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Higher FIB-4 index at baseline predicts development of liver cancer in a community-based cohort with viral hepatitis

Makiko Kimura[1,§], Tomoki Nishikawa[1,§], Tetsuro Shimakami[1,2,*], Takeshi Terashima[1,2], Rika Horii[1,2], Masako Fukuda[1], Mika Yoshita[1], Noboru Takata[1,2], Tomoyuki Hayashi[1,2], Masaya Funaki[1], Kouki Nio[1], Hajime Takatori[1], Kuniaki Arai[1,2], Tatsuya Yamashita[1,2], Masao Honda[1], Junko Tanaka[3], Shuichi Kaneko[1], Taro Yamashita[1]

[1] Department of Gastroenterology, Kanazawa University Hospital, Ishikawa, Japan;
[2] WHO Collaborating Center for Viral Hepatitis and Liver Cancer in WPRO, Kanazawa, Ishikawa, Japan;
[3] Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima City, Hiroshima, Japan.

Abstract: Hepatitis B and C (HBV and HCV) testing has been performed in Japan since 2002 and is subsidized by central and prefectural governments. A follow-up program for HBV- or HCV-infected persons was started at that time in Ishikawa Prefecture. This study analyzed the long-term follow-up data from this program. In total, 1029 participants in the Ishikawa Hepatitis Follow-up Program (HBV-infected, *n* = 535; HCV-infected, *n* = 494) were enrolled. Clinical data between the first visit and the most recent visit by March 2019 were collected. In the HBV-infected group, 384 persons (71.8%) were asymptomatic carriers, 133 (24.9%) developed chronic hepatitis, 15 (2.8%) developed compensated liver cirrhosis, and 3 (0.6%) developed decompensated liver cirrhosis. Ninety (16.8%) were treated with nucleotide/nucleoside analogs. Sixteen (3.0%) developed liver cancer. In the HCV-infected group, 427 persons (86.4%) developed chronic hepatitis, 46 (9.3%) developed compensated liver cirrhosis, and 21 (4.3%) developed decompensated liver cirrhosis. Forty-eight (9.7%) developed liver cancer. Three hundred and seventy-eight (76.5%) received antiviral therapy (a direct-acting antiviral in 166, interferon-based treatment followed by a direct-acting antiviral in 73, and interferon-based treatment in 139). The subsidy system was used by 270 persons (71.4%). Sustained virological response was confirmed in 340 persons (68.8%). A higher FIB-4 index at the first visit was a significant risk factor for liver cancer in HBV-infected and HCV-infected persons. The Ishikawa Hepatitis Follow-up Program has revealed the clinical course of HBV and HCV infection in community-dwelling individuals. The results will be used for micro-elimination at a prefectural level.

***Keywords*:** direct-acting antivirals, hepatitis B virus, hepatitis C virus, liver cancer, liver cirrhosis

Introduction

Viral hepatitis is a major public health challenge that caused an estimated 1.57 million deaths worldwide in 2019 and accounted for 2.1% of all deaths (*1*). Most mortality associated with viral hepatitis is attributable to cirrhosis and liver cancer. There are four important hepatitis viruses, namely, HAV, HBV, HCV, and HEV. While all these viruses can cause acute infection, only HBV and HCV cause chronic infection, which may progress over time to cirrhosis or liver cancer. An estimated 295.9 million people were known to have HBV infection and 57.8 million to have HCV infection worldwide in 2019 (*2*). Therefore, to reduce the mortality associated with these infections, it is important to be able to identify individuals infected with HBV or HCV, to introduce antiviral therapy, and to perform periodic surveillance for hepatic function and liver cancer.

Antiviral therapy dramatically reduces deaths from HBV- and HCV-related liver diseases (*3-5*). Highly effective direct-acting antiviral (DAA) therapy has enabled elimination of HCV in over 95% of patients treated (*6*). However, liver cancer can occur even after HCV elimination, defined as a sustained virological response (SVR). Therefore, surveillance for liver cancer is necessary after elimination of HCV as well as during persistent infection (*7*). In patients with HBV, treatment with a nucleoside/nucleotide analog reduces the viral load and ameliorates liver cirrhosis (*8*) and impedes progression to liver failure and liver cancer (*5,9,10*). Nevertheless, liver cancer can still occur after the HBV viral load is suppressed by antiviral treatment. Current HBV treatment guidelines do not recommend antiviral treatment for asymptomatic HBV carriers, which

includes those with immune-tolerant or inactive chronic HBV infection as defined by the American Association for the Study of Liver Diseases (*11*). Liver cancer is also known to occur in asymptomatic carriers, albeit with low incidence. Thus, there are multiple lines of evidence suggesting that all individuals infected with HBV or HCV should receive lifelong care.

Effective linkage of individuals with HBC or HCV infection to appropriate care is essential to achieve the World Health Organization (WHO) goal of eliminating HBV/HCV by 2030 (*12*). The first step is to provide HBV and HCV tests for as many people as possible, particularly those at high risk, and the second is to encourage infected individuals to see a liver specialist to receive the necessary care, including antiviral therapy, periodic liver function and virological monitoring, and surveillance for liver cancer.

Testing for HBV and HCV has been subsidized by central and prefectural governments in Japan since 2002 (*13,14*). In the same year, the Ishikawa Prefecture started a surveillance program for people found to be positive for HBV or HCV by government-subsidized testing. This program includes follow-up by municipal healthcare workers, who visit or telephone individuals who have tested positive for HBV or HCV to ascertain whether they are under the care of a liver specialist and encourage them to attend if not. The program was modified in 2010 and is now known as the Ishikawa Hepatitis Follow-up Program, which provides annual follow-up for people who have tested positive for HBV or HCV *via* the publicly funded testing system. This program is based at Kanazawa University Hospital, which is the sole regional core institution in Ishikawa Prefecture (*15*), and encourages people who have tested positive for HBV or HCV to attend for specialized care. Thus, the program offers linkage to care and collects long-term clinical data on people who have tested positive for hepatitis. In this study, we analyzed the long-term follow-up data for participants in the Ishikawa Hepatitis Follow-up Program to determine the clinical course of their diseases (including survival status), occurrence of liver cancer, introduction of antiviral therapy, and the use of subsidy for antiviral therapy. Our findings indicate that government-subsidized hepatitis testing has been beneficial to this local community. We hope that our findings can be used to achieve micro-elimination of HBV/HCV and reduce mortality from liver cancer at a prefectural level in Japan.

