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ORIGINAL ARTICLE

Necessity for surveillance for hepatocellualr carcinoma in older patients with chronic hepatitis C who achieved sustained virological response

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Abstract

Background and Aim: Hepatocellular carcinoma (HCC) surveillance in low-risk patients (annual incidence <1.5%) is not recommended per the American Association for the Study of Liver Diseases guidelines. Because patients with chronic hepatitis C with non-advanced fibrosis who have achieved sustained virological response (SVR) have a low risk of HCC, HCC surveillance is not recommended for them. However, aging is a risk factor for HCC; threfore, the necessity for HCC surveillance in older patients with non-advanced fibrosis needs to be verified.

Methods: This multicenter, prospective study enrolled 4993 patients with SVR (1998 patients with advanced fibrosis and 2995 patients with non-advanced fibrosis). The HCC incidence was examined with particular attention to age.

Results: The 3-year incidence of HCC in patients with advanced and non-advanced fibrosis was 9.2% (95% CI: 7.8–10.9) and 2.9% (95% CI: 2.1–3.7), respectively. HCC incidence was significantly higher in patients with advanced fibrosis ($P < 0.001$). HCC incidence stratified by age and sex was investigated in patients with non-advanced fibrosis. The HCC incidence in the 18–49, 50s, 60s, 70s, and ≥80 age groups were 0.26, 1.3, 1.8, 1.7, and 2.9 per 100 person-years in men, and 0.00, 0.32, 0.58, 0.49, and 0.57 per 100 person-years in women, respectively.

Conclusions: Male patients with non-advanced fibrosis aged ≥60 years have a higher risk of developing HCC and, thus, require HCC surveillance.

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Introduction

Hepatitis C virus infection can progress to hepatocellular carcinoma (HCC), cirrhosis, or liver failure.[1–3] Almost all patients can achieve sustained virological response (SVR) through direct-acting antiviral (DAA) therapy.[4–11] Although the risk of HCC decreases in patients who achieve SVR, some may nevertheless develop HCC.[12–15] Therefore, the identification and HCC surveillance of patients at a high risk of developing HCC after SVR are important clinical issues. Liver fibrosis is an important risk factor for HCC.[16,17] Western guidelines recommend that patients with advanced fibrosis should be screened regularly for HCC.[18–20] Various noninvasive methods have been proposed and used clinically to identify patients with advanced fibrosis and a high risk of HCC.[21–26] On the other hand, since routine HCC surveillance is not cost effective to perform in all patients, screening is not recommended for patients without advanced fibrosis.[27] In addition, older patients have been identified to be at a high risk of HCC.[28] This is due to the large number of older patients living in Japan and their need to undergo HCC surveillance. However, whether HCC surveillance is necessary or not for older patients without advanced fibrosis/cirrhosis remains unclear. This nationwide, multicenter, prospective study addresses the research gap by examining the necessity for HCC surveillance with a particular focus on age.

Methods

Study protocol. A nationwide, prospective, multicenter registry cohort of patients who received DAA treatment from September 2014 to July 2019 involving 15 institutes from the Japanese Red Cross Hospital Liver Study Group was enrolled. Patients with decompensated cirrhosis at the beginning of the DAA treatment were excluded. The following categories of patients were also excluded: (i)those who did not achieve SVR; (ii) those who had a coinfection of hepatitis B virus and human immunodeficiency virus; and (iii) those with a history of HCC and who developed HCC before the day 24 weeks after SVR (SVR24). In all, 5863 patients who received DAA therapy were registered, and after excluding patients who met the exclusion criteria, a final total of 4993 patients were enrolled in the study.

Advanced fibrosis was defined as fibrosis-4 (FIB-4) index ≥3.25 or histological fibrosis stage 3–4. Liver biopsy was used to evaluate fibrosis in 1196 patients, and FIB-4 index was used to evaluate fibrosis in 3797 patients. Where the results of liver biopsy and FIB-4 index were different, the former were used as the fibrosis stage. A total of 1998 patients had advanced fibrosis, whereas 2995 had non-advanced fibrosis. Patients were stratified by age group (18–49, 50s, 60s, 70s, and 80s), and the association between age and HCC development was investigated. The observation was started on SVR24, and subsequent HCC development was investigated.

