Research Article

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PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy

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Background & Aims: Risk scores for hepatocellular carcinoma (HCC) developed in Asians offer poor-moderate predictability in Caucasian patients with chronic hepatitis B (CHB). This nine center cohort study aimed to develop and validate an accurate HCC risk score in Caucasian CHB patients treated with the current oral antivirals, entecavir/tenofovir.

Methods: We included 1815 adult Caucasians with CHB and no HCC at baseline who received entecavir/tenofovir for ⩾12 months. Using data from eight centers (derivation dataset, n = 1325), a HCC risk score was developed based on multivariable Cox models and points system for simplification. Harrell's c-index was used as discrimination, bootstrap for internal validation and the data from the 9th and largest center (validation dataset, n = 490) for external validation.

Results: The 5-year cumulative HCC incidence rates were 5.7% and 8.4% in the derivation and validation dataset, respectively. In the derivation dataset, age, gender, platelets and cirrhosis were independently associated with HCC. The PAGE-B score was developed based on age, gender and platelets (c-index = 0.82, 0.81 after bootstrap validation). The addition of cirrhosis did not substantially improve the discrimination (c-index = 0.84). The predictability of PAGE-B score was similar (c-index = 0.82) in the validation dataset. Patients with PAGE-B ⩽9, 10–17, ⩾18 had 5-year cumulative HCC incidence rates of 0%, 3%, 17% in the derivation and 0%, 4%, 16% in the validation dataset.

Conclusion: PAGE-B, which is based only on baseline patients' age, gender and platelets, represents a simple and reliable score for prediction of the 5-year HCC risk in Caucasian CHB patients under entecavir/tenofovir.

Introduction

Monotherapy with one of the current first-line oral nucleos(t)ide analogues (NAs), entecavir (ETV) and tenofovir disoproxil fumarate (TDF), results in long-term inhibition of hepatitis B virus (HBV) replication in almost all compliant patients with chronic hepatitis B (CHB), improves liver histological lesions, often achieves regression of cirrhosis, prevents or reverses hepatic decompensation, diminishes the need for liver transplantation and improves the overall survival [1]. However, hepatocellular carcinoma (HCC) still develops in CHB patients treated with NA(s) regardless of virological response [2–4] representing the major complication and a key challenge in the management of CHB patients.

Given that the early diagnosis of HCC increases the applicability of curative therapies and eventually the patients' prognosis [5], the identification and close surveillance of CHB patients at high risk for HCC is of great importance. Most of the HCC data in CHB come from cohort studies including untreated patients or patients treated with lamivudine and/or adefovir and more recently ETV [2,3,6–9]. Recently, risk scores (GAG-HCC, CU-HCC

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Abbreviations: NA(s), nucleos(t)ide analogue(s); ETV, entecavir; TDF, tenofovir disoproxil fumarate; HBV, hepatitis B virus; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; IQR, interquartile range; HR, hazard ratio; CI, confidence interval(s).

and REACH-B) for prediction of HCC were developed and validated in cohorts of untreated Asian CHB patients [7–9], while their predictability was subsequently confirmed in Asian patients treated with entecavir [10]. We and others, however, have shown that the predictability of these HCC risk scores is poor to moderate in Caucasian CHB patients, for whom different risk scores seem to be required [11,12].

The aim of this large, multicenter, cohort study was to develop and validate an accurate HCC risk score in Caucasian CHB patients treated with the currently recommended oral antivirals, ETV or TDF.

Patients and methods

Patient population

This study was based on two datasets of Caucasian CHB patients selected by the same criteria from nine participating centers, as it has been previously described [11,12]. The derivation dataset including patients from eight centers was used as the training dataset to derive a score in predicting HCC, whereas the validation dataset including patients from the largest center (Milano, Italy) was used for external validation of the scoring system. All patients with CHB followed in the liver clinics of the nine participating centers were included if they were adults ($\geqslant$16 years old), Caucasians and had received treatment with ETV or TDF for $\geqslant$12 months. The participating centers were in Greece (Athens [2 centers], Larissa, Thessaloniki), Italy (Milano), Spain (Barcelona, Madrid), Netherlands (Rotterdam) and Turkey (Ankara). Patients naive to or previously treated with other NAs were included. Patients with decompensated cirrhosis, HCC diagnosed before the onset of ETV/TDF, patients with co-infection(s) with hepatitis D, hepatitis C or human immunodeficiency virus and liver transplant patients were excluded.