Methods

Data collection

Participants in the Ishikawa Hepatitis Follow-up Program agree to periodic collection of their data by a specialized institution or a regional core center. Accordingly, information on the following was collected by a regional core center: age, sex, aspartate transaminase (AST), alanine transaminase (ALT), and platelet count at the first visit to a specialized institution or regional core center and at the most recent visit before March 2019. The collected data were then used to calculate the AST to platelet ratio index (APRI) and FIB-4 index. Information on antiviral therapy, viral status (particularly HCV), liver status, including occurrence of liver cancer, deaths, and the cause of death between the two time points was obtained from examination letters or direct requests to specialized institutions or the regional core center. The diagnosis of compensated cirrhosis and decompensated cirrhosis was comprehensively made based on clinical data, physical examinations, or liver imaging tests by the hepatologists in specialized institutions or a regional core center. Data on subsidized antiviral therapy for participants in the program were obtained from the Ishikawa prefectural government.

Statistical analysis

The data are shown as the mean ± standard deviation and were analyzed using the Student's *t*-test, chi-squared test, the Kaplan–Meier method, receiver operating characteristic curve analysis, and Cox proportional-hazards regression analysis. All statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, Inc., La Jolla, CA). A p-value < 0.05 was considered statistically significant.

Ethics statement

The protocol for this study was approved by the Medical Ethics Committee of Kanazawa University (Approval No. 2018-105 (2871)) and conforms to the provisions of the Declaration of Helsinki.

Results

In Japan, municipal screening for HBV and HCV was performed as part of a national health promotion program for seniors between 2002 and 2008 and as part of a general health promotion program from 2008 onwards. In Ishikawa Prefecture, 222,029 individuals were tested for HBV and 221,967 were tested for HCV under these programs between 2002 and 2019, and 1,956 and 1,655 were positive for HBV and HCV, respectively. In Ishikawa Prefecture, starting in 2002, municipal public health staff followed up persons who were positive for viral hepatitis tests in local screening programs. The same personnel made annual home visits or telephone calls to ascertain whether individuals with a positive test had visited a specialized institution and recommended a visit to those who had not.

In 2010, the regional core center for hepatitis care coordination (Kanazawa University Hospital, the only regional core center in the prefecture) took over the

follow-up process. The new program was named as the Ishikawa Hepatitis Follow-up Program and is run in conjunction with the Ishikawa Prefecture. Persons who have tested positive for viral hepatitis and consent to participate in the program receive a leaflet in July each year from the regional core center recommending that they visit a specialized institution as well as an examination letter for their physician to complete with details of their visit. The patient brings this letter to the specialized institution, where the consulting hepatologist records in the letter the date of examination, diagnosis, liver imaging tests performed, recommendations for further testing and treatment, and the date of the next appointment. The regional core center then uses the completed examination letter to confirm whether a participant has visited a specialized institution and enters data concerning treatment and disease status into a database.

By the end of 2022, 1,726 (49.2%) of the 3,511 persons who tested positive for hepatitis from 2002 onwards had consented to participate in the follow-up program, 541 (15.4%) had declined to participate, and 1,244 (35.4%) had not responded to an invitation to participate.

Kanazawa University Hospital collects clinical data from the examination letters returned by specialized institutions, learns of any changes in the health of the study participants, and follows the long-term clinical course of persons with viral hepatitis. In this study, we aimed to clarify the clinical course in this community-based cohort with viral hepatitis over time using the data collected for participants in the Ishikawa Hepatitis Follow-up Program. However, the data provided in examination letters were insufficient. Therefore, we collected the necessary data directly from the specialized institutions, the regional core center, and municipal government.

Data for 1,029 of the 1,557 persons identified to have viral hepatitis during the study period were available for analysis. Five hundred and thirty-five were HBsAg-positive and 494 were HCV antibody-positive. The HBV-positive group included 199 men and 336 women with a mean age of 59.5 years (range, 15–82) at the first visit and an average length of observation of 6.4 years (range, 1–25). By March 2019 (the end of the 2018 financial year), 384 persons (71.8%) were diagnosed to be asymptomatic carriers, 133 (24.9%) to have chronic hepatitis, 15 (2.8%) to have compensated liver cirrhosis, and 3 (0.6%) to have decompensated liver cirrhosis. Ninety (16.8%) had been treated with nucleoside/nucleotide analogs; 6 were asymptomatic carriers, 70 had chronic hepatitis, 11 compensated liver cirrhosis, and 3 decompensated liver cirrhosis. The indication of nucleoside/nucleotide analogs treatments was decided by the hepatologists in the specialized institutions. During the observation period, 16 (3.0%) had developed liver cancer and 4 had died (2 from liver cancer and 2 of non-liver-related causes). The HBV-positive individuals who developed liver cancer were found to have APRI and FIB-4 index values at the first and most recent examination that were significantly higher than those in their counterparts who did not develop liver cancer. Moreover, the platelet count at the first examination was significantly lower in those who developed liver cancer and neither alcohol drinking nor complications of diabetes mellitus did not significantly affect development of liver cancer (Table 1). We performed a COX proportional-hazards regression

Table 1. Comparison of HBV-infected individuals according to whether they developed liver cancer