Written informed consent was obtained from all patients before their enrollment into the study. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki. The study was approved by the institutional ethics review committee (Approval Number: 2022).

Clinical and laboratory data. The age and sex of the patients were recorded upon enrollment into the study. Serum samples were collected at the time of SVR 24, and laboratory tests were performed on the same day at each hospital. The FIB-4 index was calculated according to the following formula[29,30]: FIB-4 = age (years) × AST (IU/L)/(platelets [10^9/L] × ALT [IU/L]$^{1/2}$), where AST stands for aspartate aminotransferase and ALT stands for alanine aminotransferase.

HCC surveillance and diagnosis. Ultrasonography and blood tests, including tests for tumor markers, were performed at the start of DAA treatment and every 3–6 months for HCC surveillance. When tumor marker levels were abnormally high, and/or abdominal ultrasonography suggested any lesion indicative of HCC, contrast-enhanced computed tomography, magnetic resonance imaging, or angiography was performed. HCC was diagnosed as tumors displaying vascular enhancement in the early phase and washout in the later phase according to the guidelines published by the American Association for the Study of Liver Disease (AASLD) and the Japan Society of

Hepatology.[18,31] Tumor biopsy was used to diagnose tumors with atypical imaging findings.

Statistical analysis. Patient characteristics were compared between those with advanced and non-advanced fibrosis using the Man–Whitney *U*-test. The cumulative incidence of HCC was evaluated using the Kaplan–Meier method, and the differences between the groups were analyzed using the log-rank test. Factors associated with HCC development were evaluated using the Cox proportional hazard model. Age, sex, and α-fetoprotein (AFP) were selected before the Cox proportional hazard model analysis.[28,32–34] Because these factors have been previously shown to be risk factors for HCC, we included these risk factors in the multivariate analysis. Platelet counts were not used in the multivariate analysis because platelet counts were included in the FIB-4 index. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics. The number of patients with advanced and non-advanced fibrosis was 1998 and 2995, respectively. The median (interquartile range) age of patients with advanced and non-advanced fibrosis was 73 (66–78) and 64 (54–71) years, respectively. The AST and ALT values were significantly higher in patients with advanced fibrosis than in those with non-advanced fibrosis. Furthermore, albumin and platelet counts were significantly lower in patients with advanced fibrosis (Table 1).

HCC incidence in patients with advanced and non-advanced fibrosis. The 1-, 2-, and 3-year incidence rates of HCC in patients with advanced fibrosis were 3.7% (95% CI: 2.9–4.7), 6.3% (95% CI: 5.1–7.6), and 9.2% (95% CI: 7.8–10.9), respectively, whereas those in patients with non-advanced fibrosis were 1.1% (95% CI: 0.7–1.6), 1.8% (95% CI: 1.2–2.4), and 2.9% (95% CI: 2.1–3.7), respectively. The HCC incidence was significantly higher in patients with advanced fibrosis than in those with non-advanced fibrosis ($P < 0.001$, Fig. 1). Among the non-advanced fibrosis group, 59 patients developed HCC. There were 1656 female and 1339 male patients in the non-advanced fibrosis group. Fifteen female patients (0.9%) and 44 male patients (3.3%) developed HCC.

Factors associated with HCC in patients with non-advanced fibrosis. Univariable analysis was performed for factors (age, sex, AFP) known to be risk factors for HCC development in patients with non-advanced fibrosis. The hazard ratios (95% confidence interval [CI]) for age (every 10 years), male sex, and AFP ≥5 ng/mL for HCC development were 1.4 (95% CI: 1.1–1.8, $P < 0.01$), 3.8 (95% CI: 2.1–6.8, $P < 0.01$), and 4.0 (95% CI: 2.1–7.8, $P < 0.01$), respectively. Multivariable analysis revealed that age (every 10 years), male sex, and AFP ≥ 5 ng/mL were independent factors associated with HCC development. The hazard ratios (95% CI) for age (every 10 years), male sex, and AFP ≥ 5 ng/mL for HCC development were 4.4 (95% CI: 2.3–8.6, $P < 0.01$), 7.0 (95% CI: 3.1–15.8, $P < 0.01$), and 1.4 (95% CI: 1.0–4.9, $P = 0.04$), respectively.

