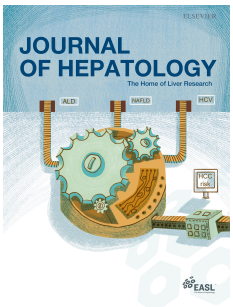

External validation of the PAGE-B score for HCC risk prediction in people living with HIV/HBV coinfection

Bernard Surial, Adrià Ramírez Mena, Marie Roumet, Andreas Limacher, Colette Smit, Olivier Leleux, Amanda Mocroft, Marc van der Valk, Fabrice Bonnet, Lars Peters, Jürgen K. Rockstroh, Huldrych F. Günthard, Annalisa Berzigotti, Andri Rauch, Gilles Wandeler, the Swiss HIV Cohort Study, ATHENA Observational Cohort Study, EuroSIDA, ANRS CO3 Aquitaine Cohort

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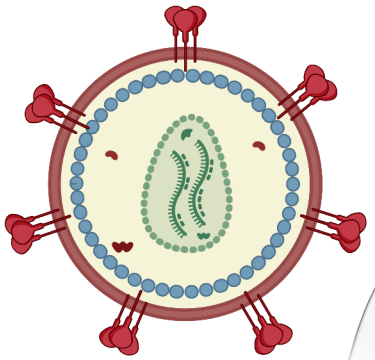
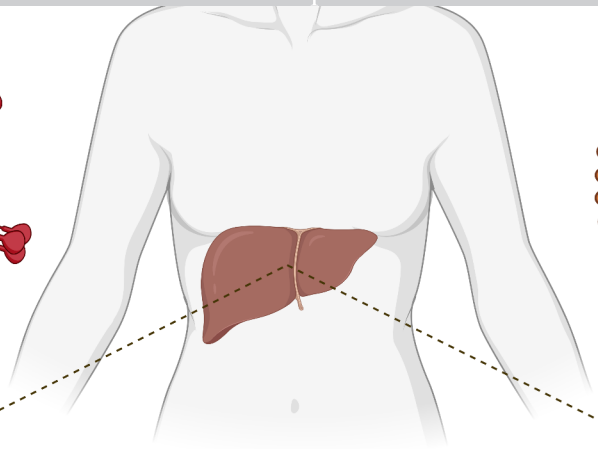
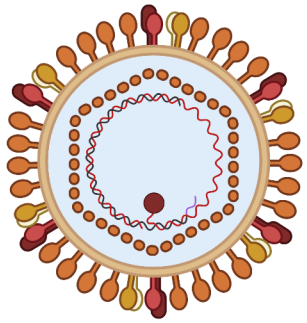
HIV

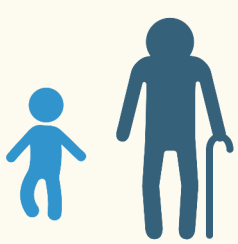




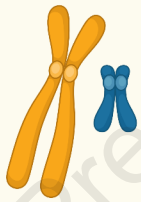


Hepatitis B

PAGE-B



Age



Gender

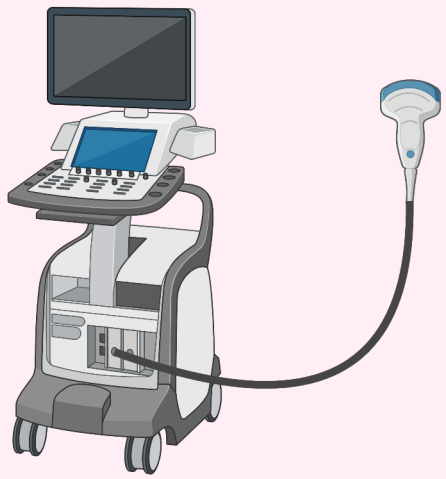
Platelets

PAGE-B below 10

99.4%

will not develop HCC

PAGE-B 10 or higher



Targeted HCC screening

External validation of the PAGE-B score for HCC risk prediction in people living with HIV/HBV coinfection

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Authors' contribution: BS, AR and GW conceived and designed the study. BS performed the statistical analyses with help from MR and AL. BS and GW wrote the first draft of the manuscript. All authors contributed to the acquisition and interpretation of the data, critically revised the manuscript, and approved its final version.

Data availability statement: Data are available upon reasonable request. The data sets generated and/or analyzed during the current study are not publicly available, since they are subject to national data protection laws and restrictions imposed by the ethics committee to ensure data privacy of the study participants. The code for the analysis is archived at https://doi.org/10.5281/zenodo.7466614.

ABSTRACT

Background & Aims

Hepatitis B virus (HBV) coinfection is common among people living with HIV (PLWH) and the most important cause of hepatocellular carcinoma (HCC). Whereas risk prediction tools for HCC exist for patients with HBV monoinfection, they have not been evaluated in PLWH. We performed an external validation of PAGE-B in people with HIV/HBV coinfection.

Methods

We included PLWH with a positive HBsAg and without HCC before starting tenofovir from four European cohorts, and estimated the predictive performance of PAGE-B on HCC occurrence over 15 years of tenofovir-containing antiretroviral therapy (ART). Model discrimination was assessed after multiple imputation using Cox regression with the prognostic index as covariate, and by calculating Harrell's c-index. Calibration was assessed by comparing cumulative incidences with the PAGE-B derivation study using Kaplan-Meier curves.

Results

In total, 2'963 individuals with HIV/HBV coinfection on tenofovir-containing ART were included. PAGE-B was <10 in 26.5%, 10–17 in 57.7%, and ≥18 in 15.7% of patients. Within a median follow-up of 9.6 years, HCC occurred in 68 individuals (2.58/1000 patient-years, 95% confidence interval [CI] 2.03–3.27). The regression slope of the prognostic index for developing HCC within 15 years was 0.93 (95% CI 0.61–1.25), and the pooled c-index was 0.77 (range 0.73–0.80), both indicating good model discrimination. Cumulative incidence of HCC was lower in our study compared to the derivation study. A PAGE-B cut-off of <10 had a negative predictive value for developing HCC within 5 years of 99.4%. Restricting efforts to individuals with a PAGE-B of ≥10 would spare HCC screening in 27% of individuals.

Conclusions

For individuals with HIV/HBV coinfection, PAGE-B is a valid tool to determine the need for HCC screening.

IMPACT AND IMPLICATIONS

Chronic hepatitis B virus (HBV) infection is the most important cause of hepatocellular carcinoma (HCC) among people living with HIV, and valid risk prediction may guide HCC screening efforts to high-risk individuals. We aimed at validating PAGE-B, a risk prediction tool that is based on age, gender, and platelets, among 2963 individuals with HIV/HBV coinfection who received tenofovir-containing antiretroviral therapy. In the present study, PAGE-B showed good discrimination, adequate calibration, and a cut-off of less than 10 had a negative predictive value for developing HCC within 5 years of 99.4%. These results indicate that PAGE-B is a simple and valid risk prediction tool to determine the need for HCC screening among people living with HIV and HBV.

INTRODUCTION

Between 5 and 15% of people living with HIV (PLWH) also have a chronic hepatitis B virus (HBV) infection, the single most important cause of end-stage liver disease and hepatocellular carcinoma (HCC) worldwide [1]. Screening individuals with HBV infection and a high risk for HCC using ultrasound every 6 months is recommended to detect cancers at an early and curable stage [2,3]. However, screening uptake remains suboptimal, and therefore represents a missed opportunity to prevent HCC-related deaths [4,5]. We previously showed that among individuals with HIV and HBV, those who were older than 46 years or had liver cirrhosis had the highest risk of developing HCC [6]. To guide clinicians in deciding whether a patient needs HCC screening or not, simple HCC risk prediction tools could help with risk stratification.

