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Prediction of long-term clinical outcome in a diverse chronic hepatitis B population: Role of the PAGE-B score

W. P. Brouwer[1] | A. J. P. van der Meer[1] | A. Boonstra[1] | E. P. C. Plompen[1] | S. D. Pas[1] | R. J. de Knegt[1] | R. A. de Man[1] | F. J. W. ten Kate[1] | H. L. A. Janssen[1,2] | B. E. Hansen[1,3]

[1]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, ZH, The Netherlands

[2]UHN Liver Clinic, Toronto Western and General Hospital, University Health Network Toronto, Toronto, ON, Canada

[3]IHPME, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

Correspondence
Willem P. Brouwer, Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam's, Rotterdam, ZH, The Netherlands.
Email: w.p.brouwer@erasmusmc.nl

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Summary

An abundance of noninvasive scores have been associated with fibrosis and hepatocellular carcinoma (HCC) development. We aimed to compare the prognostic ability of these scores in relation to liver histology in chronic hepatitis B (CHB) patients. Liver biopsies from treatment-naïve CHB patients at one tertiary care centre were scored by a single hepato-pathologist. Laboratory values at liver biopsy were used to calculate the PAGE-B, REACH-B, GAG-HCC, CU-HCC and FIB-4 scores. Any clinical event was defined as HCC development, liver failure, transplantation and mortality. HCC and mortality data were obtained from national database registries. Of 557 patients, 40 developed a clinical event within a median follow-up of 10.1 (IQR 5.7-15.9) years. The PAGE-B score predicted any clinical event (*C*-statistic.86, 95% CI: 0.80-0.92), HCC development (*C*-statistic .91) and reduced transplant-free survival (*C*-statistic .83) with good accuracy, also when stratified by ethnicity, antiviral therapy after biopsy or advanced fibrosis. The *C*-statistics (95% CI) of the REACH-B, GAG-HCC, CU-HCC and FIB-4 scores for any event were .70 (0.59-0.81), .82 (0.75-0.89), .73 (0.63-0.84) and.79 (0.69-0.89), respectively. The PAGE-B event risk assessment improved modestly when combined with the Ishak fibrosis stage (*C*-statistic .87, 95% CI: 0.82-0.93). The PAGE-B score showed the best performance in assessing the likelihood of developing a clinical event among a diverse CHB population over 15 years of follow-up. Additional liver histological characteristics did not appear to provide a clinically significant improvement.

KEYWORDS
chronic hepatitis B, hepatocellular carcinoma, long-term outcome, PAGE-B, prognosis

1 | INTRODUCTION

Approximately 350 million patients worldwide have chronic hepatitis B (CHB). Long-term CHB can lead to liver cirrhosis, decompensation, hepatocellular carcinoma (HCC) development and death. Nearly 30% of cirrhosis and 53% of all HCC is attributable to CHB, and about 650 000 patients die to the complications of CHB each year.[1,2] Disease progression may be halted by antiviral therapy (AVT), and therefore, it is important to assess the risk of deterioration for individual patients to be able to provide a timely intervention for those who benefit most.[3-5] For decades, liver biopsy has been the gold standard to assess the severity of liver disease and the patients' related prognosis.

Abbreviations: CHB, chronic hepatitis B; HAI, hepatic activity index; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis.

Janssen and Hansen are equally contributed.

However, this procedure is associated with potentially severe complications, sampling error, as well as inter- and intra-observer variation.[6,7] Noninvasive objective surrogate scores for the long-term prognosis are therefore warranted.

Recently, the FIB-4 and APRI scores have been developed to estimate the fibrosis severity with moderate to good accuracy, and the FIB-4 score has additionally been associated with survival and HCC development during 5 years of follow-up.[8-12] Furthermore, the PAGE-B score has been developed to estimate the probability of HCC development in Caucasian CHB patients treated with entecavir or tenofovir, as an alternative to the REACH-B, CU-HCC and GAG-HCC scores which were only associated with HCC development in Asian patients.[13-18] It is unknown how the prognostic accuracy of these noninvasive serum scores compares to that of liver histology with respect to the long-term outcome in CHB patients, especially with regard to event-free and transplant-free survival. Also, the prognostic benefit in performing a liver biopsy in addition to these noninvasive scores has, to our knowledge, not been assessed in detail.

The aims of the current study therefore were (i) to assess the prognostic performance of simple noninvasive risk scores in different subgroups, and (ii) to assess whether liver histological characteristics could improve this performance in CHB patients.

