and 36-month incidences were 2.5%, 5.2%, and 10.0% in patients with cirrhosis and 0.9%, 2.1%, and 2.9% in patients without cirrhosis, respectively. There was a statistically significant difference in incidence between patients with and without cirrhosis ($p < 0.0001$). In another multivariate analysis, we identified significant risk factors in the cases with or without cirrhosis as follows: sex (male) (HR, 2.30; 95% CI 1.08–4.91) and FIB-4 index (HR, 1.16; 95% CI 1.02–1.32) for the patients with cirrhosis; and sex (male) (HR, 3.23; 95% CI 1.56–7.04), age (HR, 1.82; 95% CI 1.20–2.77), and GGTP (HR, 1.04; 95% CI 1.02–1.07) for the patients without cirrhosis, respectively.

Risk factors associated with HCC development

Table 3 shows the risk factors associated with the development of HCC. Univariate analysis identified patient age, sex, AST, ALT, GGTP, platelet count, AFP, APRI, FIB-4 index, diabetes mellitus, and cirrhosis as factors significantly

Table 3 Risk factors associated with the development of HCC

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Age (by every 10 years)	1.45	1.17–1.83	0.0011	1.51	1.20–1.91	0.0005
Sex						
Female	1			1.00		
Male	2.27	1.42–3.68	0.0007	2.40	1.46–3.96	0.0006
AST (by every 40 IU/L)	1.4	1.21–1.58	< 0.0001			
ALT (by every 40 IU/L)	1.21	1.04–1.35	0.0042			
GGTP (by every 40 IU/L)	1.04	1.02–1.05	< 0.0001	1.04	1.02–1.06	< 0.0001
Platelet count (by every 5×10^4/μL)	0.55	0.44–0.69	< 0.0001			
AFP (by every 10 ng/mL)	1.06	1.008–1.097	0.0043			
APRI	1.3	1.20–1.38	$p < 0.0001$			
FIB-4 index	1.14	1.10–1.18	$p < 0.0001$	1.12	1.07–1.17	$p < 0.0001$
Geno (sero) type						
1	1					
2	0.58		0.12			
Habitual alcohol intake						
Absence	1					
Presence	1.49	0.68–2.6	0.21			
Diabetes mellitus						
Absence	1					
Presence	1.97	1.17–3.20	0.008			
Fatty liver						
Absence	1					
Presence	0.8	0.39–1.48	0.5			
Cirrhosis						
Absence	1					
Presence	3.02	1.89–4.84	$p < 0.0001$			

associated with HCC. According to the multivariate analysis, sex (male), age, FIB-4 index, and GGTP were independent factors significantly associated with HCC. In addition, we determined the cutoff values of these factors by ROC analysis. From ROC analysis, age ≥62 years old, FIB-4 index ≥4.6, and GGTP level ≥44 IU/L were identified as cutoff values. ROC analysis of sex, age, FIB-4 index, and GGTP also showed AUCs of 0.599, 0.619, 0.745, and 0.626, respectively. Among 730 patients who had GGTP ≥44 IU/L, 101 (13.8%) had no habitual alcohol intake, diabetes mellitus, or fatty liver. Figure 3 shows the cumulative HCC incidence stratified by patients with these four factors. The 12-, 24-, and 36-month incidences were 7.9%, 17.5%, and 25.0% in patients with all four factors (Line A in Fig. 3), 5.5%, 11.8%, and 17.9% in patients with three factors except sex (male) (Line B in Fig. 3), 2.9%, 6.4%, and 9.5% in patients meeting only FIB-4 index ≥4.6 (Line C in Fig. 3), and 0.4%, 0.8%, 1.8% in patients with no indicated risk factors (Line D in Fig. 3), respectively. Regarding DAA regimens, we compared cumulative HCC incidence between the 24-week treatment group ($n=1740$) and 12-week treatment group ($n=812$). There was no statistically significant difference between the two ($p=0.40$). The 12-, 24-, and 36-month incidence was 0.9%, 3.1%, and 5.5%, respectively, in the 24-week treatment group, and 1.5%, 2.7%, and 3.1%, respectively, in the 12-week treatment group.

