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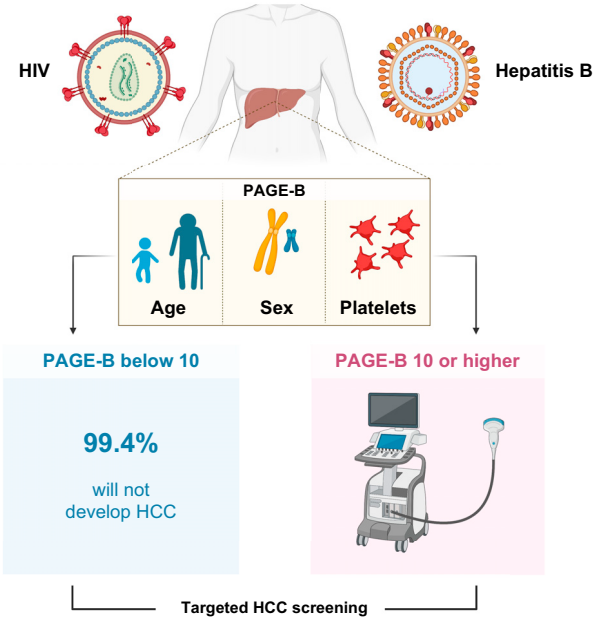
Graphical abstract



Highlights

- This external validation study included 2,963 individuals with HIV/HBV coinfection from four European cohorts.
- Within a median of 9.6 years, 68 patients developed hepatocellular carcinoma (incidence rate 2.58/1,000 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 the development of HCC within 5 years.

Impact and implications

Chronic HBV infection is the most important cause of hepatocellular carcinoma (HCC) among people living with HIV. Valid risk prediction may enable better targeting of HCC screening efforts to high-risk individuals. We aimed to validate PAGE-B, a risk prediction tool that is based on age, sex, and platelets, in 2,963 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 <10 had a negative predictive value of 99.4% for the development of HCC within 5 years. 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.

https://doi.org/10.1016/j.jhep.2022.12.029
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External validation of the PAGE-B score for HCC risk prediction in people living with HIV/HBV coinfection

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Journal of Hepatology **2023**. vol. 78 | 947–957

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Background & Aims: HBV coinfection is common among people living with HIV (PLWH) and is the most important cause of hepatocellular carcinoma (HCC). While risk prediction tools for HCC have been validated in patients with HBV monoinfection, they have not been evaluated in PLWH. Thus, we performed an external validation of PAGE-B in people with HIV/HBV coinfection.
Methods: We included data on PLWH from four European cohorts who were positive for HBsAg and did not have HCC before starting tenofovir. We estimated the predictive performance of PAGE-B for HCC occurrence over 15 years in patients receiving tenofovir-containing antiretroviral therapy. Model discrimination was assessed after multiple imputation using Cox regression with the prognostic index as a covariate, and by calculating Harrell's c-index. Calibration was assessed by comparing our cumulative incidence with the PAGE-B derivation study using Kaplan-Meier curves.
Results: In total, 2,963 individuals with HIV/HBV coinfection on tenofovir-containing antiretroviral therapy 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 (2.58/1,000 patient-years, 95% 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. The 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 of 99.4% for the development of HCC within 5 years. Restricting efforts to individuals with a PAGE-B of ≥10 would spare unnecessary 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.

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Introduction

Between 5 and 15% of people living with HIV (PLWH) also have a chronic HBV infection, the single most important cause of end-stage liver disease and hepatocellular carcinoma (HCC) worldwide.[1] Screening individuals with HBV infection who are at high risk of HCC using ultrasound every 6 months is recommended to detect cancers at an early and curable stage.[2,3] However, screening uptake remains suboptimal, representing 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 cirrhosis had the highest risk of developing HCC.[6] HCC risk prediction tools could help to guide clinicians in deciding whether a patient should undergo HCC screening or not.

PAGE-B, a prognostic score including age, sex and platelet count at initiation of antiviral therapy, was derived from a multicountry study of 1,815 European individuals with HBV monoinfection, 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 HCV and 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 patients with HIV/HBV coinfection from a large cohort collaboration in Europe.

