

Journal Pre-proof



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

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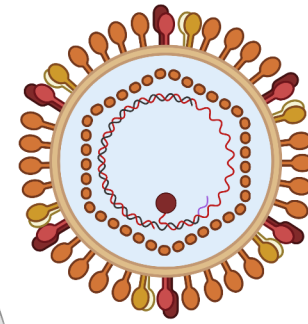
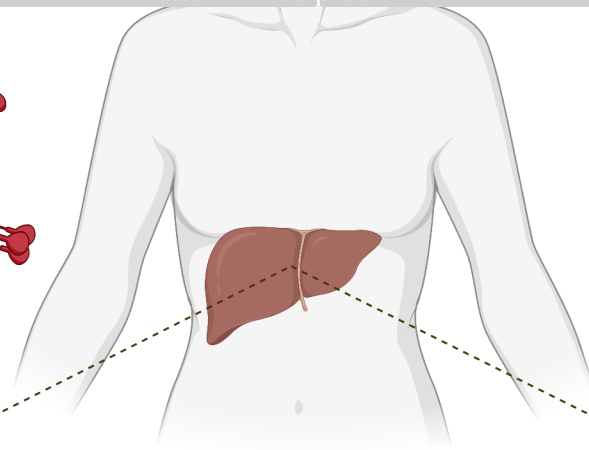
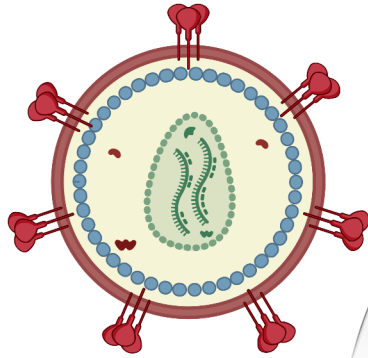
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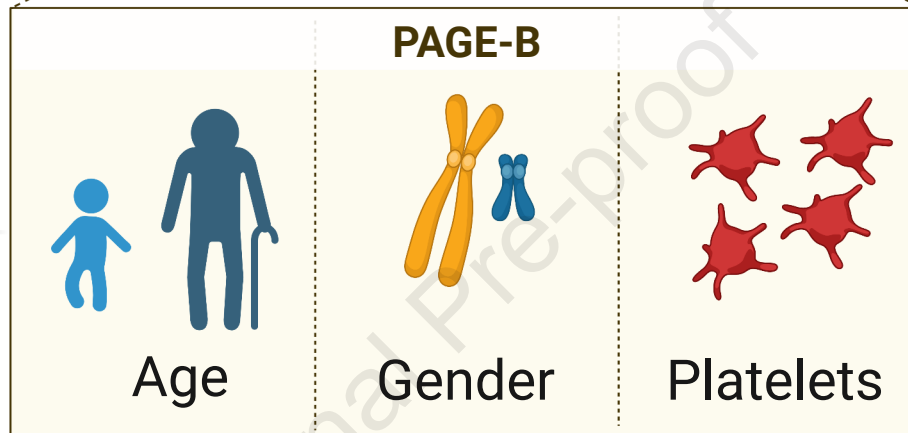
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HIV



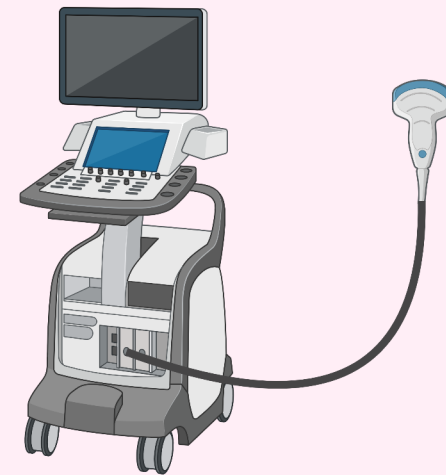
Hepatitis B



PAGE-B below 10

99.4%
will not
develop HCC

PAGE-B 10 or higher



Targeted HCC screening

1 External validation of the PAGE-B score for HCC risk prediction in 2 people living with HIV/HBV coinfection

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7 Cohort

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43

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89 and approved its final version.

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91 and/or analyzed during the current study are not publicly available, since they are subject to national
92 data protection laws and restrictions imposed by the ethics committee to ensure data privacy of the
93 study participants. The code for the analysis is archived at <https://doi.org/10.5281/zenodo.7466614>.

94

Journal Pre-proof

95 **ABSTRACT**

96 **Background & Aims**

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

101 **Methods**

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

108 **Results**

109 In total, 2'963 individuals with HIV/HBV coinfection on tenofovir-containing ART were included. PAGE-
110 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
111 years, HCC occurred in 68 individuals (2.58/1000 patient-years, 95% confidence interval [CI] 2.03–
112 3.27). The regression slope of the prognostic index for developing HCC within 15 years was 0.93 (95%
113 CI 0.61–1.25), and the pooled c-index was 0.77 (range 0.73–0.80), both indicating good model
114 discrimination. Cumulative incidence of HCC was lower in our study compared to the derivation study.
115 A PAGE-B cut-off of <10 had a negative predictive value for developing HCC within 5 years of 99.4%.
116 Restricting efforts to individuals with a PAGE-B of ≥10 would spare HCC screening in 27% of
117 individuals.