2 | MATERIALS AND METHODS

2.1 | Patient selection

The patient population and selection have been described previously.[19] In short, mono-infected treatment-naïve CHB (HBsAg positive for >6 months) patients consecutively biopsied in the period of 1985-2012 were retrospectively identified in a tertiary care centre in Rotterdam, the Netherlands. Patients were excluded in case of a history of AVT for the duration of >1 month prior to or at the time of biopsy, a current or past coinfection with hepatitis C, D, E or human immunodeficiency virus, presence of autoimmune liver disease, primary biliary cholangitis, Wilson's disease, hemochromatosis or any other coexisting primary liver disease or treatment with immune suppressive medication for more than 6 months prior to or at the time of biopsy. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the ethical review board of the Erasmus Medical Center, Rotterdam, the Netherlands.

2.2 | Data acquisition

Data on all-cause mortality were obtained from the municipal record database, and the development of HCC was obtained from the national HCC registry database. The event of liver transplantation or decompensation was obtained from the (electronic) medical chart. Data on demographics (sex, age, race, ethnicity, height, weight, route of hepatitis B virus (HBV) transmission, presumed date of infection) and clinical data (history, diagnosis of diabetes mellitus, daily alcohol intake, history of alcohol abuse, smoking) were obtained by a single investigator (WB) from the chart in a standardized way. Alcohol use was defined as ≥1 units of alcohol/day and alcohol abuse was defined as an history or current use of ≥5 units/day, corresponding to 40-50 g alcohol per day.[20] Data on chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutyltransferase [y-GT], bilirubin, albumin), haematology (platelet count, prothrombin time) and virology (HBsAg, anti-HBs, hepatitis B e antigen [HBeAg], anti-HBe, HBV DNA load, HBV genotype) at the time of biopsy were obtained from the clinical laboratory and the Department of Virology at the Erasmus Medical Center.

2.3 | Liver histology

All liver biopsies were obtained percutaneously. These biopsies were rescored by a single experienced hepato-pathologist (FK) who was blinded to the patient characteristics and outcome. Biopsies were scored in a uniform manner according to the Ishak fibrosis score, the hepatic activity index (HAI),[21] the Brunt score for steatosis and non-alcoholic steatohepatitis (NASH), defined as the combined presence of macrovesicular or microvesicular steatosis, lobular inflammation, lipogranulomas and ballooning degeneration.[22] Advanced fibrosis was defined as an Ishak score of ≥4, corresponding to portal to portal bridging and probable or definite cirrhosis. To minimize the chance of histological misclassification due to sample size, liver biopsies with a length of less than 10 mm and with less than 10 portal fields were excluded from the analysis.[23,24]

2.4 | Laboratory measurements

The gender and time-dependent upper limit of normal values were used for the analysis of serum ALT and AST. The HBV DNA level was expressed in units/millilitre (IU/mL) and, when required, calculated using the conversion of 1.0 pg/mL=5.15 × 10^4 IU/mL or 1.0 copies/mL=0.1818 IU/mL. HBV genotype was determined using the INNO-LiPA Genotype assay (Innogenetics, Ghent, Belgium) in case data on HBV genotype were missing.

2.5 | Outcome measures

The occurrence of liver failure (defined as an episode of jaundice, ascites, hepatic encephalopathy or gastroduodenal bleeding due to varices), HCC development, liver transplantation and all-cause mortality was studied. We assessed the occurrence of these events as a composite endpoint (any clinical event) as well as separately. In case of multiple events in an individual patient, only the first event was considered for the composite endpoint. The cause of death was determined by the treating physician. Death caused by liver failure or HCC was considered liver-related. The diagnosis of HCC was based on histopathology and when not available, on two imaging modalities (magnetic resonance imaging, computed tomography or contrast enhanced ultrasound).[25]

2.6 | Statistical analysis

Baseline was defined as the date of first liver biopsy. Scores for cirrhosis and outcome were constructed as previously described and their respective cut-offs were utilized in the analysis when appropriate (Table 1). The association between baseline clinical factors and (non-)invasive scores and clinical outcome at long-term follow-up was estimated using the Cox proportional hazards method. Factors with a *P*-value <.1 in univariate analysis were considered for multivariable Cox regression analysis. Deceased patients were censored at the time of death for the nonmortality outcomes. Patients who experienced liver failure were considered still at risk in the analysis for HCC, and *vice versa*. If there was no clinical event, patients were censored at the last follow-up visit. The *C*-statistic was calculated for the (non-)invasive risk scores to assess the predictive ability for any clinical outcome and risk of HCC. The risk of any clinical event was estimated for each individual patient using the baseline survival from the univariable Cox regression model using the noninvasive risk score with the highest overall *C*-statistic.

