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Behaviour-Based Predictive Scores of Hepatocellular Carcinoma in People With Chronic Hepatitis B (ANRS CO22 HEPATHER)

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ABSTRACT

Background and Aims: Early assessment of hepatocellular carcinoma (HCC) risk could improve long-term outcomes in people with chronic hepatitis B virus (HBV) infection. Some existing HCC predictive scores are not easily implementable. We developed easy-to-use HCC predictive scores based on behavioural and routine bio-clinical data in people with chronic HBV infection.

Methods: Eight-year follow-up data was analysed from people with chronic HBV infection enrolled in the French ANRS CO22 HEPATHER cohort. Patients were randomly split into two samples (training/testing). A multivariable Cox model for time to HCC was estimated on the training sample. The HCC predictive score was computed by summing the points assigned to model predictors, normalising their coefficients over a 10-year age increment, and rounding to the nearest integer. The Youden index identified the score's optimal risk threshold. Comparisons with existing predictive scores were performed on the testing sample.

Results: In the study population ($N = 4370$; 63% of men; 65% of < 50 years old), 56 HCC cases occurred during 25,900 follow-up person-years. Two HCC predictive scores were defined: SADAPTT (daily soft drink consumption, age, hepatitis Delta infection, unhealthy alcohol use, platelet count, heavy tobacco smoking, and HBV treatment) and ADAPTT (the same predictors except for daily soft drink consumption), with ranges 0–13 and 0–14, respectively, and values ≥ 3 indicating a high HCC risk. Their performances were similar to existing scores.

Abbreviations: (a)HR, (adjusted) hazard ratio; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis Delta virus; HIV, human immunodeficiency virus; MASLD, metabolic dysfunction–associated steatotic liver disease; PAF, population attributable fraction; ROC, receiver operating characteristic.

The ANRS/AFEF HEPATHER Study Group available in Appendix.

Marc Bourlière and Patrizia Carrieri contributed equally to this work.

Conclusions: We developed two effective behaviour-based HCC predictive scores, implementable in many settings, including primary care and decentralised areas. Further studies are needed to validate these scores in other datasets.

1 | Introduction

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, the sixth most prevalent cancer worldwide, and the third most common cause of cancer-related mortality worldwide, with 905,677 new cases and 830,180 deaths in 2020 [1]. Moreover, a 55% increase in HCC incidence is predicted globally by 2040 [2]. HCC mainly affects people chronically infected with hepatitis B or C viruses (HBV or HCV), those with unhealthy alcohol use [3], those exposed to aflatoxin [4], and those with metabolic dysfunction-associated steatotic liver disease (MASLD) [5]. Certain lifestyle behaviours are known to be risk factors for HCC, such as unhealthy alcohol use and tobacco smoking [3, 6]. Others, such as coffee consumption, seem to offer protection from HCC development [7]. Worldwide, 44% of HCC cases are attributable to HBV and 21% to HCV, but these percentages vary geographically [8]. The percentage is especially high in areas where HBV infection is endemic and/or undertreated. Specifically, HBV accounts for more than 50% of HCC cases in Sub-Saharan Africa, and Central, East, and Southeast Asia [8], where HBV prevalence is intermediate to high [9]. Some HBV-related factors are associated with HCC development, such as a positive HBeAg (i.e., the hepatitis B e antigen)—which is an indicator of active viral replication [10]—and HBV DNA levels [11].

Studies have shown that HBV treatment based on potent nucleos(t)ide analogues—which block HBV replication—reduces the risk of HCC in people with chronic HBV infection [12]. Nevertheless, even after HBsAg (i.e., the hepatitis B surface antigen) seroclearance, people with chronic HBV infection still risk developing HCC, as a large number of other risk factors are still present [13]. Approximately 30 predictive scores, specific to either Asian or Caucasian populations, have been developed for people with chronic HBV infection. Almost all of these scores are primarily based on HBV-related clinical and biological data not routinely collected in primary care settings. Only four of them include a behaviour-based predictor, specifically alcohol use [14–17].

Given that early identification of people with chronic HBV infection at risk of HCC can improve their long-term outcomes and potentially reduce the rate of HBV-related HCC [4], we aimed to develop easy-to-use scores, based on behavioural and routine bioclinical data, to predict HCC in people with chronic HBV infection.

