Hepatocellular Carcinoma Risk Assessment for Patients With Advanced Fibrosis After Eradication of Hepatitis C Virus

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The identification of patients with advanced fibrosis who do not need any further hepatocellular carcinoma (HCC) surveillance after the eradication of hepatitis C is pivotal. In this study, we developed a simple serum-based risk model that could identify patients with low-risk HCC. This was a nationwide multicenter study involving 16 Hospitals in Japan. Patients with advanced fibrosis (1,325 in a derivation cohort and 508 in a validation cohort) who achieved sustained virological responses at 24 weeks after treatment (SVR24) were enrolled. The HCC risk model at any point after SVR24 and its change were evaluated, and subsequent HCC development was analyzed. Based on the multivariable analysis, patients fulfilling all of the factors (GAF4 criteria: gamma-glutamyl transferase < 28 IU/L, alpha-fetoprotein < 4.0 ng/mL, and Fibrosis-4 Index < 4.28) were classified as low-risk and others were classified as high-risk. When patients were stratified at the SVR24, and 1 year, and 2 years after SVR24, subsequent HCC development was significantly lower in low-risk patients (0.5-1.1 per 100 person-years in the derivation cohort and 0.9-1.1 per 100 person-years in the validation cohort) than in high-risk patients at each point. HCC risk from 1 year after SVR24 decreased in patients whose risk improved from high-risk to low-risk (HCC incidence: 0.6 per 100 person-years [hazard ratio (HR) = 0.163 in the derivation cohort] and 1.3 per 100 person-years [HR = 0.239 in the validation cohort]) than in those with sustained high risk. *Conclusion:* The HCC risk model based on simple serum markers at any point after SVR and its change can identify patients with advanced fibrosis who are at low HCC risk, and these patients may be able to reduce HCC surveillance. (*Hepatology Communications* 2022;6:461-472).

H epatitis C virus infection could lead to cirrhosis, hepatocellular carcinoma (HCC) development, and liver failure.[1] Direct-acting antiviral (DAA) treatment makes it possible to eradicate the hepatitis C virus in nearly all patients.[2-8] The HCC development rate decreases in patients who achieve sustained virological response (SVR), but some patients develop HCC even after SVR.[9-13]

Patients with advanced fibrosis have a higher risk of HCC development even after SVR; therefore, these patients are recommended to continue HCC surveillance. On the other hand, continuing regular HCC surveillance in all patients with advanced fibrosis is not cost-effective, and identification of patients with low-risk HCC is an important clinical issue.[14] However, a method for identifying patients at low risk of HCC among patients with advanced fibrosis has not been well established. Furthermore, there are studies that assess HCC risk at the time of SVR, but HCC risk changes over time after SVR.[15] Therefore, risk stratification at any point after SVR is necessary, and studies investigating the association between HCC development and risk stratification at any point after SVR are limited.[16]

Serum tests and serum-based fibrosis markers are widely available; the utility of these markers for the stratification of HCC risk has been previously reported.[13,17,18] Furthermore, one advantage of these convenient methods is that they are suitable for repeat measurements that could assess the change in HCC risk.[19,20] However, there are limited data that identify patients at low risk of HCC by serum markers and the association between change in serum markers and change in the risk of HCC development. Hence, in this multicenter cohort study, we developed a simple serum-based risk stratification model that could identify patients at low risk of HCC at any point after SVR and investigated changes in the risk model and changes in the rate of HCC development.

Patients and Methods

STUDY DESIGN

A nation-wide multicenter prospective registry cohort involving 14 institutes from the Japanese Red Cross Hospital Liver Study Group was registered as a derivation cohort. Two institutes were enrolled in the study as a validation cohort after the HCC

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risk model was developed. The study flow chart is shown in Fig. 1. Patients who received DAA treatment from September 2014 to July 2019 were investigated. Patients without advanced fibrosis (defined by Fibrosis-4 Index [FIB-4] < 3.25[21,22] or histological fibrosis stage 0-2) before treatment were excluded, and no patient with decompensated cirrhosis at the beginning of the DAA treatment was registered. The following categories of patients were also excluded: (1) those who did not achieve SVR; (2) those who had co-infection of hepatitis B virus or human immunodeficiency virus; (3) those with past history of HCC development; and (4) follow-up periods within 6 months. Patients who may have developed HCC before SVR, and patients who developed HCC within 6 months after SVR at 24 weeks after treatment (SVR24) were excluded (29 patients in the derivation cohort and 22 patients in the validation cohort). Patients with data missing at the entry were also excluded. Finally, 1,325 patients with advanced fibrosis (266 diagnosed by liver biopsy and 1,059 diagnosed by FIB-4 ≥ 3.25) were enrolled in the derivation cohort. Using the same inclusion and exclusion criteria, 508 patients in the validation cohort were