Items	Liver cancer (+)	Liver cancer (−)	*p*-value
Cases, *n*	16	519	
First examination			
Age (years)	61.5 ± 9.4	59.5 ± 10.1	NS
AST (IU/L)	31.9 ± 11.9	25.8 ± 16.2	NS
ALT (IU/L)	26.2 ± 11.4	24.8 ± 24.4	NS
Platelets ($\times 10^4/\mu L$)	13.27 ± 5.28	21.02 ± 5.61	< 0.001
Albumin (g/dL)	4.08 ± 0.78	4.35 ± 0.35	NS
APRI	1.02 ± 0.75	0.45 ± 0.34	< 0.05
FIB-4 index	3.40 ± 2.00	1.66 ± 0.83	< 0.05
Most recent examination			
Observation period (years)	8.92 ± 6.25	6.34 ± 4.29	NS
Age (years)	70.9 ± 8.1	66.4 ± 10.1	< 0.05
Alcohol intake (> 20g/day) +/-/unknown	1/11/4	47/394/68	NS
DM +/-/unknown	0/16/0	49/455/15	NS
AST (IU/L)	38.8 ± 38.5	24.0 ± 11.7	NS
ALT (IU/L)	25.0 ± 26.0	20.0 ± 11.7	NS
Platelets ($\times 10^4/\mu L$)	16.2 ± 10.9	20.7 ± 10.9	NS
Albumin (g/dL)	3.65 ± 0.85	4.26 ± 0.41	< 0.05
APRI	0.93 ± 0.67	0.43 ± 0.39	< 0.01
FIB-4 index	4.41 ± 3.19	1.95 ± 1.09	< 0.01

Liver cancer (+), developed liver cancer during the observation period. Liver cancer (−), did not develop liver cancer during the observation period. ALT, alanine transaminase; APRI, AST to platelet ratio; AST, aspartate transaminase; HBV, hepatitis B virus; NS, not significant; DM, diabetes mellitus.

analysis to identify factors contributing to development of liver cancer in HBV-infected individuals. Univariate analysis showed that, a lower platelet count, a lower albumin level, and higher APRI and FIB-4 index values significantly increased the risk of liver cancer. Only a higher FIB-4 index remained a significant risk factor for liver cancer in multivariate analysis (Table 2). We also performed a Kaplan–Meier analysis to determine the cumulative incidence of liver cancer. Overall, the cumulative incidence was 0.56% at day 2000 after the first visit, was 4.8% at day 4000, and plateaued thereafter. However, in several cases, liver cancer was detected later than day 6000 after the first visit (Figure 1A). There was no significant sex-related difference in the cumulative incidence of liver cancer (Figure 1B). To determine the suitable cutoff of FIB-4 index at the first visit for the prediction of liver cancer, we performed the receiver operating characteristic curve (ROC) analysis, which showed that the area under curve (AUC) was 0.82 and that FIB-4 index 2.41 was a suitable cutoff with sensitivity 0.88 and specificity 0.75. Based on this analysis, we compared the cumulative incidence of liver

Table 2. Risk factors for liver cancer development in the HBV-infected group

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age (years)	1.05	0.98–1.12	NS			
Sex (male)	1.27	0.42–3.82	NS			
NA (+)	13.36	3.67–48.64	< 0.001			
AST (IU/L)	1.01	0.99–1.03	NS			
ALT (IU/L)	1	0.98–1.02	NS			
Platelets ($\times 10^4/\mu L$)	0.72	0.63–0.82	< 0.001			
Albumin (g/dL)	0.23	0.07–0.77	< 0.05	0.55	0.17–1.81	0.33
APRI	2.87	1.69–4.86	< 0.001			
FIB-4 index	2.06	1.62–2.62	< 0.001	1.97	1.47–2.63	< 0.001
T-Bil (mg/dL)	2.62	0.7–9.9	NS			

Data at the first visit were analyzed. NA (+), nucleotide/nucleoside analogs used during the observation period. ALT, alanine transaminase; APRI, AST to platelet ratio; AST, aspartate transaminase; CI, confidence interval; HBV, hepatitis B virus; NS, not significant; T-Bil, total bilirubin.

