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ORIGINAL ARTICLE

General evaluation score for predicting the development of hepatocellular carcinoma in patients with advanced liver fibrosis associated with hepatitis C virus genotype 1 or 2 after direct-acting antiviral therapy

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Key words
advanced liver fibrosis, direct-acting antiviral, general evaluation score, hepatitis C virus, hepatocellular carcinoma, sustained virologic response.

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Abstract

Background and Aim: To validate a composite predictive model for hepatocellular carcinoma (HCC) development in patients with advanced liver fibrosis associated with chronic hepatitis C virus (HCV) who have received direct-acting antiviral (DAA) therapy and achieved sustained virologic response (SVR).
Methods: This study included 1258 patients with advanced liver fibrosis associated with HCV genotype 1, 2, or both. General evaluation score (GES), which is based on sex, age, fibrosis stage, albumin, and α-fetoprotein, was used as a composite predictive model.
Results: There were 645 (51.3%) patients in the low-risk group, 228 (18.1%) in the intermediate-risk group, and 385 (30.6%) in the high-risk group based on GES categories. The 12-, 36-, and 60-month cumulative incidence of HCC was 0.7%, 5.3%, and 13.0%, respectively. Multivariable analysis with Cox proportional hazards models showed that male sex (hazard ratio [HR], 1.863; 95% confidence interval [CI], 1.204–2.883), F4 fibrosis stage (HR, 3.199; 95% CI, 1.696–6.036), and albumin (HR, 0.489; 95% CI, 0.288–0.828) are independently associated with HCC development. The incidence of HCC differed significantly by GES-based risk category ($P < 0.001$). Cox proportional hazards models showed that, with the low-risk group as the referent, the HR for HCC development was 1.875 (95% CI, 1.000–3.514) in the intermediate-risk group and 2.819 (95% CI, 1.716–4.630) in the high-risk group. GES had better predictive ability for HCC development than fibrosis-4 index according to time-dependent receiver operating characteristic analysis.
Conclusion: GES is useful for predicting HCC development in patients with advanced liver fibrosis after SVR.

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Introduction

A recent study reported that hepatitis C virus (HCV) infection affects 58 million people worldwide.[1] Persistent HCV infection might lead to cirrhosis, including decompensated cirrhosis with ascites, encephalopathy, or variceal hemorrhage, in 10–20% of patients.[2] In addition, persistent HCV infection might cause hepatocellular carcinoma (HCC).[2] In Japan, 1.0–1.5 million people have chronic HCV infection: most patients have HCV genotype 1 or 2 infection.[3]

Sustained virologic response (SVR) is defined as the elimination of HCV RNA by antiviral therapy. SVR with interferon-based antiviral therapy has been reported to decrease hepatic fibrosis and the incidence of liver-related events such as decompensated cirrhosis or HCC.[4,5] SVR also leads to decreased liver inflammation, for example, reflected by the normalization of serum alanine aminotransferase levels.[4] Several studies have reported that patients who achieve SVR with anti-HCV therapy generally have a good clinical course and outcome.[5–7] Although the development of HCC is rare in patients after HCV elimination, it sometimes occurs.[8,9] Clinical risk factors for the development of HCC in patients after SVR with anti-HCV therapy include male sex, advanced age, advanced liver fibrosis, low albumin level, and high α-fetoprotein level.[10,11] Recently, direct-acting antivirals (DAAs) have been developed to treat patients with chronic HCV infection.[12–14] DAAs have resulted in higher rates of SVR achievement, shorter and simpler therapeutic regimens, and fewer adverse events than interferon-based anti-HCV therapy.[15] Several studies have reported that patients with HCV who achieve SVR with DAA therapy also have a lower incidence of liver-related events such as decompensated cirrhosis or HCC.[16–23] The emergence of DAAs to treat HCV will dramatically increase the number of patients who achieve SVR. Therefore, in the European Association for the Study of the Liver HCV guidelines,[15] among patients who have achieved SVR, surveillance for HCC is recommended only for patients with advanced fibrosis (METAVIR score F3) or cirrhosis (METAVIR score F4)[24] every 6 months with ultrasound because the risk of de novo or incident HCC is reduced but not eliminated with SVR. No surveillance for HCC is recommended for patients with no to moderate fibrosis (METAVIR score F0–F2) after SVR, provided that they have no other comorbidities such as a history of excessive alcohol drinking, obesity, or type 2 diabetes.[15]

