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Validation Study of Scores Predicting Hepatocellular Carcinoma Risk in Chronic Hepatitis B Patients Treated With Nucleos(t)ide Analogues

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ABSTRACT

Chronic hepatitis B virus (HBV) infection is a leading cause of hepatocellular carcinoma (HCC) worldwide. Nucleos(t)ide analogues (NAs) are widely used in chronically HBV-infected patients, but the risk of HCC still remains in NA-treated patients. In this study, we aimed to validate the HCC risk scores for HBV-infected patients treated with nucleos(t)ide analogues (NAs). Among a total of 360 chronically HBV-infected patients who were treated with NAs, 253 patients without a history of HCC were used to validate the PAGE-B, mPAGE-B, PAGED-B, APA-B, and aMAP scores, as well as a recently developed score, the FAL-1 score, which consists of the FIB-4 index and ALT at 1 year of NA. In this cohort, the cumulative incidence of HCC at 5, 10, and 15 years was 2.9%, 7.8% and 11.0%, respectively. Most scores significantly stratified the HCC incidence and, for the FAL-1 score, the cumulative incidence of HCC at 10 years was 0%, 11.3% and 17.2% for the score-0 ($n = 91$), score-1 ($n = 129$) and score-2 ($n = 30$) groups, respectively. Compared with the other scores, the FAL-1 score was shown to efficiently identify patients at very low risk of HCC. An analysis using both this validation and the previously reported derivation cohorts demonstrated the utility in patients with either HBV genotype B or C. In conclusion, the utility of the FAL-1 score was reproduced in this validation study as well as other scores. In particular, the FAL-1 score may be useful to efficiently identify patients with a low risk of HCC.

1 | Introduction

Hepatitis B virus (HBV) spreads by several routes, including vertical transmission and horizontal transmission, despite the development of effective vaccines [1]. Chronic HBV infection is the leading cause of hepatocellular carcinoma (HCC) worldwide [2]. Globally, nearly 257.5 million people were estimated to be chronically infected with HBV [3], and the number of incident

cases of HCC due to HBV infection was reported to be 219,000 in 2019 [4]. Nucleos(t)ide analogues (NAs) have been widely used for chronic hepatitis B patients, and lower HCC risks have been reported in NA-treated patients than in those without NAs [5–7]. However, the risk of HCC still remains in NA-treated patients, and an effective estimation method is needed to efficiently find HCC patients in the early stage.

Several risk scores predicting HCC in HBV-infected patients treated with NAs have been reported using the data at baseline or during treatment [8]. Most scores include age, sex, and the presence of liver cirrhosis or its related factors such as platelets (PLT) and albumin [8]. In addition, some scores include alpha-fetoprotein and the presence of diabetes. We reported that non-achievement of alanine aminotransferase (ALT) normalisation at 1 year of therapy was associated with HCC development [9] and, recently, we developed a fibrosis and alanine aminotransferase-1 (FAL-1) score to predict HCC development in chronic hepatitis B patients under NA treatment with a simple method using the Fibrosis-4 (FIB-4) index and ALT at 1 year of therapy [10]. However, validation of the FAL-1 score has not been performed and its utility remains unknown. In this study, we aimed to validate scores that estimate the HCC risk in NA-treated patients, including the FAL-1 score.

2 | Patients and Methods

2.1 | Patients

A total of 360 patients with HBV chronic infection who were treated with NAs [lamivudine (LAM), entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide fumarate (TAF)] were enrolled from 6 hospitals in Aomori, Akita, Iwate, Yamagata, Miyagi and Fukushima prefectures in the Tohoku Hepatology Research Meeting (THERME) Study Group. The six hospitals were not included in the previous study that developed the FAL-1 score. After the exclusion of patients with hepatitis C virus (HCV) co-infection, very excessive alcohol intake (> 120 g/day), a history of HCC development before the start of NAs, or HCC development within 1 year, and those lacking baseline data, a total of 253 patients were retrospectively analysed (Figure 1).

This study has been approved by the medical ethics committee of Tohoku University (approval no. 2021-1-533). Informed consent was obtained in the form of an opt-out method. This means that the content of the study was made public and that the participants could withdraw from the study at any time.

2.2 | Assays of Serological Tests

The FIB-4 index was calculated as follows: FIB-4 = age (years) × aspartate aminotransferase (AST, U/l)/[(PLT, 10^3/μL) × $\sqrt{}$alanine aminotransferase (ALT, U/l)] [11]. HBsAg was determined by a chemiluminescent immunoassay (CLIA) using ARCHITECT (Abbott Japan, Tokyo, Japan) or a chemiluminescent enzyme immunoassay (CLEIA) using LUMIPULSE HBsAg-HQ (Fujirebio, Tokyo, Japan). Hepatitis B e antigen (HBeAg) was tested by CLIA using ARCHITECT. The HBV DNA levels were quantified by real-time PCR assay using Cobas TaqMan HBV Auto (Roche Diagnostics, Tokyo, Japan). HBcrAg was determined by CLEIA using LUMIPULSE (Fujirebio). HBV genotypes were determined using IMMUNIS HBV Genotype EIA Kit (Institute of Immunology, Tokyo, Japan).