HCC incidence stratified by age and sex in patients with non-advanced fibrosis. The HCC incidence stratified by age and sex was examined in patients with non-advanced fibrosis. Patients were first stratified by the age group (18–49, 50s, 60s, 70s, and 80s). The 3-year HCC incidence in the 18–49, 50s, 60s, 70s, and 80s age groups were 0.3% (95% CI: 0.04–2.1), 3.0% (95% CI: 1.6–5.6), 3.1% (95% CI: 1.9–4.8), 3.4% (95% CI: 2.0–5.4), and 4.4% (95% CI: 1.6–11.9), respectively (Fig. 2). The HCC incidence per 100 person-years calculated for the 18–49, 50s, 60s, 70s, and 80s age groups were 0.13, 0.84, 1.1, 1.3, and 1.4 per 100 person-years, respectively (Table 2).

Since age and sex were independent factors associated with HCC, patients with non-advanced fibrosis were further stratified by age group and sex. In male patients, the HCC incidence per 100 person-years for the 18–49, 50s, 60s, 70s, and 80s age groups was 0.26, 1.3, 1.8, 1.7 and 2.9, respectively. Similarly, in female patients, the HCC incidence in the 18–49, 50s, 60s, 70s,

Table 1 Patient characteristics

	Advanced fibrosis, $n = 1998$	Non-advanced fibrosis, $n = 2995$	*P*-value
Age, years	73 (66–78)	64 (54–71)	<0.001
Gender, male (%)	774 (38.7%)	1339 (44.7%)	<0.001
AST, IU/L	26 (22–32)	21 (18–25)	<0.001
ALT, IU/L	17 (13–23)	15 (11–21)	<0.001
Albumin, g/dl	4.2 (3.9–4.4)	4.3 (4.1–4.5)	<0.001
Total bilirubin, mg/dl	0.8 (0.6–1.0)	0.7 (0.5–0.9)	<0.001
GGT, IU/L	22 (16–35)	17 (13–26)	<0.001
Platelet counts, 10^9/L	115 (88–140)	189 (160–225)	<0.001
PT-INR	1.08 (1.02–1.15)	1.01 (0.97–1.06)	<0.001
AFP, ng/ml	4.0 (2.7–6.0)	3.0 (2.0–4.3)	<0.001
FIB-4 index	4.9 (3.9–6.9)	1.9 (1.3–2.5)	<0.001

Data are shown in the median interquartile range. *P*-value indicates the difference between advanced fibrosis and the non-advanced fibrosis.
AFP, α-fetoprotein ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; PT-INR, prothrombin time-international normalized ratio.