Keywords: Hepatitis B virus; HIV infection; hepatocellular carcinoma; liver cirrhosis; liver neoplasms; risk assessment; risk prediction models; model validation; tenofovir.
Received 6 October 2022; received in revised form 21 December 2022; accepted 23 December 2022; available online 21 January 2023
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https://doi.org/10.1016/j.jhep.2022.12.029

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 containing 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 of 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 analyses. 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 at 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). Cirrhosis was defined as Metavir stage F4 on liver biopsy or liver stiffness >11 kPa on TE at any timepoint. If neither of these measurements was available, we defined cirrhosis as an aspartate aminotransferase-to-platelet ratio index (APRI) >2.0 at the time of tenofovir start. Coinfection with HCV was defined as a positive HCV RNA measurement prior to tenofovir start, and HDV coinfection was defined as having a positive anti-HDV serology at any timepoint following 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 (Fig. 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 are listed in Table S2, and the distribution of imputed platelet values is shown in Fig. 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 seems 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 restricted the analyses 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 have HDV or HCV coinfection.

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 (Fig. S3). The ATHENA cohort followed the largest proportion of patients (n = 1,319, 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 (IQR 35 to 47 years), 466 (16%) participants were female, 2,023 (68%) were Caucasian, and 314 (11%) had evidence of 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 platelet counts 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 treatment (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 cases of 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

Table 1. Patient characteristics at tenofovir start, stratified by cohort.

Characteristic	Overall (N = 2,963)	Aquitaine (n = 337)	ATHENA (n = 1,319)	EuroSIDA (n = 800)	SHCS (n = 507)
Male sex	2,477 (84%)	277 (82%)	1,147 (87%)	662 (83%)	391 (77%)
Median age, years (IQR)	41 (35–47)	42 (37–48)	41 (35–48)	41 (36–47)	40 (35–46)
Caucasian	2,023 (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	2,023 (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	1,536 (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	1,596 (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	1,018 (34%)	112 (33%)	419 (32%)	298 (37%)	189 (37%)
(Missing)	159 (5.4%)	58 (17%)	32 (2.4%)	63 (7.9%)	6 (1.2%)
Median BMI, kg/m^2 (IQR)	22.8 (20.8–25.1)	22.3 (20.4–24.6)	22.9 (20.9–25.0)	22.7 (20.8–25.1)	23.0 (20.8–25.8)
(Missing)	639 (22%)	92 (27%)	185 (14%)	317 (40%)	45 (8.9%)
Median CD4 cell count, cells/μl (IQR)	323 (182–510)	376 (196–584)	310 (170–490)	346 (210–531)	314 (198–472)
(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%)
Cirrhosis	314 (11%)	27 (9.9%)	129 (15%)	94 (12%)	64 (16%)
Median ALT at baseline, IU/L (IQR)	41 (25–79)	38 (24–70)	47 (26–134)	39 (25–69)	39 (25–65)
(Missing)	731 (25%)	60 (18%)	444 (34%)	191 (24%)	36 (7.1%)
Median platelet count, G/L (IQR)	190 (141–236)	194 (144–235)	188 (133–235)	192 (152–233)	190 (148–239)
(Missing)	1,063 (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)	1,063 (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)	1,941 (66%)	250 (74%)	1,180 (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)	1,277 (43%)	124 (37%)	167 (13%)	756 (94%)	230 (45%)
XTC use before TFV	1,629 (55%)	211 (63%)	584 (44%)	550 (69%)	284 (56%)
Median time of prior XTC use, years (IQR)	3.7 (0.0–8.2)	3.8 (0.0–7.2)	0.0 (0.0–6.0)	5.2 (0.0–8.1)	9.9 (5.2–15.1)
Median follow-up on TFV, years (IQR)	9.6 (4.9–13.3)	10.8 (5.6–15.0)	9.7 (5.3–13.1)	8.4 (3.8–12.3)	10.3 (5.2–14.3)

APRI, aspartate aminotransferase-to-platelet ratio index; ALT, alanine aminotransferase; MSM, men who have sex with men; PWID, persons who inject drugs; TFV, tenofovir; XTC, lamivudine or emtricitabine.