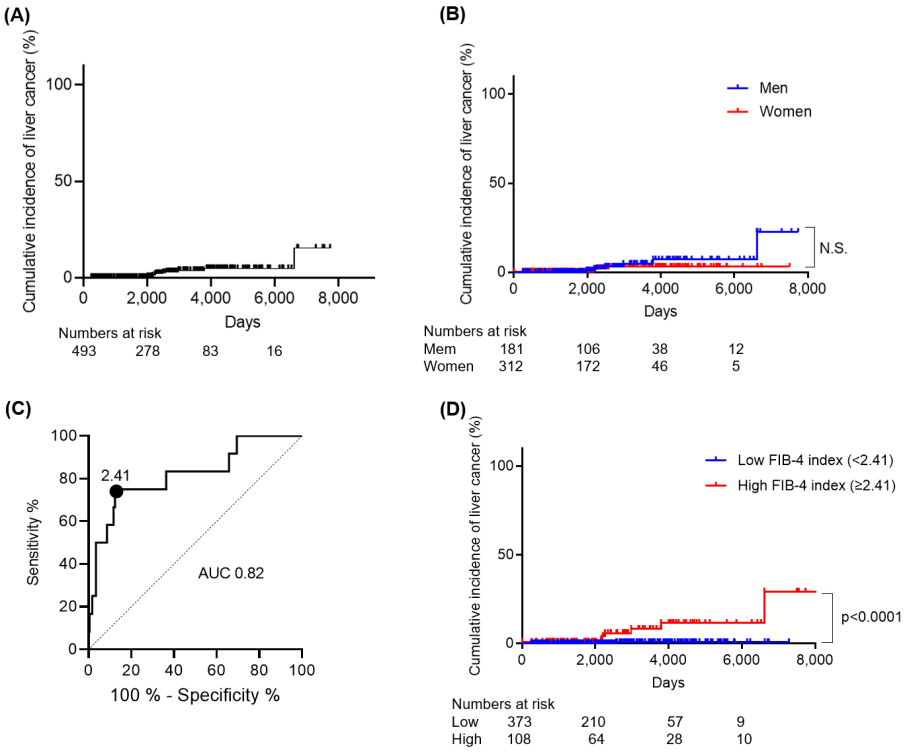

Figure 1. Cumulative incidence of liver cancer in the hepatitis B virus-infected group from the first visit. **(A)** Kaplan–Meier curve for all cases. **(B)** Comparison of Kaplan–Meier curves for the cumulative incidence of liver cancer according to sex by Cox proportional-hazards regression analysis. **(C)** Receiver operating characteristic (ROC) curve analysis for FIB-4 index at the first visit on liver cancer prediction. Area under the ROC curve was calculated. FIB-4 index at the point closest to the upper left was 2.41 (sensitivity 0.88, specificity 0.75). **(D)** Comparison of Kaplan–Meier curves for the cumulative incidence of liver cancer according to whether the FIB-4 index at the first visit was low (< 2.41) or high (≥ 2.41) by Cox proportional-hazards regression analysis. In Figure 1A, 1B and 1D, the numbers of analyzed patents were described. NS, not significant.

Table 3. Comparison of HCV-infected individuals according to whether they received antiviral treatments

Items	Antiviral treatment (−)	Antiviral treatment (+)	*p*-value
Cases, *n*	116	378	
First examination			
Age (years)	71.0 ± 7.8	60.5 ± 10.2	< 0.001
AST (IU/L)	39.7 ± 23.4	43.7 ± 33.5	NS
ALT (IU/L)	34.5 ± 22.7	47.1 ± 47.9	< 0.001
Platelets ($\times 10^4/\mu L$)	16.3 ± 6.4	18.6 ± 12.0	< 0.05
Albumin (g/dL)	4.01 ± 0.51	4.26 ± 0.37	< 0.001
APRI	1.09 ± 1.10	0.99 ± 1.06	NS
FIB-4 index	3.81 ± 2.99	2.60 ± 1.78	< 0.001
Most recent examination			
Observation period (years)	7.14 ± 4.82	8.52 ± 5.19	< 0.05
Age (years)	78.4 ± 6.9	69.1 ± 10.0	< 0.001
AST (IU/L)	64.3 ± 138.1	24.2 ± 16.1	< 0.005
ALT (IU/L)	37.7 ± 80.1	18.2 ± 14.8	< 0.05
Platelets ($\times 10^4/\mu L$)	15.2 ± 6.7	18.2 ± 6.9	< 0.001
Albumin (g/dL)	3.45 ± 0.89	4.32 ± 2.34	< 0.001
APRI	2.14 ± 5.33	0.55 ± 0.60	< 0.005
FIB-4 index	7.23 ± 15.0	2.64 ± 1.70	< 0.005
During observation period			
Liver cancer (+)/(−)	15/101	33/342[†]	*NS*

[†]Unknown: 3. Antiviral treatment (+), persons who received antiviral treatment during the observation period; Antiviral treatment (−), persons who did not receive antiviral treatment during the observation period. ALT, alanine transaminase; APRI, AST to platelet ratio; AST, aspartate transaminase; HCV, hepatitis C virus; NS, not significant.

cancer between patients with FIB-4 index at the first visit < 2.41 and ≥ 2.41, and it revealed that the incidence was significantly higher in patients whose FIB-4 index was ≥ 2.41 than in those in whom it was < 2.41 (Figure 1D).

Next, we analyzed the clinical course in 494 HCV antibody-positive individuals who were also HCV-RNA-positive. The HCV-infected group included 129 men and 365 women who had a mean age of 63.0 years (range, 29–88) at the first visit and had been observed for a mean of 8.2 years (range, 1–27). Three hundred and seventy-eight (76.5%) of these patients had received antiviral treatment (DAA therapy only, n=166; interferon-based treatment followed by DAA therapy, *n* = 73; interferon-based treatment only, *n* = 139). SVR was confirmed in 340 cases (68.8%). Persistent infection, including no SVR after antiviral treatment, was confirmed in 154 (31.2%). The clinical data were compared between the group that had received antiviral therapy and the group that had not (Table 3). Compared with the individuals who had received antiviral treatment, those who had not were significantly older, had significantly lower ALT, albumin, and platelet values, and a higher FIB-4 index at the first examination. At the most recent examination, the AST, ALT, APRI and FIB-4 index values were significantly higher and the platelet count and albumin level were lower in the group that had not received antiviral treatment. Furthermore, we compared the clinical data obtained at the first and most recent examinations between the group that achieved SVR and the group that did not (Table 4). Individuals who achieved SVR were younger, had higher ALT and albumin levels, and had a lower FIB-4 index than those who had persistent infection at the first examination. At the most recent examination, individuals who achieved SVR were significantly younger, had significantly lower AST, ALT, APRI, and FIB-4 index values, and had a higher albumin level and platelet count than those who did not achieve SVR. The group that did not achieve SVR in Table 4 contained the two groups: one group for the patients who failed to achieve SVR after antiviral treatments and the other for those who had not received antiviral treatments, therefore, we also compared these two groups. The group who underwent antiviral treatments had some beneficial effects that the FIB-4 index and APRI values were significantly lower and the albumin level was significantly higher as shown in Table 5. By the end of March 2019, 427 individuals (86.4%) were diagnosed with chronic hepatitis, 46 (9.3%) with compensated liver cirrhosis, and 21 (4.3%) with decompensated liver cirrhosis. During the study period, 48 (9.7%) developed liver cancer and 24 (4.9%) died (of liver cancer, *n* = 6; from liver failure, *n* = 3; of a non-liver-related cause, *n* = 15). We compared the clinical features of HCV-infected persons who developed liver cancer with those of their counterparts who did not (Table 6). The APRI and FIB-4 index values at the first and most recent examinations were significantly higher in the group that developed liver cancer. The patients that developed liver cancer was significantly older, had higher AST and ALT levels, and had a lower albumin level and platelet count at the first examination than those who did not develop liver cancer. These trends were almost identical to those at the most recent examination. Although SVR was not significantly frequently observed in the group of no liver cancer occurrence compared with the group with liver cancer occurrence, there was a

