JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12745

ORIGINAL ARTICLE

# Incidence and risk factors of hepatocellular carcinoma in patients with hepatitis C who achieved a sustained virological response through direct-acting antiviral agents among the working population in Japan

Hideki Hagiwara,* Yoshiki Ito,* Takashi Ohta,* Yasutoshi Nozaki,* Takayuki Iwamoto,* Atsushi Hosui,† Naoki Hiramatsu,† Yuki Tahata,‡ Ryotaro Sakamori,‡ Hayato Hikita‡ and Norio Hayashi*

*Department of Gastroenterology and Hepatology, Kansai Rosai Hospital, Amagasaki, Hyogo, †Department of Gastroenterology and Hepatology, Osaka Rosai Hospital, Sakai and ‡Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

**Key words**
hepatitis C virus treatment, hepatitis C, hepatocellular carcinoma, sustained virological response, working population.

Accepted for publication 11 April 2022.

**Correspondence**
Hideki Hagiwara, Department of Gastroenterology and Hepatology, Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki, Hyogo 660 8511, Japan.
Email: hagiwara-hideki@kansaih.johas.go.jp

**Declaration of conflict of interest**: None.

**Funding support:** Japan Organization of Occupational Health and Safety

## Abstract

**Background and Aim:** The development of hepatocarcinogenesis after a sustained virological response (SVR) remains an important issue affecting the balance between treatment and occupational life of workers with chronic hepatitis C virus (HCV) infection in Japan. Here, we aimed to evaluate the hepatocellular carcinoma (HCC) reducing effect and risk factors for developing HCC after SVR in patients treated with direct-acting antiviral agents (DAAs) among the working population.

**Methods:** We studied 2579 working patients with chronic HCV infection who achieved SVR after antiviral treatment. We compared the difference in the cumulative incidence of post-SVR HCC between the interferon (IFN)-based $n = 1615$ and DAA ($n = 964$) groups. The risk factors for post-SVR HCC development were determined in the DAA group.

**Results:** After propensity score matching ($n = 644$ in each group), the HCC development rates were not significantly different between the groups ($P = 0.186$). Multivariate Cox regression and the cutoff values determined by the receiver operating characteristic curve analyses revealed that age ≥61 years, diabetes, lower serum albumin levels <4.0 g/dL at 24 weeks after the end of treatment (EOT), and higher serum α-fetoprotein levels ≥4.1 ng/mL at 24 weeks after the EOT were associated with the development of HCC.

**Conclusion:** The HCC suppressing effect after SVR through DAA treatment is equivalent to that of IFN treatment in patients in the working population. Intensive follow-up is required after SVR with DAA treatment in Japanese workers with these risk factors to ensure the promotion of health and employment support.

## Introduction

Hepatitis C virus (HCV) remains an important health problem and a major cause of cirrhosis and hepatocellular carcinoma (HCC) in Japan.[1] Previously, patients with chronic HCV infection were treated with interferon (IFN)-based therapy; however, this treatment was not ideal because of the high IFN-related toxicity and long treatment period.[2] The development of IFN-free regimens involving a combination of direct-acting antivirals (DAAs) has resulted in a high sustained virological response (SVR) rate, fair tolerability, and shorter treatment duration.[3] Therefore, DAA treatment has brought about the elimination of restrictive inclusion criteria for screening treatment candidates.

A nationwide cross-sectional survey in Japan revealed that 0.44% of workers aged ≥40 years tested positive for the HCV antibody and that an estimated 0.14 million workers require treatment for HCV infection.[4] Recently, the balance between the treatment and occupational life of workers affected by diseases has become an important issue in the field of "Promotion of Health and Employment Support" in Japan.[5] The guidelines for treatment and work integration in the workplace issued by the Ministry of Health, Labour, and Welfare of Japan outline the precautions to be implemented in the cases of workers with diseases that require treatment, such as cancer, stroke, cardiovascular disease, diabetes, and hepatitis.[6] These guidelines indicate that businesses should consider that workers require outpatient visits for the identification of tumor development at appropriate intervals depending on the cause and progression of liver disease. In this context, the risk of post-SVR hepatocarcinogenesis has become an important issue in the balance between the treatment and

occupational life of workers with liver disease. Previous studies have demonstrated a decline in the incidence of HCC in patients with SVR achieved after conventional IFN-based treatment[7–9]; however, hepatocarcinogenesis is not completely suppressed in these patients. Japanese workers with chronic HCV infection are at risk of developing HCC and are required to visit an outpatient clinic several times a year for HCC surveillance, even after achieving SVR.