Follow-up – Definitions

CHB was diagnosed in patients with positive HBsAg for $\geqslant$6 months, elevated alanine aminotransferase (ALT) and serum HBV DNA >2000 IU/ml. Patients were classified according to their liver disease severity into: a) patients with CHB only (without cirrhosis) if they had a pretreatment liver biopsy without lesions of cirrhosis; and b) patients with compensated cirrhosis if they had histological findings and/or ultrasonographic findings (nodules in the hepatic parenchyma, spleen >12 cm, portal vein >16 mm) and/or endoscopic findings of cirrhosis (varices, portal gastropathy). Patients without a pretreatment liver biopsy and without any other sign of cirrhosis were considered as cases with unclassified disease severity.

All patients were treated with ETV and/or TDF and followed at each participating center according to international and/or national clinical practice guidelines. Clinical examination and routine laboratory tests were performed at least every 6 months. HBV DNA levels were determined every 6–12 months at the laboratory of each center by various polymerase chain reaction assays (sensitivities: 10–80 IU/ml). Virological remission was considered to be present in patients who achieved HBV DNA <80 IU/ml that was maintained throughout ETV/TDF therapy. Ultrasonography and/or alpha-fetoprotein levels were performed every 6 months in cirrhotic and every 12 months in non-cirrhotic patients. The diagnosis of HCC was based on standard histological and/or compatible radiological findings [5].

Entry into this study (baseline) was defined as the date of the onset of ETV/TDF. Follow-up was considered as the time interval between the study entry and the last available clinical information until May 2014, while treatment duration was considered the time interval between the study entry until the end of therapy or the last on-therapy follow-up. Analysis time was the time interval between the study entry and the diagnosis of HCC or the end of follow-up in the absence of HCC development.

Statistical analysis

All data were entered into and analyzed using the statistical package Stata 11.2 (StataCorp LP, USA) and R (version 3.2.1). Continuous variables are presented by their median values and interquartile range (IQR), unless otherwise stated. Their comparison was performed by the non-parametric Mann-Whitney *U*-test. The chi-squared or Fisher's exact test was used for comparisons of categorical variables. The cumulative probabilities of HCC occurrence were estimated by the Kaplan-Meier method and compared with the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to estimate the effect of various variables on the hazard of HCC occurrence. Hazard ratios (HR) and their 95% confidence intervals (CI) along with corresponding *p* values are presented. A *p* value of <0.05 was considered to be statistically significant. The proportional hazards assumption was tested on the basis of Schoenfeld residuals.

The prediction model was developed to predict the occurrence of HCC within 5 years after ETV/TDF initiation. The development of our HCC risk score was based on a multivariable Cox proportional hazards model using data from eight centers (derivation dataset). We accounted for the observed follow-up time for the patients from these centers up to the 75th percentile (5 years) to avoid the likely influence of a small number of participants with longer follow-up duration on model estimates. To develop the prediction model, we have used multiple imputation to deal with missing data in candidate predictor variables [13]. We imputed 10 values of the missing predictor for each patient. We applied backward elimination to each of the 10 completed data sets separately, resulting in 10 sets of selected predictors. The final set comprised those predictors that were selected in more than 50% of the 10 data sets. Given the finally selected predictors, a model was fitted in each of the 10 completed data sets. We used Rubin's rules to combine the estimated regression coefficients and variances from the 10 different completed data sets. To evaluate the predictive performance of the model, we examined discrimination and calibration measures. Discrimination was assessed using Harrell's c-index. A calibration plot was used to assess graphically the agreement between the 5-year probability of remaining HCC free as predicted by the model *vs.* the Kaplan-Meier estimate (observed probability). Per quintile of predicted probabilities, the Kaplan-Meier estimate and standard error were determined [14].