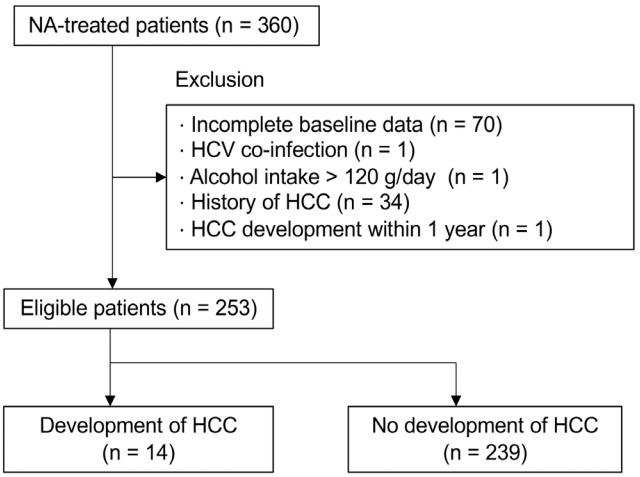

FIGURE 1 | Flow chart of patients included in this study. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NA, nucleos(t)ide analogue.

2.3 | HCC Surveillance

HCC surveillance was performed as previously reported [10]. Basically, an ultrasonography test was performed at least twice per year. The presence of hepatic steatosis was assessed by the ultrasonography at baseline. If the patient was considered to have liver cirrhosis, contrast-enhanced computed tomography or magnetic resonance imaging was performed at least once a year. Serum alpha-fetoprotein (AFP) was measured at each visit at least once every 3 months. Imaging studies were intensified if the AFP levels increased.

2.4 | HCC Risk Scores

The PAGE-B score was calculated using age, sex and PLT data as previously reported, and patients were categorised as low-risk (score ≤ 9), intermediate-risk (score 10–17), and high-risk (score ≥ 18) [12]. The mPAGE-B score was calculated using the data on age, sex, PLT, and albumin, and patients were categorised as low-risk (score ≤ 8), intermediate-risk (score 9–12) and high-risk (score ≥ 13) [13]. The PAGED-B score was calculated using the data on age, sex, PLT, diabetes mellitus, and HBV DNA, and patients were grouped into low-risk (score < 7) and high-risk (score ≥ 7) [14]. The APA-B score was calculated using the data on age, PLT and AFP at 1 year after initiation of NA, and patients were stratified into low-risk (score 0–5), intermediate-risk (score 6–9) and high-risk (score 10–15) [15]. The aMAP score was calculated using the data on age, sex, total bilirubin (T-bil), albumin, and PLT, and patients were categorised as low-risk (score < 50), medium-risk (score 50–60) and

high-risk (score > 60) [16]. The FAL-1 score was determined using FIB-4 and ALT at 1 year after the start of NAs, and with an applicable number of FIB-4 ≥ 1.58 and ALT ≥ 31, the score was determined as 0, 1 and 2 [10].

2.5 | Statistical Analysis

Statistical analyses were performed using the chi-squared test to compare proportions between two groups and the Wilcoxon rank-sum test to compare continuous variables between two groups. Cumulative incidences were estimated using the Kaplan–Meier method and were compared using the log-rank test. Differences with p values less than 0.05 were considered statistically significant. All statistical analyses were performed with JMP version 17.0.0 (SAS Institute Inc., Cary, NC). Data were plotted and graphed using GraphPad Prism version 10.3.1 (GraphPad Software Inc., La Jolla, CA).

3 | Results

3.1 | Clinical Characteristics of Patients

The clinical characteristics of the patients ($n = 253$) in this cohort are shown in Table 1. The median age was 58 years old and 159 males (65.4%) were included. The median levels of PLT, AFP and FIB-4 were 17.4, 3.8 and 2.03, respectively. The median observation period was 84 months. Among these patients, 14 patients (5.5%) developed HCC (Figure 1). Comparison of the characteristics of patients who developed HCC and those who did not is shown in Table 1. Patients who developed HCC had lower albumin (3.8 vs. 4.1 g/dL), lower PLT (12.7 vs. $17.9 \times 10^4/\mu L$) and higher AFP (10.4 vs. 3.6 ng/mL). In addition, the FIB-4 index was significantly higher in patients who developed HCC (5.00 vs. 1.98). There were no differences in the frequency of excessive alcohol intake and the presence of hepatic steatosis.

TABLE 1 | Patient characteristics in this study.