We performed additional analyses concerning the net reclassification improvement (NRI) by adding liver biopsy characteristics to the Cox regression model, in order to statistically examine the potential benefit of a liver biopsy. The *C*-statistic was calculated for the (non-)invasive risk scores to assess the predictive ability for any clinical outcome and risk of HCC. The risk of any clinical event was estimated for each individual patient using the hazard function from the univariable Cox regression model using the noninvasive risk score with the highest overall *C*-statistic. After addition of liver biopsy characteristics to the Cox regression model, we re-assessed the updated *C*-statistic and the updated estimation of this event risk using the hazard function of this multivariable model. Subsequently, the NRI at 5 and 10 years was calculated, in order to obtain the change in the estimated risk and thus to quantify the clinical added value of a liver biopsy when combined with the best performing noninvasive score.[26,27]

Skewed variables were log-transformed prior to the analyses. SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and the SAS 9.3 program (SAS Institute Inc., Cary, NC, USA) were used to perform statistical analyses. All statistical tests were two-sided and evaluated at the .05 level of significance.

2.7 | Role of the funding source

Financial support was provided by the Foundation for Liver and Gastrointestinal Research (SLO) in Rotterdam, the Netherlands, and by the Virgo consortium, funded by the Dutch government project number FES0908, and by the NGI project number 050-060-452. INNO-LiPA assays were provided by Innogenetics (Belgium). The funding sources did not have influence on study design, data collection, analysis and interpretation of the data, writing of the report or the decision to submit for publication.

3 | RESULTS

3.1 | Patient characteristics

Of 880 biopsied CHB patients, 163 did not meet eligibility criteria, 127 were excluded because of a missing chart or liver biopsy and 33 were excluded because of an inadequate liver biopsy sample. In total, 557 patients were thus included, of which 371 (67%) were male. The mean age at biopsy was 34.7 years. Patient characteristics are presented in Table 2. 47% of patients were Caucasian (n=261), 31% Asian (n=175) and 19% African (n=104). HBV genotypes A, B, C, D, E and other/mixed were present in 126 (23%), 64 (12%), 98 (18%), 171 (31%), 31 (6%) and 8 (1%) of patients, respectively. At baseline, 113 (20%) patients had advanced fibrosis and 63 (11%) cirrhosis (Table 1). Patients who received AVT after biopsy vs those who did not were more often HBeAg-positive (66% vs 25%, *P*<.001), had higher $\log_{10}$ HBV DNA load (6.8 [2.2] vs 3.9 [2.8] IU/mL, *P*<.001), ALT and AST (both *P*<.01), had lower thrombocyte counts (*P*<.001) and had more often advanced liver disease (26% vs 12%, *P*<.001).

3.2 | Events during follow-up

The mean duration of follow-up after liver biopsy was 10.1 years (interquartile range 5.7-15.9, maximum 27.3 years). Survival and HCC status was available for 515 (92.6%) patients, and 41 (7.2%) patients emigrated and were censored at the last follow-up visit; follow-up data of one patient (0.2%) could not be retrieved. Fifty-one patients lost HBsAg (median time from biopsy 3.1 years, IQR 1.2-8.2, maximum 19.2 years). During long-term follow-up, 40 patients experienced a

TABLE 1 Different risk scores and their components

Risk score	Components	Cut-offs	Ref
PAGE-B	Platelets, gender, age	<10, 10-17, >17	18
REACH-B	Gender, age, alanine aminotransferase (ALT), HBeAg status, hepatitis B virus (HBV) DNA load (copies/mL)	<8, ≥8	14
FIB-4	Platelets, age, aspartate aminotransferase (AST), ALT	≥3.25	9
Log APRI	Platelets, AST	>1.4	10
GAG-HCC	Gender, age, HBV DNA load (copies/mL), cirrhosis (US+)	<101, ≥101	15
CU-HCC	Age, albumin, bilirubin, HBV DNA load (copies/mL), cirrhosis (US+)	<5, ≥5	13

Ultrasound+ (US+): ultrasound and other factors indicating cirrhosis. In the current study, the diagnosis of cirrhosis was solely based on liver biopsy.