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 (Fig. 1A,C). 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, 1,711 (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 four (5.7%) individuals with a PAGE-B score <10 developed HCC (Fig. 1B,D). Of four individuals with HCC and a PAGE-B score <10, the median age was 37 years, three were of African and one was of Asian origin, one individual had evidence of 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 = 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 (Fig. 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 5 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).

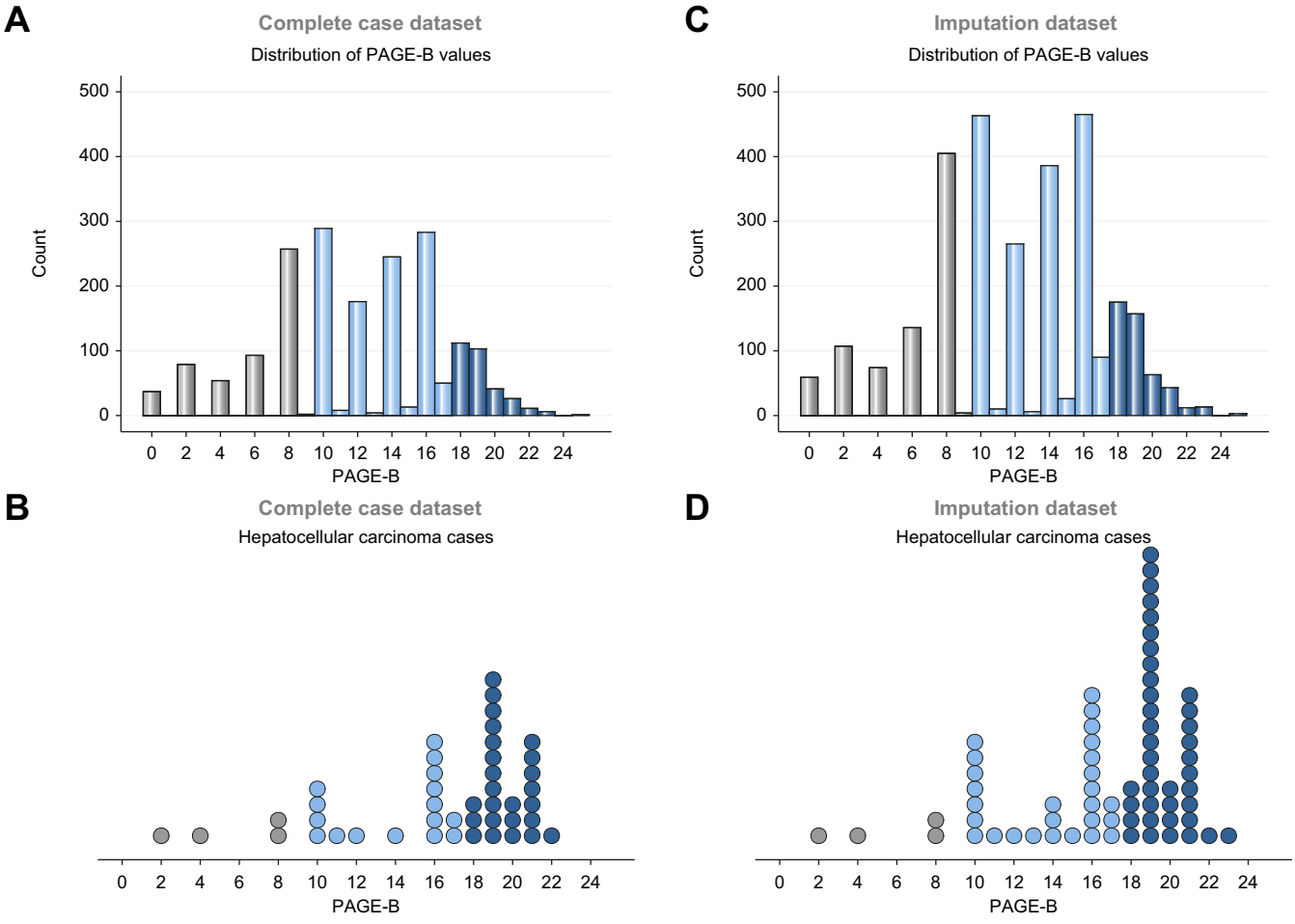


Fig. 1. Distribution of PAGE-B scores and hepatocellular carcinoma cases. Distribution of available PAGE-B scores in (A) the complete case data and (C) after multiple imputation. Hepatocellular carcinoma cases by PAGE-B score are represented as dots in (B) the complete case data and (D) after multiple imputation.