2 | Methods

2.1 | Study Design

ANRS CO22 HEPATHER is a French prospective multicentre cohort comprising 21 009 people with HBV and/or HCV infections (not infected with HIV). Enrolment occurred between 2012 and 2018 in 32 expert hepatology centres in France. Written informed consent was obtained from each participant before enrolment. The study protocol (ClinicalTrials.gov: NCT01953458) was developed in accordance with the Declaration of Helsinki and the French law for biomedical research. It was approved by the 'CPP Ile de France 3' ethics committee (Paris, France) and the French Regulatory Authority (ANSM).

2.2 | Data Collection

Socio-demographic, behavioural, and bio-clinical data were collected at the enrolment visit (hereafter, baseline visit) through interviews conducted by the medical staff in participating centres. Bio-clinical data were updated after scheduled annual clinical follow-up examinations.

2.3 | Study Population and Study Period

The study population comprised people with chronic HBV infection, defined as testing HBsAg positive for at least 6 months. In line with the EASL 2017 guidelines, both people with chronic infection status (HBeAg-positive or HBeAg-negative) and those with chronic hepatitis status (HBeAg-positive or HBeAg-negative) were included in the study population, as HCC development is possible in both sub-populations [18, 19]. Patients with current/past HCV infection, a history of HCC, or missing data for potential HCC predictors (see below) were excluded, as were those with no post-baseline follow-up visit.

For each patient, the study period was defined as the period from the baseline visit to the latest news date, with censoring at 8 years of follow-up.

2.4 | Study Outcome

The study outcome was the time between the baseline visit and HCC onset during the study period or censoring, whichever occurred first.

2.5 | Potential HCC Predictors

The sociodemographic characteristics used for score development were sex, age, place of birth, migrant status, employment status, educational level, living with a partner, and living in poverty. Place of birth was categorised as 'Europe/North America', 'Africa/Central-South America', and 'Asia' (including New Zealand). Migrants included individuals born outside of France with at least one non-French parent, with a further distinction made for those originating from regions with high HBV prevalence (> 8%) [9]. Educational level was dichotomised into having at least an upper secondary school diploma or not. Living in poverty was defined as a standard of living below the 2015 French poverty threshold (1015€/month) [20], calculated as the ratio of monthly household income to the number of consumption units.

Summary

- Although numerous studies have shown the impact of lifestyle behaviours on the risk of hepatocellular carcinoma (HCC) in people chronically infected with hepatitis B virus (HBV), behavioural predictors are often omitted from HCC predictive scores in favour of clinical and biological markers; however, the latter are not always easy to evaluate because of a lack of appropriate tools, staff, and expertise.
- This study describes the development and performances of two new scores—SADAPTT and ADAPTT—to predict HCC using only behavioural and routinely collected bio-clinical data.
- The scores' performances are similar to those of existing scores.
- They are simple to calculate and easier to implement in routine care when identifying and monitoring people chronically infected with HBV at risk of HCC.

Behavioural characteristics included past or current unhealthy alcohol use, tobacco smoking, and daily coffee, tea, and soft drink consumption. Unhealthy alcohol use was defined as consuming > 3(2) standard units/day for men (women) [21]. Tobacco smoking was evaluated in pack-years, by multiplying the average number of packs of cigarettes smoked per day by the number of smoking years, with a threshold of 20 pack-years used to identify heavy smokers. Soft drinks included carbonated beverages, both sweetened and unsweetened, whether caffeinated or not.

Routinely collected bio-clinical characteristics included family history of liver disease (i.e., viral hepatitis, HCC or cirrhosis), diabetes status, body mass index (BMI), HBV treatment status, platelet count, hepatitis Delta virus (HDV) infection, and severe liver fibrosis. We focused on overweight, defined according to the World Health Organisation classification ($25 \leq BMI < 30$ and $BMI \geq 30$, respectively). Severe liver fibrosis was defined as an FIB-4 index > 3.25 [22].

All the potential HCC predictors were recorded at baseline.

2.6 | Statistical Analyses

The Chi-squared test was used to compare the characteristics of individuals included in the study population with those excluded because of missing data or zero follow-up time.