Recently, several reports have indicated that the development of HCC is suppressed after SVR is achieved through DAA treatment.[10,11] However, to the best of our knowledge, no analysis to date has focused on the working population alone, as previous studies included both the working population and older patients. Therefore, the effect of reducing the occurrence of HCC and risk factors for developing HCC after SVR in workers receiving DAA treatment have not been clarified. In the present study, we aimed to register and follow up Japanese patients with chronic HCV infection who achieved SVR with DAA treatment in the working population and investigate the subsequent occurrence of HCC and risk factors for HCC development. These investigations would enable the identification of workers at a high risk of post-SVR hepatocarcinogenesis and the establishment of a more appropriate follow-up system, which would lead to the promotion of health and employment support.

## Methods

***Study patients.*** This was a retrospective study and included registered cohorts from Kansai Rosai Hospital, Osaka Rosai Hospital, Osaka University Hospital, and 27 other institutions participating in the Osaka Liver Forum. A total of 2579 patients with chronic HCV infection from the working population aged 20–64 years were enrolled in this study (Fig. 1). The upper age limit was set according to the definition of the working age population by the Organization for Economic Co-operation and Development. We excluded patients with HCC, human immunodeficiency virus or hepatitis B co-infection, decompensated cirrhosis, and other forms of liver disease (e.g. autoimmune hepatitis or alcoholic liver disease). Patients were divided into two groups according to the type of antiviral treatment received: IFN-based treatment (IFN-SVR group, $n = 1615$) and DAA treatment (DAA-SVR group, $n = 964$). All patients achieved SVR after antiviral therapy. The DAA treatment regimens included daclatasvir plus asunaprevir, sofosbuvir plus ribavirin, sofosbuvir plus ledipasvir, ombitasvir plus paritaprevir with ritonavir, elbasvir plus grazoprevir, and glecaprevir plus pibrentasvir. All patients were treated based on the Japanese guidelines for treating chronic HCV infection.[12,13]

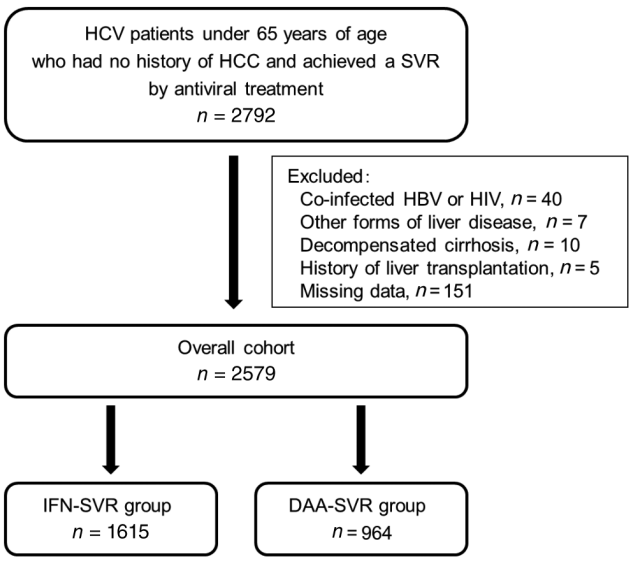


**Figure 1** Study patients. DAA, direct-acting antiviral agent; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; SVR, sustained virological response.

***Surveillance of HCC.*** After starting antiviral treatment, patients with cirrhosis were monitored every 3–4 months, and patients without cirrhosis were monitored every 6 months through abdominal ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), according to Japanese guidelines. The diagnosis of HCC was based on typical vascular findings observed on contrast-enhanced CT or MRI. The typical vascular findings included arterial enhancement with a subsequent washout appearance during the delayed phase. When vascular findings were atypical through these imaging techniques, a histological diagnosis was made through a tumor biopsy.

***Ethical considerations.*** This study was approved by the Research Ethics Committee of the Japan Organization of Occupational Health and Safety on June 27, 2018 (No. 6) and conformed to the Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology of Japan, and Ministry of Health, Labour and Welfare of Japan, 2017). Written informed consent was obtained from all patients who participated in the study.

***Statistical analyses.*** Categorical variables are expressed as numbers and were compared using chi-square tests, while continuous variables are expressed as medians with interquartile range (IQR) and were compared using Mann–Whitney $U$ tests. The difference in the cumulative incidence of HCC between the IFN-SVR and DAA-SVR groups was analyzed using the Kaplan–Meier method and log-rank test. A Cox proportional hazards model was used to identify significant risk factors associated with the occurrence of HCC. The Cox proportional hazard model was adjusted for the following 11 variables that may affect HCC occurrence: age, sex, body mass index (BMI), fibrosis-4 (FIB)-4 index, diabetes mellitus (DM), history of antiviral therapy, platelet count, serum total bilirubin level, serum alanine aminotransferase (ALT) level, serum albumin level, and serum α-fetoprotein (AFP) level. Significant factors selected in the univariate Cox regression analysis were analyzed using the multivariate Cox regression method.