Time of HCC diagnosis and HCC diameter

Figure 4 is a scatter plot showing the time of HCC diagnosis from the start of DAA treatment and the maximum diameter of the HCC at diagnosis. Numbers in the graph specify the number of HCCs diagnosed at each time-size point, if more than one. There was no relationship between the time and diameter ($p=0.74$). Five patients had HCC diameters greater than 2.0 cm and developed HCC within 6 months, or diameters greater than 3.0 cm and developed HCC within 12 months (Fig. 4 cases "a"–"e", Table 4). The duration of DAA treatment was 12 weeks in these five patients. All the patients underwent abdominal US or CT within 3 months before starting DAA treatment. However, no patients received enhanced CT or MRI. Three patients had more than 10 ng/mL of AFP at baseline, and AFP levels increased after DAA treatment in four patients. Although case "c" was clinically diagnosed as not having cirrhosis, after surgical resection, histological fibrosis of the liver was noted upon pathological examination (F4). The presence of a tumor thrombus of the portal vein (Vp2, ** in Fig. 4) was identified in a 71-year-old woman with cirrhosis. Her AFP level before DAA therapy was 66.8 ng/mL, and she received 6 months of treatment. After the therapy, the level was 58.3 ng/mL and no HCC was detected by US. Twelve months after completing treatment, her AFP level had increased to 662.9 ng/mL, and HCC 43 mm in diameter was detected in segment 4 of the liver along with portal vein thrombus on enhanced CT imaging.

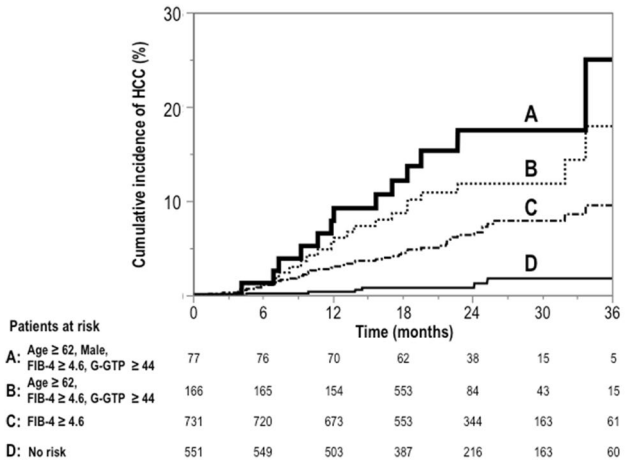

Fig. 3 Cumulative incidence of HCC stratified by patients with four factors (male sex, age ≥62 years, GGTP level ≥44 IU/L, and FIB-4 index ≥4.6). The incidences in patients meeting all four factors (**a**), three factors except sex (male) (**b**), only FIB-4 index ≥4.6 (**c**), and none (**d**), respectively, are shown

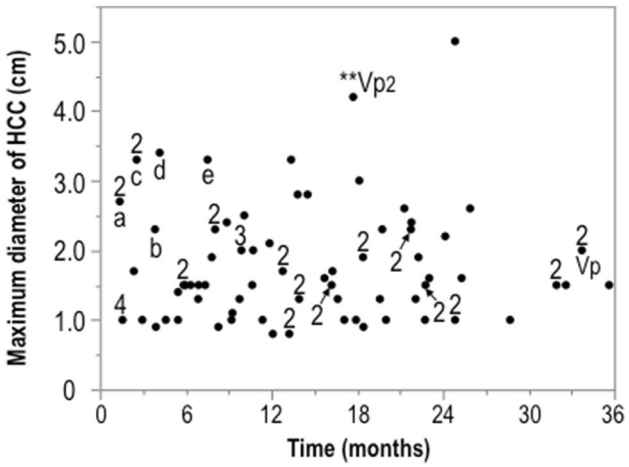

Fig. 4 Time of HCC diagnosis from DAA treatment initiation and the maximum HCC diameter at diagnosis. The number in the graph shows the number of detected HCCs. Cases "a"–"e" are described in the text and Table 4. **A patient with Vp2 (the presence of a tumor thrombus in the second-order branches of the portal vein) is also described in the text. *Vp* the presence of a tumor thrombus of the portal vein

Discussion

In Japan, the first DAA treatment (ASV plus DCV) was approved in September 2014. Many DAAs have since been approved and more than 95% of patients treated with DAAs

Table 4 Clinicopathological characteristics of cases a–e of Fig. 4

Case	Age	Sex	Cirrhosis	Diagnostic imaging/time of examination before DAA treatment (mo)	HCC		AFP (ng/mL)			FIB-4 index	Time to HCC after the start of DAA treatment (mo)	HCC treatment	Histological fibrosis of underlying liver	Tumor differentiation
					Maximum diameter (cm)	Number	Baseline	End of DAAs	1–2 Mo after DAAs	3 Mo after DAAs				
a	48	Male	Absence	US/0	2.7	2	13.4				4.7	1	TACE	
b	80	Female	Absence	US/-1	2.3	1	9.2	19.1	31.4		2.9	4	TACE	
c	62	Male	Absence	US, plain CT/0	3.3	2	36.7		82.6		5.4	4	Resection	F4	Well, Moderate
d	66	Male	Absence	Plain CT/0	3.4	1	52.0	101.0	207.0		9.1	4	Resection	F2	Moderate
e	83	Female	Absence	US/-3	3.3	1	7.9	6.9	153.7	234.4	6.1	6	Resection	F2	Moderate to poor