Of 2,438 non-African cohort 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 1.06–3.90) 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). In the analysis restricted to non-African patients, the regression slope was 1.17 (0.78–1.56), the pooled c-index 0.80 (range 0.76 to 0.82), and the Kaplan-Meier curves confirmed good model discrimination (Fig. 2B).

Sensitivity analyses

As the derivation study evaluated the PAGE-B score for the prediction of HCC within 5 years of tenofovir start, we repeated the analyses censoring all individuals at 5 years. The results remained largely unchanged, with a regression slope of 0.87 (95% CI 0.47–1.28) and a pooled c-index of 0.76 (range 0.71–0.79). Likewise, complete case analyses evaluating the HCC risk within the full follow-up period revealed similar results (regression slope 0.88, 95% CI 0.56–1.21; c-index 0.77, 95% CI 0.68–0.85). Results remained unchanged when we restricted analyses to individuals who started tenofovir after cohort registration (regression slope 0.94, 95% CI 0.58–1.30, c-index 0.77, range 0.72–0.80), and when we used cohort registration as baseline for individuals who started tenofovir prior to that date (regression slope 1.01, 95% CI 0.69–1.33, c-index 0.78, range 0.74–0.81). 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 0.55–1.23, c-index 0.76, range 0.74–0.79).

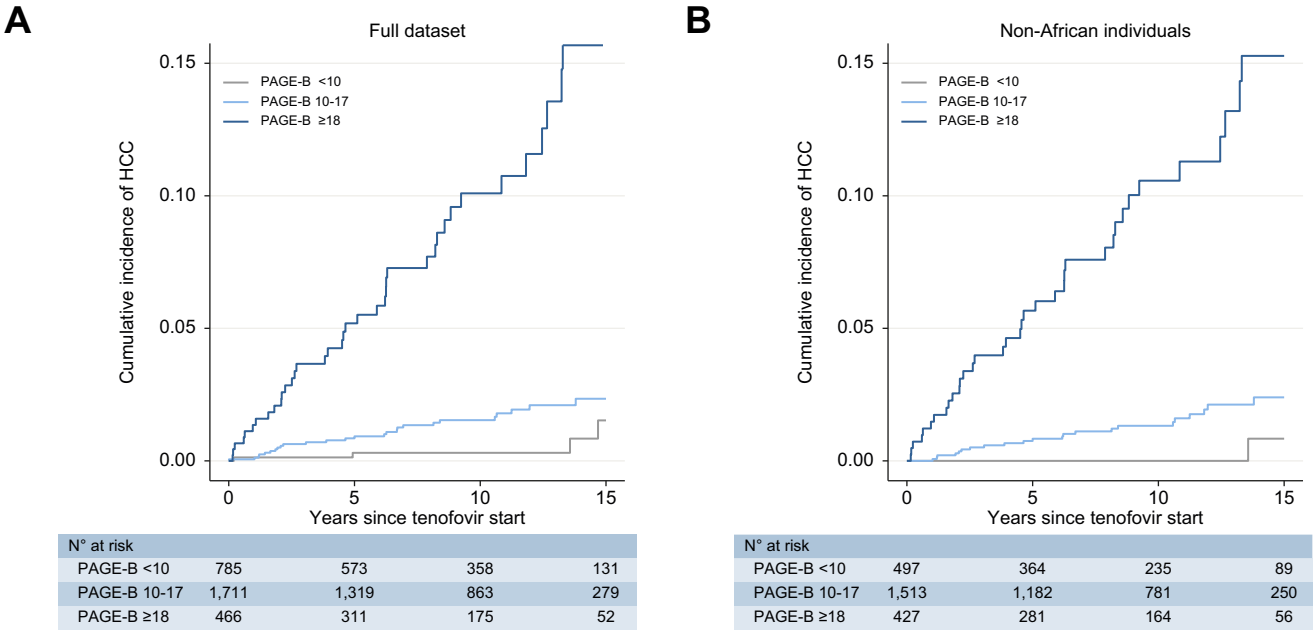
Screening cut-off

The cumulative incidence of HCC within the full follow-up period for each PAGE-B score is shown in Fig. 3. The upper limit of the 95% CI 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 5 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%, Fig. 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 individuals living with HIV and HBV coinfection from a large collaboration of European cohorts. Similar to the original derivation study,[7] individuals with a score <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, three of four HCC cases occurred in individuals of African origin.