Propensity score matching (PSM) was performed to minimize the differences in baseline characteristics between the IFN-SVR and DAA-SVR groups. The following variables were included in the multiple logistic regression to derive propensity

**Table 1** Patient characteristics at baseline before propensity score matching

| Factors | DAA-SVR ($n = 964$), median (IQR) | IFN-SVR ($n = 1615$), median (IQR) | *P*-value |
|---|---|---|---|
| Age (years) | 56 (50–61) | 54 (44–59) | <0.001 |
| Sex (male/female) | 496/468 | 841/774 | 0.76 |
| BMI (kg/m$^2$) | 22.8 (20.7–25.4) | 22.7 (21.0–25.0) | 0.546 |
| DM (presence/absence) | 141/801 | 95/1520 | <0.001 |
| HCV genotype (1/2/3/1 + 2) | 661/296/4/1 | 1005/589/0/0 | <0.001 |
| Liver histology | | | |
| Activity (A0-1/2-3) | 360/80 | 694/445 | <0.001 |
| Fibrosis (F0-2/3-4) | 373/67 | 1035/105 | 0.001 |
| Platelet count ($\times 10^4/\mu$L) | 17.4 (13.3–21.5) | 17.9 (14.3–21.8) | 0.008 |
| Total bilirubin (mg/dL) | 0.7 (0.5–0.9) | 0.7 (0.6–1.0) | 0.016 |
| AST (U/L) | 38 (28–62) | 42 (30–70) | <0.001 |
| ALT (U/L) | 43 (27–73) | 55 (34–98) | <0.001 |
| Albumin (g/dL) | 4.2 (3.9–4.4) | 4.1 (3.9–4.3) | 0.001 |
| FIB-4 index (score) | 1.89 (1.34–2.97) | 1.76 (1.13–2.65) | <0.001 |
| AFP (ng/mL) | 4.2 (3.0–8.0) | 4.9 (3.0–7.0) | 0.941 |

AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral agents; DM, diabetes mellitus; FIB-4, fibrosis 4; HCV, hepatitis C virus; IFN, interferon; IQR, interquartile range; SVR, sustained virological response.

**Table 2** Patient characteristics at baseline after propensity score matching

| Factors | DAA-SVR ($n = 644$), median (IQR) | IFN-SVR ($n = 644$), median (IQR) | Standardized difference |
|---|---|---|---|
| Age (years) | 55 (48–60) | 55 (47–60) | 0.022 |
| Sex (male/female) | 315/329 | 319/325 | 0.012 |
| BMI (kg/m$^2$) | 22.7 (20.7–25.2) | 22.8 (21.1–25.0) | 0.001 |
| DM (presence/absence) | 38/606 | 39/605 | 0.008 |
| Platelet count ($\times 10^4/\mu$L) | 17.8 (14.2–21.7) | 18.0 (14.3–22.2) | 0.034 |
| Total bilirubin (mg/dL) | 0.7 (0.5–0.9) | 0.7 (0.6–1.0) | 0.012 |
| AST (U/L) | 39 (28–62) | 40 (29–60) | 0.003 |
| ALT (U/L) | 44 (27–75) | 49 (32–81) | 0.023 |
| Albumin (g/dL) | 4.2 (3.9–4.4) | 4.1 (3.9–4.4) | 0.003 |
| FIB-4 index (score) | 1.85 (1.33–2.69) | 1.79 (1.17–2.71) | 0.02 |
| AFP (ng/mL) | 4.0 (3.0–7.3) | 4.6 (3.0–7.0) | 0.012 |

AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral agents; DM, diabetes mellitus; FIB-4, fibrosis 4; IFN, interferon; IQR, interquartile range; SVR, sustained virological response.

scores: age, sex, BMI, FIB-4 index, DM, platelet count, serum total bilirubin level, serum aspartate aminotransferase (AST) level, serum ALT level, serum albumin level, and serum AFP level. One-to-one PSM was performed between the two groups using a nearest neighbor matching method with a caliper width of 0.0324, which is a range of 0.2 of the SD of the propensity scores. All statistical analyses were performed using SPSS (version 24.0; IBM, Armonk, NY, USA). Statistical significance was defined as a two-tailed *P*-value of <0.05 in all tests.