TABLE 2 Patient characteristics

Characteristics	All patients (N=557)
Demography	
Age at biopsy, years (SD)	34.7 (12.5)
Male, n (%)	371 (67)
Body mass index kg/m^2 (SD)[a]	24.8 (4.1)
Diabetes, n (%)	29 (5)
History of alcohol abuse, n (%)[b]	25 (5)
AVT after biopsy, n (%)	348 (63)
First course/Last course	
NA only	184 (53)
(Peg)IFN only	68 (19)
(Peg)IFN/NA	84 (24)
NA/(Peg)IFN	7 (2)
Other	5 (2)
Time (wks) to AVT (IQR)	NA
Ethnicity, n (%)	
Caucasian	261 (47)
Asian	175 (31)
African/negroid	104 (19)
Other	17 (3)
Virology	
HBeAg-positive, n (%)	280 (50)
log HBV DNA, IU/mL (SD)	5.7 (2.8)
HBV genotype A/B/C/D/E[c]	126/64/98/171/31
Chemistry/haematology	
ALT, × ULN (SD)	2.6 (3.6)
AST, × ULN (SD)	1.6 (1.9)
Thrombocytes (IQR)	206 (172-243)
Histology, n (%)	
Biopsy length, mm (SD)	19.9 (6.8)
Portal fields, n (SD)	19.9 (9.1)
Median Ishak fibrosis, (IQR)	1.0 (1.0-2.0)
Advanced fibrosis, n (%)	113 (20)
Hepatic activity index (SD)	4.2 (2.3)
Steatosis (>5%), n (%)	179 (32)
Steatohepatitis, n (%)	103 (19)
Follow-up, years from biopsy (IQR)	10.1 (5.7-15.9)

AVT, antiviral therapy; NA, nucleos(t)ide analogue; (Peg)IFN, (pegylated) interferonl ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal.
[a]Available in 469 (85%) patients.
[b]Available in 477 (86%) patients.
[c]Available in 498 (90%) patients.

clinical event: 10 patients developed liver failure, 15 patients were diagnosed with HCC, seven patients underwent liver transplantation, and 31 patients died. Ten patients died of a liver-related cause (seven of whom due to HCC and three as a result of liver failure), eight died of liver-unrelated causes (of which one patient had an HCC), and for 13 patients, the cause of death was unknown. The overall 5-, 10- and 20-year event-free survival was 97.6%, 94.0% and 86.8%, respectively.

3.3 | Factors associated with long-term clinical outcome

Fifty-five per cent (22/40) of all patients with an event had advanced fibrosis at baseline. The (non-)invasive scores were all significantly associated with the development of a clinical event, HCC and a reduced transplant-free survival (Table S1). In addition to the Ishak score (hazard ratio [HR] 1.74, 95% CI: 1.5-2.1, *P*<.001), liver biopsy characteristics significantly associated with the development of any clinical event were the HAI score (HR 1.17, 95% CI: 1.1-1.3, *P*=.005) and presence of steatosis (HR 2.38, 95% CI: 1.3-1.4, *P*=.006) or NASH (HR 2.56, 95% CI: 1.3-5.2, *P*=.009). Other factors associated with any event were the three components of the PAGE-B score: older age (HR per 10 years increase 2.3, 95% CI: 1.8-2.9, *P*<.001), male gender (HR 4.8, 95% CI: 1.7-13.4, *P*=.003) and lower thrombocyte count (HR 0.85 per 10 units increase, 95% CI: 0.8-0.9, *P*<.001). Moreover, a higher body mass index (HR 1.1, 95% CI: 1.0-1.2, *P*=.002), diabetes mellitus (HR 5.7, 95% CI: 2.7-11.6, *P*<.001) and alcohol abuse (HR 4.4, 95% CI: 1.8-10.7, *P*=.001) were also associated with an adverse clinical outcome.

By multivariable analysis, factors independently associated with clinical outcome were the PAGE-B score (HR 1.27, 95% CI: 1.2-1.4, *P*<.001) and the Ishak fibrosis stage (HR 1.38, 95% CI: 1.1-1.7, *P*=.003).