Baseline parameter[a]	Total ($n = 253$)	HCC development (+) ($n = 14$)	HCC development (–) ($n = 239$)	p[b]
Age (years)	58 (46–68)	60 (56–68)	56 (45–68)	0.192
Sex (male/female)	159/94	11/3	148/91	0.193
Previous IFN (+/-)	8/245	0/14	8/231	0.336
DM (+/-)	29/224	2/12	27/212	0.741
Excessive alcohol intake (+/-)[c]	20/107	1/9	19/98	0.583
Hepatic steatosis (+/-)	43/152	3/6	40/146	0.425
Initial NA (LAM/ADV/ETV/TDF/TAF)	17/2/161/27/46	2/0/9/2/1	15/2/152/25/45	0.62
T-Bil (mg/dL)	0.7 (0.6–1.0)	0.9 (0.7–1.1)	0.7 (0.6–1.0)	0.137
AST (U/L)	39 (27–72)	44 (35–99)	38 (26–71)	0.243
ALT (U/L)	50 (29–100)	43 (34–96)	51 (28–102)	0.957
Albumin (g/dL)	4.1 (3.8–4.4)	3.8 (3.5–4.2)	4.1 (3.8–4.4)	**0.04**
Creatinine (mg/dL)	0.7 (0.6–0.8)	0.7 (0.6–0.9)	0.7 (0.6–0.8)	0.645
PLT ($\times 10^4/\mu L$)	17.4 (14.0–22.0)	12.3 (7.1–14.7)	17.9 (14.3–22.1)	**< 0.001**
AFP (ng/mL)	3.8 (2.7–6.9)	10.4 (4.4–15.7)	3.6 (2.6–5.9)	**0.019**
HBV DNA (log IU/mL)	5.9 (3.9–7.6)	5.9 (3.8–7.4)	5.9 (3.9–7.7)	0.627
HBsAg (IU/mL)	816 (114–2781)	694 (60–1984)	853 (114–2955)	0.549
HBeAg (+/-)	47/131	2/9	45/122	0.508
HBcrAg (log U/mL)	5.2 (3.7–6.8)	5.5 (4.2–6.8)	5.2 (3.6–6.8)	0.809
HBV genotype (A/B/C)	2/78/75	0/2/5	2/76/70	0.723
FIB-4 index	2.03 (1.21–3.29)	5.0 (3.1–8.0)	1.98 (1.19–3.03)	**< 0.001**
Observation period (months)	84 (48–133)	106 (81–149)	84 (48–132)	0.111

Abbreviations: AFP, alfa-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; ETV, entecavir; FIB-4, Fibrosis-4; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN, interferon; LAM, lamivudine; NA, nucleos(t)ide analogue; PLT, platelets; TAF, tenofovir alafenamide fumarate; T-Bil, total bilirubin; TDF, tenofovir disoproxil fumarate.

[a]Median (interquartile ranges) or patient numbers are shown.

[b]P values less than 0.05 are shown in bold type.

[c]Male, ≥ 30 g/day; female, ≥ 20 g/day.

3.2 | Kaplan–Meier Analysis of Cumulative HCC Incidence With Several Risk Scores That Were Previously Reported

The cumulative incidence of HCC was evaluated with Kaplan–Meier analysis using the data from the entire cohort, and the incidence was 2.9%, 7.8% and 11.0% at 5, 10 and 15 years of NA treatment, respectively (Figure 2A). Using this cohort, we evaluated several reported scores predictive of HCC risk during NA treatment, including a PAGE-B score [12], a mPAGE-B score [13], a PAGED-B score [14] and an APA-B score [15] as well as a FAL-1 score [10]. In addition, we evaluated an aMAP score, which has