Current guidelines suggest that HCC screening is not warranted in individuals with HBV monoinfection and a PAGE-B score <10 because of their 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 of the present study, 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 monoinfection.[25,26] Although the risk for HCC with a score <10



N° at risk				
PAGE-B <10	785	573	358	131
PAGE-B 10-17	1,711	1,319	863	279
PAGE-B ≥18	466	311	175	52

N° at risk				
PAGE-B <10	497	364	235	89
PAGE-B 10-17	1,513	1,182	781	250
PAGE-B ≥18	427	281	164	56

Fig. 2. Cumulative incidence of hepatocellular carcinoma since tenofovir start. The Kaplan-Meier curves show the cumulative incidence of developing hepatocellular carcinoma after starting tenofovir in (A) the full study population (N = 2,963) and (B) after excluding individuals of African origin (n = 2,438).

Table 2. Life table comparison of hepatocellular carcinoma (HCC) cases in the present study and the original derivation study.

Category	Years	N at risk		Cumulative HCCs (cumulative incidence)		Cumulative incidence, derivation study[1]	
		Complete case	Imputation	Complete case	Imputation	Derivation	Validation
PAGE-B <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.
PAGE-B 10-17							
	1	1,001	1,625	1 (0.1%)	1 (0.1%)	0%	0%
	2	937	1,534	3 (0.3%	8 (0.5%)	1%	1%
	3	877	1,442	5 (0.5%)	10 (0.6%)	1%	1%
	5	794	1,319	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.
PAGE-B ≥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.

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.

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 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