We performed validity assessment of the model using internal and external validation. Internal validation was performed using bootstrap. Bootstrap samples are random samples drawn with replacement from the original sample. We repeatedly fitted the model in 1000 bootstrap samples and evaluated its performance on the original sample. In external validation, the model developed in the derivation dataset was applied on the patients of the 9th (largest) center (validation dataset). The predictive performance of the model was assessed in the validation dataset as in the derivation dataset.

The next step was to develop a risk score based on a points system to simplify the computation of HCC risk estimate [15] (Supplementary material). We evaluated the agreement between risk estimates based on the points system and on the multivariable model (risk categories: <2%, 2–8.9%, $\geqslant$9%) using weighted kappa.

We assessed the discrimination and the calibration of the risk score in the derivation and the validation datasets by inspection of the Kaplan-Meier curves for risk groups stratified by the 25th and 75th percentiles of the risk score distribution [16].

We estimated the sensitivity, specificity, positive predictive value and negative predictive value (NPV) for various cut-offs of the risk score using appropriate methodology for censored data [17].

Results

There were 1325 patients in the derivation and 490 patients in the validation dataset. The patients in the two datasets differ in most of their characteristics at the onset of ETV/TDF (Table 1). The diagnosis of cirrhosis was based on histological findings before antiviral therapy in 172/269 (64%) and 164/234 (70%) cirrhotic patients in the derivation and validation datasets, respectively. Virological remission was achieved in 89% and 96% of patients in the derivation and validation datasets at year-1 of ETV/TDF therapy (p <0.001) and in 92% and 97% of patients beyond the first year of therapy, respectively (p <0.001). The median serum HBV DNA levels in patients without virological remission at year-1 in the derivation and validation datasets were 1000 (IQR: 6062) and 292 (913) IU/ml, respectively.

During a median follow-up of 50 (31–62) months, HCC was diagnosed in 51 (3.8%) patients in the derivation and 34 (6.9%) patients in the validation dataset. The cumulative 1-, 3- and 5-year rates of HCC were 0.9%, 3.1% and 5.7% in the derivation and 1.2%, 3.9% and 8.4% in the validation dataset, respectively (p = 0.108) (Fig. 1).

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Table 1. Main characteristics of Caucasian patients with chronic hepatitis B (CHB) who were treated with entecavir (ETV) or tenofovir (TDF).

	Derivation dataset (N = 1325, 8 centers)	Validation dataset (N = 490, 1 center)	*p* value
Age, years	52 (21)	56 (14)	<0.001
Male gender, n (%)	923 (70)	370 (76)	0.017
HBeAg positive patients, n (%)	210 (16)	88 (18)	0.314
Body mass index[1], kg/m^2	26.1 (4.4)	24.9 (4.5)	<0.001
Patients with normal ALT, n/N (%)	518/1225 (42)	313/490 (64)	<0.001
ALT in cases with abnormal ALT, IU/L	82 (85)	108 (162)	0.002
Platelets[2], x10^3/mm^3	191 (76)	177 (68)	<0.001
Patients with HBV DNA <80 IU/ml, n/N (%)	220/1220 (18)	251/470 (53)	<0.001
HBV DNA in cases with HBV DNA ≥80 IU/ml, $\log_{10}$ IU/ml	5.6 (2.7)	5.9 (2.9)	0.841
PegIFNα in the past, n (%)	305 (23)	141 (29)	0.014
NA(s) before ETV/TDF, n (%)	438 (33)	291 (59)	<0.001
Disease severity, n (%)			<0.001
CHB without cirrhosis	1037 (78)	232 (47)	
Compensated cirrhosis	269 (20)	234 (48)	
Unclassified	19 (1)	24 (5)	
Follow-up under therapy, months	44 (32)	60 (15)	<0.001
HCC cases during ETV/TDF, n (%)	51 (3.8)	34 (6.9)	0.008

[1]Available in 1055 and 480 patients of the derivation and validation dataset. [2]Available in 1268 and 484 patients of the derivation and validation dataset. Quantitative variables: median (IQR) values.
(Peg-)IFNa, pegylated interferon-alfa; NA(s), nucleos(t)ide analogue(s); HCC, hepatocellular carcinoma.