3.4 | Noninvasive scores vs liver biopsy for the prediction of clinical outcome

The *C*-statistic for the PAGE-B score for the prediction of any clinical event was .86 (95% CI: 0.80-0.92, Table 3) and was .83 (95% CI: 0.76-0.91) for reduced transplant-free survival and .91 (95% CI: 0.82-0.99) for HCC development. The other noninvasive prognostic measures showed a lower *C*-statistic for all respective outcomes (Table 3). When the Ishak stage was combined with the PAGE-B, the prediction for any clinical event improved (*C*-statistic .87, 95% CI: 0.82-0.93). For PAGE-B scores <10, 10-17 and >17, the observed cumulative probability of any clinical event was 0.9%, 1.9% and 14.2% at year 5, 0.9%, 3.1% and 39.3% at year 10 and 2.0%, 8.7% and 61.2% at year 15, respectively (log-rank *P*<.001, Figure 1). The estimated event risk and HCC risk for individual patients using the PAGE-B score are shown in Figure 2. For patients with a PAGE-B score <10, 10-17 and >17, the estimated 5-year event risk was <0.7%, 0.7%-8.0% and ≥8.0%; the 10-year event risk <1.5%, 1.5%-17.5% and ≥17.5%; and the 15-year event risk <3.0%, 3.0%-32.0% and ≥32%, respectively.

3.5 | Performance of noninvasive risk scores for clinical outcome in subgroups

For the prediction of any clinical event, the PAGE-B had the overall highest *C*-statistic compared to the other noninvasive scores

TABLE 3 *C*-statistic for the prediction of clinical outcome by prognostic biomarkers

Biomarker *C*-statistic (95% CI)	Any event (n=40)	Transplantation or mortality (n=31)	HCC development (n=15)
Noninvasive			
PAGE-B	**.86 (0.80-0.92)**	**.83 (0.76-0.91)**	**.91 (0.82-0.99)**
REACH-B	.70 (0.59-0.81)	.66 (0.53-0.80)	.83 (0.75-0.92)
FIB-4	.79 (0.69-0.89)	.76 (0.65-0.88)	.86 (0.75-0.98)
Log APRI	.69 (0.58-0.80)	.65 (0.53-0.78)	.81 (0.70-0.91)
Invasive			
PAGE-B + Ishak	**.87 (0.82-0.93)**	**.84 (0.78-0.91)**	**.92 (0.85-0.99)**
GAG-HCC[a]	.82 (0.75-0.89)	.78 (0.70-0.87)	.91 (0.86-0.96)
CU-HCC[a]	.73 (0.63-0.84)	.69 (0.55-0.82)	.84 (0.73-0.95)
Ishak fibrosis	.78 (0.70-0.86)	.75 (0.66-0.84)	.87 (0.81-0.94)

[a]The GAG-HCC and CU-HCC scores already include the diagnosis of cirrhosis, which in the current study is solely based on liver biopsy, and are therefore "invasive markers".
In bold, the noninvasive or invasive marker with the highest *C*-statistic.

stratified by AVT, advanced fibrosis and ethnicity (Table 4). Within patients with advanced fibrosis or Asian patients, the *C*-statistics were comparable to the FIB-4 and REACH-B, respectively. The *C*-statistics obtained with the PAGE-B for the prediction of HCC development in Asian patients who received AVT after liver biopsy was higher than the REACH-B: this was .75 (95% CI: 0.53-0.97) for the PAGE-B vs .69 (95% CI: 0.61-0.78) for the REACH-B, respectively.

3.6 | Additional prognostic value of the Ishak stage combined with PAGE-B

The individual risk of any event for patients was estimated for the combination of the PAGE-B with the Ishak fibrosis stage using the hazard function derived from this multivariable Cox regression model. This updated risk was compared to the original estimated risk (hazard function obtained with PAGE-B only) vs the actual observed events and nonevents at 5- and 10-year intervals to obtain the NRI. With the addition of the Ishak fibrosis stage, two of 12 (16.7%) of events were correctly reclassified into the intermediate-to-high risk group (PAGE-B score >10, corresponding to a 5-year event risk ≥0.7%), and three of 430 (0.7%) were incorrectly reclassified into the intermediate-to-high risk group at year 5 (total NRI=.160). At year 10, there was no additional value of the Ishak score to classify an event as the PAGE-B alone correctly classified all 24 events into the intermediate-to-high risk group (10-year event risk ≥1.5%). At year 10, 36 of 269 (13%) patients were correctly reclassified into the low-risk group by addition of the Ishak score, and no patients were incorrectly reclassified (total NRI=.134).

Using the same method, we also assessed the NRI for HCC prediction. Within the first 10 years of follow-up, the PAGE-B score alone correctly classified all patients who developed HCC into the intermediate HCC and high HCC risk groups (PAGE-B >10 corresponding to an HCC risk >0.2% at year 5 [4/4 cases] and >0.6% at year 10 [10/10 cases]) and no patients were incorrectly reclassified (NRI=0).