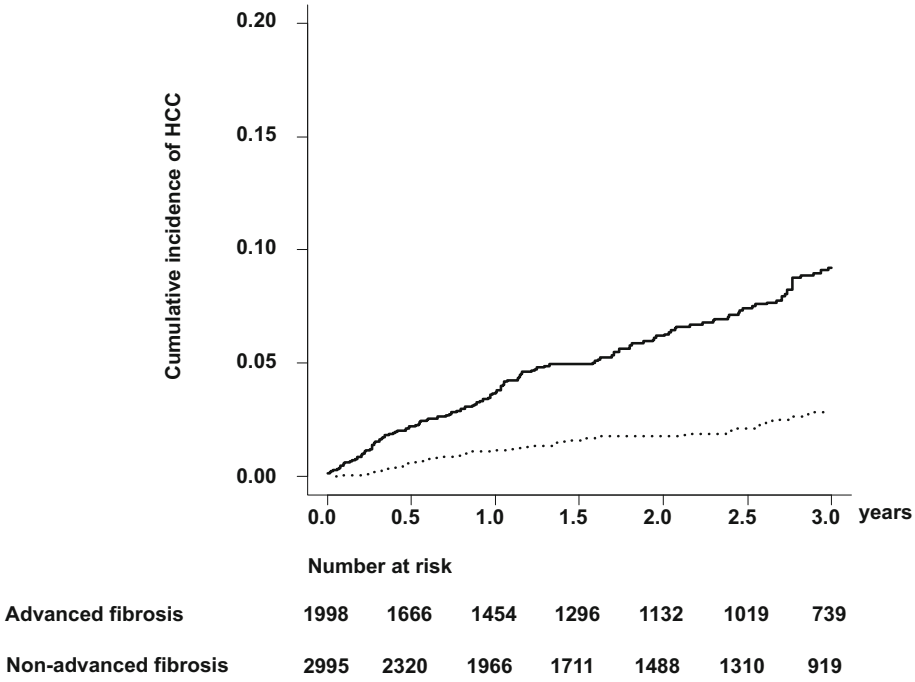

Figure 1 Cumulative incidence of hepatocellular carcinoma (HCC) stratified by fibrosis status. HCC incidence in patients with advanced and non-advanced fibrosis is shown. Advanced fibrosis is defined as fibrosis-4 (FIB-4) index ≥3.25 or histological fibrosis stage 3–4. —— , advanced fibrosis; ····· , non-advanced fibrosis.

and 80s age groups was 0, 0.32, 0.58, 0.49, and 0.57 per 100 person-years, respectively (Table 2).

Discussion

Main findings. In this multicenter, prospective study, we found that HCC incidence was significantly higher in patients with advanced fibrosis and that HCC surveillance was needed in these patients. The AASLD guidelines recommend HCC surveillance in patients with HCC incidence >1.5%/year.[18] Based on the study results, it is also recommended for patients with non-advanced fibrosis who are aged ≥60 years and males who had HCC incidence >1.5%/year. Although the AASLD guidelines do not recommend HCC surveillance in patients with non-advanced fibrosis, age ≥60 years and males exposed to a high risk of HCC development and it indicates HCC surveillance neccesity for these patients.

In context with published literature. The lack of HCC surveillance after SVR is associated with advanced HCC development and poor prognosis.[35] However, HCC surveillance of all patients is not cost effective. Therefore, the AASLD guidelines advocate HCC surveillance in patients with cirrhosis. Various models have been proposed to stratify HCC risk in all patients or patients with advanced fibrosis/cirrhosis.[21–24] However, data on HCC development in patients with non-advanced fibrosis are limited.[36] Because age has been associated with increased risk of HCC,[37] and Japan has a large older population, we specifically investigated the association between age and HCC development. A previous study found that age ≥65 years, ALT ≥ 30 IU/L, and AFP ≥ 5 ng/mL at SVR24 were independent factors for HCC development in patients with non-advanced fibrosis.[38] We found that, as in the previous study, age is an important risk factor for HCC development. Furthermore, we investigated the optimal threshold of age in this study, and even in patients with non-advanced fibrosis, those aged ≥60 years have a high risk for HCC development. Even in patients with non-advanced fibrosis, the annual HCC rate is more than 1.5% in men >60 years. Therefore, HCC surveillance is necessary for the non-advanced fibrosis group.

A late onset HCC has been observed in the group of patients in their 50s with non-advanced fibrosis. The median age of these patients was 56 (53–59) years (data not shown). Aging is a known risk factor for HCC development, and the late onset of HCC also suggests the association of aging and HCC development. On the other hand, the 1-year HCC incidence in the 50s age group with advanced fibrosis was 7.0% (data not shown). These patients with advanced fibrosis had a high risk of HCC development due to advanced fibrosis even just after SVR. Therefore, the effect of aging may be more important in patients with non-advanced fibrosis.