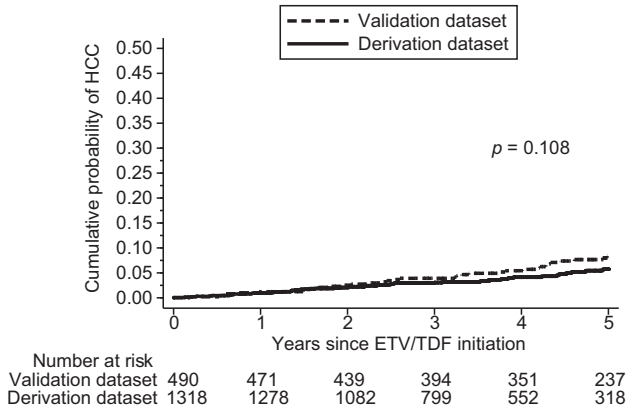

Fig. 1. Five-year cumulative probability of hepatocellular carcinoma (HCC) in the derivation and validation datasets of Caucasian chronic hepatitis B (CHB) patients treated with entecavir (ETV) or tenofovir (TDF).

Predictors of HCC within the first 5 years after ETV/TDF onset

In the univariable analyses of patients in the derivation dataset, older age, male gender, lower platelets, no prior use of (pegylated-)interferon-alfa and cirrhosis at baseline were associated with the development of HCC (Table 2). In particular, HCC developed in 0.5% (3/581), 4.6% (16/347) and 7.8% (31/397) of patients <50, 50–60 and >60 years old, in 0.9% (5/573), 5.6% (34/604) and 12.1% (11/91) of patients with platelets ⩾200, 100–199 and <100 × 10^3/mm^3, and in 1.8% (19/1037) and 11.2% (30/269) of patients without and with cirrhosis, respectively (p <0.001 for all comparisons). Virological remission at year-1 or beyond year-1 of ETV/TDF therapy was not found to affect the HCC incidence (p >0.757). In particular, HCC developed in 3.7% and 4.7% of patients with and without virological remission at year-1 (p = 0.716) or in 3.8% and 4.1% of patients with or without virological remission beyond year-1 (p = 1.00). The predictability of all variables did not significantly change when values at year-1 of ETV/TDF therapy were taken into account (data not shown). In the multivariable analysis, older age, male gender, lower platelets and cirrhosis remained independent significant predictors of HCC development (Table 2).

Derivation and internal validation of PAGE-B risk score

Since the diagnosis of cirrhosis may vary among centers and often requires liver biopsy and availability of an expert pathologist, the development of the PAGE-B HCC risk score was initially based on the three other independent predictors of HCC (platelets, age, gender). These predictors – with platelets included in the model as a categorical variable (<100,000/100,000–199,999/⩾200,000/mm^3) – were selected in all models developed from the imputed datasets. The combined regression coefficients estimated from the application of the model in the 10 different completed data sets are shown in Supplementary Table 1. The calibration plot is shown in Supplementary Fig. 1A. The c-index of the model was 0.82. We assessed internal validation using bootstrap and the resulting c-index was 0.81. The c-index did not improve substantially when cirrhosis was included in the model (c-index: 0.84). The c-index of the PAGE-B score including platelets at year 1 was the same (0.82) with that of the score including platelets before ETV/TDF.

We also evaluated the c-index of the model that included platelets, age and gender in different subgroups of the patients in the derivation dataset. The c-index was 0.86 in NA(s) naive patients and 0.74 in patients with exposure to other NA(s) before the onset of ETV/TDF as well as 0.88 and 0.65 in patients without or with cirrhosis at the onset of ETV/TDF.