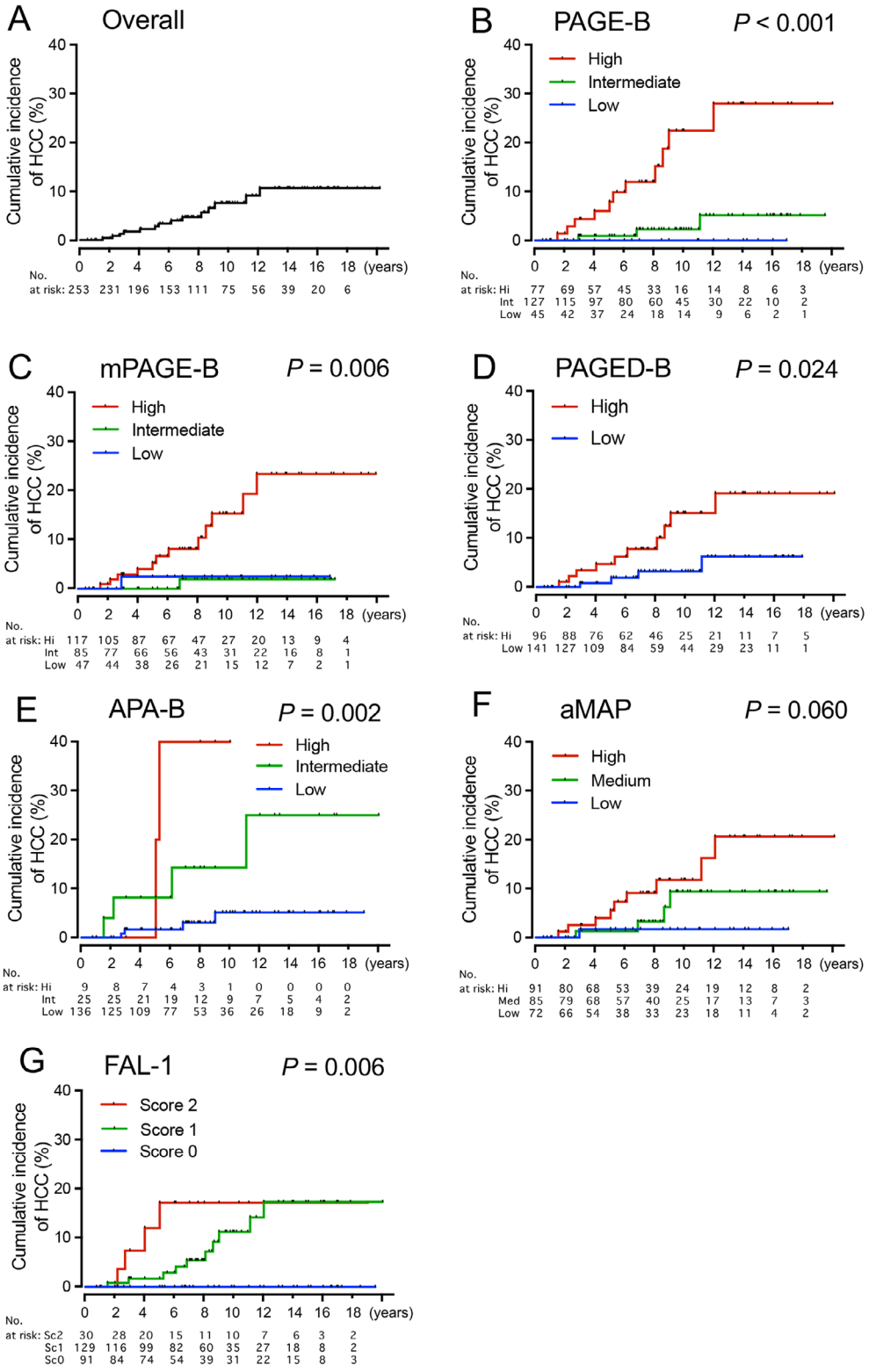

FIGURE 2 | Kaplan–Meier analyses of the cumulative HCC incidences in NA-treated patients with chronic HBV infection. (A) Result of overall patients. (B–G) Results of PAGE-B (B), mPAGE-B (C), PAGED-B (D), APA-B (E), aMAP (F), and FAL-1 (G) scores according to each risk group are shown.

been reported to predict HCC risk in various chronic liver diseases, including chronic hepatitis B patients treated with NAs, chronic hepatitis C patients, and patients with non-alcoholic fatty liver disease [16]. In an evaluation of the PAGE-B score, 45, 127, and 77 patients were categorised into low-risk, intermediate-risk, and high-risk groups, respectively. Kaplan–Meier analysis showed that the cumulative incidence of HCC in each group was 0%, 2.3% and 22.4% at 10 years, respectively ($p < 0.001$, Figure 2B). Next, the mPAGE-B score was evaluated, and 47, 85 and 117 patients were divided into low-risk, intermediate-risk and high-risk groups, respectively. The cumulative incidence of HCC in each group was 2.5%, 2.0% and 15.4% at 10 years, respectively (Figure 2C, $p = 0.006$). When the recently reported PAGED-B score was evaluated, 141 and 96 patients were classified as the low-risk and high-risk groups, respectively. The cumulative incidence of HCC in each group was 3.2% and 15.1% at 10 years, respectively (Figure 2D, $p = 0.024$). In the analysis of the APA-B score, a portion of the patients could not be evaluated due to the lack of AFP data at 1 year of NA treatment. As a result, 136, 25 and 9 patients were classified as low-risk, intermediate-risk, and high-risk groups, respectively. The cumulative incidence of HCC in each group was 5.1%, 14.3%, and 40.0% at 10 years, respectively (Figure 2E, $p = 0.002$). Based on the aMAP score, 72, 85 and 91 patients were categorised into low-risk, medium-risk and high-risk groups, respectively. The cumulative incidence of HCC in each group was 1.7%, 9.3% and 11.7% at 10 years, respectively (Figure 2F, $p = 0.060$).

3.3 | Analysis of Cumulative Incidences of HCC With the FAL-1 Score

When the FAL-1 score was evaluated, 91, 129 and 30 patients had a score of 0, 1 and 2, respectively. The cumulative incidence of HCC in each group was 0%, 11.3% and 17.2% at 10 years, respectively (Figure 2G, $p = 0.006$). The Kaplan–Meier curve was similar to that in the derivation cohort [10], showing that the patients with score 2 developed HCC relatively rapidly within a few years, and that the HCC incidence in the patients with score 1 gradually increased to 17.4% at 12 years. Interestingly, the HCC incidence of the score-2 patients reached a plateau at 5 years, and the incidence of the score-1 patients caught up with that of score-2 patients at 12 years. Notably, there were no patients who developed HCC among the score-0 patients. The FAL-1 score is potentially affected by hepatic steatosis, but the result excluding patients with hepatic steatosis was similar (Figure S1).