PAGE-B, a prognostic score including age, sex and platelet count at initiation of antiviral therapy, was derived from a multi-country study of 1'815 European individuals with HBV mono-infection, and reliably predicted their 5-year HCC risk [7]. As the score is based on inexpensive and readily available measurements that do not include the evaluation of cirrhosis, PAGE-B has become an established tool for clinicians to discuss HCC screening with patients, including in settings with limited access to liver biopsy or transient elastography (TE) [8]. The use of PAGE-B is also suggested by the European AIDS Clinical Society guidelines to assess the HCC risk in individuals with HIV/HBV coinfection [9], despite the lack of evaluation of its predictive value in this population. The validity of this score in PLWH is challenged by differences in HCC incidence, the presence of HIV-induced thrombocytopenia and the high prevalence of additional HCC risk factors such as hepatitis C virus (HCV) and hepatitis delta virus (HDV) infections, as well as alcohol use [6].

To provide scientific evidence for HCC surveillance recommendations, we conducted an external validation of the prognostic performance of the PAGE-B score in persons living with HIV and HBV from a large cohort collaboration in Europe.

PATIENTS AND METHODS

Study setting and participants

We considered participants with HBV from four prospective longitudinal cohorts: the Swiss HIV Cohort Study (SHCS) [10], the AIDS Therapy Evaluation in the Netherlands (ATHENA) Cohort [11], the Agence Nationale de Recherches sur le Sida (ANRS) CO3 Aquitaine Cohort-AQUIVIH-NA (Aquitaine) [12], and EuroSIDA [13]. Laboratory values as well as sociodemographic and clinical data are prospectively recorded using standardized protocols. All study sites' ethical committees approved the cohort studies, and all patients provided written or verbal informed consent according to local regulations. The study is presented following the TRIPOD statement [14].

We included all PLWH with a positive HBsAg test before starting an antiretroviral therapy (ART) regimen including tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). Patients who developed HCC prior to the start of tenofovir, and those without follow-up data available after this date were excluded. Differences in study eligibility between the original PAGE-B derivation study among people with HBV monoinfection [7] and the present validation study are shown in **Table S1**. Unlike in the derivation study, individuals of African or Asian origin and those with known HCV or HDV coinfection were included in our main analysis. Follow-up was measured from tenofovir start until the earliest of HCC diagnosis, death, loss to follow-up, last follow-up visit, or database closure (01.12.2020 for SHCS and ATHENA, 01.01.2021 for EuroSIDA, and 01.01.2022 for Aquitaine). Patients who stopped tenofovir during follow-up remained included in all analyses.

Outcomes and definitions

We aimed to estimate the predictive performance of the PAGE-B score on the occurrence of HCC. Whereas PAGE-B was derived to predict the 5-year risk of HCC, we assessed its performance within the full follow-up period of our study population (15 years). Information on HCC diagnosis was prospectively collected from all cohorts with standardized case-report forms, using hospital discharge reports, imaging studies and liver histology reports to verify the diagnosis. The choice of whether and how HCC screening was performed was left to the discretion of the treating physician. In accordance with the original publication, the PAGE-B score was calculated based on values for sex, age, and platelet categories (≥200 G/L, 100-199 G/L, <100 G/L). Liver cirrhosis was defined as Metavir stage F4

on liver biopsy or liver stiffness >11 kPa in TE at any time-point. If neither of these measurements was available, we used the AST to platelet ratio index (APRI) >2.0 at the time of tenofovir start to indicate cirrhosis. Coinfection with HCV was defined as a positive HCV-RNA prior to tenofovir start, and HDV coinfection was defined as having a positive anti-HDV serology at any time point since cohort registration.

Statistical Analyses

Cumulative incidence of HCC stratified by the same PAGE-B categories as in the original derivation study (<10, 10-17, ≥18) was presented using Kaplan Meier curves [7]. The predictive performance of the PAGE-B score during follow-up was assessed using discrimination and calibration, as recommended by Royston and Altman [15]. Observation time was right-censored at 15 years to limit the excess influence of individuals with longer follow-up. To assess model discrimination, we first calculated the prognostic index using the linear predictor based on the regression coefficients of the PAGE-B model (**Figure S1**). We then fitted a Cox regression model with the prognostic index as a covariate, where a slope <1 indicates poorer discrimination compared to the original study, and >1 indicates better discrimination. We further measured discrimination using Harrell's c-index, which gives the proportion of patients where predictions and outcomes are concordant, and is equivalent to the area under the receiver operating curve. Calibration was assessed by comparing cumulative incidence estimates, calculated using the Kaplan-Meier method, between the present validation and the original validation study. Screening for HCC is considered effective if the yearly risk is above 0.2% (equal to 3% in 15 years assuming a stable risk per year) [16]. To calculate the PAGE-B cut-off that reflects a risk above that threshold, we calculated cumulative incidence of HCC within 15 years using the Kaplan-Meier method. Sensitivity, specificity, negative and positive predictive values at 5 years (as in the original derivation study) were calculated from a time-dependent ROC curve analysis using the *timeROC* package [17].

As information on platelets at tenofovir start was missing in 36% of patients, model validation was performed after multiple imputation of predictors. Assuming missingness at random, we performed multivariable imputation by chained equations using the *mice* package [18]. The variables used for the multiple imputation model were the outcome (HCC) and 19 covariates (**Table S2**). The distribution of imputed platelet values is shown in **Figure S2**. After imputing 50 datasets, all calculations were

performed individually on each dataset, and estimates were combined using Rubin's rules [19] or by providing the median and the range of values (c-index) [20]. All analyses were performed using R, version 4.1.3 [21,22].

Sensitivity Analyses

To evaluate the robustness of our results, we performed five types of sensitivity analyses. First, we repeated the analyses censoring all individuals at five years after tenofovir start as done in the derivation study. Second, we evaluated the robustness of the multiple imputation process comparing the results with complete case analyses. Third, we excluded individuals of African origin in accordance with the derivation study, as HCC seem to occur at a younger age in this population compared to individuals of non-African origin [23]. Fourth, we explored the possibility of immortal time bias as some individuals started tenofovir prior to registration in the cohorts. Therefore, we repeated the analyses restricted to individuals who started tenofovir after cohort registration and performed analyses where baseline was defined as the start of tenofovir if this date was after cohort registration, and as cohort registration date otherwise. Finally, we performed a sensitivity analysis excluding all individuals known to be coinfected with HDV or HCV.