Strengths and limitations. The present study is a prospective registered cohort study involving over 5000 patients from hospitals across Japan. HCC surveillance has been conducted under a unified protocol. Furthermore, because this study was conducted in Japan, the generalizability of this recommendation should be validated in other regions. Although diabetes mellitus and alcohol intake are also known risk factors for HCC,

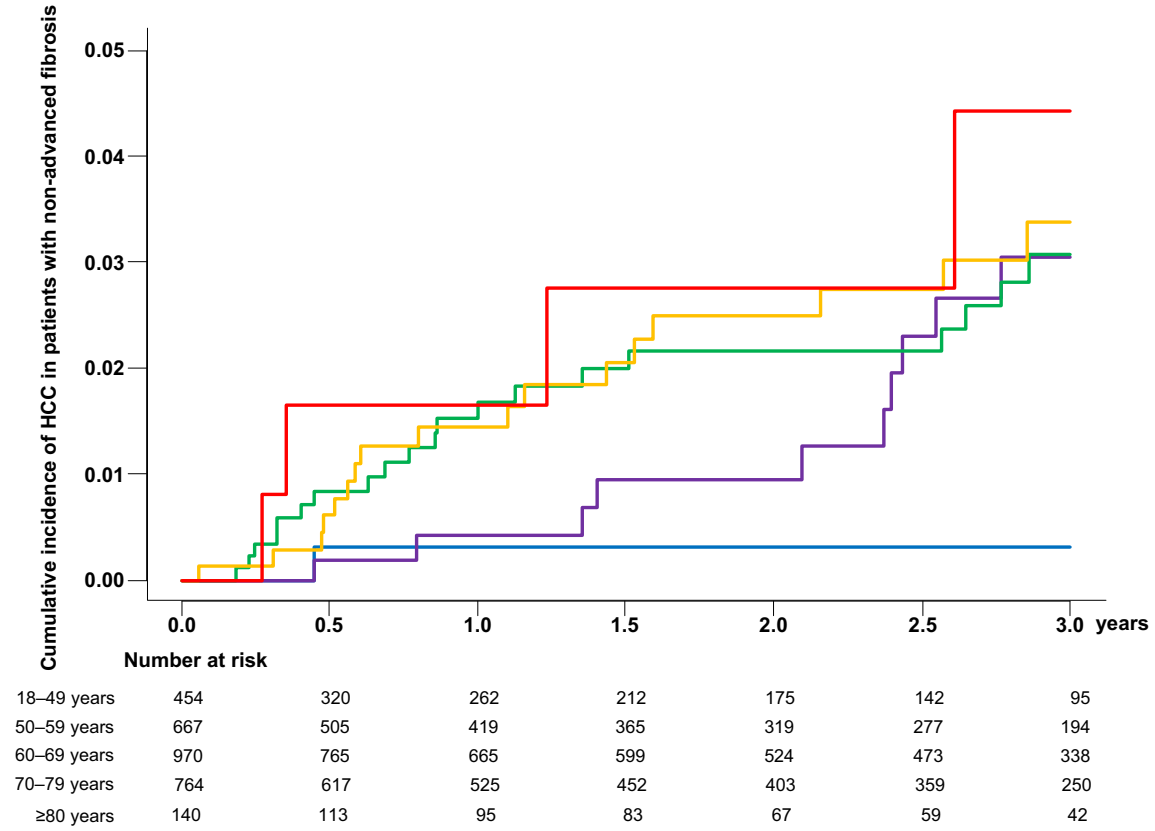

Figure 2 Cumulative incidence of hepatocellular carcinoma (HCC) in patients with non-advanced fibrosis stratified by age. HCC incidence stratified by age (over 10 years) in patients with non-advanced fibrosis is shown. —— , 18–49 years; —— , 50–59 years; —— , 60–69 years; —— , 70–79 years; —— , ≥80 years.

we had not collected these data in the study.[39–42] Even in those aged <60 years, some may have a high risk of HCC development due to diabetes mellitus and alcohol intake, and further studies are also needed to identify high-risk patients aged <60 years. However, we found that HCC risk could be accurately stratified using only age and sex and that HCC surveillance was necessary