118 **Conclusions**

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

121 **IMPACT AND IMPLICATIONS**

122 Chronic hepatitis B virus (HBV) infection is the most important cause of hepatocellular carcinoma (HCC)
123 among people living with HIV, and valid risk prediction may guide HCC screening efforts to high-risk
124 individuals. We aimed at validating PAGE-B, a risk prediction tool that is based on age, gender, and
125 platelets, among 2963 individuals with HIV/HBV coinfection who received tenofovir-containing
126 antiretroviral therapy. In the present study, PAGE-B showed good discrimination, adequate calibration,
127 and a cut-off of less than 10 had a negative predictive value for developing HCC within 5 years of
128 99.4%. These results indicate that PAGE-B is a simple and valid risk prediction tool to determine the
129 need for HCC screening among people living with HIV and HBV.

130

131 INTRODUCTION

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

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

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

155

156 PATIENTS AND METHODS

157 Study setting and participants

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

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

175 Outcomes and definitions

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

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

189 **Statistical Analyses**

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

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

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

216 **Sensitivity Analyses**

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

228

229 RESULTS

230 Study population

231 Of 2'988 eligible patients with the last HBsAg prior to tenofovir start being positive, we excluded 10
232 patients who developed HCC before starting tenofovir, and 15 patients without available follow-up data
233 after tenofovir start, resulting in a study population of 2'963 patients (**Figure S3**). The ATHENA cohort
234 followed the largest proportion of patients (n = 1319, 44.5%), followed by EuroSIDA (800, 27.0%), the
235 SHCS (507, 17.1%) and the Aquitaine cohort (337, 11.4%). At tenofovir start, the median age was 41
236 years (interquartile range [IQR] 35 to 47 years), 466 (16%) participants were female, 2'023 (68%) were
237 Caucasian, and 314 (11%) had evidence of liver cirrhosis (48.4% diagnosed with TE, 39.8% with APRI,
238 and 11.8% with liver biopsy). Although most patient characteristics were similar across cohorts, the
239 amount of missing data on platelets and HDV coinfection varied markedly (**Table 1**). Compared to the
240 original PAGE-B derivation study [7], individuals in the current validation study were younger (median
241 age 41 years in our study vs. 52 years in the derivation study), more likely to be male (84% vs. 70%),
242 had a lower median body mass index (22.8 vs. 26.1 kg/m²), and more commonly received other
243 nucleoside analogues prior to tenofovir (55% vs. 33%), whereas the median platelet count was similar
244 in both studies (190 vs. 191 G/L, **Table S3**).

245 Occurrence of HCC

246 Within a median follow-up of 9.6 years (IQR 4.9 to 13.3 years), HCC was diagnosed in 68 individuals
247 (2.3%, incidence rate 2.58 per 1'000 patient-years, 95% CI 2.03 to 3.27). Overall, 24 HCC (35.3%)
248 occurred in ATHENA, 17 (25.0%) in EuroSIDA, 16 (23.5%) in the SHCS, and 13 (19.1%) in the
249 Aquitaine cohort. Within 5 years of follow-up – the observation period used in the PAGE-B derivation
250 study – HCC occurred in 36 individuals (1.2%, incidence rate 2.82 per 1'000 patient-years, 95% CI 2.03
251 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
252 10 years, and 3.93% at 15 years. Of all patients who developed HCC, 90% were male, 81% were
253 Caucasian, and 51 individuals died (overall survival rate 25%), with a median survival after HCC
254 diagnosis of 11.7 months (95% CI 5.9 to 19.2).

255 PAGE-B model validation

256 For 1'890 individuals (63.8%), a PAGE-B score at the time of tenofovir start could be calculated based
257 on complete case data. The distributions of PAGE-B values were similar in the complete case and
258 imputation datasets (**Figure 1A** and **1C**). In the complete case dataset, the PAGE-B score was <10 in
259 522 (27.6%), between 10 and 17 in 1'068 (56.5%), and ≥ 18 in 300 individuals (15.9%). After multiple
260 imputation, 785 individuals (26.5%) had a score <10, 1711 (57.7%) had a score between 10 and 17,
261 and 466 (15.7%) had a score ≥ 18 . Thirty-nine HCC cases (55.7%) occurred in individuals with a PAGE-
262 B of 18 or higher, 27 (38.6%) occurred in individuals with a PAGE-B between 10 and 17, whereas only
263 4 (5.7%) individuals with a PAGE-B score <10 developed an HCC (**Figure 1B** and **1D**). Of 4 individuals
264 with an HCC and a PAGE-B score <10, the median age was 37 years, 3 were of African and one was
265 of Asian origin, one individual had evidence of liver cirrhosis on TE, and another individual had
266 coinfection with HDV.

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

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

284 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-
285 Meier curves confirmed good model discrimination (**Figure 2B**).

