Multicentre external validation of the GES score for predicting HCC risk in Japanese HCV patients who achieved SVR following DAAs

Kazumichi Abe¹ | Masashi Fujita¹ | Manabu Hayashi¹ | Atsushi Takahashi¹
Hiromasa Ohira¹ | Nabiel Mikhail²,³ | Reham Soliman²,⁴ | Gamal Shiha²,⁵

Abstract
A simple score combining clinical and biochemical parameters (general evaluation score (GES)) has shown value in predicting hepatocellular carcinoma (HCC) risk after hepatitis C virus (HCV) eradication in Egyptian patients with HCV genotype 4. We aimed to apply the GES to predict HCC risk in Japanese HCV patients who achieved sustained virological response (SVR) following direct-acting antivirals (DAAs). This multicentre retrospective cohort study included 187 HCV patients without a history of HCC treatment who achieved SVR. The GES was calculated using pre- and post-treatment data. The median age of the patients was 66 years; 49% were male, 89% had cirrhosis and 69% had HCV genotype 1. During the mean 36-month follow-up, 19 (10.2%) developed HCC. Regarding the pretreatment scores, 75 (40.1%), 58 (31.0%) and 54 (28.9%) patients had low-, intermediate- and high-risk scores, respectively. The 4-year cumulative incidence (CumI) was 1.64% in the low-risk group, 2.82% in the intermediate-risk group and 6.88% in the high-risk group (log-rank \( P = .029 \)). In patients with cirrhosis, 60 (36.1%), 57 (34.3%) and 49 (29.5%) had low-, intermediate- and high-risk scores respectively. The 4-year CumI was 0.98% in the low-risk group, 2.86% in the intermediate-risk group and 6.67% in the high-risk group (log-rank \( P = .02 \)). The GES calculated with pretreatment data was more useful than that calculated with post-treatment data (Harrell’s C statistic: 0.670 vs 0.587). This tool incorporates changes over time to estimate variations in HCC risk and could help identify low-risk patients for whom HCC surveillance can be discontinued.

KEYWORDS
cirrhosis, DAAs, HCC risk score, HCV, SVR

1 INTRODUCTION

The eradication of hepatitis C virus (HCV) with direct-acting antivirals (DAAs) has been shown to significantly reduce the risk of hepatocellular carcinoma (HCC).¹⁻³ However, whether the risk of HCC will decrease over time after the eradication of HCV remains unclear. Moreover, predictors of HCC occurrence after DAA therapy in patients without a history of HCC treatment have not been clearly elucidated. Over the past few decades, several HCC risk scores have been developed and validated to stratify the risk of developing HCC.
Shiha et al demonstrated and validated the usefulness of a simple HCC risk score, the general evaluation score (GES), which could identify three patient groups with different levels of HCC risk during follow-up, utilizing simple and readily available predictors and thus can be easily assessed in clinical practice, namely, older age, male sex, low albumin and high AFP levels and the presence of cirrhosis at baseline.\(^6\)

In response to the authors' recommendation to evaluate the GES in different patient populations and ethnicities, we attempted to validate the GES in 187 Japanese HCV patients with cirrhosis and advanced liver fibrosis, who achieved a sustained virological response (SVR) following DAA therapy and were recruited from the Fukushima Liver Academic Group (FLAG) and its satellite centres between December 2014 and April 2019. The average duration of follow-up was 35 months after the initiation of DAA therapy.