registered in the study. The HCC risk model was developed in the derivation cohort using serum markers at SVR24, and subsequent HCC development was examined. The HCC risk model was assessed at 1 year and 2 years after SVR24, and subsequent HCC development was also examined. Furthermore, the association between changes in the HCC risk and the rate of HCC development was investigated. Patients who fulfilled all of the gamma-glutamyltransferase (GGT), alpha-fetoprotein (AFP), and FIB-4 (GAF4) criteria (GGT < 28 IU/L, AFP < 4.0 ng/mL, and FIB-4 < 4.28) were classified as low-risk (detailed in the Results section), and others as high-risk. In the high-risk group at baseline (SVR24), patients who fulfilled the low-risk criteria at the last observation were classified as belonging to the improvement group. Patients who persistently fulfilled the high-risk criteria were classified as belonging to the non-improvement group. Written informed consent was obtained from each patient before enrollment into the study. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki. The study was approved by the institutional ethics review committee (approval number 2022).
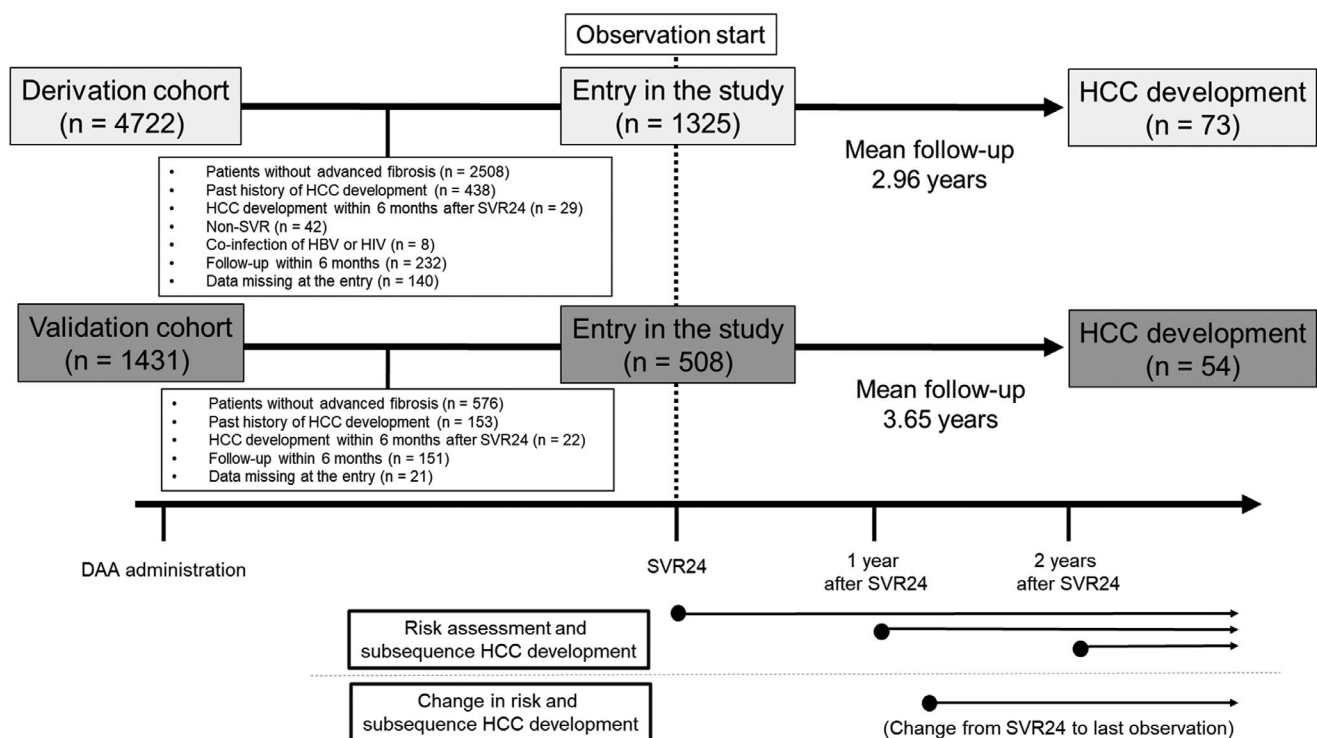

FIG. 1. Study flow chart. Abbreviations: HBV, hepatitis B virus; and HIV, human immunodeficiency virus.

CLINICAL AND LABORATORY DATA

The ages and genders of the patients were recorded at entry into the study. Serum samples were collected at SVR24, and 1, 2, and 3 years after SVR24. The FIB-4 index was calculated according to the following formula: FIB-4 = age [years] × AST [aspartate aminotransferase; IU/L] / (platelets [10^9/L] × ALT [alanine aminotransferase; IU/L]$^{1/2}$).[21]

HCC SURVEILLANCE AND DIAGNOSIS

Ultrasonography and blood tests, including tests for tumor markers, were performed at the start of DAA treatment and every 3-6 months for HCC surveillance. When tumor marker levels rose abnormally and/or abdominal ultrasonography suggested any lesion suspicious of HCC, contrast-enhanced computed tomography, magnetic resonance imaging, or angiography were performed. HCC was diagnosed for tumors displaying vascular enhancement at the early phase and washout at the later phase according to guidelines published by the American Association for the Study of Liver Diseases (AASLD) and the Japan Society of Hepatology.[23,24] Tumor biopsy was used to diagnose tumors with nontypical imaging findings.

