



Impact of COVID-19 pandemic on surveillance of hepatocellular carcinoma: A study in patients with chronic hepatitis C after sustained virologic response

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Funding information

None.

Abstract

Background: The current coronavirus disease 2019 (COVID-19) pandemic has strongly influenced many aspects of the medical care, including cancer surveillance.

Aims: We investigated how the COVID-19 pandemic influenced surveillance for hepatocellular carcinoma (HCC), focusing on patients with hepatitis C virus infection who were receiving surveillance for HCC after sustained virologic response (SVR) in Japan.

Methods: Patients who achieved SVR between 1995 and 2017 and continued receiving surveillance were compared by month in terms of the rate at which they kept their scheduled visits for HCC surveillance from July 2019 to May 2020.

Results: The percentage of kept scheduled visits was above 97% before February 2020. By contrast, it declined sharply after March 2020 when COVID-19 became pandemic; the percentages were 75.5% in March, 63.0% in April and 49.1% in May 2020 (July 2019–February 2020 vs March–May 2020, $P < 0.0001$). Similar declines were observed in patients with cirrhosis or advanced fibrosis and in those with a history of HCC. Whereas most patients who cancelled a scheduled visit before February 2020 did not reschedule it, the majority of patients with cancellations after March 2020 did want to reschedule.

Conclusions: The percentages of scheduled visits that were kept declined rapidly after COVID-19 became pandemic in Japan, although the spread of COVID-19 is relatively mild and the legal restriction of people's behaviour and movement is absent. Instituting measures to follow-up with cancelled patients and resume surveillance will be necessary in the future.

1 | INTRODUCTION

Surveillance for hepatocellular carcinoma (HCC) impacts favourably on prognosis of patients with chronic liver disease by increasing the rate of early HCC detection and the use of curative treatments,

when it develops.¹⁻⁵ The risk of HCC persists in patients with chronic hepatitis C virus (HCV) infection even after the achievement of sustained virologic response (SVR), that is the eradication of HCV,⁶ and it remains necessary for patients with SVR continuing to visit the hospital and receive examinations regularly. In particular,

the risk of HCC development after SVR has increased since interferon (IFN)-free, oral direct-acting antivirals (DAAs) were first used to treat HCV in Japan, where patients with SVR after DAA therapy are older and frequently have advanced liver fibrosis or cirrhosis.^{7,8} In Japan, it is recommended that all patients with previous HCV infection fundamentally continue visiting hospitals regularly for surveillance of HCC.

Since social distancing and stay-at-home policies have been instituted to slow the spread of coronavirus disease 2019 (COVID-19), unexpected outcomes have been observed among patients with chronic diseases, including those who are under surveillance for HCC. The COVID-19 pandemic may restrict patients' daily behaviour, and may prevent some from making their regular hospital visits. This also applies to patients under surveillance for HCC and to those participating in other cancer-screening programs.⁹ Therefore, in this study, we investigated how the current COVID-19 pandemic influenced surveillance for HCC, focusing on patients who are surveyed after SVR in Japan.

2 | METHODS

2.1 | Study patients

A total of 1405 patients with chronic HCV infection achieved SVR between 1992 and 2017 at Ogaki Municipal Hospital (578 by IFN-based therapy and 827 by IFN-free DAA therapy). Of these patients, 432 patients had discontinued HCC surveillance before study initiation in July 2019. In addition, 38 patients had active HCC that required continuous treatment or follow-up. The remaining 935 patients who continued to regularly visit the hospital for HCC surveillance and who did not have active HCC in July 2019 were enrolled in the study (Figure 1).

The study protocol complied with the Helsinki Declaration and was approved by our institutional review board. The requirement for

informed consent was waived, as we used only de-identified data collected from medical records.

2.2 | Policy regarding patient surveillance after SVR and during the COVID-19 pandemic

At our hospital, all patients with chronic HCV infection who have achieved SVR are advised to continue regular visits for HCC surveillance. Principally, patients are advised to visit the hospital at 6- to 8-month intervals and to undergo laboratory tests and ultrasonography examination. Patients with a history of HCC are advised to visit the hospital at 3- to 6-month intervals. Patients usually visit the hospital, undergo laboratory tests and an ultrasonography examination before meeting with their doctors, meet with their doctor on the same day of examination and then schedule their next appointment. If they miss a scheduled visit without contacting the hospital beforehand, we telephone them to ask them why they did not keep their appointment and advise them to reschedule.