US ultrasonography, *CT* computed tomography, *AFP* -fetoprotein, *FIB-4 index* fibrosis-4 index, *HCC* hepatocellular carcinoma, *TACE* transcatheter arterial chemoembolization

have achieved SVR. The HCC occurrence risk after achieving SVR by DAAs is similar to that of IFN therapy [13–16]. From these studies, Roche et al. 13 suggest that DAAs do not increase the risk of de novo HCC after achieving an SVR, even after considering that many patients have other HCC risk factors. In Japanese patients, the natural incidence rate of HCC was 1.8% in patients with chronic hepatitis and 7.1% in those with cirrhosis [17]. Although compared against a different treatment era, our incidence (0.9% in chronic hepatitis and 2.5% in cirrhosis) was not higher. Recently, Calvaruso et al. [6] reported that SVR by DAA treatment reduced the incidence of HCC in a large prospective study of patients with cirrhosis. They reported that HCC developed in 2.1% of patients with Child–Pugh class A disease after SVR at one year, which increased to 5.7% at two years. This is consistent with the findings of our study (2.5% and 5.2%, respectively). Based on these data, we anticipate that DAA treatments can reduce the incidence of HCC development. Accurate comparison of HCC occurrence rates requires comparison with the rate in patients not receiving treatment; however, it is not ethically possible to conduct such a study.

Contrarily, Conti et al. [8] reported that DAA-induced SVR does not reduce the short-term occurrence of HCC. In addition, Nakao et al.[9] reported six patients who developed rapidly growing HCC after DAA treatment, with a moderate pathological degree of tumor differentiation in all six patients. There was a significant difference in the well-to less-differentiated ratio of tumor between the control group and those in these six patients. We also focused on five cases with large HCC that developed within six months after the start of DAA treatment. In cases “c”, “d”, and “e”, the tumor differentiation grade was moderate, consistent with those reported by Nakao et al. [9] However, our cases had high AFP levels before DAA treatment and the AFP levels increased even after starting DAA treatment. Our cases also had advanced liver fibrosis, based on the FIB-4 index, although they were clinically diagnosed as those without liver cirrhosis. HCC might have existed before DAA treatment, although none were detected by US or plain CT imaging. No patients received contrast imaging examinations. Therefore, enhanced CT or MRI should be performed in cirrhotic patients with high serum AFP levels before DAA treatment. In addition, we should pay more attention to high FIB-4 index, especially in patients with liver cirrhosis.

Regarding factors associated with HCC, we found four: old age, male sex, high GGTP, and high FIB-4 index. Patients who had these had approximately six—seven times higher risk for HCC development compared with other patients. These risk factors have been previously reported in patients treated with IFN-based therapy [18]. In particular, age, sex, and advanced liver fibrosis are important factors [19, 20]. We also found a high GGTP level to be associated with HCC development. The GGTP level increases due

to habitual alcohol intake, diabetes mellitus [21], and fatty liver. However, many patients in our study had high GGTP values even though they did not have these characteristics. Therefore, the GGTP level might be upregulated through an unknown mechanism in patients at high risk for HCC development after DAA-induced SVR. Of note, Wang et al. 22 suggested that GGTP was associated with DNA damage, genomic instability, and genetic mutation by increasing the uptake of iron, leading to the progression of HCC. Further study is needed to clarify the mechanism of the possible promoting role of GGTP in hepatocarcinogenesis.

In summary, the results of this study suggest that DAAs do not increase the risk of HCC after achieving SVR. Old age, male sex, high serum GGTP level, and high FIB-4 index were important risk factors to predict the occurrence of HCC. Patients with large and early tumor occurrence did not receive sufficient diagnostic imaging. We recommend enhanced abdominal CT or MRI before treatment with DAAs is initiated. Careful follow-up is important in patients with these risk factors.

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Compliance with ethical standards

Conflict of interest: Akio Ido has COI as follows: (1) Speaking fees or honoraria; AbbVie GK, Bristol Myers Squibb Co. Ltd., Gilead Sciences Inc., and Eisai Co. Ltd. (2) Research grants; AbbVie GK, Otsuka Pharmaceutical Co. Ltd., MSD K.K., Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Astellas Pharmaceutical Inc., and Takeda Pharmaceutical Co. Ltd. The other authors disclose no conflicts.

Ethical approval The protocol was approved by all hospital institutional review boards and carried out in compliance with the Declaration of Helsinki.