STATISTICAL ANALYSIS

Patient characteristics between the derivation cohort and the validation cohort were compared using Mann-Whitney U test or Fisher's exact test. A receiver operating characteristic (ROC) curve analysis and Youden index were used to determine an optimal threshold of serum markers for HCC development. The association between HCC development and serum risk factors was evaluated using the Cox proportional hazard model. All serum factors using for the investigation are listed in Tables 1 and 2. Factors with $P < 0.05$ on univariate analysis were selected for multivariable backward stepwise regression analysis. The cumulative incidence of HCC was evaluated using the Kaplan-Meier method, and the differences between groups were analyzed by the log-rank test. Changes in serum markers were analyzed by the Wilcoxon rank-sum test. Values of

TABLE 1. PATIENT CHARACTERISTICS

	Derivation Cohort	Validation Cohort	
	n = 1,325	n = 508	P Value
Age, years	72 (64-77)	74 (67-79)	<0.001
Gender, male (%)	533 (40.2%)	210 (41.3%)	0.7
AST, IU/L	26 (21-31)	26 (22-33)	0.2
ALT, IU/L	17 (13-23)	16 (12-24)	0.6
Albumin, g/dL	4.2 (4.0-4.6)	4.2 (4.0-4.5)	0.7
Bilirubin, mg/dL	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.5
GGT, IU/L	21 (16-31)	22 (16-33)	0.09
Platelet counts, 10^9/L	131 (102-160)	129 (102-155)	0.2
AFP, ng/mL	4.0 (2.7-5.6)	3.6 (2.3-6.2)	0.2
FIB-4	3.41 (2.7-4.6)	3.63 (2.9-4.8)	0.002
Follow-up, years	2.96 (1.9-3.5)	3.65 (2.3-4.5)	<0.001

Note: Continuous data are shown in median (IQR). P value indicates difference between the derivation cohort and the validation cohort.
Abbreviations: ALT, alanine aminotransferase; and AST, aspartate aminotransferase.

$P < 0.05$ were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan),[25] a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

PATIENT CHARACTERISTICS

A total of 1,325 and 508 patients with advanced fibrosis were enrolled in the deviation cohort and the validation cohort, respectively (Fig. 1). Patient characteristics at SVR24 are provided in Table 1. The median (interquartile range [IQR]) age was 72 (64-77) years in the derivation cohort and 74 (67-79) in the validation cohort, respectively. AST, ALT, GGT, and AFP levels were within the upper limit of the normal in both cohorts, and there were no significant differences between the two cohorts. The median (IQR) FIB-4 was 3.41 (2.7-4.6) in the derivation cohort and 3.63 (2.9-4.8) in the validation cohort, respectively. The median (IQR) observation periods were 2.96 (1.9-3.5) years, and 73 patients developed HCC during the observation periods in the derivation cohort. Furthermore, the median (IQR) observation

TABLE 2. FACTORS ASSOCIATED WITH HCC DEVELOPMENT

	Derivation Cohort						Validation cohort		
	Univariable Analysis			Multivariable Analysis			Multivariate analysis		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	p value	Hazard ratio	95% CI	p value
AST ≥ 25 IU/L	3.02	1.7-5.3	<0.001						
ALT ≥ 23 IU/L	2.03	1.4-2.9	<0.001						
Albumin ≤ 4.3 g/dL	2.28	1.2-4.5	0.02						
Bilirubin ≥ 1.0 mg/dL	2.06	1.3-3.3	0.002						
GGT ≥ 28 IU/L	2.04	1.3-3.2	0.002	1.88	1.2–3.0	0.01	2.57	1.4–4.6	0.001
Platelet count ≤ 114 (10^9/L)	2.44	1.5-3.9	<0.001						
AFP ≥ 4.0 ng/mL	2.23	1.3-3.7	0.002	1.97	1.2–3.3	0.01	2.36	1.2–4.5	0.01
FIB-4 ≥ 4.28	2.38	1.5-3.8	<0.001	2.33	1.5–3.7	<0.001	2.25	1.3–3.9	0.003

Note: Factors with $P < 0.05$ in the univariate analysis were used for the multivariable analysis. AST, ALT, and platelet counts were not used for the multivariable analysis because these factors were included in FIB–4. The threshold of each factor for HCC development within 3 years was defined by ROC analysis.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; and CI, confidence interval.

HCC RISK MODEL DEVELOPMENT

The association between serum factors at SVR24 and HCC development were investigated in the derivation cohort (Table 2). The threshold value for each marker was determined by ROC analysis and Youden index, and the thresholds of GGT ≥ 28 IU/L, AFP ≥ 4.0 ng/mL, and FIB-4 ≥ 4.28 for HCC development within 3 years after SVR24 were selected. In the univariate analysis, GGT ≥ 28 IU/L, AFP ≥ 4.0 ng/mL, FIB-4 ≥ 4.28, albumin, and bilirubin were significantly associated with HCC development, and these factors were chosen for the multivariable backward stepwise regression analysis. AST, ALT, and platelet counts were not used for the multivariable analysis, as these factors were included in the FIB-4. In the multivariable analysis, GGT ≥ 28 IU/L (hazard ratio [HR]: 1.88, 95% confidence interval [CI]: 1.2-3.0, $P = 0.01$), AFP ≥ 4.0 ng/mL (HR: 1.97, 95% CI: 1.2-3.3, $P = 0.01$), and FIB-4 ≥ 4.28 (HR: 2.33, 95% CI: 1.5-3.7, $P < 0.001$) were independent factors significantly associated with HCC development. Next, factors associated with HCC development were investigated in the validation cohort using GGT ≥ 28 IU/L, AFP ≥ 4.0 ng/mL, FIB-4 ≥ 4.28, albumin, and bilirubin. In the multivariable analysis of the validation cohort, GGT ≥ 28 IU/L (HR: 2.57, 95% CI: 1.4-4.6, $P = 0.001$), AFP ≥ 4.0 ng/mL (HR: 2.36, 95% CI: 1.2-4.5, $P = 0.01$), and FIB-4 ≥ 4.28 (HR: 2.25, 95% CI: 1.3-3.9, $P = 0.003$) were independent factors significantly associated with HCC development similar to the derivation cohort. Based on the results, patients fulfilling all of the following GAF4 criteria were classified into the low-risk group: GGT < 28 IU/L, AFP < 4.0 ng/mL, and FIB-4 < 4.28. Others were classified into the high-risk group.