2 \| \textbf{PATIENTS AND METHODS}

2.1 \| Cohorts

Of the 689 patients enrolled, this study included 187 HCV patients with cirrhosis and advanced liver fibrosis, who achieved SVR between 17 September 2014 and 4 April 2019. Patients were included if they met the following inclusion criteria: 18 years or older, diagnosed with HCV, history of DAA therapy and no history or current HCC. Patients with either HBV or HIV coinfection, renal impairment or other malignancies were excluded. All participants received a course of one of several DAAs for the treatment of chronic hepatitis C infection. The treatments for HCV genotype 1 infection included a 24-week combined regimen of NS5A and NS3 protease-targeted DAAs (daclatasvir [DCV] and asunaprevir [ASV]) in 53 patients and a 12-week treatment with NS5A protease- and NS5B polymerase-targeted DAAs (sofosbuvir [SOF] and ledipasvir [LDV]) in 59 patients; a 12-week combined regimen of NS5A and NS3 protease-targeted DAAs (elbasvir [EVR] and grazoprevir [GZR]) in nine patients and ombitasvir/paritaprevir/ritonavir (OBV/PTR/r) in two patients. The treatments for HCV genotype 2 infection included a 12-week combined regimen of SOF and ribavirin (RBV) in 47 patients. Two brands of RBV were given: Copegus (Chugai Pharmaceutical) and Rebetol (Merck Sharp & Dohme). Ribavirin was administered as an oral tablet (600–1000 mg total daily dose, depending on the body weight). The need for dose changes, temporary interruptions, or the discontinuation of RBV was determined based on the manufacturer's prescribing information. A total of 17 patients were treated with glecaprevir/pibrentasvir (G/P), HCV genotype 1- or genotype 2-infected patients without cirrhosis were treated with G/P for 8 weeks, and HCV genotype 1- or genotype 2-infected patients with compensated cirrhosis were treated with G/P for 12 weeks. Patients with HCV genotype 3/4 infections were treated with G/P for 12 weeks.

The study protocol conformed to the ethics guidelines outlined in the Declaration of Helsinki. The study protocol was reviewed, and opt-out consent was approved by the Ethics Committee of Fukushima Medical University (No. 29021). The need to obtain informed consent from the participants was waived by the Ethics Committee of Fukushima Medical University because of the retrospective nature of the study. The study was conducted according to the relevant guidelines.

2.2 \| Patient evaluation

Clinical and laboratory data were collected before the initiation of antiviral treatment until the last visit at 6-month intervals of follow-up, according to a standardized protocol. All patients underwent virological, haematological and biochemical laboratory testing, abdominal ultrasound examination and triphasic MSCT if indicated. The follow-up duration was calculated as the time between the end of treatment and the last follow-up or the date of event development (HCC occurrence), whichever occurred first. Clinical and demographic information, including patient age, sex, HCV genotypes, presence of diabetes mellitus (DM) and DAA treatment, was collected. The biochemical parameters collected included ALT, AST, albumin, platelets, alpha-foetoprotein (AFP) and fibrosis-4 (FIB-4) (Age x AST)/(Platelet count x √ALT). DM was defined by any of the following criteria: (a) a documented history of diabetes, (b) the administration of a diabetes medication or (c) a fasting glucose level ≥126 mg/dl or an HbA1c level ≥6.5 on two separate occasions.

2.3 \| Diagnosis of cirrhosis

Patients were diagnosed with cirrhosis (F4) when they fulfilled more than one of the following criteria;

- Definite clinical signs and laboratory parameters of cirrhosis (eg splenomegaly, ascites, albumin ≤3.5 g/dL, platelet count ≤100,000/μL);

Lay Summary

The eradication of hepatitis C virus (HCV) with direct-acting antivirals (DAAs) has been shown to significantly reduce the risk of hepatocellular carcinoma (HCC). Moreover, the predictors of HCC occurrence after DAA therapy in patients without a history of HCC treatment have not been clearly elucidated. We validated the usefulness of a simple HCC risk score, the general evaluation score (GES), which utilizes simple and readily available predictors, namely, older age, male sex, low albumin and high AFP levels and the presence of cirrhosis at baseline, that can be easily assessed in clinical practice. This dynamic tool incorporates changes over time to estimate variations in HCC risk and might help to identify patients with low risk for whom could be followed up at longer intervals.
2.4 Diagnosis of HCC