The study population was randomly split into a training sample (70%) and a testing sample (30%) in order to build and validate, respectively, the prediction model. The Chi-squared test compared the characteristics of patients in both samples.

Factors associated with HCC risk were identified using Cox proportional hazards models on the training sample. Two models were built: the first used all potential predictors; the second omitted coffee, tea, and soft drink consumption, as these behaviours are not systematically collected in observational settings. Variables were first tested in univariable analyses; those with a p-value < 0.20 (Wald test) were considered eligible for the multivariable analysis. The final multivariable models were built using a backward stepwise selection procedure with a significance level of 5%. The robust sandwich estimator was used to estimate the variance of model coefficients. Population attributable fractions (PAF) were estimated for behavioural predictors in the two models to quantify the proportion of HCC cases attributable to each behaviour.

Two predictive scores were computed by summing points assigned to predictors in the two final multivariable models. These points were calculated by dividing each coefficient by that of a 10-year age increment (so that a 10-year increment increased the score by 1 point), then rounding to the nearest integer. Time-dependent receiver operating characteristic (ROC) curves were estimated on the training sample for each score using the kernel nearest-neighbour estimator of the conditional survival function [23]. The area under the ROC curve (AUROC) was calculated at 8 years on 1000 bootstrap resamples to evaluate score performances, and an optimal risk threshold was determined for each score using the Youden index. Discrimination performances of the final models were assessed on the training sample computing Harrell's C-index [24], Gönen and Heller's concordance coefficient [25] and Royston and Sauerbrei R^2_D statistic [26]. The discrimination performances of the two predictive scores were estimated on the testing sample by plotting Kaplan–Meier curves stratified using the risk threshold and computing the log-rank test. Calibration slopes were calculated using 1000 bootstrap resamples to evaluate the spread of estimated HCC risk. Time-dependent ROC curves were plotted on the testing sample, and AUROC at 3, 5 and 8 years on 1000 bootstrap resamples was used to compare the performances of the two new HCC predictive scores with those of existing scores.

Three sensitivity analyses were also performed. First, we replaced HBV treatment and platelet count with an indicator of severe liver fibrosis based on the FIB-4 index. This change was made to take into account areas where a physician's decision to initiate HBV treatment cannot be assessed due to a lack of data, especially in settings where no HBV DNA quantification is available. Second, we built our two main predictive scores and the two scores with FIB-4 a second time, including only participants with chronic hepatitis status (HBeAg-positive or HBeAg-negative) and excluding individuals with chronic infection status from the study population. Third, we built our four predictive scores a third time by excluding participants who developed HCC during the first year of follow-up in order to exclude potential pre-existing cases of HCC not diagnosed at baseline.

All analyses were performed with Stata version 17.0 for Windows software (StataCorp LP, College Station, TX).

3 | Results

3.1 | Study Population Characteristics

The selection and characteristics of the study population are presented in Figure 1 and Table S1, respectively.

The study population included 4370 individuals, with a median follow-up time of 6.4 years [interquartile range: 5.0–7.3]. Fifty-six HCC cases occurred during the eight-year study period, corresponding to 25,900 person-years. Most of the study participants were male (63.0%), under 50 years old (65.0%), and had chronic hepatitis B status (73%). The majority of participants were migrants (68.5%), 43% being born in Africa and 15% in Asia. No significant differences were found in participants' characteristics between the training ($N = 3056$) and the testing ($N = 1314$) samples (Table S1).

Table S2 highlights differences between the 1472 excluded participants and the 4370 participants included in the study population.

3.2 | Computation of HCC Predictive Scores

The results from the univariable analyses are provided in Table S3. In the first final multivariable model, which included all eligible variables, older age, HBV treatment, low platelet count, and HDV infection were associated with a higher risk of HCC (Table 1). Heavy smoking (adjusted hazard ratio [95% confidence interval]: 2.40 [1.23–4.66], $p = 0.010$) was associated with a near twofold higher HCC risk, whereas past or current unhealthy alcohol use (2.92 [1.35–6.34], $p = 0.007$) and daily soft drink consumption (3.18 [1.44–7.02], $p = 0.004$) were associated with almost threefold higher HCC risk.