Table 4. Comparison of HCV-infected individuals according to whether they achieved SVR

Items	SVR (+)	SVR (–)	*p*-value
Cases, *n*	340	154: 116 antiviral treatments (-) 38 antiviral treatments (+)	
First examination			
Age (years)	60.3 ± 10.1	69.0 ± 9.3	< 0.001
AST (IU/L)	44.1 ± 33.9	40.0 ± 25.1	NS
ALT (IU/L)	47.6 ± 48.8	36.5 ± 28.0	< 0.005
Platelets ($\times 10^4/\mu L$)	18.7 ± 12.5	16.6 ± 6.3	< 0.05
Albumin (g/dL)	4.27 ± 0.36	4.05 ± 0.48	< 0.001
APRI	0.99 ± 1.06	1.06 ± 1.07	NS
FIB-4 index	2.58 ± 1.78	3.53 ± 2.77	< 0.001
Most recent examination			
Observation period (years)	8.71 ± 5.21	7.08 ± 4.79	< 0.005
Age (years)	69.0 ± 9.9	76.2 ± 9.0	< 0.001
AST (IU/L)	23.4 ± 15.4	56.1 ± 121.0	< 0.005
ALT (IU/L)	17.0 ± 10.5	35.7 ± 71.5	< 0.005
Platelets ($\times 10^4/\mu L$)	18.5 ± 6.9	15.4 ± 6.5	< 0.001
Albumin (g/dL)	4.35 ± 2.45	3.59 ± 0.89	< 0.001
APRI	0.51 ± 0.54	1.83 ± 4.70	< 0.001
FIB-4 index	2.58 ± 1.64	6.26 ± 13.23	< 0.001

SVR (+), persons who achieved SVR; SVR (–), persons who did not achieve SVR. ALT, alanine transaminase; APRI, AST to platelet ratio; AST, aspartate transaminase; HCV, hepatitis C virus; NS, not significant; SVR, sustained virological response.

Table 5. Comparison of HCV-infected individuals who did not achieve SVR whether they underwent antiviral treatments

Items	Antiviral treatments (+)	Antiviral treatments (–)	*p*-value
Cases, *n*	38	116	
Liver cancer (+)/(–)	4/34	14/102	NS
First examination			
Age (years)	62.7 ± 10.6	71.0 ± 7.8	< 0.001
AST (IU/L)	40.7 ± 30.0	39.7 ± 23.4	NS
ALT (IU/L)	42.7 ± 39.6	34.5 ± 22.7	NS
Platelets ($\times 10^4/\mu L$)	17.5 ± 6.1	16.3 ± 6.4	NS
Albumin (g/dL)	4.15 ± 0.36	4.01 ± 0.51	NS
APRI	0.97 ± 0.99	1.09 ± 1.10	NS
FIB-4 index	2.72 ± 1.82	3.81 ± 2.99	< 0.05
Most recent examination			
Observation period (years)	6.89 ± 4.77	7.14 ± 4.82	NS
Age (years)	69.4 ± 11.2	78.4 ± 6.9	< 0.001
AST (IU/L)	31.1 ± 20.0	64.3 ± 138.1	< 0.05
ALT (IU/L)	29.3 ± 33.2	37.7 ± 80.1	NS
Platelets ($\times 10^4/\mu L$)	16.2 ± 5.8	15.2 ± 6.7	NS
Albumin (g/dL)	4.05 ± 0.73	3.45 ± 0.89	< 0.001
APRI	0.85 ± 0.92	2.14 ± 5.33	< 0.05
FIB-4 index	3.18 ± 2.16	7.23 ± 15.00	< 0.01

tendency that SVR was frequently observed in the group with no liver cancer occurrence ($p = 0.054$). Neither alcohol drinking nor complications of diabetes mellitus did not significantly affect development of liver cancer. A Cox proportional-hazards regression analysis was performed to identify factors contributing to development of liver cancer in the HCV-infected group (Table 7). Univariate analysis identified older age, no SVR, male sex, a lower platelet count, a lower albumin level, and higher AST, ALT, APRI and FIB-4 index values at the first examination to be significant risk factors for liver cancer. In multivariate analysis, only a higher FIB-4 index and male sex remained as significant risk factors (Table 7). Finally, we performed a Kaplan–Meier analysis to clarify the cumulative incidence of liver cancer. Overall, the cumulative incidence was 3.2% on day 2500 after the first visit, 10.4% by day 5000, and plateaued thereafter (Figure 2A). The incidence of liver cancer was significantly higher in men than in women (Figure 2B). To determine the suitable cutoff of FIB-4 index at the first visit for the prediction of liver cancer, we performed ROC analysis, which showed that AUC of 0.77 and FIB-4 index 2.54 was a suitable cutoff with sensitivity 0.62 and specificity 0.88 (Figure 2C). Based on this analysis, we compared the cumulative incidence of liver cancer incidence between patients with FIB-4 index at the

Table 6. Comparison of HCV-infected individuals according to whether they developed liver cancer

Items	Liver cancer (+)	Liver cancer (−)	*p*-value
Cases, *n*	48	446	
First examination			
Age (years)	67.0 ± 8.0	62.5 ± 10.8	< 0.01
AST (IU/L)	57.4 ± 34.1	41.2 ± 30.8	< 0.005
ALT (IU/L)	62.2 ± 60.7	42.2 ± 41.0	< 0.05
Platelets ($\times 10^4/\mu L$)	13.3 ± 5.9	18.6 ± 11.3	< 0.001
Albumin (g/dL)	4.04 ± 0.35	4.22 ± 0.42	< 0.005
APRI	1.73 ± 1.37	0.93 ± 1.00	< 0.001
FIB-4 index	4.45 ± 2.44	2.71 ± 2.08	< 0.001
Most recent examination			
Observation period (years)	8.02 ± 4.74	8.22 ± 5.18	NS
Age (years)	74.7 ± 8.1	70.9 ± 10.3	< 0.005
SVR/no SVR	29/19	312/134	NS
Alcohol intake (>20g/day) +/-/unknown	5/34/9	27/363/86	NS
DM +/-/unknown	9/38/1	70/370/6	NS
AST (IU/L)	88.7 ± 201.4	27.7 ± 28.7	< 0.05
ALT (IU/L)	50.3 ± 121.6	19.9 ± 16.4	NS
Platelets ($\times 10^4/\mu L$)	13.7 ± 6.3	18.0 ± 6.9	< 0.001
Albumin (g/dL)	3.61 ± 0.84	4.18 ± 2.23	< 0.005
APRI	2.38 ± 4.24	0.77 ± 2.46	< 0.05
FIB-4 index	7.01 ± 7.67	3.37 ± 7.61	< 0.005