4 | DISCUSSION

In the current study, we have compared different prognostic scores for their ability to predict the clinical outcome over more than 15 years of follow-up in CHB patients of diverse ethnic origin and infected with all major HBV genotypes. We found that the PAGE-B score was the overall best performing risk score to predict any clinical outcome, transplant-free and HCC-free survival when compared to the REACH-B, FIB-4, APRI, GAG-HCC and CU-HCC risk scores. The PAGE-B score also showed a better prognostic performance stratified by AVT, or among subgroups of different ethnicity and severity of liver disease. After addition of the Ishak fibrosis stage to the PAGE-B risk score, the risk assessment obtained by the PAGE-B risk score only modestly improved, which was further underlined by the modest NRI.

Since timely diagnosis of severe liver disease may improve patients' prognosis through treatment with highly potent AVT, it is of great importance to select those patients in need for intervention and parallel HCC surveillance by assessing the risk of clinical disease progression as early as possible. The classical division of CHB in a five-stage disease continuum has its limitations, in that there are grey areas in which there is doubt whether patients should or should not receive therapy. Therefore, previous research has provided us with an abundance of (non-)invasive risk scores to assess the extent of liver disease, and long-term outcome. This may further add to uncertainty which score to use best in clinical practice. To our knowledge, there have not been comparisons within different subgroups between these risk scores. Comparing the different scores in the current study, we have shown that the PAGE-B score had the best overall discriminative ability to predict the risk of any clinical event, reduced transplant-free survival and HCC development over more than 15 years of follow-up and across different ethnicities. Importantly, in the current cohort we observed a better ability for the PAGE-B score to assess the HCC risk among treated Asian patients compared to the REACH-B. The validated PAGE-B score was previously constructed in a selected group