Recently, several composite models such as the age–male–ALBI–platelets score,[25] after DAAs recommendation for surveillance (ADRES) score,[26,27] and general evaluation score (GES)[28] have been reported as predictors of incident HCC in patients with HCV who have received DAA therapy and achieved SVR. Among these composite models, GES was developed as an indicator for HCC development in patients with advanced fibrosis associated with HCV genotype 4 infection who have received DAA therapy and achieved SVR.[28] However, this model has not been sufficiently validated in patients with other HCV genotypes.

In this study, we validated the utility of GES for predicting HCC development in patients with HCV genotype 1, 2, or both who have received DAA therapy and achieved SVR. To compare the ability of GES *versus* fibrosis-4 (FIB-4) index in predicting HCC development, we generated time-dependent receiver operating characteristic (ROC) curves[29] for censored data and evaluated the areas under the ROC curves (AUROCs).

Materials and methods

A nationwide multicenter registry cohort involving 15 institutions from the Japanese Red Cross Hospital Liver Study Group was registered as a derivation cohort. A total of 5863 patients with HCV received DAA-based therapy at participating institutions between September 2014 and March 2020. Of these, 3263 patients met the following eligibility criteria and were enrolled in this study: (i) achievement of SVR; (ii) infection with HCV genotype 1, 2 or both; (iii) no history of HCC; (iv) no evidence of HCC development for at least 6 months after SVR; and (v) no missing clinical data. We excluded patients with non-advanced liver fibrosis ($n = 2005$). Consequently, 1258 patients were included in the analysis.

Indications for DAA therapy and DAA regimens were based on the Japan Society of Hepatology guidelines for the management of HCV infection.[3] SVR was defined as undetectable serum HCV RNA at 24 weeks after the end of treatment. The date when DAA therapy started was defined as the start of follow-up (baseline). The end of follow-up was defined as the date of the final visit for patients who had not developed HCC and as the date of HCC diagnosis for patients who developed HCC during follow-up.

Written informed consent was obtained from each patient before study enrollment. The study protocol conformed to the ethical guidelines in the Declaration of Helsinki. The study was approved by the institutional ethics review committee (approval number, 2022).

Clinical and laboratory data. Patient age and sex were recorded at the time of study entry. Serum samples were collected at the time of SVR. FIB-4 index was calculated according to the following formula[30]: aspartate aminotransferase (IU/L) × age (years)/platelet count (10^9/L) × alanine aminotransferase (IU/L)$^{1/2}$.

General evaluation score. GES was based on sex, age, fibrosis stage, albumin level, and α-fetoprotein level at the start of DAA therapy, based on a previous report.[28] Table S1, Supporting information shows GES components and scoring.

GES was defined as the sum of the points. Risk for development of HCC was categorized by GES as follows: low risk, ≤6 points; intermediate risk, 6–7.5 points; and high risk, >7.5 points, based on a previous report.[28]

In this study, we diagnosed advanced liver fibrosis (≥F3) based on liver biopsy findings.[24] In patients for whom liver biopsy data were not available, FIB-4 index levels were used as the basis for diagnosing advanced liver fibrosis. The FIB-4 index cutoff values for F3 and F4 fibrosis were set to 3.26 and 3.61, respectively, based on a previous report.[31]

HCC surveillance and diagnosis. Blood tests, including tests for tumor markers, and abdominal ultrasonography were carried out at the start of DAA treatment, SVR, and every 3–6 months thereafter for HCC surveillance. When tumor marker levels became higher than the reference range or ultrasonography suggested any lesions that were suspicious for HCC, contrast-enhanced computed tomography, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging, contrast-enhanced ultrasonography with perflubutane, angiography, or any combination of these procedures was performed. HCC was diagnosed when typical imaging findings were observed based on the guidelines published by the American Association for the Study of Liver Diseases and the Japan Society of Hepatology.[32,33] Liver tumor biopsy was performed to diagnose tumors with atypical imaging findings.