RESULTS

Study population

Of 2'988 eligible patients with the last HBsAg prior to tenofovir start being positive, we excluded 10 patients who developed HCC before starting tenofovir, and 15 patients without available follow-up data after tenofovir start, resulting in a study population of 2'963 patients (**Figure S3**). The ATHENA cohort followed the largest proportion of patients (n = 1319, 44.5%), followed by EuroSIDA (800, 27.0%), the SHCS (507, 17.1%) and the Aquitaine cohort (337, 11.4%). At tenofovir start, the median age was 41 years (interquartile range [IQR] 35 to 47 years), 466 (16%) participants were female, 2'023 (68%) were Caucasian, and 314 (11%) had evidence of liver cirrhosis (48.4% diagnosed with TE, 39.8% with APRI, and 11.8% with liver biopsy). Although most patient characteristics were similar across cohorts, the amount of missing data on platelets and HDV coinfection varied markedly (**Table 1**). Compared to the original PAGE-B derivation study [7], individuals in the current validation study were younger (median age 41 years in our study vs. 52 years in the derivation study), more likely to be male (84% vs. 70%), had a lower median body mass index (22.8 vs. 26.1 kg/m^2), and more commonly received other nucleoside analogues prior to tenofovir (55% vs. 33%), whereas the median platelet count was similar in both studies (190 vs. 191 G/L, **Table S3**).

Occurrence of HCC

Within a median follow-up of 9.6 years (IQR 4.9 to 13.3 years), HCC was diagnosed in 68 individuals (2.3%, incidence rate 2.58 per 1'000 patient-years, 95% CI 2.03 to 3.27). Overall, 24 HCC (35.3%) occurred in ATHENA, 17 (25.0%) in EuroSIDA, 16 (23.5%) in the SHCS, and 13 (19.1%) in the Aquitaine cohort. Within 5 years of follow-up – the observation period used in the PAGE-B derivation study – HCC occurred in 36 individuals (1.2%, incidence rate 2.82 per 1'000 patient-years, 95% CI 2.03 to 3.91). The cumulative incidence was 0.28% at 1 year, 0.96% at 3 years, 1.39% at 5 years, 2.42% at 10 years, and 3.93% at 15 years. Of all patients who developed HCC, 90% were male, 81% were Caucasian, and 51 individuals died (overall survival rate 25%), with a median survival after HCC diagnosis of 11.7 months (95% CI 5.9 to 19.2).

PAGE-B model validation

For 1’890 individuals (63.8%), a PAGE-B score at the time of tenofovir start could be calculated based on complete case data. The distributions of PAGE-B values were similar in the complete case and imputation datasets (**Figure 1A** and **1C**). In the complete case dataset, the PAGE-B score was <10 in 522 (27.6%), between 10 and 17 in 1’068 (56.5%), and ≥18 in 300 individuals (15.9%). After multiple imputation, 785 individuals (26.5%) had a score <10, 1711 (57.7%) had a score between 10 and 17, and 466 (15.7%) had a score ≥18. Thirty-nine HCC cases (55.7%) occurred in individuals with a PAGE-B of 18 or higher, 27 (38.6%) occurred in individuals with a PAGE-B between 10 and 17, whereas only 4 (5.7%) individuals with a PAGE-B score <10 developed an HCC (**Figure 1B** and **1D**). Of 4 individuals with an HCC and a PAGE-B score <10, the median age was 37 years, 3 were of African and one was of Asian origin, one individual had evidence of liver cirrhosis on TE, and another individual had coinfection with HDV.

The regression slope of the prognostic index for the development of HCC within 15 years after tenofovir start was 0.93 (95% CI 0.61 to 1.25). This value was close to 1.0 (p-value = 0.67) and indicated preserved discrimination compared to the derivation study. Similarly, PAGE-B showed good discrimination with a pooled c-index of 0.77 (range 0.73 to 0.80), which was close to the results after internal (c-index: 0.81) and external (c-index: 0.82) validation performed in the original PAGE-B derivation study [7]. Visual inspection of the Kaplan-Meier curves showed that the highest cumulative incidence of HCC was in individuals with a PAGE-B ≥18, followed by those with a PAGE-B between 10 and 17, whereas the lowest incidence was seen in individuals with a PAGE-B <10 (**Figure 2A**). Model calibration was assessed by comparing the cumulative incidence of HCC from our study with the results of the derivation study. The cumulative incidence of HCC over five years was 5.6% in individuals with a PAGE-B score ≥18 in our study compared to 17% in the derivation study. We also found a lower cumulative incidence in individuals with a PAGE-B score between 10 and 17 compared to the derivation study and this difference was observed throughout the full follow-up time (**Table 2**).

Of 2438 non-African participants, 61 developed HCC: 37 (60.7%) had a PAGE-B ≥18, 23 (37.7%) had a PAGE-B between 10 and 17, and only one individual (1.6%) had a PAGE-B <10. HCC incidence rates between individuals of African (2.03 per 1’000 patient-years, 95% CI 1.06 to 3.90) and of non-African origin (2.69 per 1’000 patient-years, 95% CI 2.08 - 3.47) did not differ significantly (p = 0.43). The

regression slope was 1.17 (0.78 to 1.56), the pooled c-index 0.80 (range 0.76 to 0.82), and the Kaplan-Meier curves confirmed good model discrimination (**Figure 2B**).

Sensitivity analyses

As the derivation study evaluated the PAGE-B score for the prediction of HCC within five years of tenofovir start, we repeated the analyses censoring all individuals at five years. The results remained largely unchanged, with a regression slope of 0.87 (95% CI 0.47 to 1.28) and a pooled c-index of 0.76 (range 0.71 to 0.79). Likewise, complete case analyses evaluating the HCC risk within the full follow-up period revealed similar results (regression slope 0.88, 95% CI 0.56 to 1.21; c-index 0.77, 95% CI 0.68 to 0.85). Results remained unchanged when we restricted analyses to individuals who started tenofovir after cohort registration (regression slope 0.94, 95% CI 0.58 to 1.30, c-index 0.77, range 0.72 to 0.80), and when we used cohort registration as baseline for individuals who started tenofovir prior to that date (regression slope 1.01, 95% CI 0.69 to 1.33, c-index 0.78, range 0.74 to 0.81). Similarly, excluding 382 individuals who were known to have HCV or HDV coinfection did not change the interpretation of our results (regression slope 0.89, 95% CI 0.55 to 1.23, c-index 0.76, range 0.74 to 0.79).

Screening cut-off

The cumulative incidence of HCC within the full follow-up period for each PAGE-B score is shown in **Figure 3**. The upper limit of the 95% confidence interval of the cumulative HCC risk was above the accepted screening threshold (HCC risk of 0.2% per year) for a PAGE-B score of >12 in the full dataset, and >13 after excluding individuals of African origin. Using a cut-off of >10 as in the original derivation study [7], the sensitivity and specificity for developing HCC within five years of tenofovir start were 81.0% and 42.9%, respectively (negative predictive value 99.4%, **Table S4**). After excluding individuals of African origin, the sensitivity of a cut-off of >10 improved to 93.6% (negative predictive value 99.8%, **Figure S4**). When increasing the cut-off to >12 in the full dataset, sensitivity was 77.7%, specificity was 51.8%, and the negative predictive value was 99.4%.

DISCUSSION

In this external validation study, the PAGE-B score showed good accuracy in predicting the HCC risk in a large collaboration of European cohorts of individuals living with HIV and HBV infection. Similar to the original derivation study [7], individuals with a score below 10 were at very low risk of HCC, with a negative predictive value above 99%, confirming the usefulness of PAGE-B to target HCC surveillance efforts in individuals with HIV/HBV coinfection. In the subset of participants with a low PAGE-B score, 3 of 4 HCC cases occurred in individuals of African origin.