We have not restricted hospital visits during the COVID-19 pandemic. The hospital is located in the countryside in central Japan, and there were relatively few cases of COVID-19 in our region in March, April and May (150 cases and seven deaths as of May 31, 2020). During this period, we did not telephone patients to ask them to postpone their visits, and laboratory test, imaging examinations and meetings with doctors were performed as usual.

2.3 | Data collection and analysis

We used electronic medical records to collect information on the visits of 935 patients. When patients visited on the scheduled day, this was counted as a visit. When a visit was postponed to another date, this was counted as rescheduling. When patients informed us that they would miss their visit but did not set up another date, this

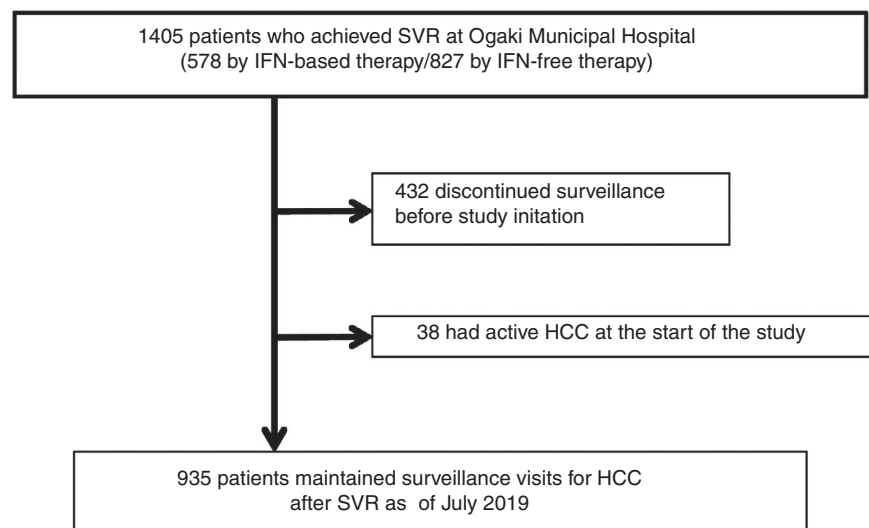


FIGURE 1 Schematic representation of study patient enrolment

was defined as failure to reschedule. When patients missed their visit and did not inform us ahead of time, we telephoned them once and advised them to set up another date. If they agreed, this was defined as rescheduling. When patients refused to set up another date or if we could not contact them, this was counted as failure to reschedule.

We compared the monthly percentages of patients who successfully visited the hospital for their scheduled visit. We also compared the corresponding percentages in patients with cirrhosis or advanced fibrosis, and in those with a history of HCC. The presence of cirrhosis was assessed clinically prior to anti-HCV therapy based on imaging and endoscopic findings, including the presence of oesophageal or gastric varices, collateral veins due to portal hypertension and splenomegaly. Advanced fibrosis was defined by a FIB-4 index¹⁰ above 3.25 before anti-HCV therapy. For patients who cancelled their visits, we compared the distribution of patients who did and did not reschedule their visits.

TABLE 1 Background of study patients (n = 935)

Age (y) ^a	70.1 (63.0-77.0)
Gender (male/female)	430 (46.6)/505 (54.0)
Treatment (IFN-based/DAA-based) ^b	306 (32.7)/629 (67.3)
Advanced fibrosis/cirrhosis (no/yes)	579 (61.9)/356 (38.1)
History of HCC (no/yes)	815 (87.2)/120 (12.8)

Note: Values in parentheses are interquartile ranges or percentages. Abbreviations: DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; IFN, interferon.

^aAge in July 2019.

^bAntiviral treatment used to achieve SVR.