The first predictive score (i.e. SADAPTT)—based on daily soft drink consumption, age, hepatitis Delta status, unhealthy alcohol use, platelet count, heavy tobacco smoking, and HBV treatment status—ranged from 0 to 13. The threshold to identify people at high risk of developing HCC was ≥ 3 (Table 2).

Similar results were found in the second multivariable model, which was not adjusted for daily soft drink consumption (Table 1). The second score (i.e., ADAPTT)—based on age, hepatitis Delta status, unhealthy alcohol use, platelet count, heavy tobacco smoking, and HBV treatment status—ranged from 0 to 14, with a threshold of ≥ 3 indicating high risk.

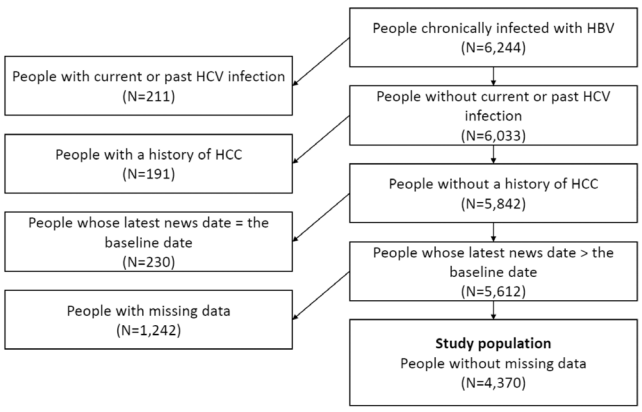

FIGURE 1 | Selection of the study population (ANRS CO22 HEPATHER). HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

In both multivariable models, according to the PAF values, heavy smoking and past or current unhealthy alcohol use accounted for 19% and 13.5% of HCC cases, respectively. In the first model, daily soft drink consumption accounted for 19.3% of HCC cases (Table 1).

The first sensitivity analysis replacing HBV treatment with severe liver fibrosis assessment showed similar results, with the addition of male sex in both predictive scores (Table S4). Results did not change in the two other sensitivity analyses when omitting individuals with chronic infection status and those who developed HCC during the first year of follow-up (Tables S5 and S6).

3.3 | Discrimination and Calibration

Both predictive models exhibited good discrimination performances on the training sample, as indicated by Harrell's C-index and Gönen and Heller's coefficient (Table 2). Additionally, the Royston and Sauerbrei R_D^2 was acceptable for both predictive models. The log-rank test yielded significant p-values for both predictive scores on the testing sample ($p = 0.002$ for SADAPTT; $p < 0.001$ for ADAPTT). Kaplan–Meier curves for each score, stratified using its specific threshold, are presented for the testing sample in Figure 2. Calibration slopes were acceptable, with values of 0.885 for SADAPTT and 1.090 for ADAPTT (Table 3).

The AUROC at 8 years for both scores on the testing sample is presented in Table 2. Good performances were found for both scores, with an AUROC of 0.79 for SADAPTT and 0.84 for ADAPTT.

Similar results were found in the three sensitivity analyses; however, the predictive scores built using the FIB-4 index exhibited lower performances than ADAPTT and SADAPTT scores (Tables S4–S6).

3.4 | Comparison With Other Existing Scores

The AUROC for the two new scores and for existing HCC predictive scores at 3, 5, and 8 years on the testing sample are presented in Table 3. The ADAPTT score had a higher AUROC than the SADAPTT score at each of the three time points. There were no differences between the performances of the two new scores and the other scores tested, except for AGED, which had a lower AUROC at all three time points. When observing the evolution of the AUROC over time, the performances of the SADAPTT and ADAPTT scores were similar to or superior to that of other scores after 3 years (Figure S1).

4 | Discussion

We developed two easy-to-use scores calculated from behavioural and routinely-collected bio-clinical data to predict the risk of HCC in people with chronic HBV infection. The scores were SADAPTT (daily soft drink consumption, age, HDV infection, unhealthy alcohol use, platelet count, heavy tobacco

TABLE 1 | Factors associated with HCC risk in the training sample, multivariable Cox proportional hazards models (ANRS CO22 HEPATHER, $N = 3056$).