286 **Sensitivity analyses**

287 As the derivation study evaluated the PAGE-B score for the prediction of HCC within five years of
288 tenofovir start, we repeated the analyses censoring all individuals at five years. The results remained
289 largely unchanged, with a regression slope of 0.87 (95% CI 0.47 to 1.28) and a pooled c-index of 0.76
290 (range 0.71 to 0.79). Likewise, complete case analyses evaluating the HCC risk within the full follow-
291 up period revealed similar results (regression slope 0.88, 95% CI 0.56 to 1.21; c-index 0.77, 95% CI
292 0.68 to 0.85). Results remained unchanged when we restricted analyses to individuals who started
293 tenofovir after cohort registration (regression slope 0.94, 95% CI 0.58 to 1.30, c-index 0.77, range 0.72
294 to 0.80), and when we used cohort registration as baseline for individuals who started tenofovir prior to
295 that date (regression slope 1.01, 95% CI 0.69 to 1.33, c-index 0.78, range 0.74 to 0.81). Similarly,
296 excluding 382 individuals who were known to have HCV or HDV coinfection did not change the
297 interpretation of our results (regression slope 0.89, 95% CI 0.55 to 1.23, c-index 0.76, range 0.74 to
298 0.79).

299 **Screening cut-off**

300 The cumulative incidence of HCC within the full follow-up period for each PAGE-B score is shown in
301 **Figure 3**. The upper limit of the 95% confidence interval of the cumulative HCC risk was above the
302 accepted screening threshold (HCC risk of 0.2% per year) for a PAGE-B score of >12 in the full dataset,
303 and >13 after excluding individuals of African origin. Using a cut-off of >10 as in the original derivation
304 study [7], the sensitivity and specificity for developing HCC within five years of tenofovir start were
305 81.0% and 42.9%, respectively (negative predictive value 99.4%, **Table S4**). After excluding individuals
306 of African origin, the sensitivity of a cut-off of >10 improved to 93.6% (negative predictive value 99.8%,
307 **Figure S4**). When increasing the cut-off to >12 in the full dataset, sensitivity was 77.7%, specificity was
308 51.8%, and the negative predictive value was 99.4%.

309 DISCUSSION

310 In this external validation study, the PAGE-B score showed good accuracy in predicting the HCC risk
311 in a large collaboration of European cohorts of individuals living with HIV and HBV infection. Similar to
312 the original derivation study [7], individuals with a score below 10 were at very low risk of HCC, with a
313 negative predictive value above 99%, confirming the usefulness of PAGE-B to target HCC surveillance
314 efforts in individuals with HIV/HBV coinfection. In the subset of participants with a low PAGE-B score,
315 3 of 4 HCC cases occurred in individuals of African origin.

316 Current guidelines suggest that individuals with HBV mono-infection and a PAGE-B score <10 do not
317 need HCC screening because of a very low risk of HCC [24]. In the original derivation study, a score of
318 <10 had a negative predictive value of 100%, meaning that no patient experienced HCC below that cut-
319 off [7]. We found a slightly lower negative predictive value of 99.4% in the full study population, and
320 99.8% after excluding individuals of African origin. These estimates are in line with the findings of
321 previous PAGE-B external validation studies in individuals with HBV mono-infection [25,26]. Although
322 the risk for HCC with a score <10 was not 0% in our study, the yearly risk for HCC was below the
323 recommended threshold of 0.2%, and therefore it seems justified to apply the same cut-offs to
324 individuals with and without HIV coinfection. Since 27% of individuals in our study had a PAGE-B <10,
325 targeting screening efforts to individuals with a PAGE-B of 10 and higher would substantially reduce
326 the need for HCC surveillance. Based on our results, even a higher threshold of <12 could be
327 considered, as the yearly HCC risk remained below 0.2% in those individuals, which would spare HCC
328 screening in 473 (16%) additional individuals. However, the potential benefits of using a higher PAGE-
329 B score cut-off than in the original derivation study need to be confirmed in other cohorts of individuals
330 with HIV/HBV coinfection.

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

339 guidelines [7,8]. In our study, we considered every participant with a positive HBsAg prior to tenofovir
340 start irrespective of whether they had evidence of liver inflammation, since tenofovir-containing ART is
341 recommended in all individuals with HIV/HBV coinfection [9]. Therefore, our study population was more
342 likely to include participants with no or mild liver disease than the derivation study, which is also reflected
343 by the lower prevalence of liver cirrhosis compared to the HBV mono-infection cohorts [26]. In addition,
344 the lower HCC incidence observed in our study may also have been influenced by the higher proportion
345 of individuals with HBV-active treatment prior to tenofovir start (55%) compared to the derivation study
346 (33%).