Statistical analysis. Continuous variables are expressed as medians (interquartile range). The Kruskal–Wallis test was used for continuous variables. The chi-square test or Fisher's exact test was used for categorical variables. Actuarial analysis of the cumulative incidence of HCC was performed using the Kaplan–Meier method; differences were tested using the log-rank test. Multivariable Cox proportional hazards models were used to calculate hazard ratios (HRs) for the development of HCC. We performed multivariable analysis with the following covariates, which are GES components: sex, age, fibrosis stage, albumin, and α-fetoprotein.[28] In addition, we performed multivariable analysis with GES-based risk category. Time-dependent ROC curves for HCC development were obtained using the nearest neighbor estimation method (span, 0.05) with GES and FIB-4 index. We calculated sensitivity and specificity for each year of HCC development using the maximum value of sensitivity+-specificity−1 as the cutoff level.[34]

Statistical significance was defined as $P < 0.05$. Statistical analyses were performed with EZR, version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[35] More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

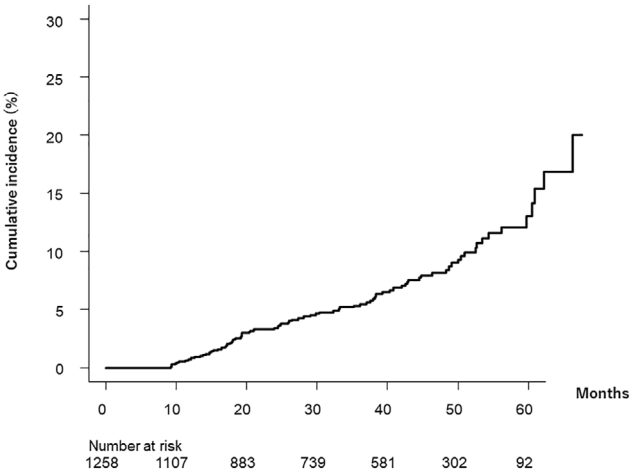


Figure 1 Cumulative incidence of HCC. The 12-, 36-, and 60-month cumulative incidence of HCC was 0.7%, 5.3%, and 13.0%, respectively. HCC, hepatocellular carcinoma.

Table 1 Characteristics of study patients

		GES-based risk group			
	Overall ($n = 1258$)	Low ($n = 645$)	Intermediate ($n = 228$)	High ($n = 385$)	*P* value
Age (years)†	72.3 (66.0–78.0)	73.0 (66.0–78.0)	70.4 (61.8–77.4)	74.0 (67.0–79.0)	0.001
Sex (female/male)	746/512	486/159	68/160	192/193	<0.001
Aspartate aminotransferase (IU/L)†	55 (38–85)	50 (35–74)	54 (39–91)	65 (45–95)	<0.001
Alanine aminotransferase (IU/L)†	48 (28–81)	43 (25–74)	50 (30–96)	53 (33–86)	<0.001
Albumin (g/dL)†	3.9 (3.6–4.2)	4.1 (3.9–4.3)	4.0 (3.7–4.1)	3.5 (3.3–3.6)	<0.001
Total bilirubin (mg/dL)†	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.7–1.1)	0.8 (0.6–1.1)	0.001
Platelet count ($\times 10^9$/L)†	117 (89–142)	126 (101–147)	116 (90–142)	100 (72–129)	<0.001
α-fetoprotein (ng/mL)†	7.0 (4.0–13.6)	5.9 (3.5–9.9)	7.1 (4.0–14.0)	10.0 (5.1–25.0)	<0.001
HCV genotype (1/2/both 1 and 2)	957/299/2	482/161/2	161/67/0	314/71/0	0.014
FIB-4 index†	4.92 (3.86–7.16)	4.33 (3.62–5.78)	4.80 (3.91–6.27)	6.92 (4.81–9.64)	<0.001
Fibrosis stage (F3/F4)	500/758	391/254	58/170	51/334	<0.001
GES†	6.0 (4.0–8.0)	4.0 (2.5–4.0)	7.5 (6.5–7.5)	9.0 (8.0–11.5)	<0.001
Developed HCC	83	25	16	42	<0.001
Follow-up duration (months)†	37.9 (17.5–49.1)	39.9 (17.7–48.9)	36.1 (15.1–49.6)	35.4 (18.0–49.5)	0.522

†Values are expressed as medians (interquartile range).