The diagnosis of HCC was made in accordance with EASL\textsuperscript{8} and AASLD\textsuperscript{9} guidelines. Multiphase CT or MRI was performed if there were any focal hepatic lesions diagnosed by abdominal ultrasound and/or if AFP was >20 ng/mL. MSCT. The diagnosis of HCC was based on the characteristic arterial enhancement and early washout in the delayed phase. The macroscopic classification, histological differentiation and architectural pattern were evaluated according to the general guidelines and standards for clinical and pathological studies of primary liver cancer.\textsuperscript{10}

2.5 GES score

The General Evaluation Score (GES) was then derived using hazard ratios (HRs) of the variables in the multivariable model (Table S1).\textsuperscript{6} Patients were then stratified into three groups based on the GES score (the low-risk group [≤6 points], the intermediate-risk group [≥6-7.5 points] and the high-risk group [≥7.5 points]). The GES score was calculated twice: at baseline (pretreatment) and 24 weeks after the end of treatment (post-treatment).

2.6 Statistical analysis

Statistical analyses were performed using SPSS version 26 (Statistical Package for Social Sciences) (IBM Corp.). Continuous variables are reported as the median (IQR). Categorical variables are reported as frequencies (%). Nonparametric tests, the Mann-Whitney test for quantitative comparisons and Fisher’s exact test for qualitative comparisons were used. Kaplan-Meier analysis, Cox regression analysis and the log-rank test were used to evaluate the effect of the risk score on the cumulative hazard. The performance of the GES was evaluated using Harrell's C statistic. A rough rule for interpretation is that C-statistic values above 0.80 indicate very good models, values between 0.70 and 0.80 indicate good models, and values between 0.50 and 0.70 indicate fair models.

2.7 Ethical consideration

The study protocol conformed to the ethics guidelines outlined in the Declaration of Helsinki. The study protocol was reviewed, and opt-out consent was approved by the Ethics Committee of Fukushima Medical University (No. 29021). The need to obtain informed consent from the participants was waived by the Ethics Committee of Fukushima Medical University because of the retrospective nature of the study. The study was conducted in accordance with relevant guidelines.

3 RESULTS

3.1 Analysis according to pretreatment risk

The total number of patients included in the analysis was 187 (21 non-cirrhotic F3 patients and 166 cirrhotic patients). A total of 91 (48.7%) were male, with an average age of 68.24 ± 10.32 years. The observation period was 36.40 ± 14.31 (range 0-55) months (Table 1). Among the study patients for whom the pretreatment score could be calculated, 75 (40.1%), 58 (31.0%) and 54 (28.9%) had low-, intermediate- and high-risk scores respectively. HCC developed in 19 cases during the study period. Four cases of HCC developed in the low-risk group (4/75, 5.3%), five developed in the intermediate-risk group (5/58, 8.6%) and 10 developed in the high-risk group (10/54, 18.5%) (Table 2). The 4-year cumulative incidence was 1.64% (95% CI = 0.52-3.95) in the low-risk group, 2.82% (95% CI = 1.03-6.24) in the intermediate-risk group and 6.88% (95% CI = 3.49-12.26) in the high-risk group. Analysis of the cumulative incidence of HCC showed a significant difference among the three risk groups (P = .029, Figure 1A). Harrell’s C statistic for this external validation group was 0.6703.

3.2 Analysis of cirrhotic subgroups according to pretreatment risk

This study included 166 cirrhotic chronic HCV patients, 79 (47.6%) of whom were male, and their average age was 68.78 ± 10.46 years. Of the study patients with the score calculated, 60 (36.1%), 57 (34.3%) and 49 (29.5%) had low-, intermediate- and high-risk scores respectively. HCC developed in 16 cases during the study period. Two cases of HCC developed in the low-risk group (2/60, 3.3%), five developed in the intermediate-risk group (5/57, 8.8%) and nine developed in the high-risk group (10/54, 18.5%) (Table 1). The 4-year cumulative incidence was 0.98% (95% CI = 0.16-3.23) in the low-risk group, 2.86% (95% CI = 1.05-6.34) in the intermediate-risk group and 6.67% (95% CI = 3.25-12.24) in the high-risk group. Analysis of the cumulative incidence of HCC showed a significant difference among the three risk groups (P = .020, Figure 1B). Harrell’s C statistic for this external validation group was 0.6960.