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

357 We present the first external validation of an HCC risk prediction model in a multinational population of
358 individuals living with HIV and HBV, providing robust evidence for the current recommendation by the
359 European AIDS Clinical Society guidelines to use PAGE-B for HCC risk stratification [9]. However,
360 despite our best efforts to pool data from large European cohorts, the statistical power of our study was
361 limited, since a minimum of one hundred events is commonly suggested for external validation studies
362 [31]. Furthermore, the proportion of participants with missing platelet measurements was high,
363 exceeding 50% in one cohort. Although we used multiple imputation and confirmed its robustness by
364 comparing results from imputed with complete case data, some bias in the estimates of model
365 performance cannot be excluded. In addition, information on HDV coinfection was limited in most
366 cohorts. Since HDV acts as an additional risk factor for HCC [32], restricting our analyses to patients
367 without HDV coinfection might have led to better model performance. Finally, participants in our
368 collaboration of real-life cohorts underwent HCC screening according to the judgement of their treating

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

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

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629 *Author names in bold designate shared co-first authorship.*

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723 TABLES

724 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)
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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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727 **Table 2** Life table comparison of hepatocellular carcinoma (HCC) cases in the
 728 present study and the original derivation study

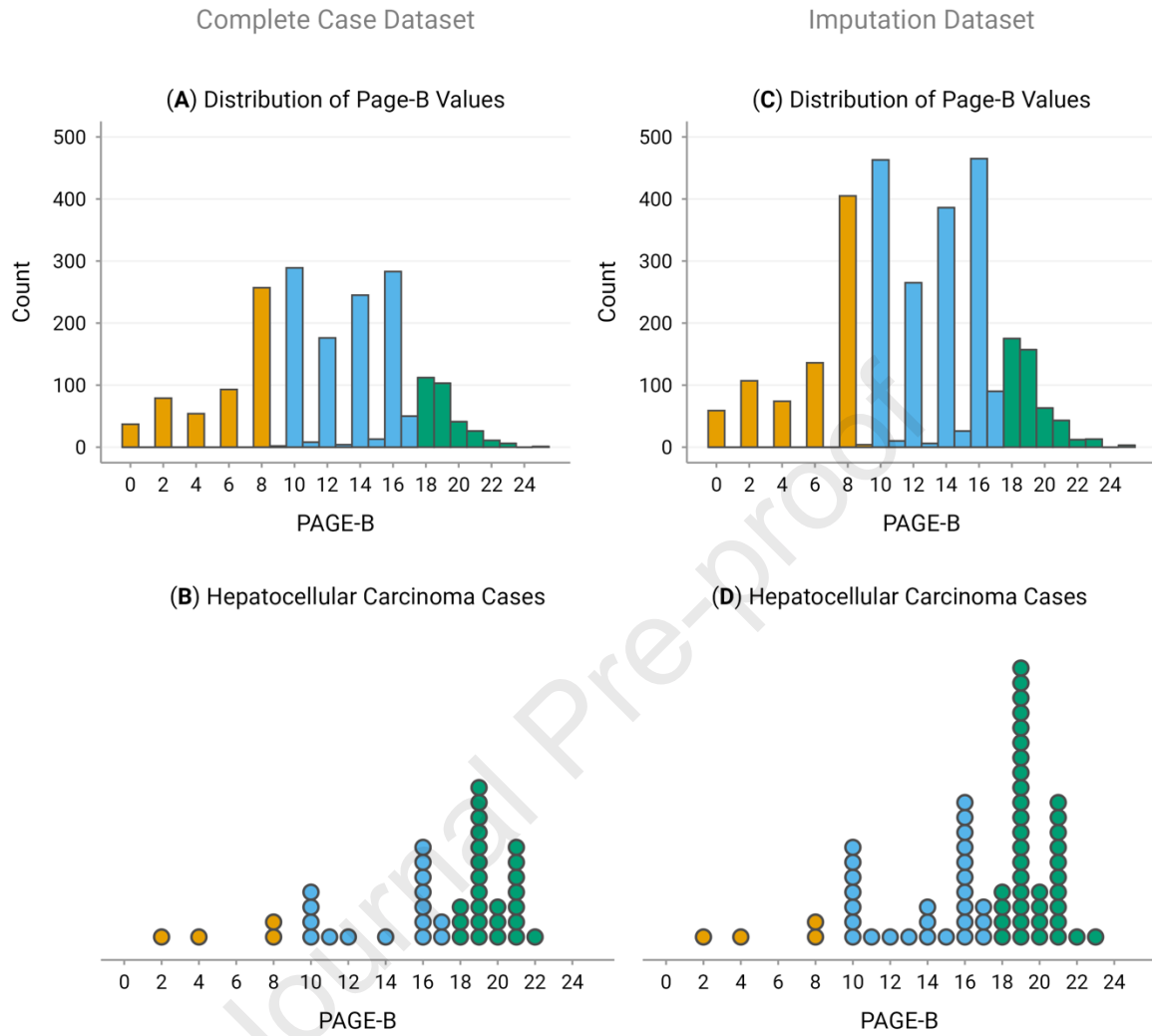
729

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

¹Papatheodoridis 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

731 **FIGURES**

732

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

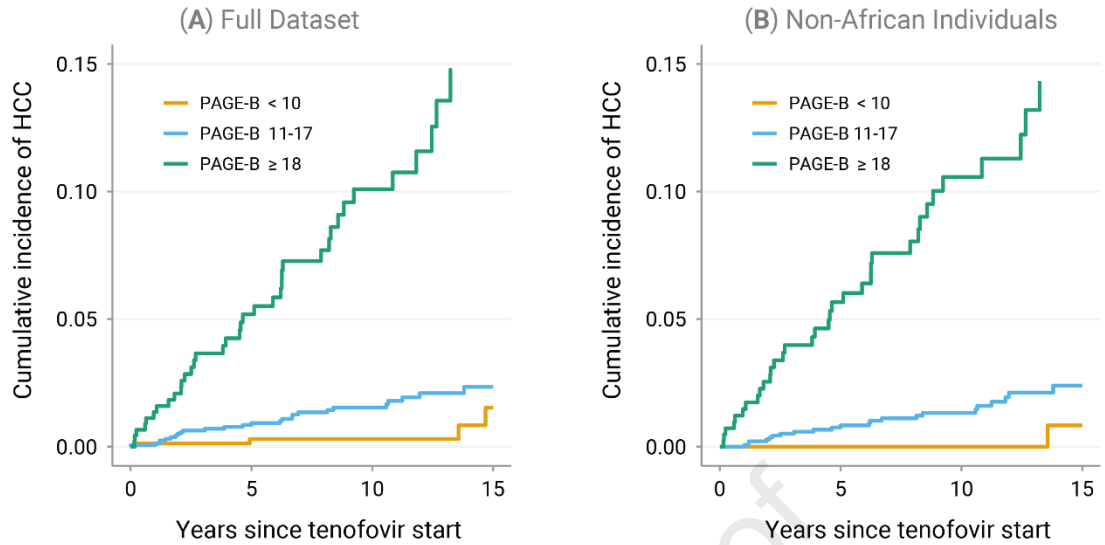
734 Distribution of available PAGE-B scores in the complete case data (A) and after multiple imputation

735 (C). Hepatocellular carcinoma cases by PAGE-B score are represented as dots in the complete case

736 data (B) and after multiple imputation (D).

737

738

**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

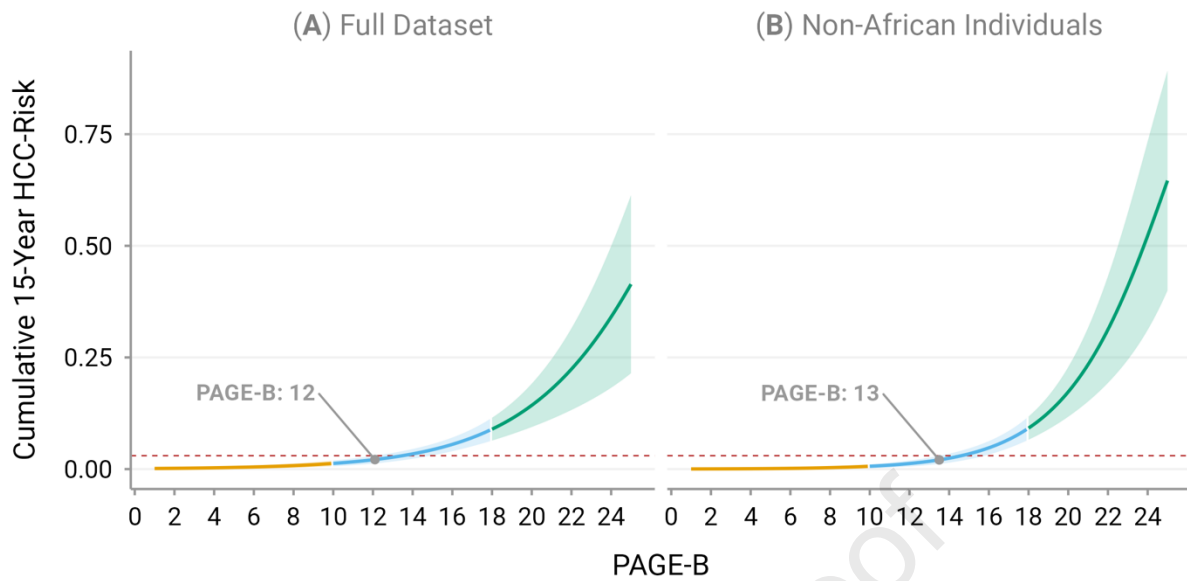
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740 **Figure 2 Cumulative incidence of hepatocellular carcinoma since tenofovir start**

741 The Kaplan-Meier curves show the cumulative incidence of developing hepatocellular carcinoma

742 (HCC) after starting tenofovir in the full study population (**A**, n = 2963) and after excluding individuals743 of African origin (**B**, n = 2438)

744



745

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.