The model score was simplified to an integer scoring system (Table 3). The score ranged from 0 to 25. There was a very good

Table 2. Baseline variables associated with hepatocellular carcinoma (HCC) in the derivation dataset of 1325 chronic hepatitis B patients.

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age (per year increase)	1.06 (1.04-1.09)	<0.001	1.05 (1.02-1.08)	<0.001
Gender (male *vs.* female)	5.00 (1.80-13.90)	<0.001	4.63 (1.66-12.90)	0.003
HBeAg status (negative *vs.* positive)	1.28 (0.57-2.84)	0.549		
Body mass index (per 1 kg/m^2)	1.06 (0.99-1.13)	0.124		
ALT (per IU/L)	1.00 (0.99-1.00)	0.179		
Platelets, x10^3/mm^3	0.985 (0.98-0.99)	<0.001	0.99 (0.984-0.996)	0.001
HBV DNA (per $\log_{10}$ IU/ml)	0.91 (0.80-1.04)	0.165		
PegIFNα in the past (yes *vs.* no)	0.40 (0.17-0.95)	0.037	0.52 (0.22-1.24)	0.141
NA(s) before ETV/TDF (yes *vs.* no)	0.74 (0.40-1.37)	0.339		
Cirrhosis (yes *vs.* no)	6.64 (3.74-11.81)	<0.001	2.68 (1.39-5.18)	0.003

CI, confidence interval; (Peg-)IFNa, pegylated interferon-alfa; NA(s), nucleos(t)ide analogue(s); ETV, entecavir; TDF, tenofovir.

Table 3. Construction of the PAGE-B risk score for prediction of hepatocellular carcinoma in Caucasian chronic hepatitis B patients under entecavir or tenofovir. The score ranges from 0 to 25.

Age (years)	Gender	Platelets (/mm^3)
16-29: 0	Female: 0	≥200,000: 0
30-39: 2	Male: 6	100,000-199,999: 6
40-49: 4		<100,000: 9
50-59: 6		
60-69: 8		
≥70: 10		

agreement between the point system and the multivariable model with a weighted kappa of 0.88 (Supplementary Table 2). The 5-year HCC risk according to PAGE-B risk score is shown in Fig. 2. In clinical practice, physicians can calculate the score of each patient at treatment initiation based on the values provided in Table 3. The 5-year risk of HCC occurrence corresponding to this score can be obtained from Fig. 2 or Supplementary Table 3.

We further assessed the discrimination of the PAGE-B score by inspection of the Kaplan-Meier curves for risk groups stratified by the 25th and 75th percentiles of the risk score distribution in the derivation dataset (10 and 18 points, respectively). Of the 1264 patients with evaluable PAGE-B score in the derivation dataset, 312 (24.7%), had low (⩽9), 597 (47.2%) intermediate (10–17) and 355 (28.1%) had high (⩾18) PAGE-B score. The proportion of patients with cirrhosis was 3.9% (12/309), 18.0% (105/584) and 40.9% (144/352) in cases with PAGE-B score ⩽9, 10–17 and ⩾18 (p <0.001), while the median (IQR) score was 12 (8–16) and 18 (14–20) in patients without and with cirrhosis, respectively (p <0.001). The 5-year cumulative probability of HCC in patients in the low (⩽9), medium (10–17) and high (⩾18) PAGE-B score was 0%, 3% and 17%, respectively (p <0.001) (Fig. 3A).

The distribution of the PAGE-B score per outcome value in the derivation dataset is shown in Supplementary Fig. 2. The estimated ROC curve for PAGE-B score in the derivation dataset at 5 years is depicted in Supplementary Fig. 3. The cut-off that maximizes both sensitivity and specificity of the PAGE-B risk score for the prediction of patient outcome is 17 (sensitivity 76.0%, specificity 77.3%). The highest cut-off of PAGE-B score associated with 100% sensitivity and, as a result, 100% NPV is 10 (Table 4). Thus, 100% patients with risk score ⩽10 were HCC free at 5 years.