3.3 Analysis according to post-treatment risk

The total number of patients included in this analysis was 97 (13 F3 noncirrhotic patients and 84 cirrhotic patients), and the
TABLE 1  Baseline characteristics of the studied patients according to the development of HCC

|                | HCC patients | Non-HCC patients | All     | P-value |
|----------------|--------------|------------------|---------|---------|
| Number         | 19           | 168              | 187     |         |
| Age            | 70.0 (66.0-74.0) | 70.0 (61.0-77.0) | 70.0 (61.0-77.0) | .963    |
| Sex            |              |                  |         |         |
| Males          | 12 (63.2)    | 79 (47.0)        | 91 (48.7) | .182    |
| Females        | 7 (36.8)     | 89 (53.0)        | 96 (51.3) |         |
| Fibrosis stage |              |                  |         |         |
| No cirrhosis (F3) | 3 (15.8)   | 18 (10.7)        | 21 (11.2) | .507    |
| Cirrhosis (F4) | 16 (84.2)    | 150 (89.3)       | 166 (88.8) |         |
| Albumin (g/dL) | 3.7 (3.3-3.9) | 3.9 (3.6-4.2)   | 3.9 (3.6-4.1) | .016    |
|AFP (ng/mL)     | 14.6 (6.6-19.4) | 6.8 (3.7-18.8) | 7.3 (3.9-18.9) | .119    |
| ALT (U/L)      | 53.0 (44.0-85.0) | 45.0 (31.0-71.0) | 47.0 (31.0-72.0) | .271    |
|AST (U/L)       | 59.0 (49.0-88.0) | 53.0 (39.3-76.0) | 53.0 (40.7-60.0) | .509    |
|Platelet count (×10^3) | 81.0 (68.0-118.0) | 95.0 (73.3-123.5) | 92.0 (73.0-122.0) | .322    |
|FIB-4           | 7.45 (4.24-8.57) | 5.94 (4.13-8.58) | 6.08 (4.13-8.58) | .391    |

Genotype

| 1              | 16 (84.2) | 113 (67.3) | 129 (69.0) | .313    |
| 2              | 3 (15.8)  | 54 (32.1)  | 57 (30.5)  |         |
| ND             | 0 (0.0)   | 1 (0.6)    | 1 (0.5)    |         |
| DM             |           |            |            | .070    |
| No             | 12 (63.2) | 136 (81.0) | 148 (79.1) |         |
| Yes            | 7 (36.8)  | 32 (19.0)  | 39 (20.9)  |         |

DAAs treatment

| DCV/ASV       | 9 (47.4) | 44 (26.2) | 53 (28.3) | .156    |
| GLE/PIB       | 1 (5.3)  | 16 (9.5)  | 17 (9.1)  |         |
| GZR/EBR       | 1 (5.3)  | 8 (4.8)   | 9 (4.8)   |         |
| OBV/PTR/r     | 1 (5.3)  | 1 (0.6)   | 2 (1.1)   |         |
| SOF/LDV       | 4 (21.1) | 55 (32.7) | 59 (31.6) |         |
| SOF/RBV       | 3 (15.8) | 44 (26.2) | 47 (25.1) |         |

Note: Data are presented as frequency (%) or median (IQR).
Abbreviations: SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir; ASV, asunaprevir; GZR, grazoprevir; EBR, elbasvir; GLE/PIB, glecaprevir/pibrentasvir; OBV/PTR/r, ombitasvir/paritaprevir/ritonavir

*Patients with non-SVR status after DAA initiation were excluded from this study.