	SADAPTT model				ADAPTT model			
	aHR [95% CI]	***p***	***β***	**PAF (%)**	**aHR [95% CI]**	***p***	***β***	**PAF (%)**
Age (per 10-year increment)[a]	2.05 [1.45–2.90]	< 0.001	0.718		1.79 [1.30–2.46]	< 0.001	0.582	
Past or current unhealthy alcohol use[b]								
No (ref.)	1				1			
Yes	2.92 [1.35–6.34]	0.007	1.072	13.5	2.89 [1.33–6.27]	0.007	1.060	13.4
Tobacco smoking[c]								
< 20 pack-years (ref.)	1				1			
≥ 20 pack-years	2.40 [1.23–4.66]	0.010	0.874	19.4	2.38 [1.22–4.65]	0.011	0.868	19.3
Daily soft drink consumption								
No (ref.)	1							
Yes	3.18 [1.44–7.02]	0.004	1.157	19.3	Not included			
Receiving HBV treatment								
No (ref.)	1				1			
Yes	2.96 [1.26–6.96]	0.013	1.085		3.02 [1.29–7.08]	0.011	1.104	
Platelet count								
$\geq 200 \times 10^9$/L (ref.)	1				1			
$< 200 \times 10^9$/L	2.53 [1.28–4.99]	0.007	0.929		2.55 [1.29–5.05]	0.007	0.936	
HDV infection								
No (ref.)	1				1			
Yes	4.79 [1.73–13.24]	0.003	1.566		4.90 [1.85–12.96]	0.001	1.589	

Abbreviations: β, regression coefficient; aHR, adjusted hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis Delta virus; PAF, population attributable fraction.

[a]We used in the models the 4-category age variable as a continuous variable. We divided the β coefficient of each variable by the β coefficient of the 10-year age increment, then rounded to the nearest integer.

[b]Unhealthy alcohol use was defined as consuming > 2(3) standard units/day for women (men), respectively.

[c]Pack-years were calculated by multiplying the average number of packs of cigarettes smoked per day by the number of smoking years.

smoking, and HBV treatment) and ADAPTT (with daily soft drink consumption excluded), with ranges 0–13 and 0–14, respectively, and values ≥ 3 indicating a high HCC risk.

Both scores can be implemented in various settings, including primary care and decentralised areas. They have similar predictive performances to existing scores, most of which focus on bio-clinical predictors (only four existing scores include behaviours, specifically alcohol use). To our knowledge, this is the first study to develop predictive scores of HCC that extensively rely on behaviours. Moreover, unlike existing scores, the scores developed in this study take HDV infection into account. Additionally, they use only two easily available bio-clinical variables, HBV treatment status and low platelet count, which are proxies for advanced liver disease. Taking these strengths together, the two new scores represent a substantial advancement over existing options and may simplify early detection of people with chronic HBV infection at risk of HCC. Two alternative scores were also developed, replacing HBV treatment with a severe liver fibrosis assessment using the FIB-4 index. The choice to use the ADAPTT or SADAPTT score, or their alternative scores based on the FIB-4 index instead of HBV treatment, will depend on the variables available at the time the score is applied, thus broadening the range of possible uses.

The association between unhealthy alcohol use and HCC risk, confirmed in our study, has been consistently shown in people with chronic HBV infection and in the general population [3]. Worldwide, unhealthy alcohol use accounts for approximately 26% of HCC cases [8]. Although an interaction between hepatitis B and unhealthy alcohol use has already been demonstrated [39], the proportion of HCC cases attributable to unhealthy alcohol use in our results was half that observed in the general population, suggesting the competing role of other risk factors in accelerating HCC development. Unhealthy alcohol use is the

TABLE 2 | Calculation and performances of the SADAPTT and ADAPTT scores predicting HCC (ANRS CO22 HEPATHER, $N = 4370$).