3.4 | Comparison of Each Risk Score for the Identification of Patients at Low Risk of HCC

Next, we analysed the ability of each score to efficiently identify a group of patients with a low risk of HCC. The percentage of patients in the low-risk group in each score (x-axis) and the 10-year HCC incidence in the group (y-axis) are plotted in Figure 3. The dots in the right and lower area are considered to indicate that the score has a good ability to efficiently identify patients with a low risk of HCC. Then, the low-risk group in the FAL-1 score accounted for 36.3%, and the HCC incidence was 0%, and the FAL-1 score is considered to be a better score than other scores from this point of view. To verify the result, the FAL-1 score data of the derivation cohort were also plotted in Figure 3. The HCC incidence in the low-risk group was 0.7%, which was similar to that in this validation cohort.

3.5 | Utility of the FAL-1 Score in Patients With Either Genotype B or C

To confirm the utility of the FAL-1 score regardless of HBV genotype, we combined the derivation cohort [10] and this validation cohort (Figure 4). A total of 725 patients were included, and among patients whose HBV genotype could be determined, 8 patients had genotype A, 232 patients had genotype B, and 330 patients had genotype C. In the analysis of cumulative HCC

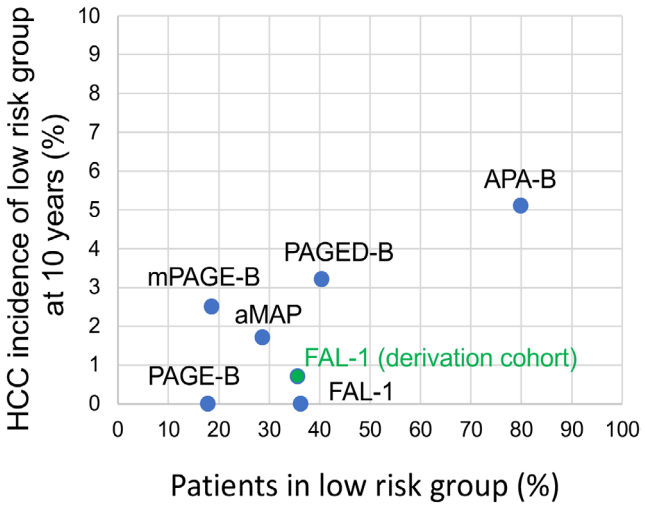

FIGURE 3 | Analysis o thef efficiency to identify patients with low risk of HCC in each risk score. A dot plot of the percentage of patients in the low-risk groups (x-axis) and HCC incidence at 10 years in the group (y-axis) by the HCC scores including PAGE-B, mPAGE-B, PAGED-B, APA-B, aMAP, and FAL-1 scores. Blue dots are based on this validation cohort and a green dot is a data of the FAL-1 score in the derivation cohort that was previously reported [10].

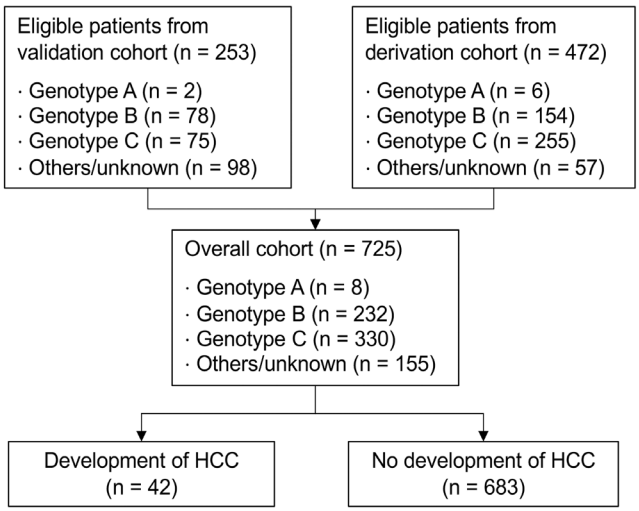

FIGURE 4 | Flow chart of patients in the analysis by HBV genotype using the validation cohort in this study and the previously reported derivation cohort [10].

incidence according to the genotype, there was no significant difference (Figure 5A). Overall, 259, 349, and 113 patients had FAL-1 scores of 0, 1 and 2, respectively. The cumulative incidence of HCC was significantly stratified ($p < 0.001$), and the 10-year incidences in each group were 0.5%, 10.6% and 22.2%, respectively (Figure 5B). When genotype C patients were analysed, the cumulative incidence of HCC in each group was 0%, 11.2% and 24.8% at 10 years, respectively (Figure 5C), similar to the overall result ($p < 0.001$). In the analysis of genotype B patients, the cumulative incidence of HCC in each group was 1.5%, 8.7% and 20.6% at 10 years, respectively (Figure 5D). The FAL-1 score also stratified the HCC risk in genotype B ($p = 0.002$), but the curve of score-1 patients was different from that of genotype C: the incidence increased sharply to 13.5% at approximately 10 years.