Informed consent Written informed consent was obtained from all participating patients.

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Affiliations

Tatsuya Ide[1] · Hironori Koga[1] · Masahito Nakano[1] · Satoru Hashimoto[2] · Hiroshi Yatsuhashi[2] · Nobito Higuchi[3] · Makoto Nakamuta[3] · Satoshi Oeda[4] · Yuichiro Eguchi[4] · Satoshi Shakado[5] · Shotaro Sakisaka[5] · Yoko Yoshimaru[6] · Yutaka Sasaki[6] · Yuichi Honma[7] · Masaru Harada[7] · Masataka Seike[8] · Tatsuji Maeshiro[9] · Satoshi Miuma[10] · Kazuhiko Nakao[10] · Seiichi Mawatari[11] · Akio Ido[11] · Kenji Nagata[12] · Shuichi Matsumoto[13] · Yuko Takami[14] · Tetsuo Sohda[15] · Tatsuyuki Kakuma[16] · Takuji Torimura[1]

Tatsuya Ide
ide@med.kurume-u.ac.jp

Masahito Nakano
nakano_masahito@kurume-u.ac.jp

Satoru Hashimoto
shashimoto@nagasaki-mc.com

Hiroshi Yatsuhashi
yatsuhashi@nagasaki-mc.com

Nobito Higuchi
nobito@kyumed.jp

Makoto Nakamuta
nakamuta.makoto.ya@mail.hosp.go.jp

Satoshi Oeda
ooedasa@edu.cc.saga-u.ac.jp

Yuichiro Eguchi
eguchiyu@me.com

Satoshi Shakado
shakado@cis.fukuoka-u.ac.jp

Shotaro Sakisaka
sakisaka@fukuoka-u.ac.jp

Yoko Yoshimaru
youko-k@fc.kuh.kumamoto-u.ac.jp

Yutaka Sasaki
sasakiy@kumamoto-u.ac.jp

Yuichi Honma
y-homma@med.uoeh-u.ac.jp

Masaru Harada
msrharada@med.uoeh-u.ac.jp

Masataka Seike
seikem@oita-u.ac.jp

Tatsuji Maeshiro
f994908@med.u-ryukyu.ac.jp

Satoshi Miuma
miuma1002@gmail.com

Kazuhiko Nakao
kazuhiko@nagasaki-u.ac.jp

Seiichi Mawatari
mawatari@m2.kufm.kagoshima-u.ac.jp

Akio Ido
ido-akio@m2.kufm.kagoshima-u.ac.jp

Kenji Nagata
nagatakj@med.miyazaki-u.ac.jp

Shuichi Matsumoto
shuuimatsumoto-gi@umin.org

Yuko Takami
takami.yuko.px@mail.hosp.go.jp

Tetsuo Sohda
t-sohda@fukuoka-med.jrc.or.jp

Tatsuyuki Kakuma
tkakuma@med.kurume-u.ac.jp

Takuji Torimura
tori@med.kurume-u.ac.jp

[1] Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

[2] Clinical Research Center, National Hospital Organization Nagasaki Medical Center, 2-1001-1 Kubara, Omura 856-8562, Japan

[3] Division of Gastroenterology, National Kyusyu Medical Center Hospital, 1-8-1 Chigyouhama, Chuou-ku, Fukuoka 810-8563, Japan

[4] Liver Center, Saga University Hospital, 5-1-1 Nabeshima, Saga 849-8501, Japan

[5] Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan

[6] Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan

[7] Third Department of Internal Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8556, Japan

[8] Department of Gastroenterology, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hazama-machi, Yufu 879-5593, Japan

[9] First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, 207 Azauehara, Nishihara-machi, Nakagashira-gun 903-0215, Japan

[10] Department of Gastroenterology and Hepatology, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki 850-0000, Japan

[11] Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1, Sakuragaoka 890-8544, Kagoshima, Japan

[12] Department of Liver Disease, University of Miyazaki Hospital, 5200 Kihara, Kiyotake-machi, Miyazaki 889-1692, Japan

[13] Fukuoka Tokushukai Medical Center, 4-5 Sugukita, Kasuga 816-0864, Japan

[14] Department of Hepato-Biliary-Pancreatic Surgery and Clinical Research Institute, National Kyushu Medical Center Hospital, 1-8-1 Chigyouhama, Chuou-ku, Fukuoka 810-8563, Japan

[15] Hepatology Division, Japanese Red Cross Fukuoka Hospital, 3-1-1 Okusu, Minami-ku, Fukuoka 815-8555, Japan

[16] Biostatistics Center, Kurume University, 67 Asahi-machi, Kurume 830-0011, Japan