Current guidelines suggest that individuals with HBV monoinfection and a PAGE-B score <10 do not need HCC screening because of a very low risk of HCC [24]. In the original derivation study, a score of <10 had a negative predictive value of 100%, meaning that no patient experienced HCC below that cut-off [7]. We found a slightly lower negative predictive value of 99.4% in the full study population, and 99.8% after excluding individuals of African origin. These estimates are in line with the findings of previous PAGE-B external validation studies in individuals with HBV mono-infection [25,26]. Although the risk for HCC with a score <10 was not 0% in our study, the yearly risk for HCC was below the recommended threshold of 0.2%, and therefore it seems justified to apply the same cut-offs to individuals with and without HIV coinfection. Since 27% of individuals in our study had a PAGE-B <10, targeting screening efforts to individuals with a PAGE-B of 10 and higher would substantially reduce the need for HCC surveillance. Based on our results, even a higher threshold of <12 could be considered, as the yearly HCC risk remained below 0.2% in those individuals, which would spare HCC screening in 473 (16%) additional individuals. However, the potential benefits of using a higher PAGE-B score cut-off than in the original derivation study need to be confirmed in other cohorts of individuals with HIV/HBV coinfection.

In our study, PAGE-B model discrimination was similar to the original derivation study [7] and comparable to other external validation studies performed among individuals with HBV monoinfection in Europe and Asia [25,27]. Our incidence of HCC was comparable to other cohorts of Caucasian participants with HIV/HBV coinfection [28], but markedly lower than in the original derivation study across all PAGE-B categories, leading to differences in model calibration. These discrepancies were most likely driven by differences in how HBV infection was defined across studies: To be included in the derivation study, individuals needed to have confirmed HBsAg positivity for at least 6 months, increased transaminases, and an HBV-DNA above 2000 IU/mL, in line with current HBV treatment

guidelines [7,8]. In our study, we considered every participant with a positive HBsAg prior to tenofovir start irrespective of whether they had evidence of liver inflammation, since tenofovir-containing ART is recommended in all individuals with HIV/HBV coinfection [9]. Therefore, our study population was more likely to include participants with no or mild liver disease than the derivation study, which is also reflected by the lower prevalence of liver cirrhosis compared to the HBV monoinfection cohorts [26]. In addition, the lower HCC incidence observed in our study may also have been influenced by the higher proportion of individuals with HBV-active treatment prior to tenofovir start (55%) compared to the derivation study (33%).

Although several models were developed to predict HCC in individuals with chronic HBV infection, PAGE-B remains the only score that has been validated for Caucasian patients. In contrast to the original PAGE-B derivation study, which was restricted to Caucasian individuals, we included all ethnic groups as PAGE-B has shown to perform well in individuals of Asian descent [26]. However, no study has evaluated its predictive performance among African individuals. In our study, most individuals with a low PAGE-B who developed HCC in our study were of African origin. As our analyses only included a small number of individuals of African origin, the predictive performance of PAGE-B in that population remains to be determined. As HCC may develop at a younger age in that population compared to non-African individuals [23,29,30], and age being an important component of PAGE-B, other risk stratification tools may be needed to guide surveillance efforts for that population.

We present the first external validation of an HCC risk prediction model in a multinational population of individuals living with HIV and HBV, providing robust evidence for the current recommendation by the European AIDS Clinical Society guidelines to use PAGE-B for HCC risk stratification [9]. However, despite our best efforts to pool data from large European cohorts, the statistical power of our study was limited, since a minimum of one hundred events is commonly suggested for external validation studies [31]. Furthermore, the proportion of participants with missing platelet measurements was high, exceeding 50% in one cohort. Although we used multiple imputation and confirmed its robustness by comparing results from imputed with complete case data, some bias in the estimates of model performance cannot be excluded. In addition, information on HDV coinfection was limited in most cohorts. Since HDV acts as an additional risk factor for HCC [32], restricting our analyses to patients without HDV coinfection might have led to better model performance. Finally, participants in our collaboration of real-life cohorts underwent HCC screening according to the judgement of their treating

physician. As individuals that clinicians perceived to be at higher risk may have been more likely to receive ultrasound examinations, the lack of systematic screening may have introduced the potential for detection bias.

In conclusion, our results confirm that PAGE-B is a simple and valid risk prediction tool to determine the need for HCC screening among people living with HIV and HBV. Better risk prediction has the potential to increase surveillance uptake in high-risk individuals, as well as to reduce healthcare costs by avoiding screening of individuals with a very low HCC risk. Although PAGE-B performs well in most populations, better risk prediction models are urgently needed to inform surveillance strategies in individuals of African origin.

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TABLES

Table 1 Patient characteristics at tenofovir start, stratified by cohort

Characteristic	Overall (n = 2963)	Aquitaine (n = 337)	ATHENA (n = 1319)	EuroSIDA (n = 800)	SHCS (n = 507)
Male sex	2477 (84%)	277 (82%)	1147 (87%)	662 (83%)	391 (77%)
Age in years (IQR)	41 (35 to 47)	42 (37 to 48)	41 (35 to 48)	41 (36 to 47)	40 (35 to 46)
Caucasian	2023 (68%)	289 (86%)	774 (59%)	641 (80%)	319 (63%)
(Missing)	69 (2.3%)	3 (0.9%)	8 (0.6%)	58 (7.2%)	0 (0%)
Region of Origin					
European or USA	2023 (68%)	289 (86%)	774 (59%)	641 (80%)	319 (63%)
African	525 (18%)	41 (12%)	293 (22%)	56 (7.0%)	135 (27%)
Latin American	162 (5.5%)	1 (0.3%)	148 (11%)	0 (0%)	13 (2.6%)
Asian	155 (5.2%)	3 (0.9%)	96 (7.3%)	18 (2.2%)	38 (7.5%)
Other	29 (1.0%)	0 (0%)	0 (0%)	27 (3.4%)	2 (0.4%)
Unknown	69 (2.3%)	3 (0.9%)	8 (0.6%)	58 (7.2%)	0 (0%)
Transmission Group					
MSM	1536 (52%)	159 (49%)	820 (67%)	330 (41%)	227 (47%)
PWID	412 (14%)	62 (19%)	41 (3.3%)	234 (29%)	75 (15%)
Heterosexual	783 (26%)	98 (30%)	350 (29%)	156 (20%)	179 (37%)
Other	50 (1.7%)	8 (2.4%)	16 (1.3%)	19 (2.4%)	7 (1.4%)
(Missing)	182 (6.1%)	10 (3.0%)	92 (7.0%)	61 (7.6%)	19 (3.7%)
HIV Viral Load					
≥ 200 cp/mL	1596 (54%)	146 (43%)	780 (59%)	382 (48%)	288 (57%)
50 – 199 cp/mL	190 (6.5%)	21 (6.2%)	88 (6.7%)	57 (7.1%)	24 (4.7%)
Below 50 cp/mL	1018 (34%)	112 (33%)	419 (32%)	298 (37%)	189 (37%)
(Missing)	159 (5.4%)	58 (17%)	32 (2.4%)	63 (7.9%)	6 (1.2%)
BMI in kg/m^2	22.8 (20.8 to 25.1)	22.3 (20.4 to 24.6)	22.9 (20.9 to 25.0)	22.7 (20.8 to 25.1)	23.0 (20.8 to 25.8)
(Missing)	639 (22%)	92 (27%)	185 (14%)	317 (40%)	45 (8.9%)
CD4 cell count, cells/µL (IQR)	323 (182 to 510)	376 (196 to 584)	310 (170 to 490)	346 (210 to 531)	314 (198 to 472)
(Missing)	181 (6.1%)	60 (18%)	32 (2.4%)	83 (10%)	6 (1.2%)
Diabetes	183 (6.2%)	38 (11%)	82 (6.2%)	39 (4.9%)	24 (4.7%)
Liver cirrhosis	314 (11%)	27 (9.9%)	129 (15%)	94 (12%)	64 (16%)
ALT at baseline in IU/L (IQR)	41 (25 to 79)	38 (24 to 70)	47 (26 to 134)	39 (25 to 69)	39 (25 to 65)
(Missing)	731 (25%)	60 (18%)	444 (34%)	191 (24%)	36 (7.1%)
Platelets in G/L (IQR)	190 (141 to 236)	194 (144 to 235)	188 (133 to 235)	192 (152 to 233)	190 (148 to 239)
(Missing)	1063 (36%)	76 (23%)	560 (42%)	406 (51%)	21 (4.1%)
Platelet count category					
≥ 200 G/L	859 (25%)	121 (36%)	347 (26%)	175 (22%)	216 (43%)
100-199 G/L	828 (28%)	102 (30%)	325 (25%)	179 (22%)	222 (46%)
<100 G/L	213 (7.2%)	38 (11%)	87 (6.6%)	40 (5%)	48 (9.5%)
(Missing)	1063 (36%)	76 (23%)	560 (42%)	406 (51%)	21 (4.1%)
HDV coinfection	147 (5%)	15 (17%)	13 (9.4%)	69 (8.6%)	50 (11%)
(Missing)	1941 (66%)	250 (74%)	1180 (89%)	451 (56%)	60 (12%)
HCV coinfection	274 (9.2%)	22 (6.5%)	51 (3.9%)	157 (20%)	44 (8.7%)
HBeAg-positivity	799 (27%)	106 (50%)	515 (45%)	26 (3.2%)	152 (55%)
(Missing)	1277 (43%)	124 (37%)	167 (13%)	756 (94%)	230 (45%)
XTC use before TFV	1629 (55%)	211 (63%)	584 (44%)	550 (69%)	284 (56%)
Prior XTC in years (IQR)	3.7 (0.0 to 8.2)	3.8 (0.0 to 7.2)	0.0 (0.0 to 6.0)	5.2 (0.0 to 8.1)	9.9 (5.2 to 15.1)
Follow-up on TFV in years (IQR)	9.6 (4.9 to 13.3)	10.8 (5.6 to 15.0)	9.7 (5.3 to 13.1)	8.4 (3.8 to 12.3)	10.3 (5.2 to 14.3)