FIB-4, fibrosis-4; GES, general evaluation score; HCC, hepatocellular carcinoma; HCV, hepatitis C.

Results

Patient characteristics. The characteristics of the 1258 patients are shown in Table 1. There were 746 (59.3%) females and 512 (40.7%) males, with a median age of 72.3 (66.0–78.0) years. Liver fibrosis stage was diagnosed based on liver biopsy findings in 166 (13.2%) patients. The remaining 1092 (86.8%) patients were diagnosed based on FIB-4 index. Median GES was 6.0 (4.0–8.0) points. There were 645 (51.3%) patients in the low-risk group; 228 (18.1%) in the intermediate-risk group; and 385 (30.6%) in the high-risk group based on GES. Median follow-up was 37.9 (17.5–41.0) months. During follow-up, 83 patients developed HCC.

Table 1 also shows the characteristics of the study patients by GES-based risk category. There were significant differences in all clinical factors except for median follow-up across GES-based risk categories.

Table 2 Multivariable analysis of HCC incidence

	HR	95% CI	*P* value
Sex (male)	1.863	1.204–2.883	0.005
Age (per 1 year)	1.019	0.994–1.044	0.146
Fibrosis stage (F4)	3.199	1.696–6.036	<0.001
Albumin (per 1 g/dL)	0.489	0.288–0.828	0.008
α-fetoprotein (per 1 ng/mL)	1.002	0.999–1.004	0.309

CI, confidence interval; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HR, hazard ratio.

Cumulative incidence of HCC. Figure 1 shows the Kaplan–Meier curve for the cumulative incidence of HCC in all study patients. The 12-, 36-, and 60-month cumulative incidence of HCC was 0.7%, 5.3%, and 13.0%, respectively.

Multivariable analysis. Multivariable analysis with Cox proportional hazards modeling including the covariates of sex, age, fibrosis stage, albumin, and α-fetoprotein showed that male sex (HR, 1.863; 95% confidence interval [CI], 1.204–2.883), F4 fibrosis (HR, 3.199; 95% CI, 1.696–6.036), and albumin (per 1 g/dL) (HR, 0.489; 95% CI, 0.288–0.828) were independently associated with HCC development (Table 2).

Cumulative incidence of HCC based on risk group according to GES. Figure 2 shows the cumulative incidence of HCC among study patients by GES-based risk group ($P < 0.001$, log-rank test). With the low-risk group as the referent, the HR for HCC development was 1.875 (95% CI, 1.000–3.514) in the intermediate-risk group ($P = 0.049$) and 2.819 (95% CI, 1.716–4.630) in the high-risk group ($P < 0.001$).

Time-dependent ROC analysis for HCC development. Figure 3a–e shows the time-dependent ROC curves (solid lines) for GES with respect to HCC development during