2.4 | Statistical analysis

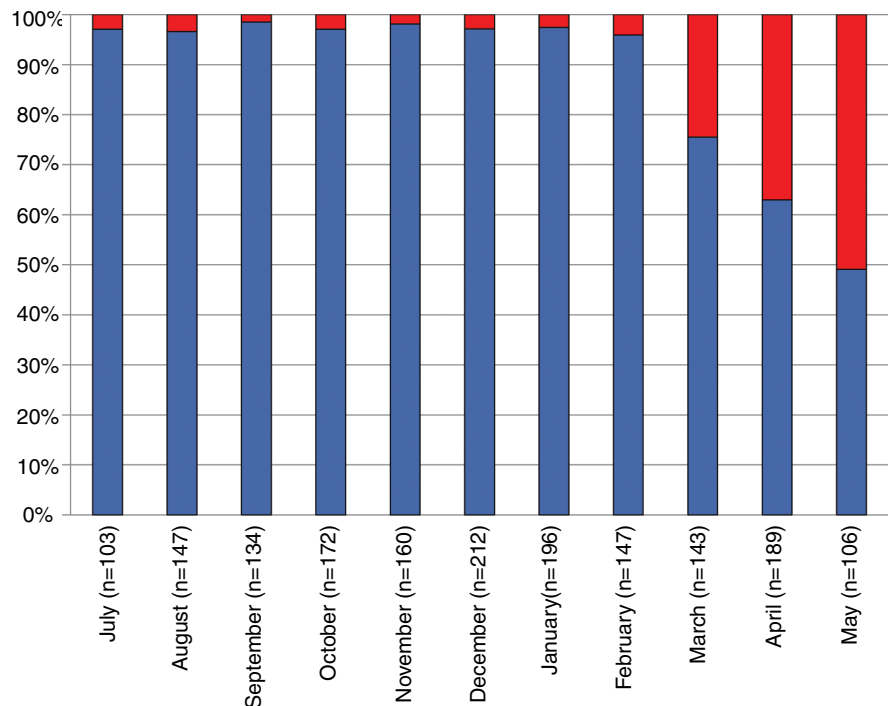
Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as medians and interquartile ranges. Monthly differences in the percentages of patients who kept their scheduled visits were analysed with the Chi-square test. Statistical analysis was performed using JMP statistical software, version 11.0 (SAS Institute). All *P* values were derived from two-tailed tests, with *P* < 0.05 accepted as statistically significant.

3 | RESULTS

Table 1 shows the characteristics of the study patients. Patients who achieved SVR by IFN-based therapy (n = 306) entered surveillance between 1995 and 2013, and those who achieved SVR by IFN-free DAA therapy (n = 629) entered surveillance between 2014 and 2017. Because Japanese patients with HCV infection are older than those in Western countries, the ages of patients who achieved SVR and who were receiving surveillance were high as of July 2019. There were 356 patients (38.1%) with cirrhosis or advanced liver fibrosis and 120 patients (12.8%) with a history of HCC.

Figure 2 shows the monthly percentages of patients who visited the hospital on the day of their appointment. These were above 95% in all months until February 2020, but they declined suddenly in March 2020. The percentages of patients who kept their scheduled visits in March, April and May 2020 were 79.7%, 63.0% and 49.1% respectively. The overall percentage from March to May 2020 was significantly lower than that from July 2019 to

FIGURE 2 Monthly percentages of patients who kept their scheduled visits (blue bars) between July 2019 and May 2020. Blue bars, the percentages of patients who kept their scheduled visits; red bars, the percentages of patients who cancelled their visits. The first COVID-19 death was reported on February 13, 2020. The Japanese government closed public school early in March; it also declared a state of emergency on April 16, which was terminated on May 14



February 2020 (1236 of 1271 visits, 97.2% vs 279 of 438 visits, 63.7% respectively; $P < 0.0001$). Subanalyses of 356 patients with cirrhosis or advanced fibrosis and of 120 patients with a history of HCC showed less marked declines in the percentage of patients who kept their scheduled visits (Figure 3). The percentages of patients who visited the hospital in March, April and May 2020 were 81.5%, 68.4% and 71.0%, respectively, in patients with cirrhosis or advanced fibrosis, and 100%, 80.6% and 76.5%, respectively, in patients with a history of HCC. However, in 257 patients with cirrhosis or advanced fibrosis but with no history of HCC, the percentages were low (72.2%, 51.9% and 38.5% respectively) despite the high risk of HCC development.