External validation of PAGE-B risk score

In the validation dataset, PAGE-B risk score offered similarly good predictability of HCC (c-index: 0.82). The estimated ROC curve for

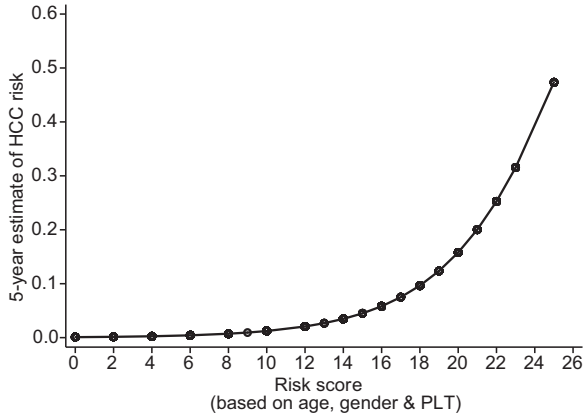

Fig. 2. Five-year cumulative probability of hepatocellular carcinoma (HCC) in the derivation dataset according to PAGE-B risk score which is based on age, gender and platelets counts (PLT).

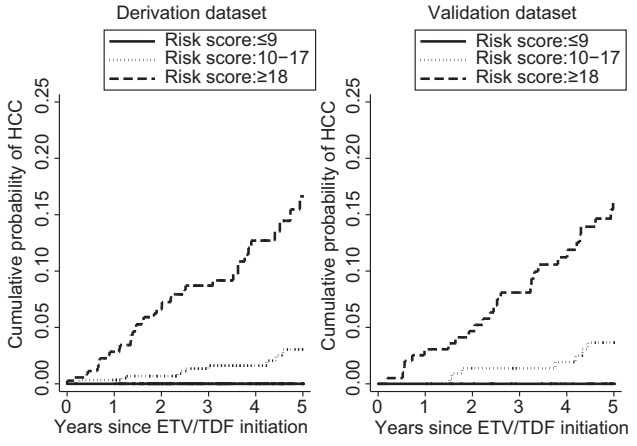

Fig. 3. Cumulative probability of hepatocellular carcinoma (HCC) in the derivation and validation dataset of patients treated with entecavir (ETV) or tenofovir (TDF) according to their PAGE-B risk scores.

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Table 4. Accuracy for prediction of hepatocellular carcinoma development within the first 5 years of entecavir or tenofovir therapy in the derivation and validation datasets using the cut-off point of >10 in the PAGE-B risk score.

	PAGE-B risk score >10	
	Derivation cohort (N = 1264)	Validation cohort (N = 484)
Sensitivity	100%	100%
Specificity	41.2%	19.6%
Positive predictive value	9.8%	10.3%
Negative predictive value	100%	100%

PAGE-B score in the validation dataset at 5 years is depicted in Supplementary Fig. 3. The calibration plot of the model is depicted in Supplementary Fig. 1B.

Of the 484 patients with evaluable PAGE-B score in the validation dataset, 55 (11.4%), 232 (47.9%) and 197 (40.7%) cases had PAGE-B score ⩽9, 10–17 and ⩾18, respectively. The 5-year cumulative probability of HCC in patients in the low (⩽9), medium (10–17) and high (⩾18) PAGE-B score was 0%, 4% and 16% (p <0.001) (Fig. 3B).

The accuracy of the cut-off point of 10 in PAGE-B score for HCC prediction within the first 5 years of ETV/TDF therapy in the validation dataset is presented in Table 4.