## Results

***Characteristics of study patients.*** Patients in the DAA-SVR group were significantly older than those in the IFN-SVR group; further, the DAA-SVR group had a larger proportion of patients with DM and advanced fibrosis (METAVIR score F3 or F4 stage). Compared with patients in the IFN-SVR group, those in the DAA-SVR group had significantly lower baseline platelet counts, serum total bilirubin levels, serum AST levels, serum ALT levels, and significantly higher serum albumin levels and FIB-4 indices (Table 1). After PSM, 644 patients were matched in each group, and all their corresponding variables were balanced because of a standardized difference of <0.1 (Table 2).

***Comparison of cumulative incidence of HCC between the IFN-SVR and DAA-SVR groups.*** The median follow-up period was 47.5 months in the IFN-SVR group and 36.6 months in the DAA-SVR group. Twenty-seven patients in the IFN-SVR group and 20 in the DAA-SVR group developed HCC. The cumulative incidence of post-SVR HCC at 1, 2, 3, and 4 years were 0.3, 0.9, 1.3, and 1.8% in the IFN-SVR group and 0.4, 0.8, 2.0, and 3.4% in the DAA-SVR group, respectively. The HCC development rates were significantly lower in the IFN-SVR group than in the DAA-SVR group ($P = 0.044$).

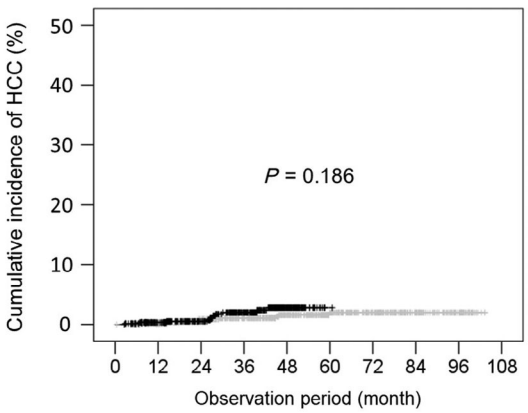


**Figure 2** Cumulative incidence of hepatocellular carcinoma (HCC) after propensity score matching. Black line, direct-acting antiviral agent-sustained virological response (SVR) group; gray line, interferon-SVR group.

After PSM, the median follow-up period was 51.0 months in the IFN-SVR group and 35.7 months in the DAA-SVR group. Nine patients in the IFN-SVR group and 11 in the DAA-SVR group developed HCC. The cumulative incidence of post-SVR HCC at 1, 2, 3, and 4 years were 0.2, 0.9, 1.1, and 1.6% in the IFN-SVR group and 0.3, 0.8, 2.0, and 2.8% in the DAA-SVR group, respectively. The HCC development rates were not significantly different between the two groups ($P = 0.186$) (Fig. 2).

***Risk factors for HCC development in the DAA-SVR group.*** The univariate analysis revealed the following significant risk factors for HCC development in 964 patients from the DAA-SVR group: older age, higher FIB-4 index, diagnosis of DM, lower platelet count, and lower serum albumin level at baseline. Lower platelet counts, higher serum ALT levels, higher serum bilirubin levels, lower serum albumin levels, and higher AFP levels at 24 weeks after the EOT were also identified as significant variables. Multivariate Cox regression analysis was conducted using the variables selected in the univariate analysis and revealed that older age, diagnosis of DM, lower serum albumin level at 24 weeks after EOT (SVR24-Alb), and higher serum AFP level at 24 weeks after EOT (SVR24-AFP) were associated with HCC development (Table 3).

The cutoff values of these factors for predicting HCC development were determined through a receiver operator characteristics (ROC) analysis. The cutoff values for age, SVR24-Alb, and SVR24-AFP were 61 years, 4.0 g/dL, and 4.1 ng/mL, respectively, after optimization using Youden's index (Fig. 3). The sensitivity and specificity of these values are shown in Table 4.

There was a significant difference in the cumulative incidence of HCC in the DAA-SVR group according to stratification by age (61 years), diagnosis of DM, SVR24-Alb of 4.0 g/dL, and SVR24-AFP of 4.1 ng/mL (Fig. 4).