Characteristic	Overall (n = 2963)	Aquitaine (n = 337)	ATHENA (n = 1319)	EuroSIDA (n = 800)	SHCS (n = 507)

IQR = interquartile range, **MSM** = men who have sex with men, **PWID** = persons who inject drugs, **XTC** = lamivudine or emtricitabine, **TFV** = tenofovir, **HDV** = hepatitis D virus, **BMI** = body mass index, **HCV** = hepatitis C virus, **APRI** = AST to platelet ratio index, **ALT** = alanine aminotransferase.

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726

727 **Table 2** Life table comparison of hepatocellular carcinoma (HCC) cases in the

728 present study and the original derivation study

729

PAGE-B Category	Years	N at risk		Cumulative N (Cumulative Incidence) of HCCs		Cumulative Incidence of Original Publication[1]	
		Complete case	Imputation	Complete case	Imputation	Derivation	Validation
Score <10	1	480	734	1 (0.2%)	1 (0.1%)	0%	0%
	2	449	694	1 (0.2%)	1 (0.1%)	0%	0%
	3	412	651	1 (0.2%)	1 (0.1%)	0%	0%
	5	357	573	2 (0.5%)	2 (0.3%)	0%	0%
	10	216	358	2 (0.5%)	2 (0.3%)	n.r.	n.r.
	15	79	131	4 (2.5%)	4 (1.5%)	n.r.	n.r.
Score 10-17	1	1001	1625	1 (0.1%)	1 (0.1%)	0%	0%
	2	937	1534	3 (0.3%	8 (0.5%)	1%	1%
	3	877	1442	5 (0.5%)	10 (0.6%)	1%	1%
	5	794	1319	8 (0.9%)	14 (0.9%)	3%	4%
	10	490	863	13 (1.6%)	21 (1.5%)	n.r.	n.r.
	15	147	279	15 (2.2%)	26 (2.3%)	n.r.	n.r.
Score ≥18	1	268	426	5 (1.8%)	6 (1.4%)	3%	3%
	2	247	396	8 (2.9%)	9 (2.1%)	6%	5%
	3	217	356	12 (4.6%)	15 (3.7%)	9%	8%
	5	185	311	14 (5.6%)	20 (5.2%)	17%	16%
	10	92	175	22 (11.2%)	32 (10.1%)	n.r.	n.r.
	15	28	52	24 (14.4%)	38 (16.0%)	n.r.	n.r.

N = Number, **HCC** = hepatocellular carcinoma, **n.r.** = not reported

[1]*Papatheodoridis G et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016; 64:800–806.*