periods were 3.65 (2.3-4.5) years, and 54 patients developed HCC during the observation periods in the validation cohort.
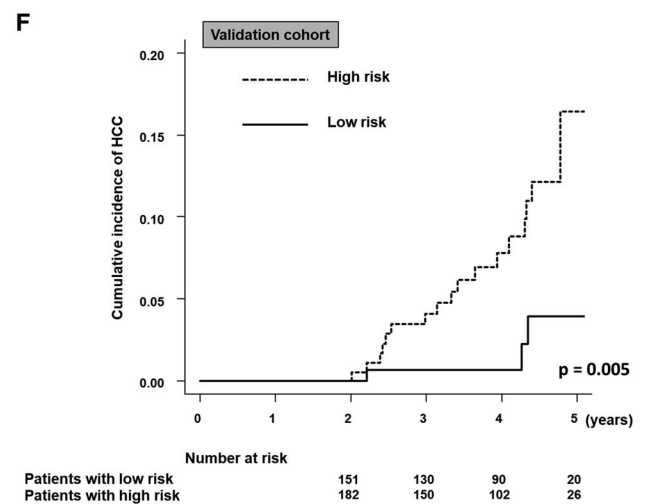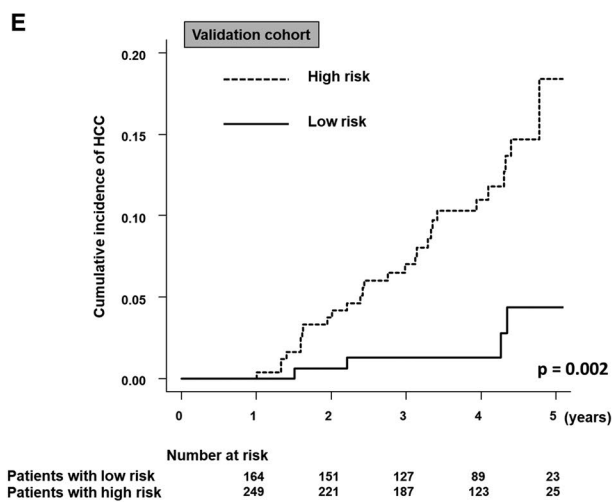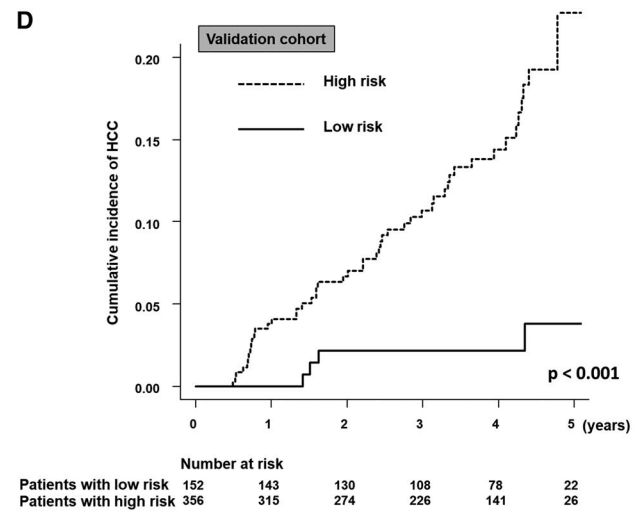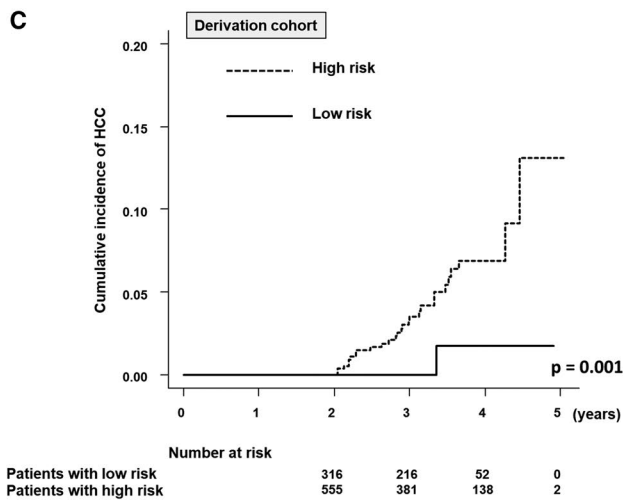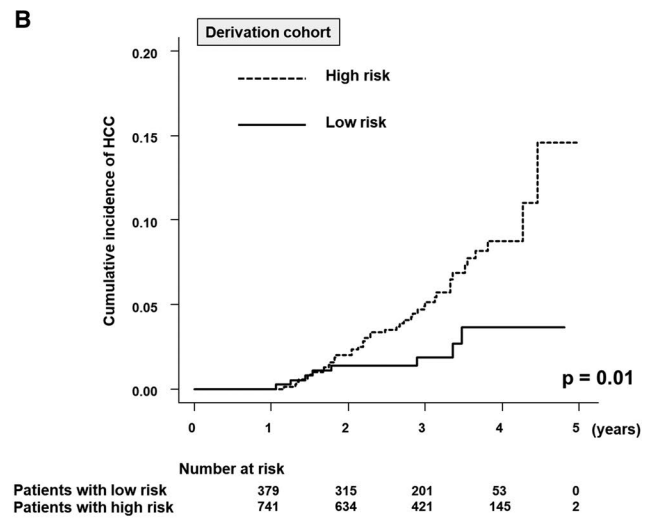
RISK MODEL AND SUBSEQUENT HCC DEVELOPMENT IN ANY YEAR