## Discussion

IFN-based treatment of chronic HCV infection frequently leads to various side effects. The duration of treatment with peginterferon is 24 weeks, even in the case of short treatment periods, and patients require weekly hospital visits and injections. These disadvantages have hindered the initiation of treatment, especially in the working populations in Japan. With IFN-free treatment involving the combination of DAAs, patients with hepatitis C can be treated with almost no side effects. Furthermore, IFN-free DAA treatment can be completed within a minimum of 8 weeks with oral drug administration.[3] This is a major step

**Table 3** Risk factors related to the incidence of hepatocellular carcinoma among patients in the working population who achieved a sustained virological response with direct-acting antiviral agents

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| Factors | Category | Hazard ratio | 95% CI | *P* value | Hazard ratio | 95% CI | *P* value |
| Age (years) | Per 1 year | 1.102 | 1.012–1.200 | 0.025 | 1.139 | 1.036–1.253 | 0.007 |
| Sex | Male/female | 0.422 | 0.162–1.097 | 0.077 | | | |
| BMI | Per 1 kg/m$^2$ | 1.109 | 0.996–1.236 | 0.059 | | | |
| FIB-4 index | Per 1 score | 1.089 | 1.033–1.148 | 0.001 | 0.901 | 0.707–1.148 | 0.398 |
| DM | Absence/presence | 3.231 | 1.289–8.099 | 0.012 | 3.4 | 1.266–9.132 | 0.015 |
| HCV treatment | Naïve/re-treatment | 1.885 | 0.780–4.558 | 0.159 | | | |
| Platelet count (pre) | Per 10$^4$/μL | 0.858 | 0.788–0.933 | <0.001 | | | |
| Platelet count (SVR24) | Per 10$^4$/μL | 0.842 | 0.771–0.919 | <0.001 | 0.881 | 0.772–1.007 | 0.062 |
| ALT (pre) | Per 1 U/L | 1.002 | 0.997–1.008 | 0.415 | | | |
| ALT (SVR24) | Per 1 U/L | 1.008 | 1.005–1.011 | <0.001 | 1.002 | 0.999–1.006 | 0.186 |
| Total bilirubin (pre) | Per 1 mg/dL | 2.359 | 0.892–6.238 | 0.084 | | | |
| Total bilirubin (SVR24) | Per 1 mg/dL | 2.266 | 1.013–5.069 | 0.046 | 1.549 | 0.576–4.170 | 0.386 |
| Albumin (pre) | Per 1 g/dL | 0.086 | 0.033–0.219 | <0.001 | | | |
| Albumin (SVR24) | Per 1 g/dL | 0.085 | 0.032–0.224 | <0.001 | 0.218 | 0.070–0.683 | 0.009 |
| AFP (pre) | Per 1 ng/mL | 1.002 | 0.997–1.006 | 0.506 | | | |
| AFP (SVR24) | Per 1 ng/mL | 1.156 | 1.115–1.199 | <0.001 | 1.273 | 1.186–1.365 | <0.001 |

AFP, α-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FIB-4, fibrosis 4; HCV, hepatitis C virus; pre, value at pretreatment; SVR24, value at 24 weeks after the end of treatment.

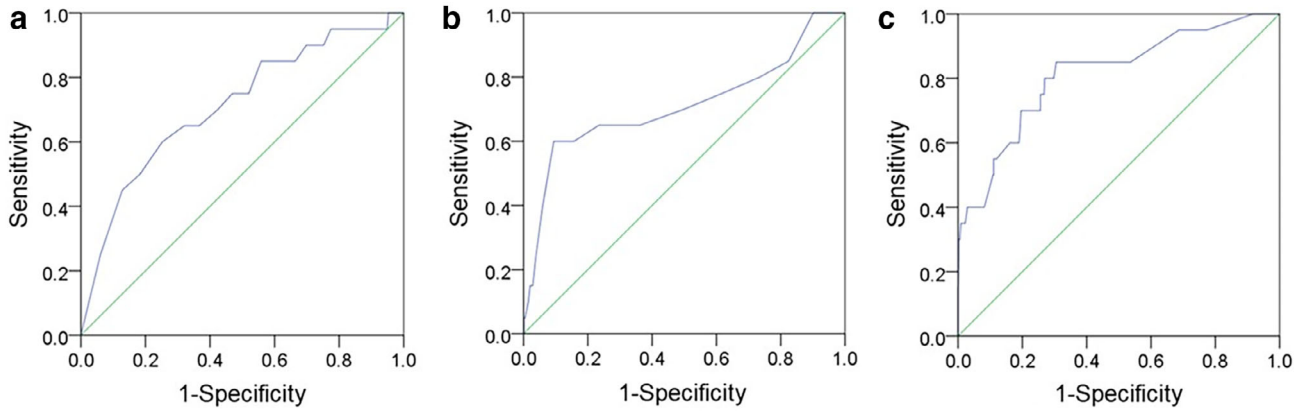


**Figure 3** Receiver operating characteristic curves of age, albumin levels, and α-fetoprotein levels. (a) age, (b) albumin (SVR24), (c) α-fetoprotein (SVR24). SVR24, value at 24 weeks after the end of treatment.