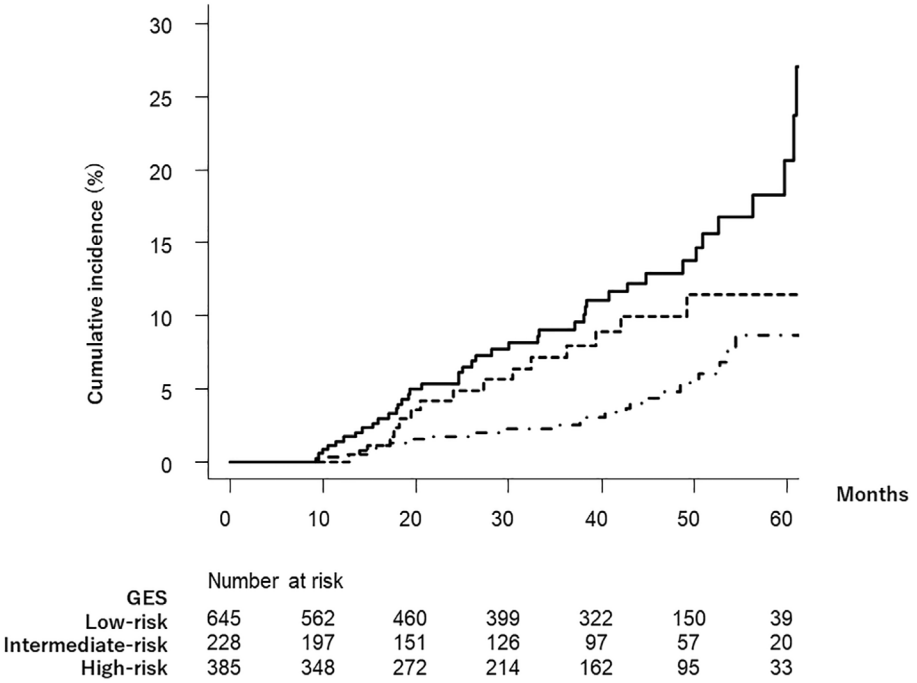
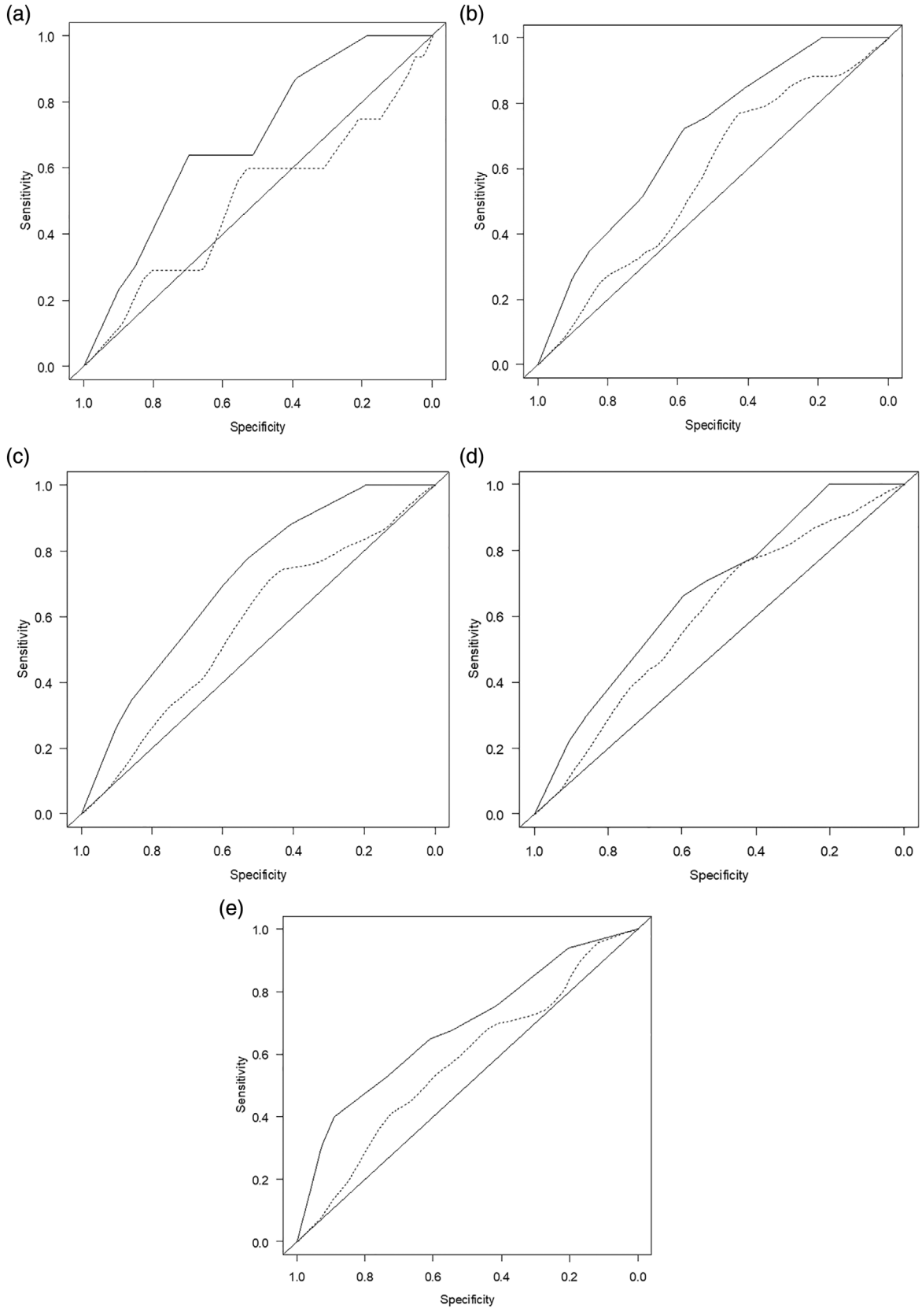