Liver cancer (+), persons who developed liver cancer during the observation period; Liver cancer (−), persons who did not develop liver cancer during the observation period. ALT, alanine transaminase; APRI, AST to platelet ratio; AST, aspartate transaminase; HCV, hepatitis C virus; NS, not significant; SVR, sustained virological response; DM, diabetes mellitus.

Table 7. Risk factors for liver cancer development in the HCV-infected group

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age at first examination	1.09	1.05–1.13	< 0.001			
Male sex	2.87	1.6–5.15	< 0.001	3.18	1.73–5.85	< 0.001
SVR achieved	0.53	0.29–0.96	< 0.05			
AST (IU/L)	1.01	1.00–1.01	< 0.01			
ALT (IU/L)	1.01	1.00–1.01	< 0.05			
Platelets ($\times 10^4/\mu L$)	0.87	0.82–0.92	< 0.001			
Albumin (g/dL)	0.47	0.30–0.74	< 0.01			
APRI	1.36	1.17–1.59	< 0.001			
FIB-4 index	1.22	1.13–1.31	< 0.001	1.12	1.15–1.34	< 0.001
T-Bil (mg/dL)	1.43	0.73–2.78	NS			

Data from the first examination were analyzed. ALT, alanine transaminase; APRI, AST to platelet ratio; AST, aspartate transaminase; CI, confidence interval; HCV, hepatitis C virus; NS, not significant; SVR, sustained virological response; T-Bil, total bilirubin.

first visit index < 2.54 and ≥ 2.54, it revealed that the incidence was significantly higher in patients whose FIB-4 index was ≥ 2.54 than in those in whom it was < 2.54 (Figure 2D). Of note, the incidence of liver cancer was significantly lower in patients who achieved SVR during the observation period (Figure 2E). Furthermore, we also compared the cumulative liver cancer incidence between the patients who did not achieve SVR even after antiviral treatment and those who did not achieve SVR because of no antiviral treatments, and the incidences were not significantly different (Figure 2F).

We compared the clinical features of individuals who developed liver cancer between the HBV and HCV groups (Table 8). The incidence of liver cancer was found to be significantly higher in the HCV group. AST, ALT, and APRI values at the first examination were also significantly higher in the HCV group, as was the APRI value at the most recent examination.

Japan has subsidized treatment for HBV and HCV at the national and prefectural levels since 2008 (*14,16*). We investigated how many participants in the Ishikawa Hepatitis Follow-up Program used this subsidy system for antiviral therapy. Of the 378 individuals who had undergone antiviral treatment in the HCV-infected group, 270 (71.4%) used the subsidy system a total of 365 times, with an average of 1.35 times per person (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=82*). One hundred and ninety-one (70.7%) of these 270 persons used the subsidy system to undergo interferon-free DAA therapy. Seventy-eight (86.7%) of 90 persons in the HBV group used the subsidy system for treatment with nucleotide analogs.