**Table 4** Cut-off value, sensitivity, and specificity of age, albumin levels, and α-fetoprotein (AFP) levels

| Factors | AUC (95% CI) | Cut-off value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| Age | 0.714 (0.593–0.835) | 61 years | 60.00 | 74.80 |
| Albumin (SVR24) | 0.711 (0.565–0.857) | 4.0 g/dL | 60.00 | 90.60 |
| AFP (SVR24) | 0.812 (0.708–0.916) | 4.1 ng/mL | 85.00 | 69.50 |

AUC, area under the curve; CI, confidence interval; SVR24, value 24 weeks after end of treatment.

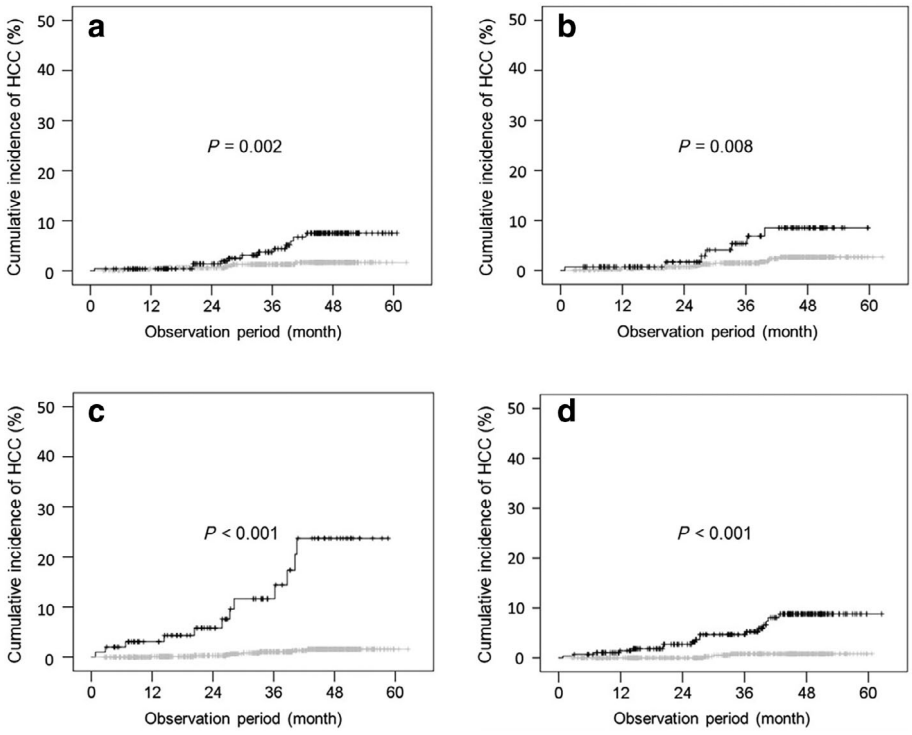


**Figure 4** Cumulative incidence of hepatocellular carcinoma (HCC) after risk factor stratification. (a) Age: black line, ≥61 years; gray line, <61 years. (b) DM: black line, present; gray line, absent. (c) Albumin (SVR24): black line, <4.0 g/dL; gray line, ≥4.0 g/dL. (d) α-fetoprotein (SVR24): black line, ≥4.1 ng/mL; gray line, <4.1 ng/mL. SVR24, value at 24 weeks after the end of treatment.

forward in eliminating barriers to treating the Japanese working population.

However, HCC occurring after SVR remains an important problem in the field of "Promotion of Health and Employment Support." Although SVR achieved through IFN-based treatment has been shown to significantly suppress hepatocarcinogenesis, it is unclear whether similar suppressive effects can be obtained after DAA treatment, especially in the working population. Clarifications regarding the suppression of HCC development after SVR achieved through DAA treatment would result in greater motivation for the working population to receive antiviral therapy, even during working periods. Our data showed no significant difference in the occurrence of HCC after SVR between the IFN-based and DAA treatment groups after adjusting for patient background through PSM. This result indicates that the effect of suppressing HCC development was equivalent between the two groups. These findings make it clear that patients with hepatitis C who belong to the working population should be treated with DAA to eliminate the virus.