Among 416 patients who had an appointment to visit the hospital between March and May 2020, 273 patients kept their scheduled visit and 143 patients did not. There was no difference in the percentage of patients who kept their scheduled visit based on the type of antiviral treatment used to achieve SVR (IFN-based, 62.5% vs DAA-based, 65.7%; $P = 1.0000$). When comparing patients with or without the maintenance of their scheduled visit, there was no difference in the duration from the achievement of SVR (median [IQR], 4.22 [3.82-4.69] years in patients who kept their visit vs 4.16 [3.66-4.61] years in patients who missed their visit; $P = 0.2809$). In 65 patients with a history of HCC, there was no difference in the duration from the last treatment of HCC based on the maintenance of their scheduled visit (median [IQR], 2.50 [1.80-3.78] years in patients who kept their visit vs 2.60 [1.55-4.40] years in patients who missed their visit; $P = 0.9736$). HCC was detected only in one patient with a history of HCC who maintained the scheduled visit

between March and May 2020. Fortunately, we experienced no patient who had the evidence of COVID-19 during the study period.

Table 2 shows the number of patients, stratified by gender and age, who kept their scheduled visits in March, April and May 2020. The only significant findings were that the frequency of missed visits was higher in females than males in April and May, and was higher in April in patients aged over 75 years than in other age groups.

Table 3 shows the monthly number of patients who missed their regular visits and then did or did not reschedule. Prior to February 2020, the majority of patients who cancelled their visits did not reschedule and quitted receiving surveillance, whereas after March 2020, most patients did reschedule. However, 16 patients subsequently cancelled their rescheduled visits (14 patients rescheduled again and the remaining two patients did not).

4 | DISCUSSION

In this study, we focused on patients with previous chronic HCV infection who achieved SVR. We did not analyse patients with active HCC who were undergoing treatment. Furthermore, patients with decompensated cirrhosis were not included because they were not candidates for IFN-based anti-HCV therapy, and IFN-free DAA-based therapy was not approved for this population in Japan before 2019. Patients with active HCC frequently visit the hospital for treatment (eg for prescription of oral molecular-targeted drugs against HCC) or for evaluation of treatment efficacy. Individuals without decompensation or active HCC who are under surveillance after SVR are relatively homogenous in that they

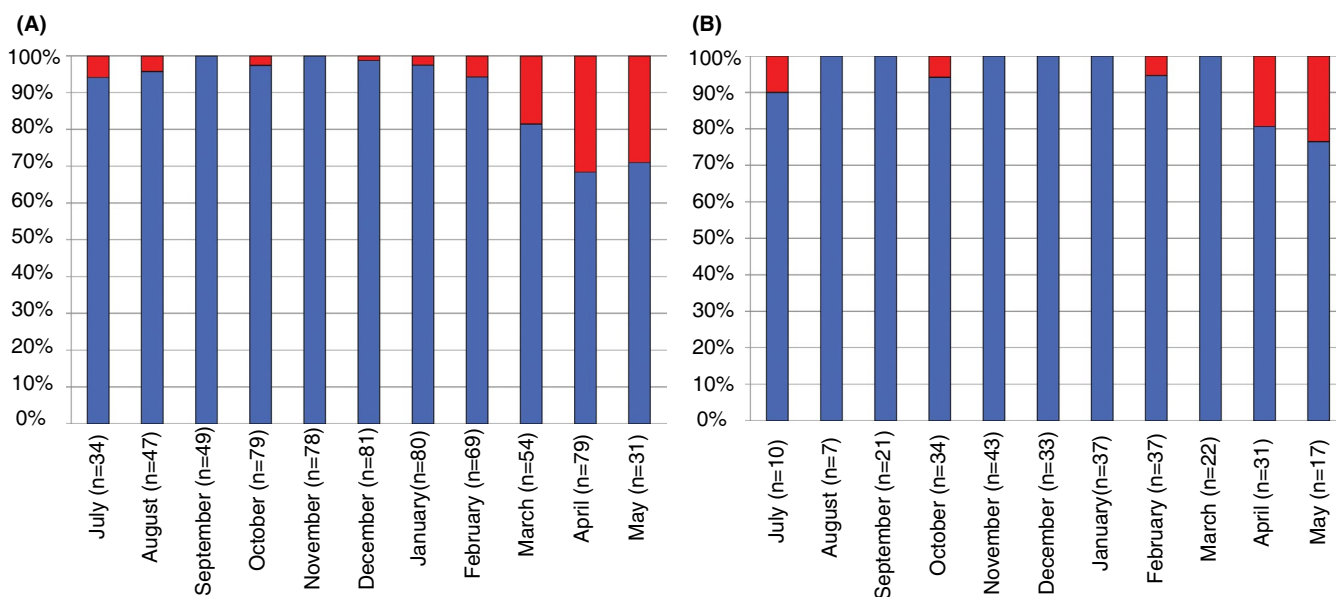


FIGURE 3 Monthly percentage of patients who kept their scheduled visits (blue bars) between July 2019 and May 2020 (A) in patients with cirrhosis or advanced fibrosis, and (B) in patients with a history of hepatocellular carcinoma. Blue bars, the percentages of patients who kept their scheduled visits; red bars, the percentages of patients who cancelled their visits