730

FIGURES

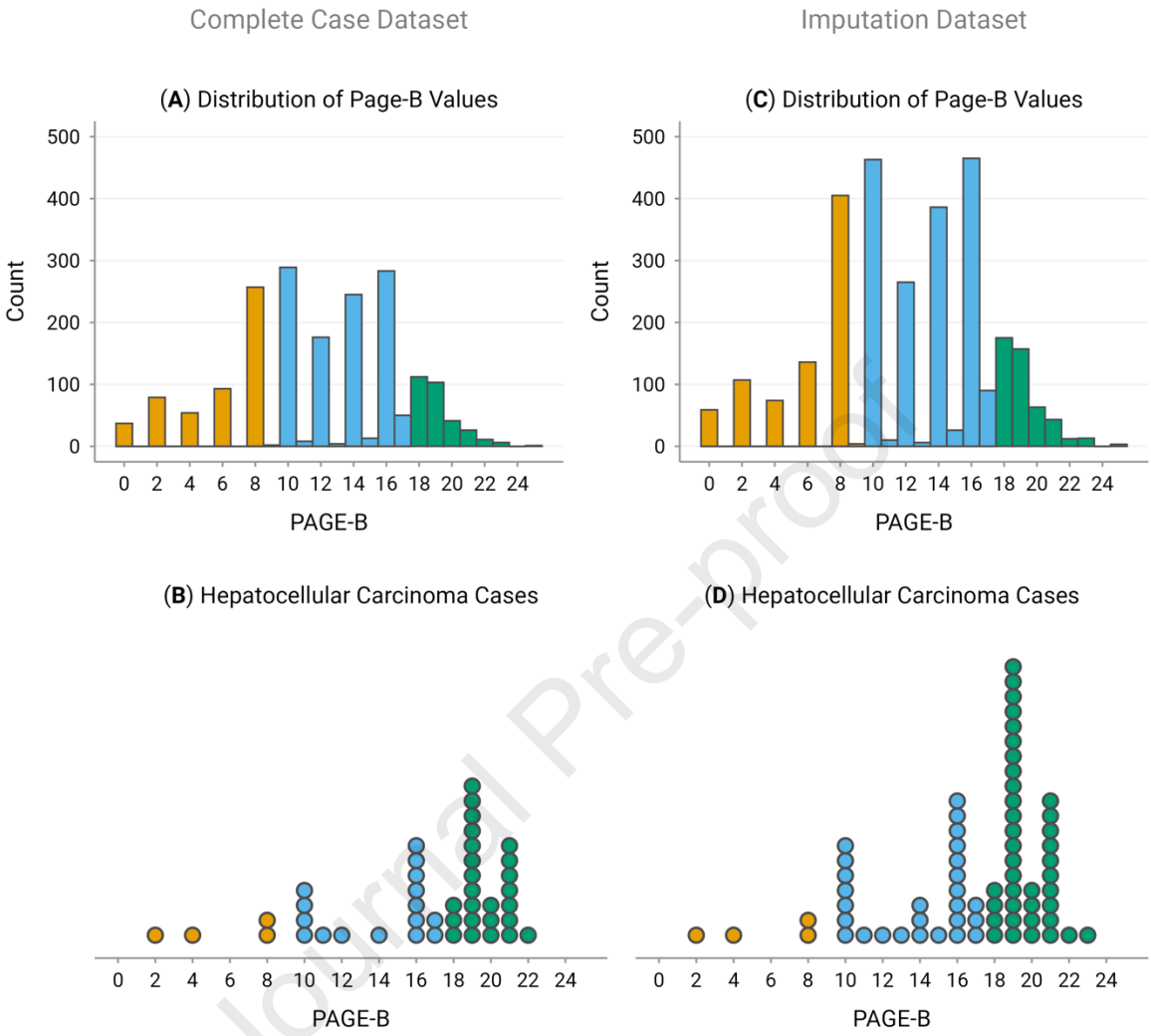
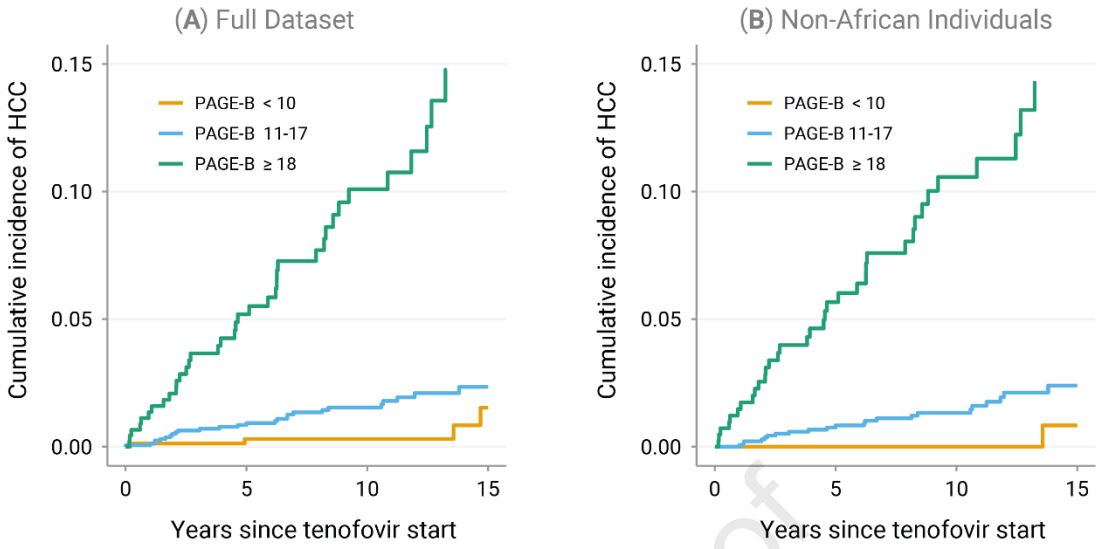


Figure 1 Distribution of PAGE-B scores and hepatocellular carcinoma cases

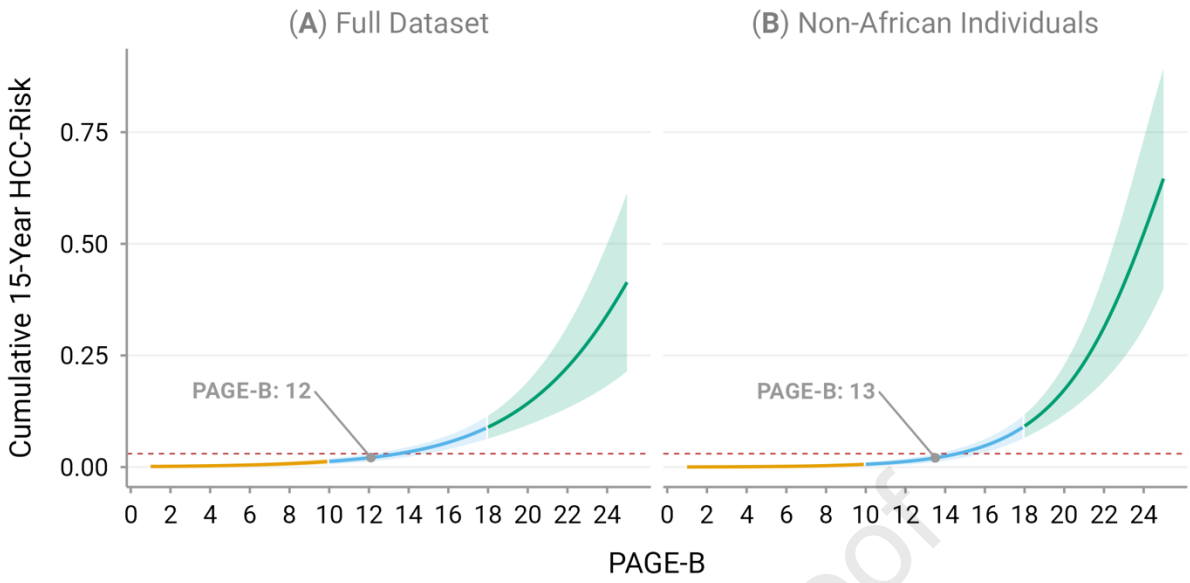
Distribution of available PAGE-B scores in the complete case data (**A**) and after multiple imputation (**C**). Hepatocellular carcinoma cases by PAGE-B score are represented as dots in the complete case data (**B**) and after multiple imputation (**D**).



No. at risk								
PAGE-B < 10	785	573	358	131	497	364	235	89
PAGE-B 11-17	1711	1319	863	279	1513	1182	781	250
PAGE-B ≥ 18	466	311	175	52	427	281	164	56

Figure 2 Cumulative incidence of hepatocellular carcinoma since tenofovir start

The Kaplan-Meier curves show the cumulative incidence of developing hepatocellular carcinoma (HCC) after starting tenofovir in the full study population (**A**, n = 2963) and after excluding individuals of African origin (**B**, n = 2438)



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746 **Figure 3 Fifteen-year probability of developing hepatocellular carcinoma, by PAGE-B score**

747 Probability (solid line) and 95% confidence interval (shaded area) of developing hepatocellular
748 carcinoma (HCC) within 15 years after tenofovir start in the full study population (**A**) and after
749 excluding individuals of African origin (**B**). The dotted red line indicates the commonly accepted
750 screening threshold (HCC risk of 0.2% per year). The upper limit of the 95% confidence interval for
751 individuals with a PAGE-B score of 12 (full dataset) or 13 (non-African individuals) remains just under
752 the accepted screening threshold.