The risk factors for developing HCC after DAA treatment in the working population are still unclear. In the multivariate analysis in this study, age, diagnosis of DM, SVR24-Alb, and SVR24-AFP were identified as factors that are significantly associated with post-SVR hepatocarcinogenesis. There was a significant difference in the cumulative incidence of HCC after SVR when the patients were stratified by age (61 years), the diagnosis of DM, SVR24-Alb level of 4.0 g/dL, and SVR24-AFP level of 4.1 ng/mL. In Japan, age,[14–20] diabetes,[15,20,21] and the post-treatment AFP level[16–20] were reported as risk factors for developing HCC after SVR was achieved through IFN therapy. This study's results show that similar background factors affect HCC development after SVR in the working population, regardless of the treatment regimen.

This study revealed that patients aged 61 years or older, those with DM, SVR24-Alb of less than 4.0 g/d, and SVR24-AFP of 4.1 ng/mL or more had a high risk of developing hepatocarcinogenesis after SVR. Thus, intensive follow-up is considered desirable for patients in the working population who have these risk factors. Early detection and treatment of cancer are important for improving prognosis, but the surveillance intervals recommended in each country are different.[22] For liver cancer surveillance in Japan, imaging examinations are generally performed every 6 months in patients with chronic hepatitis and every 3–4 months in those with liver cirrhosis.[23] Imaging examinations conducted every 3–4 months in the case of chronic hepatitis might be an option among post-SVR workers with the above-mentioned risk factors. Alternatively, imaging examinations every 12 months in the case of chronic hepatitis and every 6 months in the case of cirrhosis might be sufficient among workers without any of the above-mentioned risk factors. The number of hospital visits can be reduced for low-risk workers by extending the interval between visits, leading to a more convenient balance between treatment and occupational life. In the future, it is necessary to establish an appropriate HCC surveillance strategy according to the risk factors in post-SVR workers by further examining the relationship of the interval between imaging examinations with HCC detection and long-term prognosis.

There are some limitations to this study. First, the evaluation of liver fibrosis has not been sufficiently performed. Although liver fibrosis is a factor associated with hepatocarcinogenesis, liver histology was evaluated in less than half of the DAA-SVR group, and a non-invasive liver stiffness assessment was not performed. The FIB-4 index was selected as a factor related to liver fibrosis in this study. Second, the median follow-up period was 36.6 months in the DAA-SVR group, which may not be sufficient to assess the cumulative incidence of post-SVR HCC development. Further long-term follow-up of these cases is necessary and might significantly differ in the cumulative HCC development rate between the DAA-SVR and the IFN-SVR groups even if the patient background is adjusted. However, there are no differences in the development of post-SVR HCC between the two groups at least 3 years after the end of antiviral therapy. The third limitation of this study is patient selection bias. Age is an important factor associated with hepatocarcinogenesis after SVR. El-Serag *et al*. have shown an annual HCC incidence rate of 0.077, 0.213, 0.529, and 0.953% among 10 738 veterans with SVR aged <45 years, 45–54 years, 55–64 years, and ≥65 years.[24] van der Meer *et al*. reported that 8-year HCC incidence in SVR patients with cirrhosis was 2.6, 9.7, and 12.2% among <45 years, 45–60 years, and ≥60 years.[25] These reports indicate that the HCC development rate is very low in younger patients, especially in those under 45 years of age. Our study was hospital-based and included patients with a median age of 56 years and might be targeted at subgroups that differ from the age distribution of patients with hepatitis C infection in the true working population. Therefore, it is necessary to consider whether this study's results can be generalized to young patients in the workplace.

In conclusion, the suppression of HCC development after SVR is achieved through DAA treatment is equivalent to the suppression observed after SVR through IFN treatment in patients among the working population. Age, diabetes, SVR24-Alb, and SVR24-AFP are associated with the risk of post-SVR hepatocarcinogenesis. Intensive follow-up after SVR is achieved through DAA treatment is required for Japanese workers aged 61 years or older, those with DM, those with SVR24-Alb of less than 4.0 g/dL, and those with SVR24-AFP of 4.1 ng/mL or more. Further investigation is required to establish appropriate HCC surveillance strategies according to the risk factors in post-SVR workers.

## Acknowledgments

This study was funded by the research and development and dissemination project on the occupational injuries and illnesses of the Japan Organization of Occupational Health and Safety.