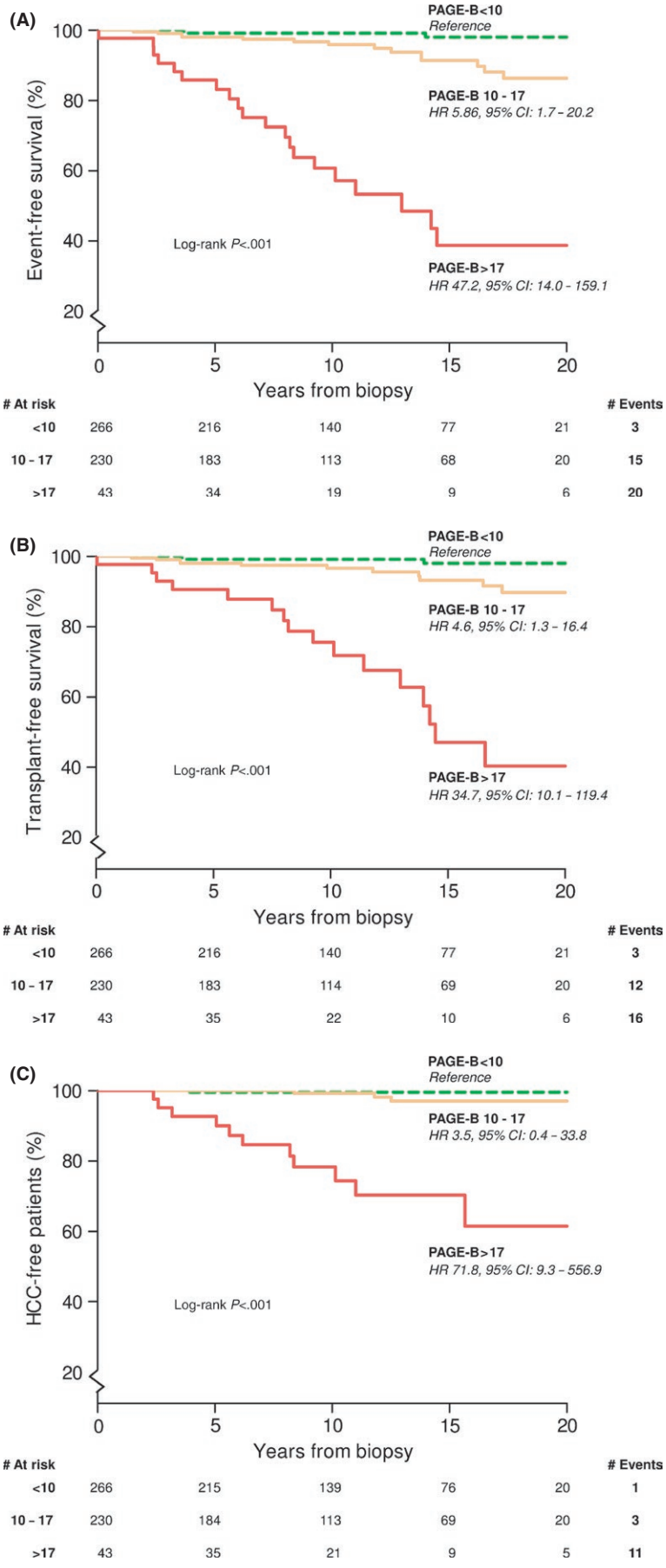

FIGURE 1 Kaplan-Meier curves for (A) event-free survival, (B) transplant-free survival and hepatocellular carcinoma (HCC), (C) free follow-up according to PAGE-B risk score <10, 10-17 and >17 points

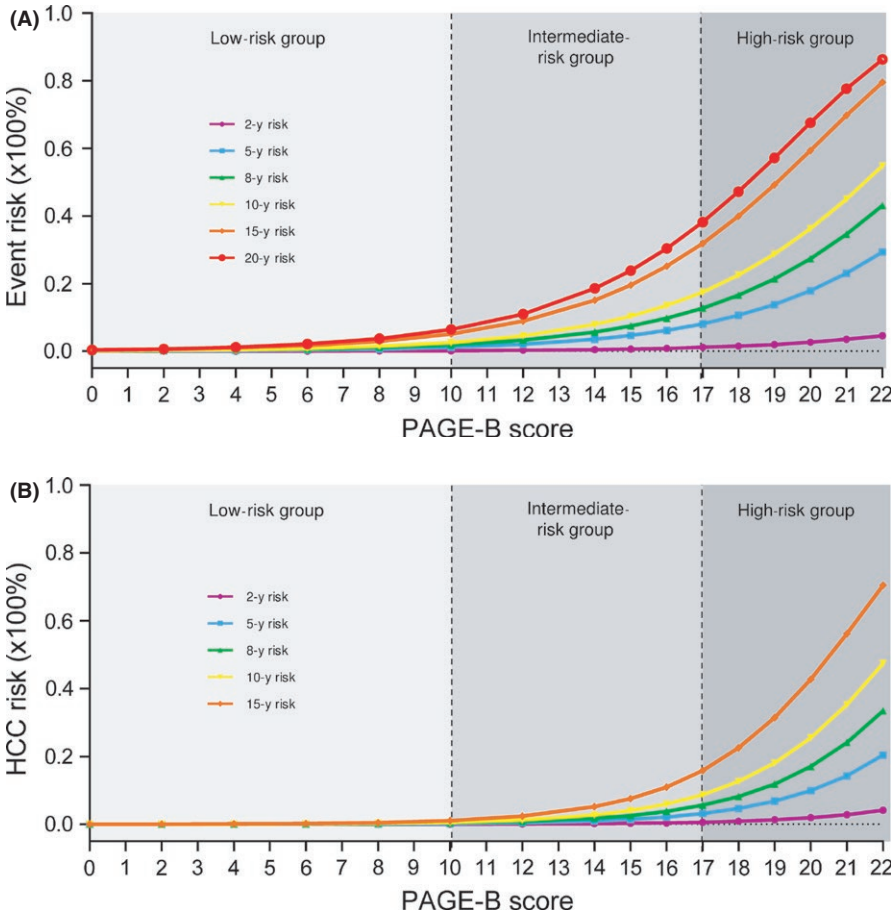

FIGURE 2 (A) Two-year to 20-year risk of any clinical event or hepatocellular carcinoma (HCC) (B) as a function of the PAGE-B score

TABLE 4 *C*-statistic for the prediction of any clinical event within different subgroups