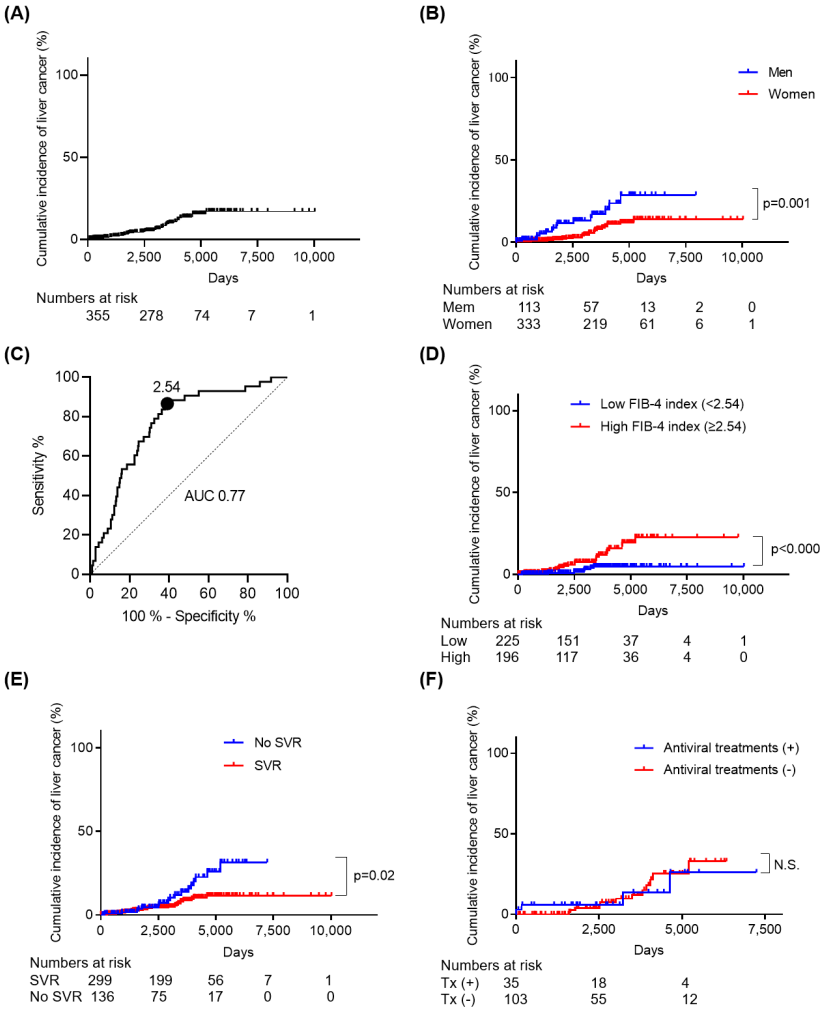

Figure 2. Cumulative incidence of liver cancer in the hepatitis C virus-infected group from the first visit. (A) Kaplan–Meier curve for all cases. **(B)** Comparison of Kaplan–Meier curves for the cumulative incidence of liver cancer according to sex by Cox proportional-hazards regression analysis. **(C)** Receiver operating characteristic (ROC) curve analysis for FIB-4 index at the first visit on liver cancer prediction. Area under the ROC curve was calculated. FIB-4 index at the point closest to the upper left was 2.54 (sensitivity 0.62, specificity 0.88). **(D)** Comparison of Kaplan–Meier curves for the cumulative incidence of liver cancer according to whether the FIB-4 index was low (< 2.54) or high (≥ 2.54) by Cox proportional-hazards regression analysis. **(E)** Comparison of Kaplan-Meier curves for the cumulative incidence of liver cancer according to whether sustained virological response (SVR) was achieved by Cox proportional-hazards regression analysis. **(F)** Comparison of Kaplan-Meier curves for the cumulative incidence of liver cancer according to whether antiviral treatments were undergone in the patients without SVR by Cox proportional-hazards regression analysis. In Figure 2A, 2B, 2D, 2E, and 2F, the numbers of analyzed patents were described. NS, not significant; Tx(+), antiviral treatments (+); Tx(-), antiviral treatments (-).

Table 8. Comparison of patients who developed liver cancer between the HBV-infected and HCV-infected groups

Items	HBV group	HCV group	*p*-value
Cases, *n*	16	48	
First examination			
Male/Female	8/8	19/29	NS
During the observation period			
Liver cancer incidence	16/535	48/494	< 0.001
First examination			
Age (years)	61.5 ± 9.4	67.0 ± 8.0	NS
AST (IU/L)	31.9 ± 11.9	57.4 ± 34.1	< 0.001
ALT (IU/L)	26.2 ± 11.4	62.2 ± 60.7	< 0.001
Platelets ($\times 10^4/\mu L$)	13.27 ± 5.28	13.3 ± 5.9	NS
Albumin (g/dL)	4.08 ± 0.78	4.04 ± 0.35	NS
APRI	1.02 ± 0.75	1.73 ± 1.37	< 0.05
FIB-4 index	3.40 ± 2.00	4.45 ± 2.44	NS
Most recent examination			
Observation period (years)	8.92 ± 6.25	8.02 ± 4.74	NS
Age (years)	70.9 ± 8.1	74.7 ± 8.1	NS
AST (IU/L)	38.8 ± 38.5	88.7 ± 201.4	NS
ALT (IU/L)	25.0 ± 26.0	50.3 ± 121.6	NS
Platelets ($\times 10^4/\mu L$)	16.2 ± 10.9	13.7 ± 6.3	NS
Albumin (g/dL)	3.65 ± 0.85	3.61 ± 0.84	NS
APRI	0.93 ± 0.67	2.38 ± 4.24	< 0.05
FIB-4 index	4.41 ± 3.19	7.01 ± 7.67	NS

ALT, alanine transaminase; APRI, AST to platelet ratio; AST, aspartate transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; NS, not significant; SVR, sustained virological response.

Discussion

In Japan, HBV and HCV are thought to be transmitted mainly *via* reuse of syringes and needles or by transfusion of contaminated blood. At the national government level, the Ministry of Health, Labour, and Welfare strongly suggests that all Japanese citizens should undergo hepatitis testing at least once in their lifetime. Nationwide hepatitis screening was started as a part of the health examination provided by municipal governments in 2002, and the cost of this screening is subsidized at the national and local government levels (*13,14*). At that time, in Ishikawa Prefecture, a program was established whereby municipal healthcare workers undertook annual and periodic follow-up for people whose government-subsidized screening test was positive for HBV or HCV. Since 2010, Kanazawa University Hospital, which is the only core institution in Ishikawa Prefecture, has provided publicly funded annual follow-up for persons with a positive HBV or HCV test through the Ishikawa Hepatitis Follow-up Program. As part of this program, a core institution can make a direct recommendation for a patient who has tested positive for hepatitis to visit a liver specialist by letter annually. The liver specialist is required to complete an examination letter and return it to the core institution, thereby confirming whether the patient has received the necessary care (*15*). A similar community-based intervention system has been implemented in Okazaki, Japan and found to be useful when encouraging HBV/HCV-infected people to attend for care by a hepatologist (*17*).

The main challenge in our follow-up system is that although we have continuously encouraged individuals with a positive hepatitis test to participate in the program, some have refused and others have not responded to our invitation to join the program. Moreover, even if persons with a positive hepatitis test agree to participate in the program, 40%–50% of examination letters are returned to the regional core center, indicating that only 40%–50% of patients visit a specialized institution each year. Furthermore, in some cases, the specialized institution receives the examination letter but does not return a completed copy to the regional core center. The regional core center enters disease and treatment data from completed examination letters into a database but can only collect a limited amount of data in this way. With advancing age, patients with viral hepatitis may develop comorbidities, such as dementia and cancers other than liver cancer, resulting in further limitations in activities of daily living or a move into a care facility for the elderly. Follow-up in a way that suits the circumstances of each patient requires an accurate knowledge of their health status. A noteworthy finding in our review of the examination letters was that some patients tried to visit a specialized institution but had seen a physician other than a hepatologist or had not undergone annual liver imaging tests. This suggests a need for more accurate data collection methods and better communication on the part of specialized institutions. We have recently started using information and communication technology to share clinical information regarding participants in this program between the core institution and specialized institutions *via* a web system that seems to be able to overcome several problems in the program. The details of this technology have been discussed elsewhere (*15*).