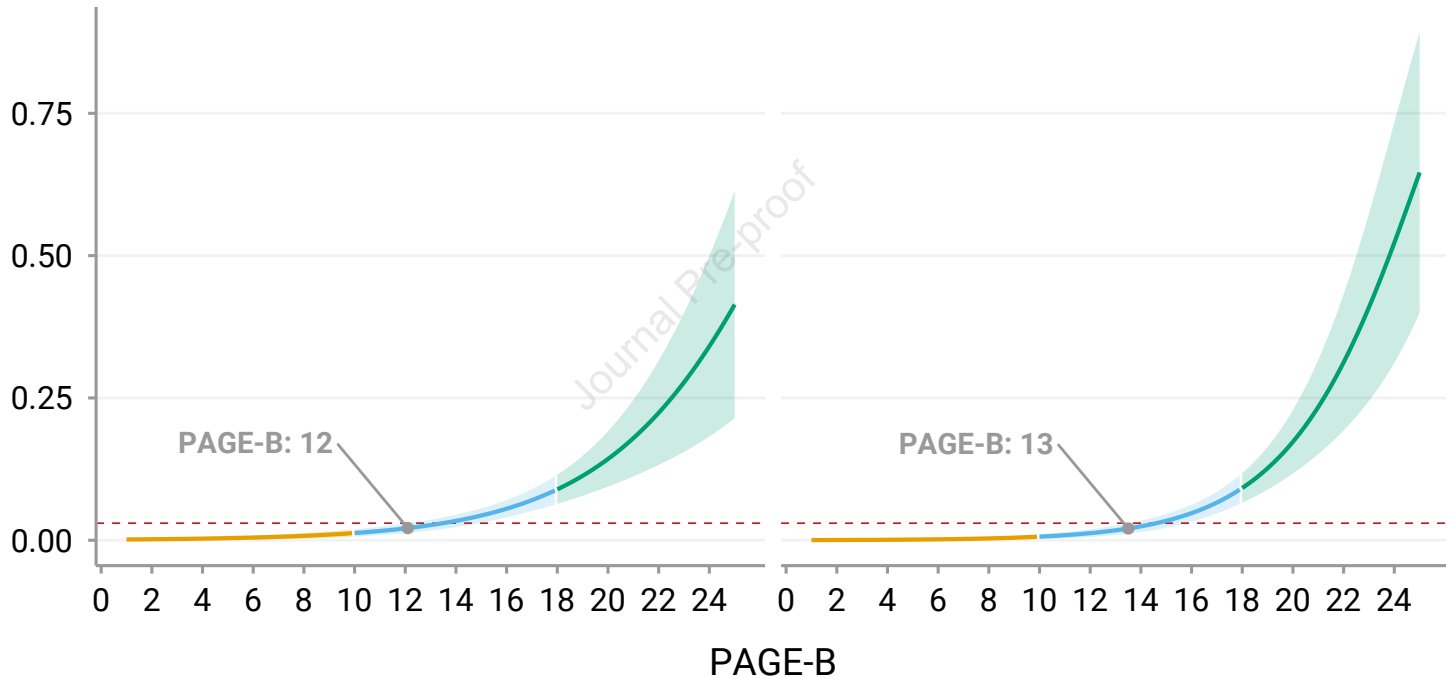
753

(A) Full Dataset

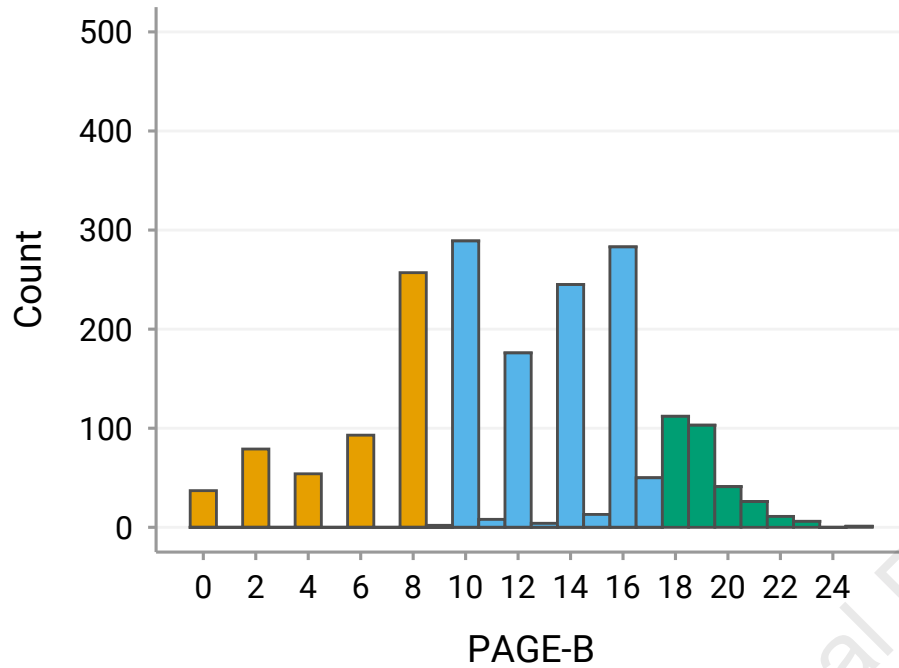
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(B) Non-African Individuals