Patients were stratified into two groups based on data at SVR24, and 1 and 2 years after SVR24; subsequent HCC development was investigated in the derivation cohort. At SVR24, 375 patients (28.3%) were classified into the low-risk group. The 1-year, 2-year, 3-year, and 4-year cumulative HCC development rates were 0.8%, 1.8%, 2.3%, and 5.9%, respectively, in patients belonging to the low-risk group, and 1.9%, 4.0%, 6.7%, and 10.4%, respectively, in patients belonging to the high-risk group (Fig. 2A). The HCC development rate was significantly lower in the low-risk group than in the high-risk group ($P = 0.008$),

A Derivation cohort

		Number at risk				
Patients with low risk	375	324	269	173	42	0
Patients with high risk	950	838	707	461	160	2

p = 0.008

B Derivation cohort

		Number at risk				
Patients with low risk	379	315	201	53	0	
Patients with high risk	741	634	421	145	2	

p = 0.01

C Derivation cohort

	Number at risk			
Patients with low risk	316	216	52	0
Patients with high risk	555	381	138	2

p = 0.001

D Validation cohort

		Number at risk				
Patients with low risk	152	143	130	108	78	22
Patients with high risk	356	315	274	226	141	26

p < 0.001

E Validation cohort

	Number at risk				
Patients with low risk	164	151	127	89	23
Patients with high risk	249	221	187	123	25

p = 0.002

F Validation cohort

	Number at risk			
Patients with low risk	151	130	90	20
Patients with high risk	182	150	102	26

p = 0.005

FIG. 2. Cumulative incidence of HCC development stratified by HCC risk model. Patients fulfilling all of the following factors were defined as low-risk: GGT < 28 IU/L, AFP < 4.0 ng/mL, and FIB-4 < 4.28. Others were defined as high risk. (A-C) Cumulative incidence of HCC development in the derivation cohort. (A) Patients were stratified using data at SVR24, and HCC development was observed from SVR24. (B) Patients were stratified using data at 1 year after SVR24, and HCC development was observed from 1 year after SVR24. (C) Patients were stratified using data at 2 years after SVR24, and HCC development was observed from 2 years after SVR24. (D-F) Cumulative incidence of HCC development in the validation cohort. (D) Patients were stratified using data at SVR24, and HCC development was observed from SVR24. (E) Patients were stratified using data at 1 year after SVR24, and HCC development was observed from 1 year after SVR24. (F) Patients were stratified using data at 2 years after SVR24, and HCC development was observed from 2 years after SVR24.

and HCC development was 1.0 per 100 person-years in the low-risk group. When patients were stratified using serum markers at 1 year after SVR24, 33.8% of them were classified into the low-risk group. The 1-year, 2-year, and 3-year HCC development rates (starting at 1 year after SVR24) were 1.4%, 1.8% and 3.6%, respectively, in the low-risk group (1.1 per 100 person-years) and 2.0%, 5.1% and 8.7%, respectively, in the high-risk group (P = 0.01; Fig. 2B). Similarly, 37.4% of patients were classified into the low-risk group using serum markers at 2 years after SVR24. The 1-year and 2-year HCC development rates (starting at 2 years after SVR24) were 0.0% and 1.7%, respectively, in the low-risk group (0.5 per 100 person-years) and 3.5% and 6.8%, respectively, in the high-risk group (P = 0.001; Fig. 2C). The cumulative rate of HCC development was significantly lower in patients belonging to the low-risk group (HCC development: 0.5-1.1 per 100 person-years) than in those belonging to the high-risk group at any point in the derivation cohort.

CHANGES IN HCC RISK AND RATE OF HCC DEVELOPMENT

Changes in HCC risk and rate of HCC development were investigated in the derivation cohort. In the high-risk group, at entry, patients who fulfilled the low-risk conditions (GAF4 criteria: GGT < 28 IU/L, AFP < 4.0 ng/mL, and FIB-4 < 4.28) at the last observation were classified into the improvement group. Patients who persisted in the high-risk conditions were classified into the non-improvement group. Approximately 21.8% of the high-risk patients improved to the low-risk level and were classified into the improvement group. The 1-year, 2-year, and 3-year incidence of HCC development was 1.1%, 1.1% and 1.1%, respectively, in the improvement group (0.6 per 100 person-years), and 2.3%, 6.0% and

10.9%, respectively, in the non-improvement group (P = 0.004; Fig. 3A). HCC development risk reduced in the improvement group with HR = 0.163 (95% CI: 0.04-0.67, P = 0.01).

HCC RISK MODEL IN THE VALIDATION COHORT

The clinical significance of the HCC risk model was validated in the validation cohort. When patients were stratified using the HCC risk model at SVR24 (Fig. 2D), 1 year after SVR24 (Fig. 2E), and 2 years after SVR24 (Fig. 2F), the cumulative rate of HCC development was significantly lower in patients belonging to the low-risk group than in those belonging to the high-risk group at any point. HCC development of the low-risk group in the stratification as of SVR24, 1 year after SVR24, and 2 years after SVR24 were 0.9, 1.1, and 1.0 per 100 person-years, respectively.