Figure 2 Cumulative incidence of HCC based on risk group according to GES. The 12-, 36-, and 60-month cumulative incidence of HCC was 0.5%, 2.5%, and 8.7%, respectively, in the low-risk group (dotted-dashed line). The 12-, 36-, and 60-month cumulative incidence of HCC was 0.0%, 7.2%, and 11.4%, respectively, in the intermediate-risk group (dashed line). The 12-, 36-, and 60-month cumulative incidence of HCC was 1.4%, 9.0%, and 20.6%, respectively, in the high-risk group (solid line). The incidence of HCC differed significantly by GES-based risk group ($P < 0.001$, log-rank test). GES, general evaluation score; HCC, hepatocellular carcinoma. GES: ——, high-risk group; ------, intermediate-risk group; - - -, low-risk group.


(a)
(b)
(c)
(d)
(e)
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0

months 12–60 after the start of follow-up. The AUROC at months 12, 24, 36, 48, and 60 was 0.685, 0.695, 0.708, 0.671, and 0.682, respectively.

Figure 3a–e shows the time-dependent ROC curves (dashed lines) for FIB-4 index with respect to HCC development during months 12–60 after the start of follow-up. The AUROC at months 12, 24, 36, 48, and 60 was 0.504, 0.573, 0.570, 0.601, and 0.573, respectively.

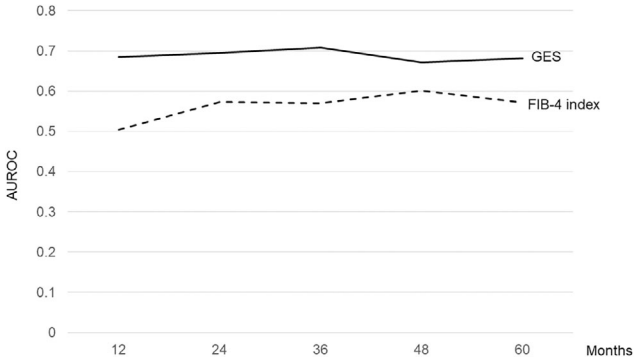


Figure 4 AUROCs for GES and FIB-4 index with respect to HCC development by months after the start of follow-up. GES (solid line) had higher predictive power for HCC development than FIB-4 index (dashed line) over all months. AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis-4; GES, general evaluation score; HCC, hepatocellular carcinoma.

Table 3 Sensitivity and specificity for predicting HCC development with GES at months 36 and 60 according to time-dependent ROC analysis

	GES	Sensitivity (%)	Specificity (%)
Month 36	6.0	77.5	53.0
	6.5	70.8	58.8
	7.0	69.8	59.6
	7.5	54.4	70.9
	8.0	34.5	85.8
Month 60	6.0	67.7	54.4
	6.5	65.0	60.8
	7.0	64.3	61.6
	7.5	53.0	73.1
	8.0	40.2	88.8

GES, general evaluation score; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic.

Figure 4 shows the AUROCs for GES and FIB-4 index with respect to HCC by month for the first 60 months after the start of follow-up based on time-dependent ROC analysis. GES had higher predictive power for the development of HCC than FIB-4 index over all months.

Table 3 shows the sensitivity and specificity of GES values associated with cutoff levels (i.e. GES 6–8) for each risk group at months 36 and 60 after the start of follow-up. The sensitivity and specificity of the optimal GES cutoff level for predicting the development of HCC were 77.5% and 53.0% with GES 6 at months 36 and 40.2% and 88.8% with GES 8 at month 60, respectively.