Score calculation	SADAPTT score	ADAPTT score
Daily soft drink consumption	+2	
Aged 50–59 years	+1	+1
Aged 60–69 years	+2	+2
Aged ≥ 70 years	+3	+3
HDV infection	+2	+3
Past or current unhealthy alcohol use[a]	+2	+2
Platelet count $< 200 \times 10^9$/L	+1	+2
Tobacco smoking ≥ 20 pack-years[b]	+1	+2
Receiving HBV treatment	+2	+2
Range	0–13	0–14
Risk threshold	≥ 3	≥ 3
Model performances		
Harrell's C-index	0.858	0.847
Gönen and Heller's coefficient	0.759	0.743
Royston and Sauerbrei R^2_D	0.550	0.518
Score performances		
On the training sample ($N = 3056$)		
AUROC [95% CI]	0.81 [0.76–0.86]	0.82 [0.76–0.87]
Log rank test p	< 0.001	< 0.001
On the testing sample ($N = 1314$)		
Calibration slope	0.885	1.090
AUROC [95% CI]	0.79 [0.67–0.90]	0.84 [0.74–0.94]
Log rank test p	0.002	< 0.001

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis Delta virus.
[a]Unhealthy alcohol use was defined as consuming > 2(3) standard units/day for women(men), respectively.
[b]Pack-years were calculated by multiplying the average number of packs of cigarettes smoked per day by the number of smoking years.

only behavioural factor recurrently included in HCC predictive scores (the existing scores and our scores). Four predictive scores include alcohol use: REAL-B [17], ACCESS-HCC [16], IPM [15] and NRHC [14]. They have all been validated in Asian populations; REAL-B was also validated in Caucasian populations. Interestingly, the points assigned to alcohol use in these four scores are similar to those estimated in our study.

Our findings indicate that one in five HCC cases could be avoided if patients were not heavy smokers (≥ 20 pack-years). This strongly supports the idea that tobacco smoking may have detrimental effects on the liver of people with chronic HBV infection, leading to a higher risk of HCC development. Our results are consistent with those published by Wang et al. who found that among people with chronic HBV infection, smokers had a higher risk of developing HCC than non-smokers [40]. Furthermore, in that study, the risk of HCC increased as the number of pack-years of smoking increased, and tobacco smoking was also associated with increased HBV viral load and alanine aminotransferase levels [40], suggesting a mediating effect on HCC development. Elsewhere, an interaction effect between HBV infection and tobacco smoking has also been found, with the estimated relative risk of HCC varying from 15.8 for non-smokers with chronic HBV infection to 21.6 for smokers with chronic HBV infection, compared to HBV-negative non-smokers [41]. Moreover, the risk of HCC increases with the duration of smoking [42]. Despite the known effect of tobacco smoking on HCC risk, it has never been included in HCC predictive scores before our study. Our results suggest that in terms of HCC prevention, a history of smoking and smoking habits should be systematically monitored in the clinical follow-up of people with chronic HBV infection.

Another noteworthy result of our study was the link between daily soft drink consumption and HCC risk. Several hypotheses may explain this result. First, soft drink consumption is associated with both prevalent MASLD—as shown in the systematic review and meta-analysis published by Wijarnpreecha et al. [43]–and incident MASLD, with a dose–response relationship [44]. Moreover, daily soft drink consumption is significantly associated with prevalent MASLD in the general population [45]. MASLD is a significant risk factor for HCC in the general population [46], with a possibly higher burden in people with chronic HBV infection [47]. Second, daily soft drink consumption may increase dietary glycaemic load, leading to igher HCC risk in people with chronic HBV infection [48] and in the general population [49]. Moreover, this consumption could also be a proxy for unhealthy dietary habits, which are under-measured in many cohorts of people with chronic HBV infection. Other studies have highlighted a protective effect of consuming fruits, white meats, milk, and yoghurt on the risk of HCC [50] and an inverse association between adherence to the Mediterranean diet and HCC risk [51]. We recommend including an assessment of soft drink consumption in the follow-up of people with chronic HBV infection, as it may be an indirect indicator of unhealthy dietary habits.

Finally, our models show that HDV infection fosters HCC development. People with HDV infection are more likely to experience liver-related complications. Indeed, HDV infection accounts for 20% of HCC cases in people with chronic HBV infection [52]. Results from a number of studies comparing HCC rates between patients mono-infected with HBV and those also infected with HDV highlighted a three- to six-fold higher risk of HCC among the latter population [53, 54]. Given the increasing availability of HDV treatment, HDV screening should be systematically performed in people with chronic HBV infection to better monitor HCC risk.