When examined changes in the HCC risk and rate of HCC development in the validation cohort, the 1-year, 2-year, and 3-year incidence of HCC development was 0%, 1.3% and 2.9%, respectively, in the improvement group (1.3 per 100 person-years), and 4.1%, 9.8% and 14.8%, respectively, in the non-improvement group. The HCC development rate was significantly lower in patients with the improvement group than those with the non-improvement group (P = 0.009; Fig. 3B). HCC development risk decreased in the improvement group with HR = 0.239 (95% CI: 0.07-0.78, P = 0.02).

CHANGES IN VARIABLES OF GAF4 CRITERIA

Changes in GGT, AFP, and FIB-4 in the non-improvement group and the improvement group of the whole cohort were investigated. The median (IQR) AFP at SVR24, and 1 and 2 years after SVR24, were 5.0 (3.7-7.0), 4.6 (3.3-6.3), and 4.3 (3.0-6.0) ng/mL
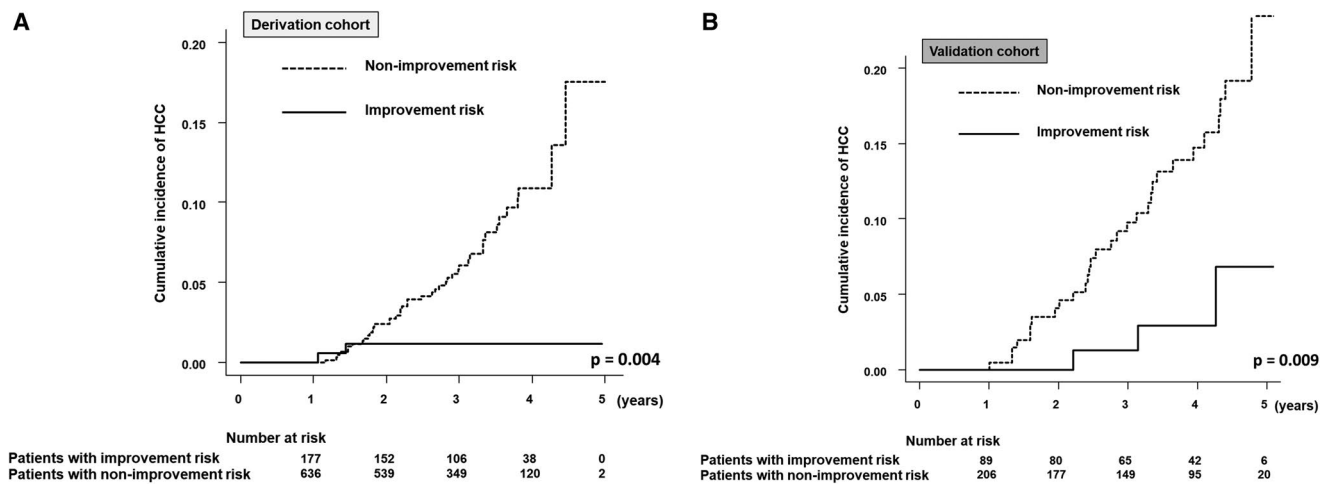
FIG. 3. Cumulative incidence of HCC development stratified by change in HCC risk model. Patients fulfilling all of the following factors were defined as low-risk: GGT < 28 IU/L, AFP < 4.0 ng/mL, and FIB-4 < 4.28. Others were defined as high risk. In the high-risk group at SVR24, patients who fulfilled the low-risk conditions at the last observation were defined as an improvement group. Patients who persisted in the high-risk conditions were defined as a non-improvement group. (A) Cumulative incidence of HCC development in the derivation cohort. (B) Cumulative incidence of HCC development in the validation cohort.

in the non-improvement group, and 4.0 (3.0-5.0), 3.2 (2.5-4.0), and 3.0 (2.3-3.6) ng/mL in the improvement group, respectively (Fig. 4A). AFP values had improved significantly over time in both groups, but the median value of AFP at each point was higher than the threshold of AFP of 4 ng/mL in the non-improvement group. Similarly, The median (IQR) FIB-4 values at SVR24, and 1 and 2 years after SVR24, were 4.04 (2.8-5.6), 3.76 (2.7-5.3), and 3.71 (2.5-4.9) in the non-improvement group, and 3.60 (2.8-4.5), 3.27 (2.6-4.0), and 3.08 (2.4-3.7), respectively (Fig. 4B), and FIB-4 values had improved significantly over time in both groups. The median (IQR) GGT values at SVR24, and 1 and 2 years after SVR24, were 28 (20-41), 27 (19-42), and 28 (18-43) mg/dL in the non-improvement group, and 21 (16-30), 19 (15-25), and 18 (14-23) mg/dL in the improvement group (Fig. 4C). GGT values had improved in the improvement group over time, but no significant improvement was found in the non-improvement group.

SUBGROUP ANALYSIS BY AGE AND SEX

Subgroup analyses were conducted by age and sex in the whole cohort. Patients were stratified by age of <70, 70-79, and ≥80 years. In patients with age <70 years, the HCC incidence was 0.9 per 100 person-years in the low-risk group, and 2.8 per 100 person-years in the high-risk group, respectively (Supporting Fig. S1A). Similarly, in patients with age of 70-79 years, the HCC incidence was 1.2 per 100 person-years in the low-risk group, and 3.3 per 100 person-years in the high-risk group (Supporting Fig. 1B), and in patients with age ≥80 years, the HCC incidence was 0 per 100 person-years in the low-risk group, and 2.7 per 100 person-years in the high-risk group, respectively (Supporting Fig. S1C). The HCC incidence was significantly lower in the low-risk groups. When patients were stratified by sex, the HCC incidence in males was 1.7 per 100 person-years in the low-risk group, and 3.7 per 100 person-years in the high-risk group, respectively (Supporting Fig. S2A). The HCC incidence in females was 0.5 per 100 person-years in the low-risk group, and 2.4 per 100 person-years in the high-risk group, respectively (Supporting Fig. S2B).