## References

1 Enomoto H, Ueno Y, Hiasa Y *et al*. The transition in the etiologies of hepatocellular carcinoma-complicated liver cirrhosis in a nationwide survey of Japan. *J. Gastroenterol.* 2021; **56**: 158–67.
2 Hayashi N, Takehara T. Antiviral therapy for chronic hepatitis C: past, present, and future. *J. Gastroenterol.* 2006; **41**: 17–27.
3 Tahata Y, Sakamori R, Takehara T. Treatment progress and expansion in Japan: from interferon to direct-acting antiviral. *Glob. Health Med.* 2021; **3**: 321–34.

4 Tatemichi M, Furuya H, Nagahama S *et al*. A nationwide cross-sectional survey on hepatitis B and C screening among workers in Japan. *Sci. Rep.* 2020; **10**: 11435.
5 The Ministry of Health. *Labour and Welfare of Japan. Annual health, labour and welfare report 2020. (4). Working Cond/Lab Relat.* Available from URL: https://www.mhlw.go.jp/english/wp/wp-hw13/dl/04e.pdf
6 The Ministry of Health, Labour and Welfare of Japan. *Guidelines for supporting treatment and work integration in the workplace* (in Japanese). [revised version March 2021]. Available from URL: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000115267.html
7 Kasahara A, Hayashi N, Mochizuki K *et al*. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. *Hepatology*. 1998; **27**: 1394–402.
8 Ikeda K, Saitoh S, Arase Y *et al*. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology*. 1999; **29**: 1124–30.
9 Hiramatsu N, Oze T, Takehara T. Suppression of hepatocellular carcinoma development in hepatitis C patients given interferon-based antiviral therapy. *Hepatol. Res.* 2015; **45**: 152–61.
10 Singal AG, Lim JK, Kanwal F. AGA clinical practice update on interaction between oral direct-acting antivirals for chronic hepatitis C infection and hepatocellular carcinoma: expert review. *Gastroenterology*. 2019; **156**: 2149–57.
11 Muzica CM, Stanciu C, Huiban L *et al*. Hepatocellular carcinoma after direct-acting antiviral hepatitis C virus therapy: a debate near the end. *World J. Gastroenterol.* 2020; **26**: 6770–81.
12 Asahina Y, Izumi N, Hiromitsu K *et al*. JSH guidelines for the management of hepatitis C virus infection: a 2016 update for genotype 1 and 2. *Hepatol. Res.* 2016; **46**: 129–65.
13 Drafting Committee for Hepatitis Management guidelines, the Japan Society of Hepatology. Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update. *Hepatol. Res.* 2022; **50**: 791–816.
14 Ikeda M, Fujiyama S, Tanaka M *et al*. Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon. *J. Gastroenterol.* 2005; **40**: 148–56.
15 Arase Y, Kobayashi M, Suzuki F *et al*. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. *Hepatology*. 2013; **57**: 964–73.
16 Asahina Y, Tsuchiya K, Nishimura T *et al*. Alpha-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. *Hepatology*. 2013; **58**: 1253–62.
17 Oze T, Hiramatsu N, Yakushijin T *et al*. Post-treatment levels of α-fetoprotein predict incidence of hepatocellular carcinoma after interferon therapy. *Clin. Gastroenterol. Hepatol.* 2014; **12**: 1186–95.
18 Yamashita N, Ohho A, Yamasaki A, Kurokawa M, Kotoh K, Kajiwara E. Hepatocarcinogenesis in chronic hepatitis C patients achieving a sustained virological response to interferon: significance of lifelong periodic cancer screening for improving outcomes. *J. Gastroenterol.* 2014; **49**: 1504–13.
19 Tada T, Kumada T, Toyoda H *et al*. Post-treatment levels of α-fetoprotein predict long-term hepatocellular carcinoma development after sustained virological response in patients with hepatitis C. *Hepatol. Res.* 2017; **47**: 1021–31.
20 Yamada R, Hiramatsu N, Oze T *et al*. Incidence and risk factors of hepatocellular carcinoma change over time in patients with hepatitis C virus infection who achieved sustained virologic response. *Hepatol. Res.* 2019; **49**: 570–8.
21 Toyoda H, Kumada T, Tada T *et al*. Risk factors of hepatocellular carcinoma development in non-cirrhotic patients with sustained virologic response for chronic hepatitis C virus infection. *J. Gastroenterol. Hepatol.* 2015; **30**: 1183–9.
22 Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J. Hepatol.* 2020; **72**: 250–61.
23 Kokudo N, Takemura N, Hasegawa K *et al*. Clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatol. Res.* 2019; **49**: 1109–13.
24 El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. *Hepatology*. 2016; **64**: 130–7.
25 van der Meer AJ, Feld JJ, Hofer H *et al*. Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication. *J. Hepatol.* 2017; **66**: 485–93.