TABLE 2  Characteristics of studied patients according to the development of HCC and pretreatment risk

|                | HCC patients | Non-HCC patients | All     | Log Rank P-value |
|----------------|--------------|------------------|---------|------------------|
| A. All patients|              |                  |         |                  |
| Number         | 19           | 168              | 187     |                  |
| GES risk categories |          |                  |         | .029             |
| Low            | 4 (21.1)     | 71 (42.3)        | 75 (40.1) |         |
| Intermediate   | 5 (26.3)     | 53 (31.5)        | 58 (31.0) |         |
| High           | 10 (52.6)    | 44 (26.2)        | 54 (28.9) |         |

B. Cirrhotic patients

|                | HCC patients | Non-HCC patients | All     | Log Rank P-value |
|----------------|--------------|------------------|---------|------------------|
| Number         | 16           | 150              | 166     |                  |
| GES pretreatment risk categories |          |                  |         | .020             |
| Low            | 2 (12.5)     | 58 (38.7)        | 60 (36.1) |         |
| Intermediate   | 5 (31.3)     | 52 (34.7)        | 57 (34.3) |         |
| High           | 9 (56.3)     | 40 (26.7)        | 49 (29.5) |         |
observation period was 34.67 ± 14.29 (range 0-54) months. Among the patients for whom post-treatment scores could be calculated, 58 (59.8%), 27 (27.8%) and 12 (12.4%) had low-, intermediate- and high-risk scores respectively. HCC developed in 12 cases during the study period. Seven cases of HCC developed in the low-risk group (7/58, 12.1%), three developed in the intermediate-risk group (3/27, 11.1%) and two developed in the high-risk group (2/12, 16.7%) (Table 3).

The 4-year cumulative incidence was 3.82% (95% CI = 1.67-7.55) in the low-risk group, 4.09% (95% CI = 1.04-11.13) in the intermediate-risk group and 8.54% (95% CI = 1.43-28.21) in the high-risk group. Analysis of the cumulative incidence of HCC showed no significant difference among the three risk groups ($P = .491$, Figure 2A). Harrell’s C statistic for this external validation group was 0.5874.

### Analysis of cirrhotic subgroups according to post-treatment risk

The study included 84 cirrhotic chronic HCV patients. Among the patients for whom post-treatment scores could be calculated, 46 (54.8%), 27 (32.1%) and 11 (13.1%) had low-, intermediate- and high-risk scores respectively. HCC developed in nine cases during the study period. Four cases of HCC developed in the low-risk group (4/46, 8.7%), three developed in the intermediate-risk group (3/27, 11.1%) and two developed in the high-risk group (2/11, 18.2%).

The 4-year cumulative incidence was 2.64% (95% CI = 0.84-6.38) in the low-risk group, 4.09% (95% CI = 1.04-11.13) in the intermediate-risk group and 10.39% (95% CI = 1.74-34.33) in the high-risk group. Analysis of the cumulative incidence of HCC showed no significant difference among the three risk groups ($P = .208$, Figure 2B).
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Figure 2B). Harrell’s C statistic for this external validation group was 0.6196.

4 | DISCUSSION

In this study, we externally validated a simple predictive score for HCC (called the GES) comprising routinely available laboratory parameters (albumin and AFP) plus age and sex. The original GES study has some limitations, as all patients in the discovery and validation cohorts had genotype 4; thus, it remains unclear whether their findings are valid in DAA-treated HCV patients with other genotypes.6 The GES in our Japanese FLAG cohort (mainly genotypes 1 and 2) successfully stratified the patients with pretreatment scores into three risk categories: low, 75 (40.1%); intermediate, 58 (31.0%) and high, 54 (28.9%). Interestingly, the 4-year cumulative IR was only 1.64% in the low-risk group, so those patients can be followed up at longer intervals. Because they have a low risk of developing HCC. If the GES could be used in the FLAG cohort for HCC risk stratification, it would not only save many resources but also reduce the physical harm related to unnecessary investigations, such as repeated CT, MRI and expensive laboratory tests. On the other hand, patients with greater risk (intermediate with 4Y C-IR 3.11% and high-risk C-IR 4.73%), which accounted for 59.9% of the patients in this cohort, may require more intense screening, with CT and MRI even at shorter intervals than that recommended by the current guidelines. Focusing HCV surveillance on those patients in the FLAG cohort with the highest risk (28.9%) will lead to the identification of many patients with early HCC who could benefit from curative treatment and will ultimately result in improved survival.8 Furthermore, GES was able to stratify the patients with post-treatment scores into three risk categories: low, 58 (59.8%); intermediate, 27 (27.8%) and high, 12 (12.4%). The 4-year cumulative incidence was 3.82% (95% CI = 1.67-7.55) in the low-risk group, 4.09% (95% CI = 1.04-11.13) in the intermediate-risk group and 8.54% (95% CI = 1.43-28.21) in the high-risk group. Remarkably, when using the post-treatment GES, the percentage of patients in the at-risk groups (high-intermediate risk) decreased, which was likely significantly attributed to the beneficial effect of viral clearance and concomitant fibrosis regression and improvement in serum albumin and AFP after treatment. Although AFP is the most widely used biomarker in HCC surveillance, it is not included in international guidelines because of its suboptimal sensitivity and specificity.8-11 However, several recent reports have confirmed that longitudinal AFP measurement, rather than an absolute cut-off value of,10,12 may further increase the sensitivity of HCC detection.