Discussion

MAIN FINDINGS

In this multicenter nation-wide study, we demonstrated that the simple HCC risk model (GAF4 criteria) consisting of GGT, AFP, and FIB-4 at any point after
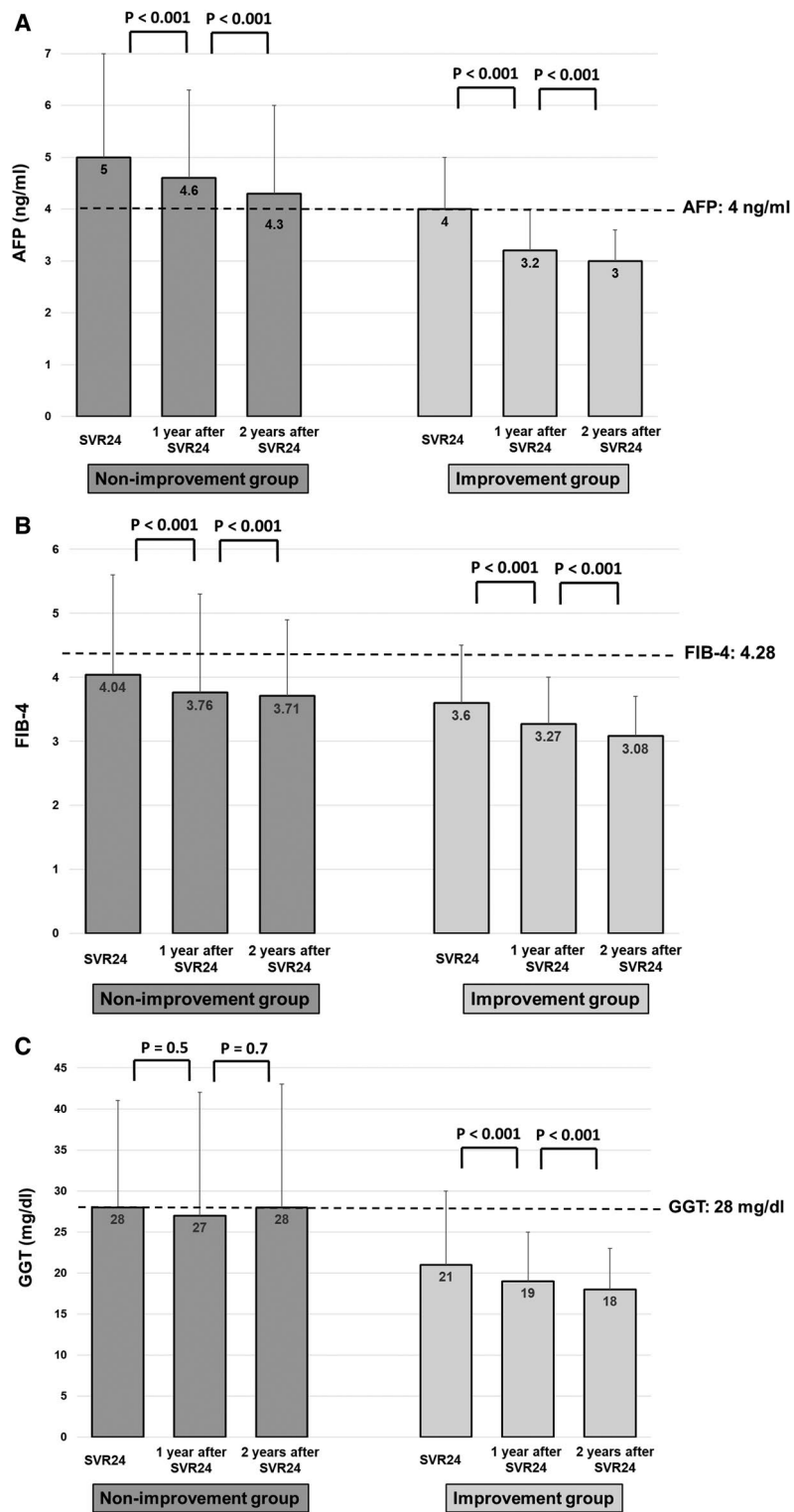
FIG. 4. Changes in AFP (A), FIB-4 (B), and GGT (C) after SVR. The bar chart indicates the median value of valuables, and the error bar indicates 75 percentiles.

SVR was associated with HCC development among patients with advanced fibrosis. Patients with low HCC risk (HCC development: 0.5-1.1 per 100 person-years in the derivation cohort and 0.9-1.1 per 100 person-years in the validation cohort) could be easily identified by GAF4 criteria, and these patients may be able to reduce HCC surveillance. The HCC incidence was especially low (0.5 per person-years) in the low-risk group of females, and HCC surveillance may be able to stop in these patients. Furthermore, even if patients had a high risk of HCC at entry, the HCC risk decreased in patients who improved to the low-risk level at the subsequent assessment. These risk-improvement patients could also reduce regular HCC surveillance. Because the risk model can be assessed easily and repeatedly, the model provides an HCC surveillance strategy after the eradication of the hepatitis C virus.