4 | Discussion

This study analysed the usefulness of the reported HCC risk scores in HBV-infected patients treated with NA in a validation cohort, and scores other than the aMAP score were shown to significantly stratify the HCC risk. In particular, our recently developed FAL-1 score showed almost the same result as the derivation cohort. The common findings of the FAL-1 score in the two cohorts were: (1) the score-2 patients developed HCC rapidly in the 5 years, and the HCC incidence reached a plateau; (2) the HCC incidence of the score-1 patients gradually increased, and the incidence caught up with that of the score-2 patients; (3) the HCC incidence of the score-0 patients was very low (0.7% in the derivation cohort and 0% in this validation cohort). In particular, the efficiency for identifying low-risk patients (more than 35%) was considered to be better than the other previously reported scores. In clinical practice, the FAL-1 score-2 patients should receive more intensive HCC surveillance during the first 5 years of NA treatment. Also, the score-0 patients, who account for one-third of NA-treated patients, can avoid frequent HCC surveillance. Another strength of the FAL-1 score is the simplicity: only two parameters, FIB-4 index and ALT after 1 year of NA treatment, are required. The FIB-4 index consists of four parameters that are obtained in routine practice, and its usefulness as a non-invasive test for liver fibrosis in various chronic liver diseases, including chronic hepatitis B, has been established [17].

The genotypes of HBV are known to affect the outcome of the disease [18], and the prevalence of HBV genotype varies in areas of the world [19]. In Japan, genotype C HBV was reported to be the most prevalent (79.0%) and genotype B followed (16.2%) in 2015–2016 [20]. In this cohort, the prevalence of genotype B was 50.3% and higher than the whole of Japan. A previous report showed a high prevalence of genotype B HBV in the same area, the Tohoku district [20–22], but the percentage of genotype B in this cohort was even higher. As a feature of this cohort, data from all six prefectures in the Tohoku district were included and, in particular, the percentage of genotype B was more than 50% in Aomori, Akita, and Yamagata prefectures, which are located in the western part of the Tohoku district (data not shown). Such a deviation of the HBV genotype distribution may exist even

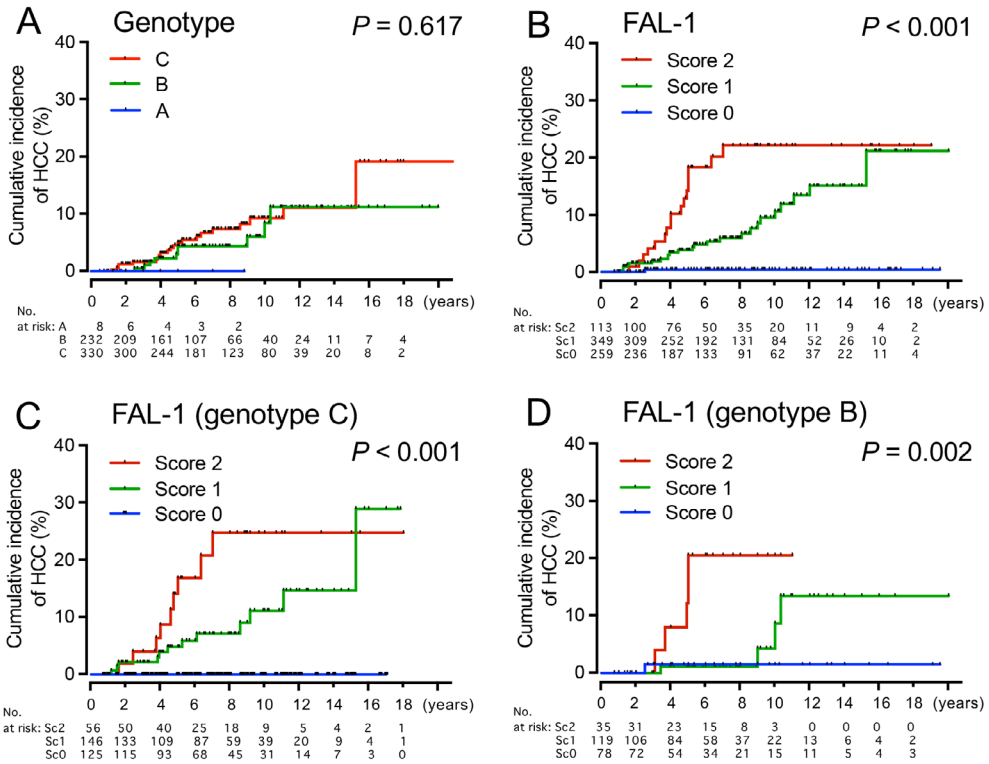

FIGURE 5 | Kaplan–Meier analyses of cumulative HCC incidences by HBV genotype using both the derivation and the validation cohorts. (A) Result of HCC incidences in patients with genotypes A, B, and C. (B) Result of HCC incidences in total patients including both cohorts, according to FAL-1 score 0, 1, and 2 groups. (C, D) Result of HCC incidences in genotype C patients (C) and genotype B patients (D), according to FAL-1 score 0, 1, and 2 groups.

within the Tohoku district, and inclusion of such areas may affect the high percentage of genotype B. The high percentage of patients with genotype B HBV is one of the strengths of this study, making it reliable to compare the characteristics of genotype B and those of genotype C.