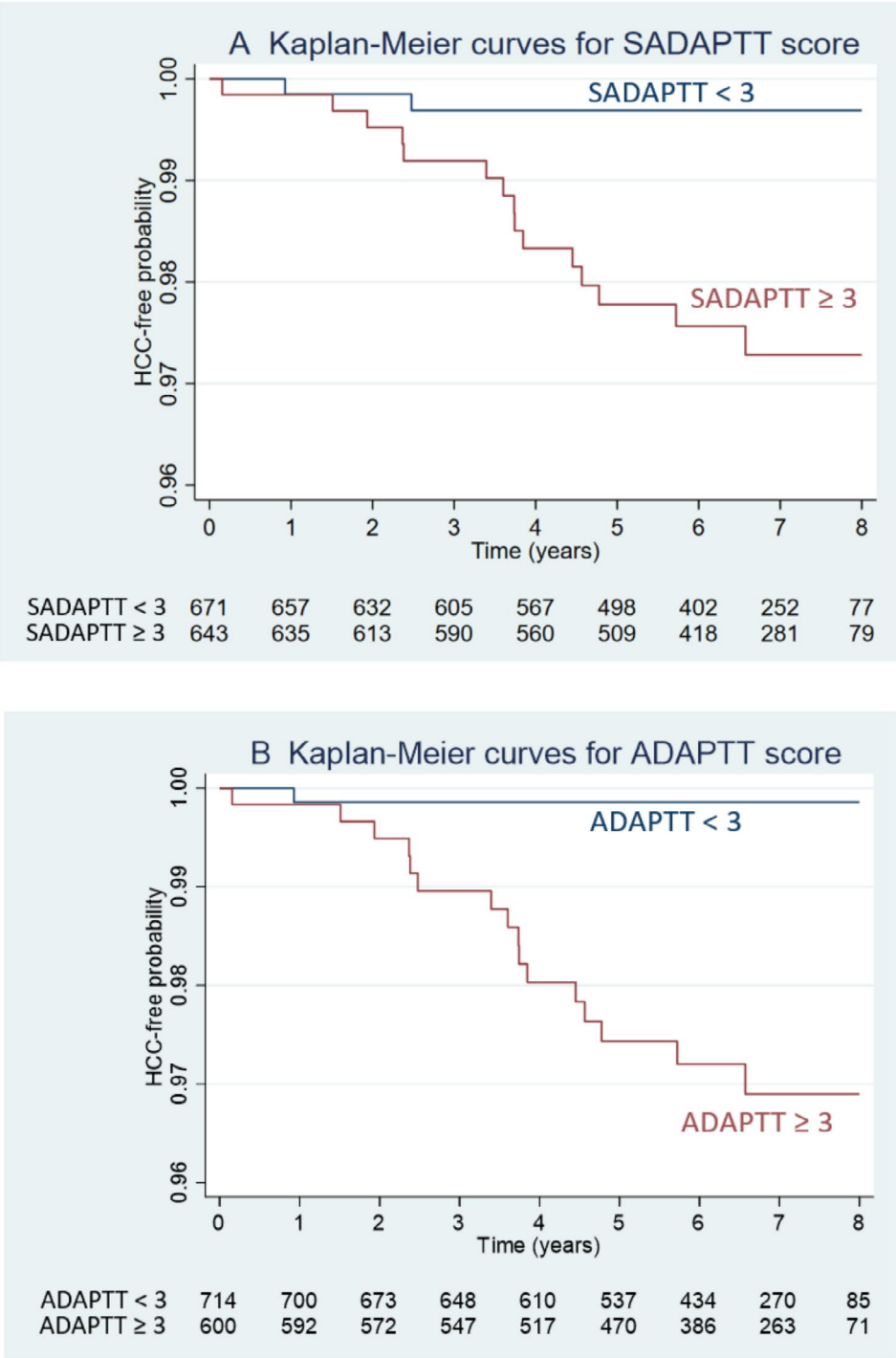

FIGURE 2 | Kaplan–Meier curves for the SADAPTT and ADAPTT scores on the testing sample, stratified by each score's specific threshold (ANRS CO22 HEPATHER, $N = 1314$).