TABLE 2 Number of patients who kept scheduled visits in March, April and May 2020 based on patient gender and age

	March 2020	April 2020	May 2020
Total	108/143 (75.5)	119/189 (63.0)	52/106 (49.1)
Male	43/58 (74.1)	66/89 (74.2)	27/50 (54.0)
Female	65/85 (76.5)	53/100 (53.0)	25/56 (44.6)
Age (y)			
<55	10/14 (71.4)	15/23 (65.2)	5/8 (62.5)
55-65	23/29 (79.3)	27/37 (73.0)	7/19 (36.8)
65-75	38/52 (73.1)	46/65 (72.3)	19/39 (48.7)
≥75	37/48 (77.1)	31/64 (48.4)	21/40 (52.5)

Note: Values in parentheses are percentages.

TABLE 3 Number of patients by month who did and did not reschedule cancelled visits

Period	Action after cancellation	Patient number (percentage)
July, 2019 (n = 3)	No reschedule	3 (100)
	Reschedule	0
August, 2019 (n = 5)	No reschedule	5 (100)
	Reschedule	0
September, 2019 (n = 2)	No reschedule	2 (100)
	Reschedule	0
October, 2019 (n = 5)	No reschedule	3 (60.0)
	Reschedule	2 (40.0)
November, 2019 (n = 3)	No reschedule	3 (100)
	Reschedule	0
December, 2019 (n = 6)	No reschedule	5 (83.3)
	Reschedule	1 (16.7)
January, 2020 (n = 5)	No reschedule	4 (80.0)
	Reschedule	1 (20.0)
February, 2020 (n = 6)	No reschedule	4 (66.7)
	Reschedule	2 (33.3)
March, 2020 (n = 29)	No reschedule	3 (10.3)
	Reschedule	26 (89.7)
April, 2020 (n = 70)	No reschedule	15 (21.4)
	Reschedule	55 (78.6)
May, 2020 (n = 54)	No reschedule	4 (7.4)
	Reschedule	50 (92.6)

Note: Values in parentheses are percentages.

regularly visit the hospital purely for surveillance and not drug treatment, so we considered this population to be useful for evaluating the impact of the COVID-19 pandemic on the HCC surveillance system.

The influence of the COVID-19 pandemic on medical care varies largely by countries and regions. In Japan, the impact is less marked than in European countries or the United States because of less widespread disease. The first COVID-19 death was reported on February 13, 2020, but the subsequent increase in number was not very rapid. Indeed, the number of patients who have died due to

COVID-19 is under 1000 as of May 31, 2020, whereas it is more than 100 000 in Europe and in the United States. In addition, the Japanese government did not issue strict stay-at-home orders, although in early March it closed public schools and on April 16 it declared a state of emergency that was terminated on May 14. The Japanese government requested that individuals stay at home and practice social distancing behaviour, but these were not legal requirements. The Japanese constitution makes it difficult for the government to establish laws restricting people's behaviour. Importantly, public transportation was functioning as usual even during the state of emergency. Individuals still may have been reluctant to use public transportation, but the hospital where this study was conducted is located in the countryside, and most patients access it by car. This resulted in a less marked decline in the number of patient visits and examinations than in the United States or Singapore.¹¹

Despite this, we found that the number of patients with SVR who kept their scheduled visits declined rapidly after March 2020. Strikingly, more than 97% of patients had kept their scheduled visits before February 2020, which indicates that Japanese patients are highly interested in their health and are well-educated regarding the importance of surveillance. By contrast, the percentage of patients who kept their scheduled visits declined to 75% in March, 60% in April and below 50% in May. These results show that the COVID-19 pandemic had a strong impact on the surveillance system for HCC and may destroy it, even in patients with a high interest in HCC surveillance and in an area where COVID-19 spread has been mild.