Discussion

To our knowledge, this is the first study trying to develop a HCC risk score in Caucasian CHB patients. Moreover, this is the first score developed for patients treated with the current first-line oral antivirals, ETV and TDF, which represent the best in class anti-HBV agents offering virological remission in almost all compliant patients and minimizing the risk of viral resistance over time and its potential effects on hepatocarcinogenesis [1–4]. Our findings show that the PAGE-B score can be rather useful in the assessment of the 5-year risk of HCC in Caucasian CHB patients with compensated liver disease who are treated with the current first-line oral antivirals, ETV or TDF. A major advantage of the PAGE-B risk score is that it is very simple and easy to use in routine clinical practice, as it is based only on the patient's age, gender and platelet count without the need for any complicated mathematical calculation. The PAGE-B risk score developed in a large dataset and was validated in another dataset of Caucasian CHB patients treated with ETV or TDF. There were several differences in the characteristics of the patients in the derivation and validation datasets, but this strengthens the reliability of our score, which was shown to offer similar predictability in different patient populations.

Cirrhosis is a well known risk factor for HCC in CHB patients [1,5], which was also confirmed in our study. However, the diagnosis of cirrhosis may not be always straightforward, as it requires liver biopsy or at least a reliable non-invasive method of fibrosis assessment. Even if a liver biopsy or non-invasive assessment of fibrosis is available, their sensitivity and specificity is not 100% and they can have substantial inter-observer and intra-observer variations particularly in daily clinical practice [18–22]. According to our results, the addition of cirrhosis does not substantially improve the predictability of the PAGE-B score simplifying its use in clinical practice. Platelet count, which is routinely and reliably determined in all CHB patients, most probably represents a marker of liver disease severity. Cirrhosis has been included in some [7,8] but not all previous HCC risk scores [9] or has been diagnosed by suboptimal methods like ultrasonography in other cohort studies [10], while platelet count has never been evaluated and included in HCC risk scores in the past.

PAGE-B scores ⩽9 mean no or perhaps minimal 5-year HCC risk, while PAGE-B scores ⩾10 and particularly ⩾18 indicate increased HCC risk requiring continuous and careful surveillance. In particular, the cut-off point of 10 in PAGE-B score offered 100% sensitivity and NPV for HCC prediction in both the derivation and validation datasets. Thus, if these findings are confirmed in other cohorts, CHB patients treated with ETV/TDF who belong to the low risk group by the PAGE-B score may safely avoid HCC surveillance. The proportion of patients who may be classified in the low or high risk group by the PAGE-B score can vary in different cohorts depending on the patients' characteristics. In our study, the proportion of patients who were classified in the low risk group and might have avoided HCC surveillance was 25% in the derivation and 11% in the validation dataset, whereas the proportion of patients who were classified in the high risk group and would require intense HCC surveillance was 28% in the derivation and 41% in the validation dataset.

A rather limited proportion of patients (4%) in the low risk group by the PAGE-B score had cirrhosis, while >50% of the patients (59%) in the high risk group by the PAGE-B score did not have cirrhosis. Given that the number of patients with cirrhosis in the low risk group by the PAGE-B score was limited and the predictability of the PAGE-B score was suboptimal in the cirrhotic patients of our derivation cohort, all cirrhotic patients under ETV/TDF therapy may better remain under surveillance for HCC.

The PAGE-B score, which is mostly based on parameters that are not usually affected by antiviral treatment, predicts the HCC risk within the first 5 years of therapy. Thus, in contrast to previous scores including variables (e.g. HBV DNA levels) that change completely during antiviral treatment [10], the predictability of the PAGE-B score was not found to improve during therapy. Although the annual HCC incidence may be lower in CHB patients treated with NA(s) compared to matched untreated controls [2,23,24], the cumulative HCC incidence in treated CHB patients is progressively increasing within the first 5 years of therapy, at least partly due to the stabilization and even improvement of patients with cirrhosis who live longer being at relatively high risk for development of HCC [3,23]. At the same time, effective long-term NA therapy has been shown to improve liver histology and even to reverse histological cirrhosis [25], which can result in some decrease of the HCC risk. Given that hepatocarcinogenesis may have started a long time ago before the clinical diagnosis of HCC [5], several years will be required before a potential beneficial effect of antiviral therapy on HCC development can become clinically evident.