Table 2 Hepatocellular carcinoma (HCC) development rate in patients with non-advanced fibrosis

	HCC development rate (95% confidence interval)			
All patients	1 year	2 years	3 years	Per 100 person-years
18–49 years	0.3% (0.04–2.1)	0.3% (0.04–2.1)	0.3% (0.04–2.1)	0.13
50–59 years	0.4% (0.1–1.7)	0.9% (0.3–2.5)	3.0% (1.6–5.6)	0.84
60–69 years	1.5% (0.8–2.6)	2.2% (1.3–3.5)	3.1% (1.9–4.8)	1.1
70–79 years	1.4% (0.7–2.7)	2.5% (1.4–4.2)	3.4% (2.0–5.4)	1.3
≥80 years	1.7% (0.4–6.4)	2.8% (0.9–8.4)	4.4% (1.6–11.9)	1.4
Female	1 year	2 years	3 years	Per 100 person-years
18–49 years	0%	0%	0%	0
50–59 years	0%	0%	0.6% (0.4–6.9)	0.32
60–69 years	1.4% (0.6–3.0)	1.4% (0.6–3.0)	1.7% (0.8–3.6)	0.58
70–79 years	0.2% (0.03–1.5)	0.8% (0.2–2.6)	1.3% (0.4–3.4)	0.49
≥80 years	0%	1.7% (0.2–11.4)	1.7% (0.2–11.4)	0.57
Male	1 year	2 years	3 years	Per 100 person-years
18–49 years	0.4% (0.09–4.5)	0.4% (0.09–4.5)	0.4% (0.09–4.5)	0.26
50–59 years	0.8% (0.2–3.2)	1.8% (0.7–4.8)	5.2% (2.7–9.9)	1.3
60–69 years	1.7% (0.7–3.8)	3.2% (1.7–5.8)	4.9% (2.7–8.4)	1.8
70–79 years	3.2% (1.7–7.0)	5.3% (2.9–9.4)	7.0% (4.0–11.9)	1.7
≥80 years	4.4% (1.1–16.3)	4.4% (1.1–16.3)	8.3% (2.6–24.9)	2.9

for male patients aged ≥60 years. Since this recommendation is easy to apply, it may benefit all clinicians. The determination of fibrosis may be inaccurate because many patients were assessed for fibrosis using the FIB-4 index. Since the FIB-4 index includes age in the formula, HCC risk in patients with non-advanced fibrosis may be underestimated. Therefore, HCC risk should be evaluated in patients with more accurate assessment of fibrosis using liver biopsy or elastography.

Future implications. Routine HCC surveillance improves prognosis, but it is not cost effective to perform in all patients. The Japanese Society of Hepatology guidelines recommend regular HCC surveillance based on HCC risk, but they do not specify in which patients.[43] In this study, we demonstrated that patients with advanced fibrosis are at a high risk of HCC and should be screened regularly. In addition to this, we demonstrated that male patients with non-advanced fibrosis aged ≥60 years have a higher risk of developing HCC (>1.5%), so at least these patients should be regularly screened for HCC. However, because the threshold for cost-effective HCC surveillance in patients with non-advanced fibrosis who achieved SVR may be less than 1.5%, the optimal threshold for HCC surveillance and cost-effectiveness analysis in patients with SVR should be verified in future studies. Long-term observation is necessary to determine whether DAA prolongs the prognosis in patients with SVR, and the appropriate threshold should be examined after that. This study clarifies the criteria for patients requiring HCC surveillance. Furthermore, HCC incidence also increases over time in patients aged 50 years onwards, which may also reflect the effects of aging. The effects of aging on younger patients (<60 years) require further long-term observation. Since this recommendation of identifying patients who require HCC surveillance after SVR can be easily adopted without the need for special testing, we believe it is useful for all clinicians.

Conclusion

In conclusion, male patients aged ≥60 years with non-advanced fibrosis have a high risk of HCC development and thus require HCC surveillance.

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