The main reason for the cancellation of scheduled visits after March 2020 was concern about COVID-19, as indicated by medical record data on telephone contacts with patients. Most of the time, patients who cancelled their scheduled visits after March 2020 rescheduled them, indicating that the majority did not want to discontinue surveillance. However, some patients rescheduled multiple times, which may ultimately result in complete failure to follow-up. By contrast, no patients indicated that they had economic reasons for not visiting the hospital during the study period. This is partly because the national insurance system covers the medical costs of all Japanese citizens. Although patients who missed visits, with or without rescheduling, are expected to return to surveillance, this is not certain. Indeed, the percentage of patients who kept their scheduled visits remained low in May 2020, despite the fact that the state of emergency was terminated in this region on May 14. It is unclear when this pandemic will end. In addition, the worldwide economic crisis that is expected to occur in the near future will also involve Japan, and at that point some patients may cancel their visits for economic reasons.

There are several limitations to this study. The study sample was restricted to HCV patients who had achieved SVR. Therefore, the influence of the COVID-19 pandemic on HCC surveillance should also be studied in patients with HBV infection or those with nonviral liver diseases. In addition, it is necessary to compare the progression of HCC at detection and survival of HCC patients diagnosed between before and after the COVID-19 pandemic in long-term observation to determine the real impact of the pandemic on HCC surveillance. Finally, this was a single-institution study. The policy for dealing

with patients during the COVID-19 pandemic differs largely among regions and hospitals. For instance, some hospitals have advised patients to cancel non-urgent appointments, which will of course strongly influence the rate of patient visits. Further nationwide and global assessment of the impact of the COVID-19 pandemic on HCC surveillance will be necessary in the future.

In conclusion, the results of this study showed that the COVID-19 pandemic strongly hampered the surveillance system for HCC in HCV patients who achieved SVR. Clinicians should carefully monitor the outcomes of patients who do not attend their scheduled visits, and take measures to ensure that they resume surveillance for HCC.

CONFLICT OF INTEREST

No other authors had conflict and interest.

AUTHORSHIP

Guarantor of the article: Hidenori Toyoda.

Specific author contributions: All authors collected the data, Hidenori Toyoda analysed the data, designed the research study, and wrote the paper. All authors approved the final version of the manuscript.

Declaration of personal interests: Hidenori Toyoda has served as a speaker for AbbVie, MSD, and Bayer, and Takashi Kumada has served as a speaker for AbbVie and Gilead Sciences.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/ygh2.418>.

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REFERENCES

1. Sangiovanni A, Del Ninno E, Fasani P, et al. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology*. 2004;126:1005-1014.
2. Toyoda H, Kumada T, Kiriyaama S, et al. Impact of surveillance on survival of patients with initial hepatocellular carcinoma: a study from Japan. *Clin Gastroenterol Hepatol*. 2006;4:1170-1176.
3. Wong GL-M, Wong VW-S, Tan G-M, et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. *Liver Int*. 2008;28:79-87.
4. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS Med*. 2014;11:e1001624.
5. Kansagara D, Papak J, Pasha AS, et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. *Ann Intern Med*. 2014;161:261-269.
6. Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. *Clin Infect Dis*. 2013;57:230-236.
7. Toyoda H, Kumada T, Tada T. Changes in patient backgrounds may increase the incidence of HCC after SVR in the era of IFN-free therapy for HCV. *Hepatology*. 2016;64:1818-1819.
8. Toyoda H, Tada T, Takaguchi K, et al. Difference in background characteristics of patients with chronic hepatitis C who achieved sustained virologic response with interferon-free versus interferon-based therapy and the risk of developing hepatocellular carcinoma after eradication of hepatitis C virus in Japan. *J Viral Hepat*. 2017;24:472-476.
9. Dinmohamed AG, Visser O, Verhoeven RHA, et al. Fewer cancer diagnoses during the COVID-19 endemic in the Netherland. *Lancet Oncol*. 2020;21:750-751.
10. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest. *Hepatology*. 2007;46:32-36.
11. Toyoda H, Huang DQ, Le MH, Nguyen MH. Liver care and surveillance: the global impact of COVID-19 pandemic. *Hepatol Commun* (in press).

How to cite this article: Toyoda H, Yasuda S, Kiriyaama S, et al. Impact of COVID-19 pandemic on surveillance of hepatocellular carcinoma: A study in patients with chronic hepatitis C after sustained virologic response. *GastroHep*. 2020;00:1-6. <https://doi.org/10.1002/ygh2.418>