Noninvasive methods for diagnosis of liver fibrosis have recently been investigated. The WHO recommends transient elastography with ultrasound, APRI, and the FIB-4 index as noninvasive methods for diagnosis of liver fibrosis in patients with chronic viral hepatitis (*18*). The clinical guidelines published by the European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver recommend noninvasive assessment of hepatic fibrosis (*19,20*). Furthermore, in the clinical guidelines for HBV and HCV issued by the American Association for the Study of Liver Diseases, APRI and the FIB-4 index are recommended for diagnosis of liver fibrosis (*11,21*). Many studies have found that a higher FIB-4 index can be useful for prediction of liver failure and/or development of liver cancer in various clinical conditions, including nonalcoholic steatohepatitis/nonalcoholic fatty liver disease (*22*) and HBV (*23*) and HCV (*24*) infection. The FIB-4 index has been found to be particularly helpful for predicting liver failure and/or development of liver cancer in various clinical situations, including symptomatic hepatitis carriers, patients with HBV treated by nucleotide/nucleoside analogs (*25,26*), and patients with HCV who have achieved SVR (*27*). This study identified a higher FIB-4 index at baseline to be a risk factor for development of liver cancer during follow-up. Therefore, individuals with a higher FIB-4 index at baseline should be followed up more intensively. Moreover, monitoring of changes in the FIB-4 index over time is reportedly useful for noninvasive real-time estimation of progression of liver fibrosis (*28,29*). FIB-4 index can be easily calculated by simple and familiar parameters, such as AST, ALT, platelet count, and age, however, transient elastography or MR electrospray seems to be a more accurate and straightforward way to assess liver fibrosis than FIB-4 index among the noninvasive methods. Therefore, FIB-4 index should be used for the first screening for liver fibrosis, then, ideally, the assessment should be followed or combined with transient elastography or MR electrospray if these are available. A regional core center can calculate the FIB-4 index for participants in the Ishikawa Hepatitis Follow-up Program using data in the returned examination letters or by information and communication technology. A regional core center can also recommend intensive follow-up for individuals with changes in their FIB-4 index over time that suggest progression of liver fibrosis. An elevated FIB-4 index has recently been reported to be related to the following: an increased risk of

cardiovascular events, cardiovascular mortality, and all-cause mortality in patients with cardiovascular disease (*30*); severity of illness and mortality in patients with COVID-19 (*31*); and an increased incidence of renal failure (*32*) and depression (*33*). The FIB-4 index can be calculated easily for individuals who attend regular follow-ups, so could be used not only for screening patients for liver disease but also for non-liver diseases as part of regular wellness checks.

This study has several important findings. Although highly effective DAAs are now available and the subsidy system can greatly reduce the copayment amount, approximately one-third of HCV-infected participants in the Ishikawa Hepatitis Follow-up Program had not yet received antiviral therapy. In a global modeling study of the HCV care cascade between 2015 and 2020, 23% of all HCV viremic patients were estimated to be diagnosed with HCV infection, and 45% of diagnosed patients were estimated to receive antiviral treatment (*34*). However, the rates of antiviral therapy for people with HCV viremia vary from region to region, being 15% in the USA (*35*), 42.2% in Canada (*36*), and 56.8%–58.1% in South Korea (*37,38*). In our cohort, 76.5% of HCV-infected persons received antiviral therapy. This rate is not satisfactory in view of the World Health Organization target of 80% of eligible people with chronic HCV infection being treated by 2030 (*39*) but is higher than those in the above mentioned reports. Although barriers to introduction of antiviral therapy vary from region to region, lower income, limited access to health services, long wait times, provider shortages, and discrimination against persons with HCV infection are thought to be common reasons (*36,37*). In addition to these social factors, we have identified clinical features of patients who have not been referred to receive antiviral therapy after diagnosis. Patients who have not received antiviral therapy are significantly older than patients who have been treated. Generally, older patients are likely to have comorbid conditions, including dementia and paralysis as a result of cerebrovascular events, resulting in limited ability to perform activities of daily living or residence in a care home, either of which makes it difficult for them to attend appointments at specialized institutions, receive antiviral therapy if necessary, and undergo periodic screening for liver function and liver cancer. We found that baseline transaminase levels were significantly higher in patients who have received antiviral therapy than in those who have not. This suggests that specialist clinicians might hesitate to treat an HCV-infected patient with normal liver function or if the patient has reduced ability to perform activities of daily living or comorbid conditions.

The risk of liver cancer is greatly reduced in HCV-infected patients who achieve SVR but can still occur after SVR. Therefore, it is recommended that surveillance for liver cancer be continued lifelong, even after achievement of SVR (*7*). Some primary care physicians may not strongly recommend surveillance for liver cancer after SVR. However, our follow-up mailing system consistently reminds patients that they should continue with periodic specialist care despite SVR. Regarding HBV-infected patients, nucleoside/nucleotide analogs treatments seemed to significantly increase risk of liver cancer occurrence as shown in Table 2. Some patients started nucleoside/nucleotide analogs treatments just after diagnosis of liver cancer, which might cause this unexpected result. Furthermore, the present study is not a prospective study to examine the effect of antiviral treatments on liver cancer occurrence, thus, our result does not show the promotional effect of antiviral treatment on liver cancer in HBV-infected patients.

In conclusion, this study has provided valuable information on the clinical course in a hepatitis-infected community-based cohort in Ishikawa Prefecture using data from the innovative Ishikawa Hepatitis Follow-up Program. An important finding was that higher FIB-4 index at baseline was significantly associated with development of liver cancer during follow-up. We hope that this analysis will be repeated in other prefectures and that the data generated will be used to achieve micro-elimination and reduce mortality from liver cancer at the prefectural level in Japan.

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[§]*These authors contributed equally to this work.*
**Address correspondence to*:
Tetsuro Shimakami, Department of Gastroenterology, Kanazawa University Hospital, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan.
E-mail: shimakami@m-kanazawa.jp