IN CONTEXT OF PUBLISHED LITERATURE

This study found that the HCC risk model based on simple serum markers at any point after SVR is associated with HCC development in patients with advanced fibrosis, and patients at low HCC risk can be identified by the model. HCC surveillance is necessary even after SVR because the lack of HCC surveillance leads to advanced HCC development and poor prognosis.[26,27] However, it is not cost-effective to screen all patients who achieved SVR, and the identification of patients at low HCC risk is an important clinical issue. GGT, AFP, and FIB-4 after SVR are known as factors associated with HCC development.[10,28,29] However, when these factors were used alone, patients at low HCC risk cannot be identified sufficiently. In this study, we found that patients with low HCC risk are able to be identified by combining these simple serum factors (GAF4 criteria).

Recently, some studies demonstrated that liver stiffness or serum markers are associated with HCC development after SVR, and low-risk patients could be detected by combining these factors.[28,30,31] However, one limitation of these studies is that the models are calculated based on the time of SVR. Liver stiffness that correlates fibrosis in the liver is associated with HCC risk.[32-34] Because liver stiffness changes over time, not only during DAA treatment but also after SVR, this indicates that HCC risk changes over time.[35-37] Therefore, HCC risk should be evaluated not only at the time of SVR but also at any point after

SVR. In addition, some patients cannot evaluate the HCC risk at SVR due to insufficient data on SVR. In this study, we demonstrated that the HCC risk model at any time was associated with HCC development, and the significance of GAF4 criteria is that it can be applied whenever laboratory data are measured.

One advantage of serum markers is that it is easy to repeat measurements. We previously reported that time-course changes in serum markers are associated with changes in HCC risk.[22,38,39] In this study, we demonstrated that if the HCC risk improves from high risk to low risk, HCC development rate also decreases in these patients. Recent studies also demonstrated that changes in FIB-4 or liver stiffness are associated with changes in HCC risk,[19,40] and our results espouse these findings. Therefore, patients at high risk of HCC are still at high risk of HCC and should continue HCC surveillance; however, if the risk improves to the low level at a subsequent point, these patients could afford to reduce HCC surveillance. Furthermore, the HCC development in female patients with GAF4 low-risk criteria was significantly low (0.5 per person-years), and HCC surveillance may be stopped in these patients. One advantage of our model is that observing a change in the risk model can identify patients who could afford to reduce or stop HCC surveillance, and this point was not established in previous studies.

STRENGTHS AND LIMITATIONS

This study was a multicenter nation-wide cohort study, which included over 1,800 patients with advanced fibrosis. Because our HCC risk model needs only standard laboratory tests, there is no examiner dependency like liver stiffness measurement.[41] It is easy to evaluate, and risk assessment at any point after SVR and repeat assessment is associated with HCC development. Therefore, this risk model can be adapted to another cohort easily and immediately without specific equipment. Although patient characteristics and HCC development rate were significantly different between the derivation cohort and the validation cohort, GAF4 criteria were able to identify patients at low risk of HCC development, even in the validation cohort. This indicates that GAF4 criteria have generalities. However, this study was conducted only in Japan, and relatively elderly patients were enrolled. FIB-4 was used as a screening method for patients with advanced fibrosis, but the diagnostic

accuracy is affected by age and liver fibrosis may be overestimated in elderly patients.[42] On the other hand, age is a risk factor for HCC development, and FIB-4 (>3.25) is associated with a high risk of HCC development[22,43]; therefore, using FIB-4 as a surrogate marker for patients with a high risk of HCC is thought to be valid. However, to strengthen the utility of the risk model, verification by a cohort in another region with a different age proportion is necessary. Moreover, the observation period of the study was short, and a further long-term follow-up study is necessary to demonstrate the utility of GAF4 criteria.

FUTURE IMPLICATIONS AND DIRECTIONS

In this study, we demonstrated patients within GAF4 criteria (GGT < 28 IU/L, AFP < 4.0 ng/mL, and FIB-4 < 4.28) at any point after SVR are at low risk of HCC development (HCC development: 0.5-1.1 per 100 person-years in the derivation cohort and 0.9-1.1 per 100 person-years in the validation cohort). Furthermore, if the HCC risk improves to the low-risk level in high-risk patients at baseline, these patients also reduce the HCC risk (HCC development: 0.6 per 100 person-years in the derivation cohort and 1.3 per 100 person-years in the validation cohort). Patients with the annual incidence of HCC risk <1.5% are not recommended HCC surveillance in the AASLD guideline.[22] Furthermore, a previous study indicated that HCC screening after SVR in patients with the annual incidence of HCC < 1.32% is not cost-effective.[14] Therefore, patients who were at low risk of the model at any time and improved from the high-risk level to the low-risk level may be able to reduce regular HCC surveillance.

The significance of the model is that GAF4 criteria do not need evaluation at a specific time point and can be applied whenever laboratory data are measured. Because this strategy is easy to adapt to detect patients at low risk of developing HCC, these data have important implications for HCC surveillance in patients with the eradication of the hepatitis C virus and help all physicians engaged in the management of liver disease.

Several studies demonstrated that liver stiffness by elastography or complication status (e.g., diabetes, alcohol intake) are associated with HCC development after SVR.[10,13,15,35] These data were not collected and evaluated in the study. GGT value is associated with diabetes or alcohol intake, and non-improvement of GGT value observed in the non-improvement group may be associated with the presence of these complications.[44] Therefore, more accurate risk estimation may be possible by combining these factors with GAF4 criteria, and further studies are needed.

In conclusion, the HCC risk model based on simple serum markers (GGT, AFP, and FIB-4) at any point after SVR and its change can identify patients at low risk of HCC, and these low-risk patients may be able to reduce HCC surveillance.

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