Discussion

In this multicenter study of patients with HCV genotype 1, 2, or both infection who had associated advanced fibrosis and achieved SVR after DAA therapy, Cox proportional hazards modeling showed that sex, fibrosis stage, and albumin are independently associated with the development of HCC after SVR. We also found that GES-based risk groups can be used to stratify the risk of HCC development in this cohort. In addition, time-dependent ROC analysis demonstrated that GES has superior predictive power for the development of HCC after SVR than FIB-4 index. Therefore, GES, which is based on sex, age, fibrosis stage, albumin, and α-fetoprotein, was considered a reasonable model for predicting HCC development in patients with advanced fibrosis who have received DAA therapy and achieved SVR.

Clinical factors such as sex, age, liver stiffness, type 2 diabetes, and levels of α-fetoprotein, albumin, and mac2 binding protein glycosylation isomer have been reported as predictors of HCC development in patients with HCV who have achieved SVR with antiviral therapy.[36–40] In addition, FIB-4 index, which is a simple composite index, has been validated to be correlated with liver fibrosis in various studies of patients with chronic HCV infection, chronic hepatitis B virus infection, or nonalcoholic fatty liver disease, including nonalcoholic steatohepatitis.[31,41] FIB-4 index has been reported as a predictor of HCC development in patients with HCV who achieved SVR with antiviral therapy such as interferon or DAAs.[38,39] Hiraoka *et al.*[26] developed the ADRES score as a composite model using clinical factors in 1069 patients with HCV who have received DAA therapy and achieved SVR in Japan. The ADRES score was based on sex, FIB-4 index, and α-fetoprotein level upon achieving SVR. They reported that the cumulative incidence of HCC at 1 and 2 years after SVR was 0.0% and 0.0% for patients with ADRES score 0, 0.5% and 1.6% for patients with ADRES score 1, 8.4% and 13.4% for patients with ADRES score 2, and 18.0% and 32.8% for patients with ADRES score 3 ($P < 0.001$).[26] In addition, we validated the

Figure 3 Time-dependent ROC curves for GES and FIB-4 index with respect to HCC development. (a) Month 12: The AUROC was 0.685 for GES (solid line) and 0.504 for FIB-4 index (dashed line). (b) Month 24: The AUROC was 0.695 for GES (solid line) and 0.573 for FIB-4 index (dashed line). (c) Month 36: The AUROC was 0.708 for GES (solid line) and 0.570 for FIB-4 index (dashed line). (d) Month 48: The AUROC was 0.671 for GES (solid line) and 0.601 for FIB-4 index (dashed line). (e) Month 60: The AUROC was 0.682 for GES (solid line) and 0.573 for FIB-4 index (dashed line). AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis-4; GES, general evaluation score; ROC, receiver operating characteristic

usefulness of the ADRES score for predicting HCC development in another cohort of patients with HCV who achieved SVR with DAA therapy.[27] However, the prediction of HCC development in Japanese patients with HCV-related advanced fibrosis and high risk of hepatocarcinogenesis who achieved SVR with DAA therapy has not been sufficiently studied.