There was no significant difference in the cumulative HCC incidence between genotype B and C. However, patients with genotype B were older, and our previous study with age- and sex-matched study showed a significantly lower HCC incidence in genotype B than in genotype C [22]. The HCC incidence in genotype B could be stratified by the FAL-1 score, but the curve of the score-1 patients was distinctive, and it increased suddenly at around 10 years. The reason is unclear, but it corresponds to the previous result that the HCC incidence of genotype B patients increased later than that of genotype C [22, 23]. Therefore, the score-1 patients should receive careful surveillance of HCC for a long time, regardless of the HBV genotype, B or C.

The PAGE-B, mPAGE-B, PAGED-B, APA-B and aMAP scores were validated in this study (Figures 2 and 3). Among these scores, the PAGE-B score appears to be better at predicting HCC at long-term follow-up; the incidence of HCC in the high-risk group increased to 28% at 12 years and that in the low-risk group was 0%. We suggest that patients with low/intermediate risk of the PAGE-B score should be evaluated with the FAL-1 score at 1 year of NA, and if the score was 0, the frequency of HCC surveillance can be reduced (e.g., ultrasonography once a year) or followed up by a general practitioner. Our tentative proposal for HCC surveillance is shown in Figure S2. So far, several other scores have been reported to predict the HCC risk in NA-treated chronic hepatitis B patients, such as HCC-RESCUE [24], CAMD [25], AASL-HCC [26], REAL-B [27] and ASPAM-B [28]. As a limitation of this study, we could not analyse these scores because there were many missing data regarding the presence of liver cirrhosis, alcohol consumption and M2BPGi. In another cohort with such data, these scores should be compared with the FAL-1 score. Another limitation is that the number of patients in the validation cohort is relatively small. Further large studies in different areas should be performed in the future.

In conclusion, this study validated the utility of various reported HCC scores in NA-treated patients with chronic HBV infection. The FAL-1 score was useful to efficiently identify the very low-risk patients regardless of the HBV genotypes, B or C.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. J. Inoue, T. Akahane, Y. Miyazaki, et al., "Long-Read Deep Sequencing Analysis of Hepatitis B Virus Quasispecies in Two Elderly Cases of Interspousal Transmission," *Journal of Infection and Chemotherapy* 31, no. 1 (2024): 102521.

2. Z. M. Younossi, G. Wong, Q. M. Anstee, and L. Henry, "The Global Burden of Liver Disease," *Clinical Gastroenterology and Hepatology* 21, no. 8 (2023): 1978–1991.

3. Polaris Observatory C, "Global Prevalence, Cascade of Care, and Prophylaxis Coverage of Hepatitis B in 2022: A Modelling Study," *Lancet Gastroenterology & Hepatology* 8, no. 10 (2023): 879–907.

4. G. Cao, W. Jing, J. Liu, and M. Liu, "Countdown on Hepatitis B Elimination by 2030: The Global Burden of Liver Disease Related to Hepatitis B and Association With Socioeconomic Status," *Hepatology International* 16, no. 6 (2022): 1282–1296.

5. T. Hosaka, F. Suzuki, M. Kobayashi, et al., "Long-Term Entecavir Treatment Reduces Hepatocellular Carcinoma Incidence in Patients With Hepatitis B Virus Infection," *Hepatology* 58, no. 1 (2013): 98–107.

6. G. L. Wong, H. L. Chan, C. W. Mak, et al., "Entecavir Treatment Reduces Hepatic Events and Deaths in Chronic Hepatitis B Patients With Liver Cirrhosis," *Hepatology* 58, no. 5 (2013): 1537–1547.

7. C. Y. Wu, J. T. Lin, H. J. Ho, et al., "Association of Nucleos(t)ide Analogue Therapy With Reduced Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B: A Nationwide Cohort Study," *Gastroenterology* 147, no. 1 (2014): 143–151.

8. C. L. Lin and J. H. Kao, "Development of Hepatocellular Carcinoma in Treated and Untreated Patients With Chronic Hepatitis B Virus Infection," *Clinical and Molecular Hepatology* 29, no. 3 (2023): 605–622.

9. J. Inoue, T. Kobayashi, T. Akahane, et al., "Non-Achievement of Alanine Aminotransferase Normalization Associated With the Risk of Hepatocellular Carcinoma During Nucleos(t)ide Analogue Therapies: A Multicenter Retrospective Study," *Journal of Clinical Medicine* 11, no. 9 (2022): 2354.

10. J. Inoue, T. Akahane, T. Kobayashi, et al., "Usefulness of the Fibrosis-4 Index and Alanine Aminotransferase at 1 Year of Nucleos(t)ide Analog Treatment for Prediction of Hepatocellular Carcinoma in Chronic Hepatitis B Patients," *Hepatology Research* 54, no. 2 (2024): 131–141.

11. A. Vallet-Pichard, V. Mallet, B. Nalpas, et al., "FIB-4: An Inexpensive and Accurate Marker of Fibrosis in HCV Infection. Comparison With Liver Biopsy and Fibrotest," *Hepatology* 46, no. 1 (2007): 32–36, https://doi.org/10.1002/hep.21669.

12. G. Papatheodoridis, G. Dalekos, V. Sypsa, et al., "PAGE-B Predicts the Risk of Developing Hepatocellular Carcinoma in Caucasians With Chronic Hepatitis B on 5-Year Antiviral Therapy," *Journal of Hepatology* 64, no. 4 (2016): 800–806.