An important finding that the percentage of at-risk patients using post-treatment GES was associated with an increase in the 4-year cumulative IR (6.9% vs 8.5% in the high-risk group and 2.8% vs 4.1% in the intermediate-risk group), which clearly showed the more accurate selection of at-risk patients who required more intense screening. The performance of GES was similar when applied to a subset of patients with cirrhosis.

GES was externally validated in a single-centre cohort of European patients with cirrhosis in the Italy study. The authors stated that the GES was able to stratify the patients into three groups: low risk, 188 (32.5%); intermediate risk, 243 (42.1%) and high risk, 146 (25.3%). The 5-year cumulative incidence of HCC was 4.7% in the low-risk group, 10% in the intermediate-risk group and 13.8% in the high-risk group (P = .01). They concluded that the accuracy of GES was suboptimal because there was no significant difference in the 5-year risk between the intermediate- and high-risk groups (P = .2).13 However, Shiha et al, in their reply to this external validation report,12 stated...
that only 42 patients (out of 577) completed the 5-year follow-up. Their patients were categorized into three patient subgroups, namely, 8, 18 and 16 patients, and unfortunately, this small number of patients could strongly limit the statistical power of the analysis. If the same analysis was conducted with the 4-year data, 324 patients would have been categorized into three patient subgroups, namely, 104, 142 and 78 patients, which could have allowed for a more powerful statistical analysis. It should also be noted that Bergna et al did not report Harrell's C index for the GES in their cohort in the Italy study, which is crucial for the evaluation of HCC risk prediction scores. Larger cohorts in the European population, predominantly with HCV genotype 1, are needed for a more accurate external evaluation of the GES.

A new assessment tool for hepatic function, the ALBI score, which consists of only albumin and bilirubin measurements, has recently been proposed. Several HCC risk models using the ALBI score have been developed and validated to stratify patients based on their risk of HCC development. The GES utilizes simple and readily available predictors and thus can be easily employed in clinical practice.

To our knowledge, this is the first study to assess the performance of an HCC risk score (GES) among DAA-treated Japanese patients with HCV genotypes 1 and 2. These findings showed that the GES had excellent performance for HCC risk stratification in DAA-treated HCV patients with other genotypes. However, our study has several limitations, which should be noted. First, the sample size was relatively small. In addition, we used a retrospective design; thus, our results need further confirmation in a prospective study. Moreover, Harrell’s C-statistic was only 0.6703, which is fair.

In conclusion, the GES was a useful score for Japanese patients after HCV eradication. Post-SVR patients with high-risk scores should be monitored carefully for the possible development of HCC.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

AUTHORS’ CONTRIBUTION
GS designed the study. KA provided the external validation Cohort. KA, MF, MH, AT and HO supervised clinical work. NM performed the statistical analyses. GS, NM and RS interpreted the data. All authors drafted the paper, provided input for the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, [K.A], upon reasonable request.

ORCID
Kazumichi Abe https://orcid.org/0000-0001-5359-9465

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of the article at the publisher’s website.

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