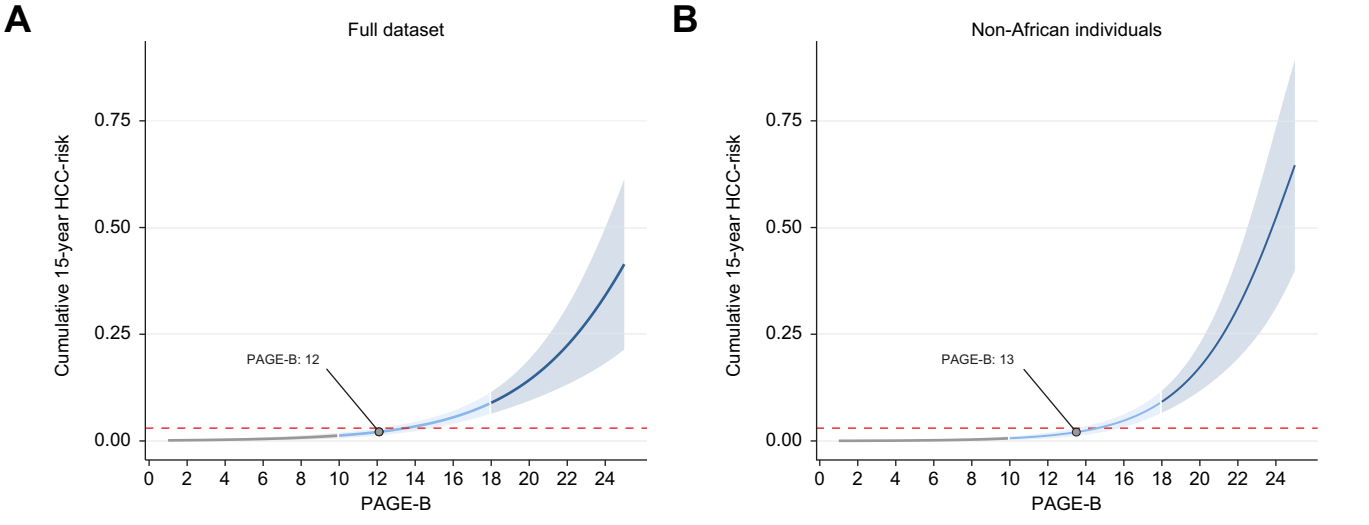


Fig. 3. Fifteen-year probability of developing hepatocellular carcinoma, by PAGE-B score. Probability (solid line) and 95% CI (shaded area) of developing hepatocellular carcinoma within 15 years after tenofovir start in (A) the full study population and (B) after excluding individuals of African origin. The dashed red line indicates the commonly accepted screening threshold (hepatocellular carcinoma risk of 0.2% per year). The upper limit of the 95% CI for individuals with a PAGE-B score of 12 (full dataset) or 13 (non-African individuals) remains just under the accepted screening threshold.

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 HBV DNA >2,000 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 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 receiving 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 been 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 earlier (in younger individuals) in African populations,[23,29,30] and because age is an important component of PAGE-B, other risk stratification tools may be needed to guide surveillance efforts for populations of African origin.

We present the first external validation of an HCC risk prediction model in a multinational population of people 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 100 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 following imputation 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 who were 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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Abbreviations

ANRS, Agence Nationale de Recherches sur le Sida; APRI, aspartate aminotransferase-to-platelet ratio index; ART, antiretroviral therapy; ATHENA, AIDS Therapy Evaluation in the Netherlands; HCC, hepatocellular carcinoma; PLWH, people living with HIV; SHCS, Swiss HIV Cohort Study; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TE, transient elastography.

Financial support

EuroSIDA was supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement #260694. Current support includes unrestricted grants by ViiV Healthcare LLC, GlaxoSmithKline R&D Limited, Janssen Scientific Affairs, Janssen R&D, Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp, Gilead Sciences. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant #148522 and #201369). The study is also supported by the Danish National Research Foundation (Grant #DNRF126) and by the International Cohort Consortium of Infectious Disease (RESPOND).

The ATHENA cohort is managed by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment. The ANRS CO3 Aquitaine- AquiVIH- NA cohort is supported by the ANRS|MIE and the CHU de Bordeaux. This study has been financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (Grant #148522 and #201369), by SHCS project #751 and by the SHCS research foundation. The SHCS data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers http://www.shcs.ch/180-health-care-providers). Further funding was obtained from the NEAT-ID Foundation. GW was supported by a Professorship (PP00P3_211025) from the Swiss National Science Foundation. BS was supported by an institutional research grant (CTU Grant). The funders had no role in the study design, data collection, analysis, and decision to publish.

Conflict of interest

BS reports support to his institution for advisory boards and travel grants from Gilead Sciences and ViiV, outside of the present work. AM has received honoraria, travel support, lecture fees and/or consultancy fees from ViiV, Gilead and Eiland and Bonnin. MvdV reports support to his institution for advisory boards and unrestricted research grants from Gilead Sciences, Merck and ViiV. FB has received travel grants and honoraria from ViiV Healthcare, Gilead, ViiV, Janssen, and MSD, and support for attending meetings from Gilead, Janssen, MSD, and ViiV Healthcare. JKR reports honoraria for himself for advisory boards or DSMB participation and speaking at educational events from Abivax, Galapagos, Gilead Sciences, Janssen, Merck, Theratechnologies and ViiV, outside of the submitted

work. HFG has received unrestricted research grants from Gilead Sciences; fees for data and safety monitoring board membership from Merck; consulting/advisory board membership fees from Gilead Sciences, Merck, Johnson and Johnson, Novartis and ViiV Healthcare; and grants from the Swiss National Science Foundation, the Yvonne Jacob Foundation and from National Institutes of Health. AR reports support to his institution for advisory boards and/or travel grants from MSD, Gilead Sciences, Pfizer and Abbvie, and an investigator-initiated trial (IIT) grant from Gilead Sciences. All remuneration went to his home institution and not to AR personally, and all remuneration was provided outside the submitted work. GW reports unrestricted research grants from Gilead Sciences and Roche Diagnostics, as well as travel grants and advisory board/lecture fees from ViiV, Gilead Sciences and MSD, all paid to his institution. All other authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

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.

Acknowledgements

The authors thank all patients, physicians and nurses associated with the participating cohorts.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.12.029.

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