Biomarker *C*-statistic (95% CI) n (cases)/N (subgroup)	Within AVT after biopsy (n/N=27/348)	Within no AVT after biopsy (n/N=13/209)	Within Advanced fibrosis (n/N=22/113)	Within no advanced fibrosis (n/N=18/444)	Caucasian patients (n/N=27/261)	Asian patients (n/N=7/175)	African patients (n/N=5/104)
Noninvasive							
PAGE-B	**.83 (0.75-0.92)**	**.91 (0.82-0.99)**	.81 (0.70-0.93)	**.81 (0.72-0.91)**	**.89 (0.82-0.96)**	**.87 (0.75-0.99)**	**.78 (0.58-0.98)**
REACH-B	.73 (0.62-0.85)	.66 (0.46-0.86)	.65 (0.49-0.82)	.65 (0.46-0.84)	.71 (0.57-0.85)	**.87 (0.77-0.98)**	.49 (0.23-0.76)
FIB-4	.79 (0.69-0.88)	.77 (0.53-0.99)	**.82 (0.70-0.93)**	.65 (0.47-0.83)	.83 (0.73-0.92)	.81 (0.67-0.96)	.61 (0.24-0.99)
Log APRI	.67 (0.56-0.78)	.68 (0.42-0.98)	.68 (0.55-0.82)	.50 (0.31-0.68)	.72 (0.62-0.83)	.77 (0.62-0.91)	.48 (0.10-0.86)
Invasive							
PAGE-B + Ishak	**.85 (0.78-0.92)**	**.90 (0.81-0.99)**	**.82 (0.73-0.92)**	**.79 (0.69-0.89)**	**.88 (0.81-0.95)**	.94 (0.87-0.99)	**.80 (0.62-0.98)**
GAG-HCC[a]	.83 (0.76-0.90)	.82 (0.70-0.94)	.71 (0.58-0.83)	.74 (0.62-0.86)	.79 (0.70-0.88)	**.97 (0.94-0.99)**	.68 (0.46-0.91)
CU-HCC[a]	.78 (0.68-0.88)	.67 (0.46-0.88)	.77 (0.64-0.90)	.52 (0.36-0.68)	.68 (0.54-0.82)	.95 (0.90-0.99)	.61 (0.28-0.94)
Ishak fibrosis	.77 (0.68-0.87)	.80 (0.67-0.93)	.72 (0.61-0.83)	.61 (0.49-0.72)	.73 (0.63-0.84)	.92 (0.85-0.99)	.75 (0.52-0.98)

[a]The GAG-HCC and CU-HCC scores already include the diagnosis of cirrhosis, which in the current study is solely based on liver biopsy, and are therefore "invasive markers."
AVT, antiviral therapy.
In bold, the noninvasive or invasive marker with the highest *C*-statistic.

of Caucasian CHB patients under highly potent NA therapy only.[17,18] Because of the different composition of the cohort in the current study in terms of untreated CHB patients and those of different ethnic origin and with different severity of liver disease, our findings further underline the robustness and generalizability of the PAGE-B score for the use in clinical practice.

For decades, the gold standard to assess the severity of liver disease has been liver biopsy.[7] With the combination of the PAGE-B score and the Ishak stage, the long-term risk prediction improved only minimally (from a *C*-statistic of .86 to .87). It could be debated whether the slight improvement in the detection of events justifies a liver biopsy with its accompanying risk for potentially severe complications, observer and sampling limitations, while the PAGE-B score is an objective, readily available and relative simple risk score.

A strength of the current study is that all liver biopsies were scored by a single experienced hepato-pathologist, which excludes interobserver and also minimizes intra-observer variation.[23] Moreover, the long-term follow-up data were both obtained from the municipal record database as well as from the national HCC registry database. As a result, data on HCC development and survival were complete for 93% of the cohort. We were not able to assess the effect of AVT on outcome because of different AVT regimens, different response criteria and significant differences between patients who were or were not treated. Although this is an important question, this analysis was outside the scope of this article, and more importantly, we have shown that the PAGE-B score had the best predictive ability for treated or untreated patients separately. Furthermore, we could not obtain repeated measurements to evaluate the longitudinal behaviour of the risk scores, and did not have data on transient elastography or HBsAg levels. It would be important to assess the added value of these factors to the PAGE-B score in future research.[28-31]

In conclusion, we have shown that the PAGE-B score was the best performing noninvasive score to predict the clinical outcome of CHB patients of different origin and within different subgroups. The Ishak stage did not clinically improve the risk prediction of the PAGE-B score. When further validated, this score could additionally be used to assess the need for AVT and HCC surveillance.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

WPB and AJM contributed to study coordination and design, collected data, performed data analysis, wrote the manuscript and approved the final version. HLAJ contributed to study coordination and design, collected data, critically reviewed the manuscript and approved the final version. FK performed histological assessment, collected data, critically reviewed the manuscript and approved the final version. RK, RM and EP collected data, critically reviewed the manuscript and approved the final version. BEH performed statistical analysis, critically reviewed the manuscript and approved the final version. AB and SP assessed the performance and coordination of assays, critically reviewed the manuscript and approved the final version. HLAJ, WPB and AJM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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