Recently, Shiha *et al.*[28] developed GES as a new composite model for predicting HCC development using clinical factors in 2372 patients with HCV genotype 4-associated advanced liver fibrosis who have received DAA therapy and achieved SVR. In their cohort, the patients were followed for an average of 23.60 ± 8.25 months after the cessation of DAA therapy. They defined advanced liver fibrosis according to transient elastography findings or clinical signs as well as laboratory parameters of cirrhosis such as splenomegaly, ascites, albumin ≤3.5 g/dL, or platelet count $\leq 100 \times 10^9$/L. In their multivariable analysis with Cox proportional hazards modeling, older age (HR, 1.07; 95% CI, 1.04–1.10; $P < 0.001$), male sex (HR, 3.61; 95% CI, 2.00–6.52; $P = 0.011$), presence of cirrhosis (HR, 3.48; 95% CI, 1.69–7.17; $P = 0.001$), high α-fetoprotein levels (HR, 2.83; 95% CI, 1.55–5.18; $P = 0.001$), and low albumin levels (HR, 1.86; 95% CI, 1.15–3.00; $P = 0.012$) were identified independent predictors of HCC development. Therefore, GES included those clinical factors. By GES-based risk group, the 12-, 24-, and 36-month cumulative incidence of HCC was 0.1% (95% CI, 0.0–0.3), 1.2% (95% CI, 0.8–1.7), and 1.9% (95% CI, 1.4–2.5), respectively, in the low-risk group ($n = 1368$, 55.7%); 0.7% (95% CI, 0.3–1.3), 3.3 (95% CI, 2.4–4.5), and 5.8% (95% CI, 4.6–7.3), respectively, in the intermediate-risk group ($n = 590$, 24.9%); and 1.2% (95% CI, 0.6–2.2), 7.1 (95% CI, 5.6–9.2), and 9.5% (95% CI, 7.6–11.7), respectively, in the high-risk group ($n = 414$, 17.5%) ($P < 0.001$, log-rank test). In a study by Shiha *et al.*,[28] sex, age, fibrosis stage, albumin level, and α-fetoprotein level were determined to be independent factors for predicting HCC development in patients with HCV genotype 4-associated advanced liver fibrosis who have received DAA therapy and achieved SVR by multivariate analysis, and these factors were determined to be components of GES. Therefore, in the present study, we aimed to validate a multivariate analysis whether these five factors are also independent factors associated with HCC development in patients with HCV genotype 1 or 2-associated advanced liver fibrosis who have received DAA therapy and achieved SVR. In this study, we also found significant differences in the proportion of patients who developed HCC by GES-based risk group ($P < 0.001$, log-rank test). The advantage of this study was that, unlike the original report,[28] it included patients with genotype 1, 2, or both; the majority of patients in Japan are infected with HCV genotype 1 or 2.

ROC analysis is generally used to assess the diagnostic ability of a continuous variable for a binary disease outcome (e.g. positive or negative for disease). However, clinical outcomes of some diseases, especially chronic diseases such as malignancy, might be dependent on time. Therefore, time-dependent ROC curve analysis has been introduced to assess the ability of predictive indicators for time-dependent disease outcomes. No previous studies have used time-dependent ROC analysis to assess a clinical composite model in terms of its association with HCC development in patients with HCV-associated advanced liver fibrosis who have received DAA therapy and achieved SVR. There are numerous reports on the usefulness of the FIB-4 index in predicting the development of HCC in patients with HCV who have received DAA therapy and achieved SVR. Therefore, in this study, we aimed to compare GES and FIB-4 index in those with advanced fibrosis to clarify that GES is more effective than FIB-4 index alone for predicting HCC development using time-dependent ROC analysis. In this study, we used time-dependent ROC analysis to show that GES is superior to FIB-4 index in terms of predicting development of HCC more than 5 years after HCV elimination with DAA therapy. In addition, we clarified the sensitivity and specificity of GES cutoff values (i.e. GES 6–8) for HCC development at 36 and 60 months in the present cohort using time-dependent ROC analysis. We found that the optimal GES cutoff levels were 6 and 8 at 36 and 60 months after the start of follow-up. Therefore, patients with GES ≥6 (especially intermediate-risk or high-risk groups) are considered to need stricter HCC surveillance, including not only ultrasonography but also contrast-enhanced computed tomography or gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging, after SVR.

The main limitations of this study include its hospital-based study population and retrospective nature. Although this study included a large number of patients with advanced liver fibrosis associated with HCV genotype 1 or 2 from multiple liver disease centers across Japan, further prospective studies with community-based subjects are warranted. In addition, approximately 90% of the patients in this study were diagnosed with advanced liver fibrosis based on FIB-4 index. Studies with advanced liver fibrosis diagnosed with magnetic resonance-based or ultrasound-based elastography should be performed for GES validation in the future.

In conclusion, GES, which is a composite model of simple clinical parameters, was useful for predicting HCC development in patients with advanced liver fibrosis associated with HCV genotype 1 or 2 infection who have received DAA therapy and achieved SVR. In addition, GES had better predictive ability for HCC development than FIB-4 index in patients with HCV-associated advanced liver fibrosis who have achieved SVR with DAA therapy. Further studies should be conducted to confirm these findings in other populations.

Data availability statement. The datasets are available from the corresponding authors on reasonable request.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. GES components and scoring.