Our study has a few limitations. HBV DNA was assessed at each center by various polymerase chain reaction assays, which were all standardised and with similar sensitivities of 10–80 IU/ml. In addition, the diagnosis of HCC was based on ultrasonographic findings performed by different radiologists and perhaps the compliance to HCC surveillance varied across the centers and even among the patients of the same center. The HCC surveillance might have not been optimal in all the patients and particularly the 12-month interval for HCC

surveillance in our non-cirrhotic patients might have resulted in delayed diagnosis of some HCC cases. Such problems, however, reflect the daily clinical practice and are present in almost any large cohort study and even in more carefully designed prospective large studies. The diagnosis of cirrhosis was based on histological, ultrasonographic and/or endoscopic findings interpreted by different pathologists, radiologists and/or endoscopists. Thus, a stronger predictability by the presence of cirrhosis cannot be excluded in case of a more accurate and universal diagnosis. On the other hand, such an approach to the diagnosis of cirrhosis is closer to the routine clinical practice and therefore the fact that cirrhosis was not included in the PAGE-B score most probably represents a great advantage. Recent data have suggested that serum HBsAg levels may represent an additional factor associated with the risk of HCC development in chronic hepatitis B patients [26,27]. Unfortunately, HBsAg levels were not available for the majority of our patients and therefore the possible role of such a marker could not be evaluated in our study. Given the characteristics of our patient population, it is not known yet whether PAGE-B score may be useful in untreated CHB cases of any origin and in treated Asian CHB patients. Finally, since PAGE-B score was developed and validated in patients treated with ETV/TDF, it is also not clear whether it may be useful in patients treated with other NA(s), such as lamivudine or telbivudine.

In conclusion, PAGE-B, which is based only on baseline patients' age, gender and platelets, represents a reliable and simple to use risk score for the prediction of HCC during the first 5 years of ETV or TDF therapy in Caucasians CHB patients. If these data are confirmed in other studies, non-cirrhotic patients in the low risk group by the PAGE-B score who have no or minimal 5-year probability for HCC will not need HCC surveillance, while patients in the moderate and particularly in the high risk group who are at increased 5-year HCC risk will require close surveillance for HCC.

Conflict of interest

GV Papatheodoridis: advisor/lecturer for Abbott/Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche; research grants Abbvie, Bristol- Myers Squibb, Gilead, Janssen, Roche; consultant for Roche; Data Safety Management Board for Gilead.
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V Sypsa: advisor/lecturer for Gilead.
C Yurdaydin: speaker's bureau and/or advisor for AbbVie, Bristol-Myers Squibb, Gilead, Merck, Roche; research grant from Bristol-Myers Squibb.
M Buti: advisor/lecturer for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Glaxo Smith-Kleine, Janssen, Merck, Novartis.
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I Vlachogiannakos: advisor/lecturer for Abbvie, Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme, Novartis, Roche.
M Colombo: advisor for Abbott/Abbvie, Achillion, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GenSpera, Glaxo Smith-Kleine, Janssen, Lundbeck, Merck, Novartis, Roche, Tibotec, Vertex; speaking and teaching for Bayer, Bristol-Myers Squibb, Gilead, Novartis, Roche, Tibotec, Vertex; grant and research support from Bristol-Myers Squibb, Gilead Merck, Roche.
R Esteban: advisor/lecturer for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis.
HLA Janssen: consultant for and grants from Bristol-Myers Squibb, Gilead, Novartis, Roche, Merck, Santaris, Medtronic; grants from Anadys, Innogenetics, Kirin; consultant for Abbott, Debio.
P Lampertico: speaking bureau/advisor for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Roche.
All other authors declared no conflict of interest in relation to this manuscript.

Authors' contributions

GV Papatheodoridis: Conception and design of the study; Assembly, analysis and interpretation of data; Drafting of the manuscript; Approval of the final version of the manuscript.
GN Dalekos: Design of the study; Interpretation of data; Revision of the manuscript; Approval of the final version of the manuscript.
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P Lampertico: Conception and design of the study; Interpretation of data; Drafting of the manuscript; Approval of the final version of the manuscript.

Supplementary data

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