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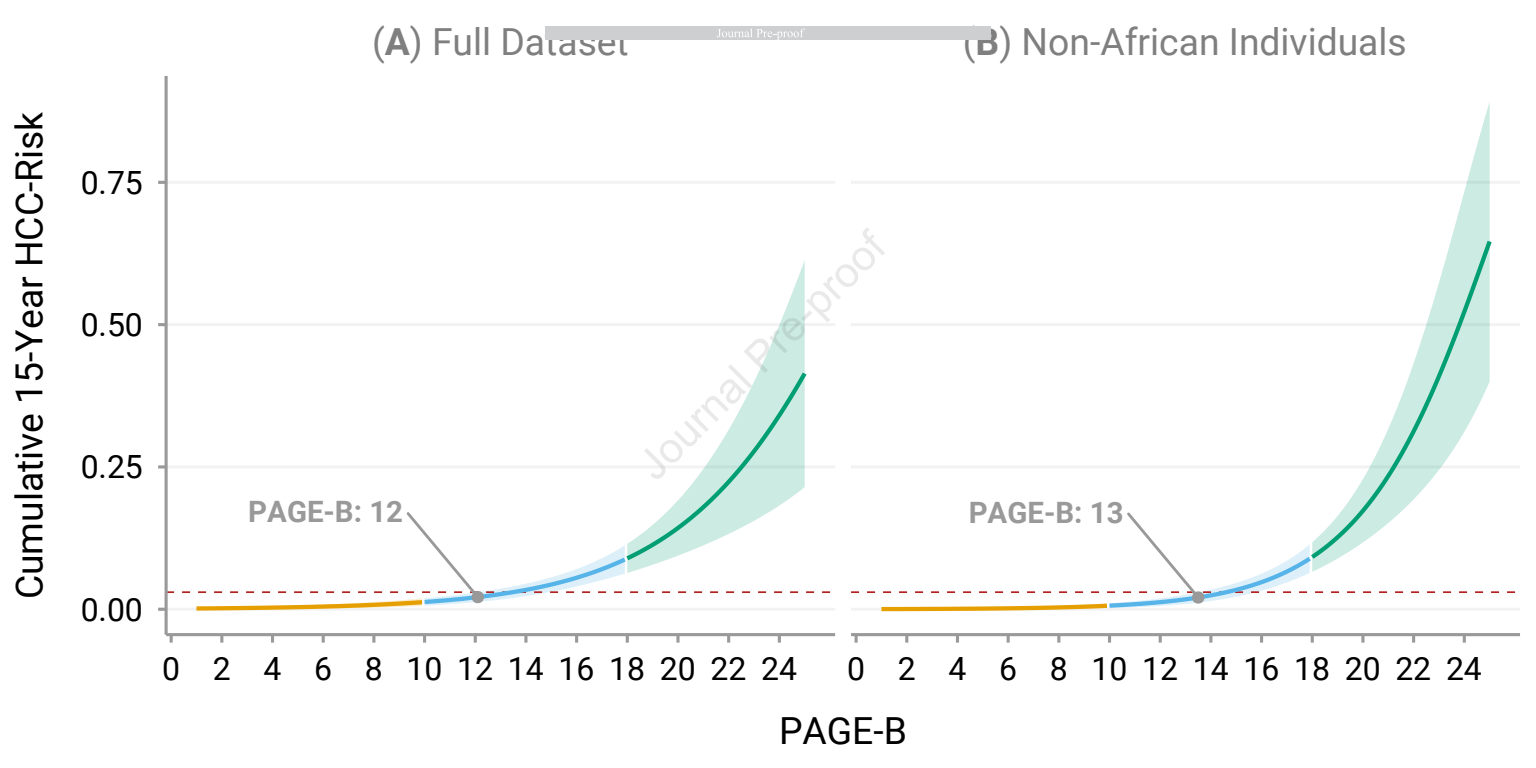