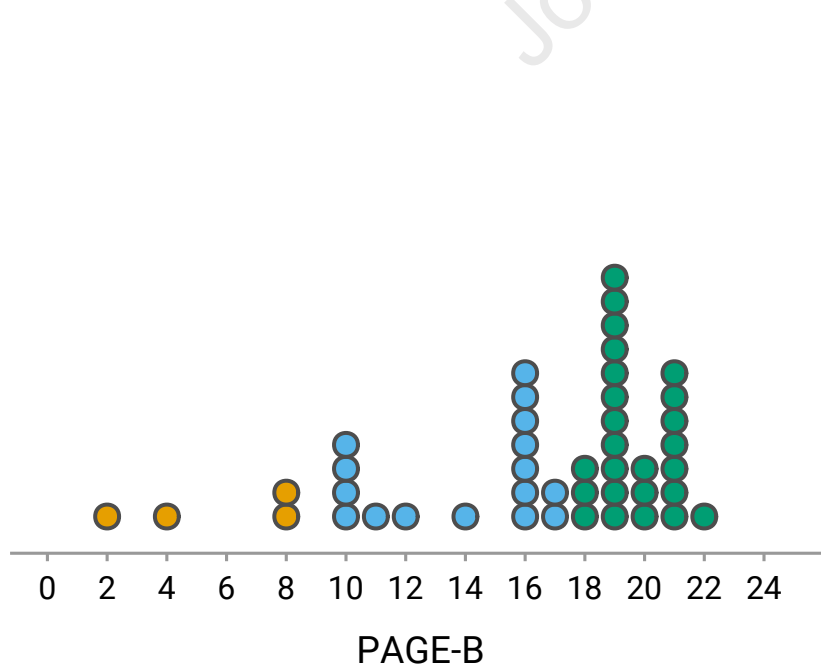
Cumulative 15-Year HCC-Risk



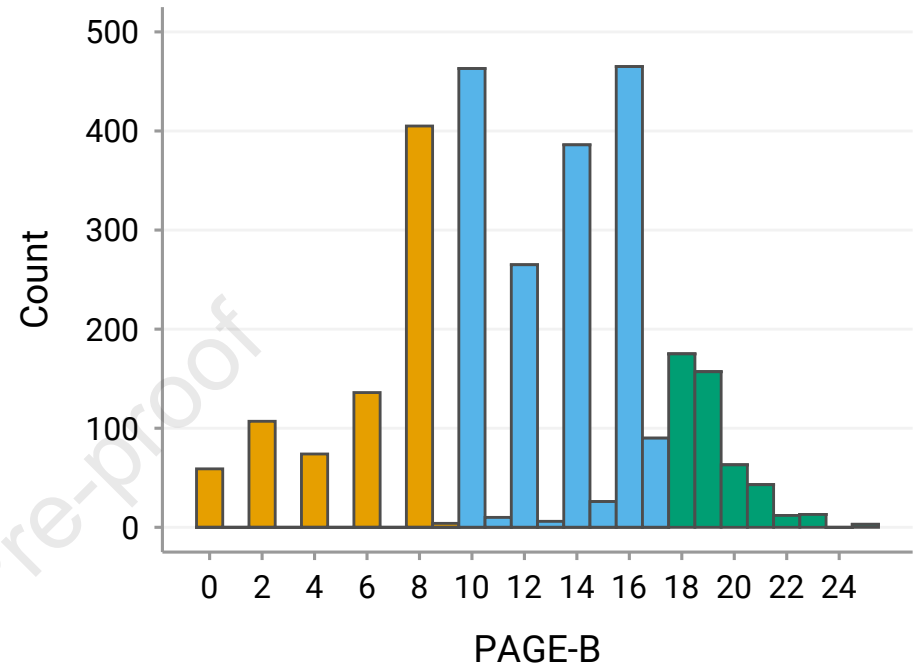
(A) Distribution of Page-B Values



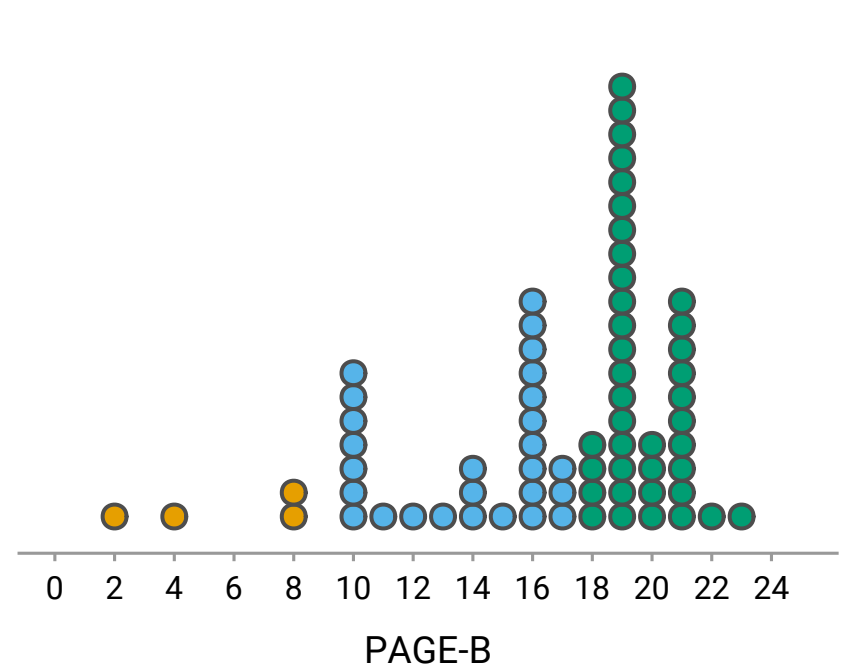
(B) Hepatocellular Carcinoma Cases



(C) Distribution of Page-B Values

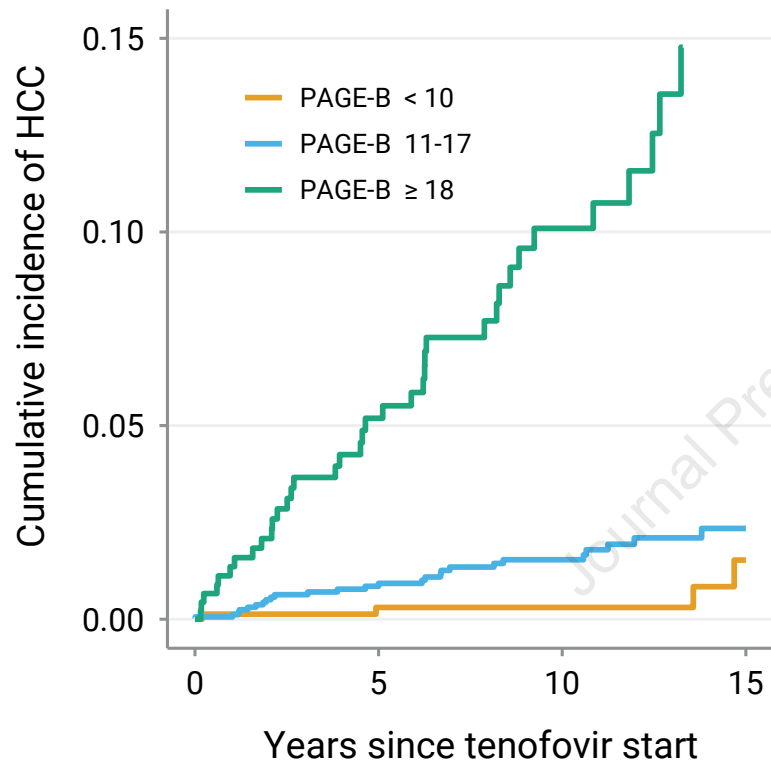
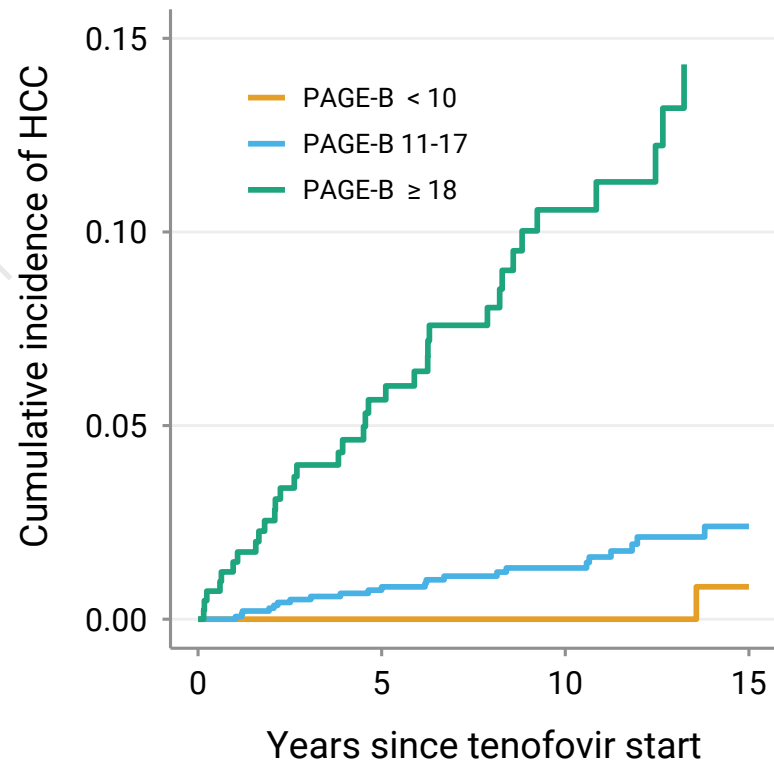


(D) Hepatocellular Carcinoma Cases



(A) Full Dataset

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**(B) Non-African Individuals****No. at risk**

PAGE-B < 10	785	573	358	131
PAGE-B 11-17	1711	1319	863	279
PAGE-B ≥ 18	466	311	175	52

497	364	235	89
1513	1182	781	250
427	281	164	56

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

3

4 Benrard Surial et al.

5

6 **Highlights**

7 • This external validation study included 2963 individuals with HIV/HBV coinfection from 4
8 European cohorts.

9 • Within a median of 9.6 years, 68 patients developed hepatocellular carcinoma (incidence rate
10 2.58/1000 person-years).

11 • Among individuals with HIV/HBV coinfection, PAGE-B (based on age, sex and platelets) showed
12 good model discrimination.

13 • A PAGE-B score <10 had a negative predictive value of 99.4% for developing hepatocellular
14 carcinoma within 5 years.