13. J. H. Kim, Y. D. Kim, M. Lee, et al., "Modified PAGE-B Score Predicts the Risk of Hepatocellular Carcinoma in Asians With Chronic Hepatitis B on Antiviral Therapy," *Journal of Hepatology* 69, no. 5 (2018): 1066–1073.

14. H. S. Chun, G. V. Papatheodoridis, M. Lee, et al., "PAGE-B Incorporating Moderate HBV DNA Levels Predicts Risk of HCC Among

Patients Entering Into HBeAg-Positive Chronic Hepatitis B," *Journal of Hepatology* 80, no. 1 (2024): 20–30.

15. C. H. Chen, C. M. Lee, H. C. Lai, et al., "Prediction Model of Hepatocellular Carcinoma Risk in Asian Patients With Chronic Hepatitis B Treated With Entecavir," *Oncotarget* 8, no. 54 (2017): 92431–92441.

16. R. Fan, G. Papatheodoridis, J. Sun, et al., "aMAP Risk Score Predicts Hepatocellular Carcinoma Development in Patients With Chronic Hepatitis," *Journal of Hepatology* 73, no. 6 (2020): 1368–1378.

17. K. Patel, S. K. Asrani, M. I. Fiel, et al., "Accuracy of Blood-Based Biomarkers for Staging Liver Fibrosis in Chronic Liver Disease: A Systematic Review Supporting the AASLD Practice Guideline," *Hepatology* 81, no. 1 (2024): 358–379, https://doi.org/10.1097/HEP.0000000000000842.

18. P. A. Revill, T. Tu, H. J. Netter, L. K. W. Yuen, S. A. Locarnini, and M. Littlejohn, "The Evolution and Clinical Impact of Hepatitis B Virus Genome Diversity," *Nature Reviews. Gastroenterology & Hepatology* 17, no. 10 (2020): 618–634.

19. J. Chen, L. Li, Q. Yin, and T. Shen, "A Review of Epidemiology and Clinical Relevance of Hepatitis B Virus Genotypes and Subgenotypes," *Clinics and Research in Hepatology and Gastroenterology* 47, no. 7 (2023): 102180.

20. K. Sakamoto, K. Ito, H. Yotsuyanagi, et al., "Trends of Hepatitis B Virus Genotype Distribution in Chronic Hepatitis B Patients in Japan," *Journal of Gastroenterology* 57, no. 12 (2022): 971–980.

21. K. Ito, H. Yotsuyanagi, M. Sugiyama, et al., "Geographic Distribution and Characteristics of Genotype A Hepatitis B Virus Infection in Acute and Chronic Hepatitis B Patients in Japan," *Journal of Gastroenterology and Hepatology* 31, no. 1 (2016): 180–189.

22. J. Inoue, T. Akahane, H. Nakayama, et al., "Comparison of Hepatitis B Virus Genotypes B and C Among Chronically Hepatitis B Virus-Infected Patients Who Received Nucleos(t)ide Analogs: A Multicenter Retrospective Study," *Hepatology Research* 49, no. 11 (2019): 1263–1274.

23. H. Haga, T. Saito, K. Okumoto, et al., "Incidence of Development of Hepatocellular Carcinoma in Japanese Patients Infected With Hepatitis B Virus Is Equivalent Between Genotype B and C in Long Term," *Journal of Viral Hepatitis* 26, no. 7 (2019): 866–872.

24. W. Sohn, J. Y. Cho, J. H. Kim, et al., "Risk Score Model for the Development of Hepatocellular Carcinoma in Treatment-Naive Patients Receiving Oral Antiviral Treatment for Chronic Hepatitis B," *Clinical and Molecular Hepatology* 23, no. 2 (2017): 170–178, https://doi.org/10.3350/cmh.2016.0086.

25. Y. C. Hsu, T. C. Yip, H. J. Ho, et al., "Development of a Scoring System to Predict Hepatocellular Carcinoma in Asians on Antivirals for Chronic Hepatitis B," *Journal of Hepatology* 69, no. 2 (2018): 278–285.

26. J. H. Yu, Y. J. Suh, Y. J. Jin, et al., "Prediction Model for Hepatocellular Carcinoma Risk in Treatment-Naive Chronic Hepatitis B Patients Receiving Entecavir/Tenofovir," *European Journal of Gastroenterology & Hepatology* 31, no. 7 (2019): 865–872.

27. H. I. Yang, M. L. Yeh, G. L. Wong, et al., "Real-World Effectiveness From the Asia Pacific Rim Liver Consortium for HBV Risk Score for the Prediction of Hepatocellular Carcinoma in Chronic Hepatitis B Patients Treated With Oral Antiviral Therapy," *Journal of Infectious Diseases* 221, no. 3 (2020): 389–399.

28. C. H. Chen, T. H. Hu, J. H. Wang, et al., "A mac-2 Binding Protein Glycosylation Isomer-Based Risk Model Predicts Hepatocellular Carcinoma in HBV-Related Cirrhotic Patients on Antiviral Therapy," *Cancers (Basel)* 14, no. 20 (2022): 5063.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.