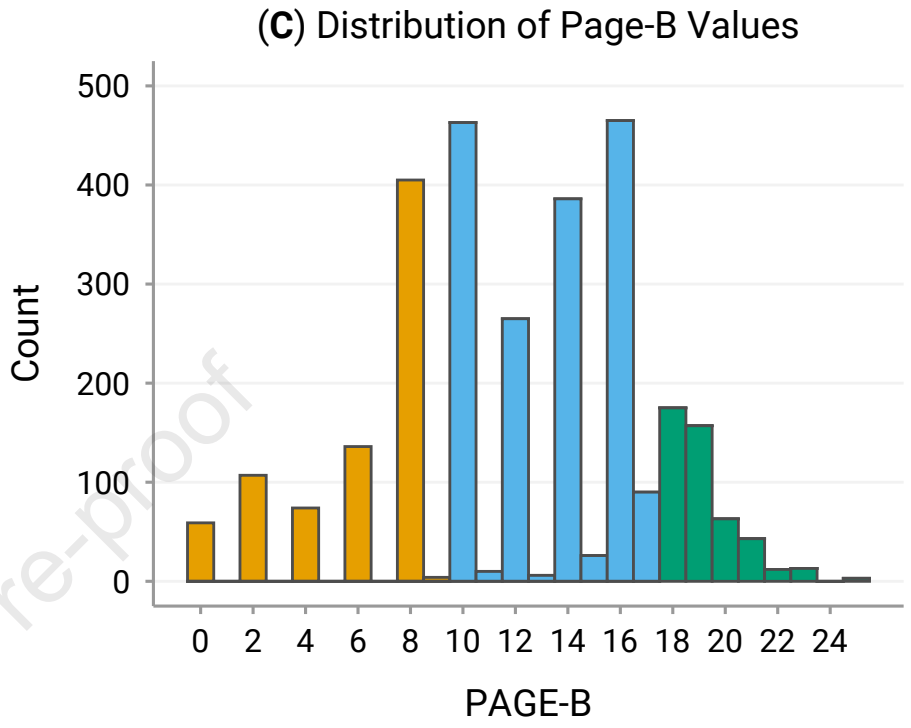

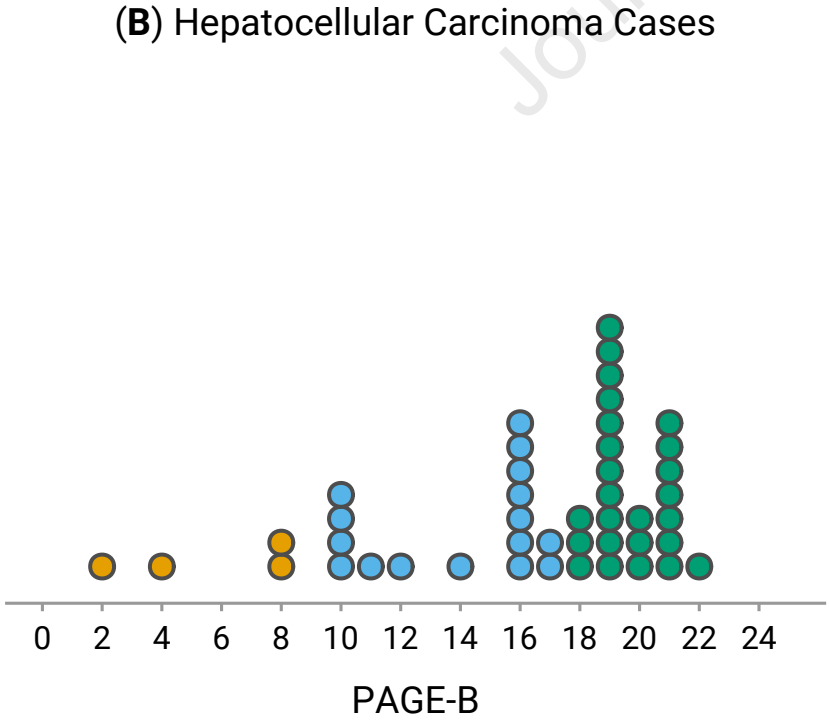

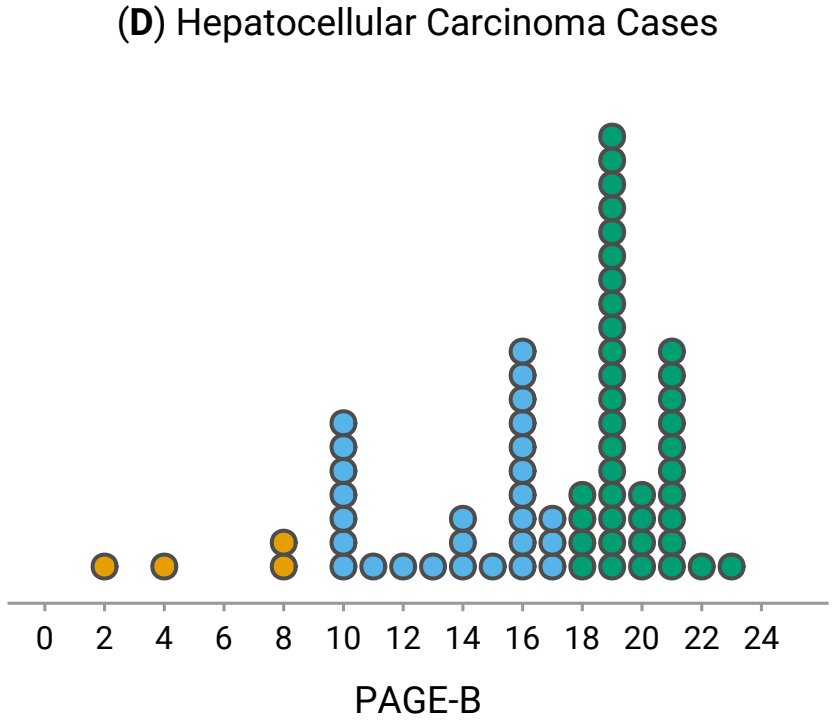

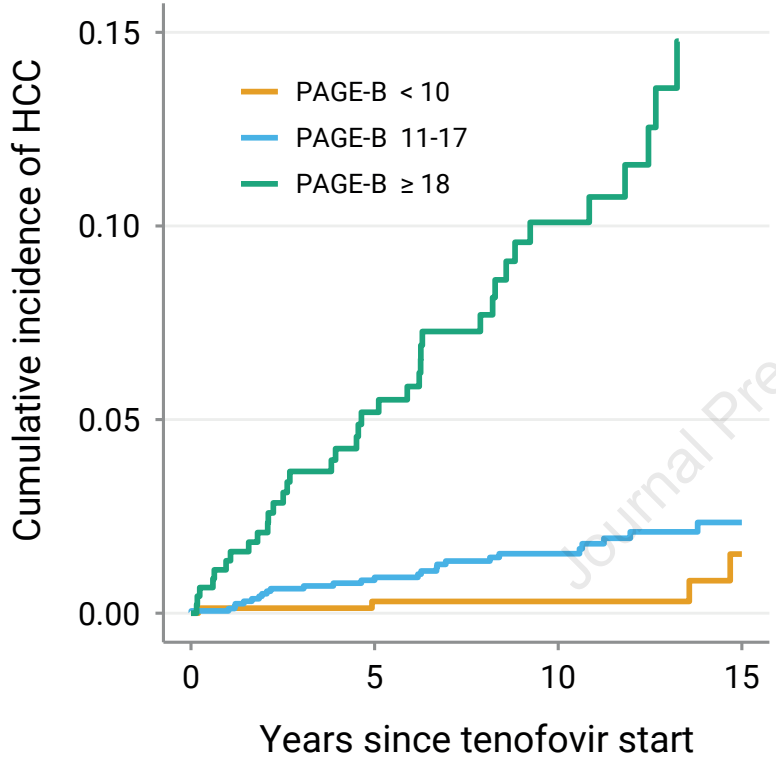

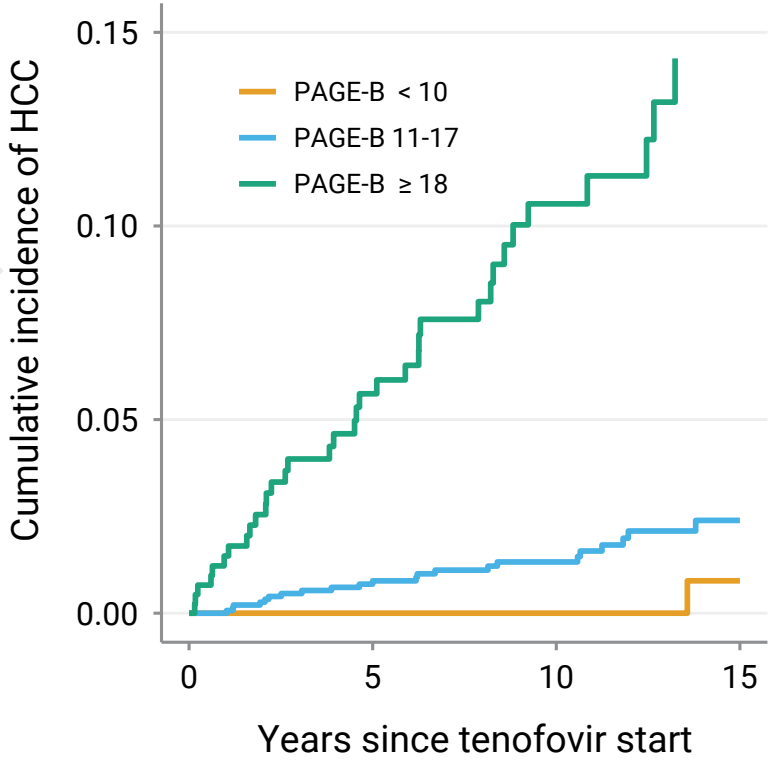

No. at risk

PAGE-B < 10	785	573	358	131	497	364	235	89
PAGE-B 11-17	1711	1319	863	279	1513	1182	781	250
PAGE-B ≥ 18	466	311	175	52	427	281	164	56

External validation of the PAGE-B score to estimate the risk of hepatocellular carcinoma in persons living with HIV and hepatitis B

Benrard Surial et al.

Highlights

- This external validation study included 2963 individuals with HIV/HBV coinfection from 4 European cohorts.
- Within a median of 9.6 years, 68 patients developed hepatocellular carcinoma (incidence rate 2.58/1000 person-years).
- Among individuals with HIV/HBV coinfection, PAGE-B (based on age, sex and platelets) showed good model discrimination.
- A PAGE-B score <10 had a negative predictive value of 99.4% for developing hepatocellular carcinoma within 5 years.