4.1 | Study Strengths and Limitations

This study has several strengths. First, easy-to-collect behavioural data were integrated into two novel HCC risk predictive scores, thanks to the collection of clinical data throughout the ANRS CO22 HEPATHER cohort follow-up and the collection of socio-behavioural data at enrolment. Second, the large cohort sample size ensured good statistical power. A third strength is the diversity of patients included in terms of their geographic origin. This diversity ensured that the two scores developed are not limited to a specific ethnicity; consequently, they can be used across various world regions. In addition, since the scores developed are based solely on data collected during routine care, they can be used in multiple contexts, including primary care and decentralised areas.

Some limitations must be acknowledged. First, the classification of soft drinks according to their sugar or caffeine content was not available in the cohort. Second, certain behaviours, such

TABLE 3 | Performances comparison of SADAPTT and ADAPTT scores with existing scores predicting HCC on the testing sample using 1000 bootstrap resamples (ANRS CO22 HEPATHER, $N = 1314$).

	Testing sample	3 years	5 years	8 years
Scores	***N***	**AUROC [95% CI]**	**AUROC [95% CI]**	**AUROC [95% CI]**
SADAPTT	1314	0.63 [0.36–0.89]	0.77 [0.64–0.90]	0.79 [0.67–0.90]
ADAPTT	1314	0.71 [0.45–0.97]	0.83 [0.71–0.95]	0.84 [0.74–0.94]
mPAGE-B [27]	896	0.76 [0.61–0.90]	0.82 [0.73–0.91]	0.81 [0.73–0.90]
HCC-RESCUE [28]	1314	0.77 [0.57–0.97]	0.84 [0.75–0.94]	0.84 [0.76–0.93]
CAMD [29]	1314	0.70 [0.55–0.84]	0.80 [0.72–0.87]	0.79 [0.70–0.87]
NRHC1 [14]	1198	0.65 [0.41–0.90]	0.79 [0.66–0.90]	0.79 [0.69–0.90]
REAL-B [17]	974	0.63 [0.41–0.86]	0.72 [0.61–0.83]	0.71 [0.59–0.82]
THRI [30]	1314	0.64 [0.41–0.88]	0.72 [0.60–0.83]	0.73 [0.62–0.84]
aMAP [31]	869	0.76 [0.57–0.95]	0.81 [0.70–0.92]	0.83 [0.73–0.93]
REACH-B [32]	1119	0.64 [0.44–0.84]	0.75 [0.64–0.86]	0.77 [0.67–0.87]
PAGE-B [33]	1314	0.68 [0.46–0.89]	0.76 [0.65–0.87]	0.75 [0.64–0.86]
AASL [34]	896	0.73 [0.59–0.87]	0.77 [0.69–0.86]	0.75 [0.67–0.84]
NRHC2 [14]	1174	0.59 [0.36–0.82]	0.70 [0.59–0.81]	0.74 [0.63–0.84]
APA-B [35]	974	0.62 [0.47–0.77]	0.69 [0.61–0.77]	0.69 [0.62–0.75]
CU-HCC [36]	800	0.73 [0.60–0.85]	0.73 [0.64–0.82]	0.67 [0.56–0.79]
IPM [15]	964	0.66 [0.47–0.84]	0.62 [0.52–0.73]	0.66 [0.55–0.77]
RWS-HCC [37]	974	0.50 [0.25–0.76]	0.61 [0.46–0.77]	0.64 [0.50–0.77]
AGED [38]	1139	0.47 [0.24–0.70]	0.51 [0.36–0.66]	0.53 [0.39–0.67]

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

as alcohol consumption, may have been under-reported due to social desirability bias. This may have led to a unidirectional misclassification (e.g. alcohol users classified as abstinent), thereby weakening the association between specific behaviours and HCC risk. Having said that, our results are consistent with the international literature. Third, the ethnicity of the participants was not available in the HEPATHER cohort; therefore, the place of birth was used instead in this study. Fourth, we could not compute all existing predictive HCC scores for comparison, as certain biological and clinical measures were not available in our study (e.g. core promoter mutations) and because for some scores, details concerning how they are calculated were missing. Fifth, other dietary data were not collected in the cohort, including exposure to aflatoxin, which is a known factor for HCC development. Finally, the two novel scores need to be validated in other datasets and adapted to specific populations. We plan to do this in a second phase of our research.

5 | Conclusion

In existing predictive HCC risk scores, behavioural characteristics are all too often ignored in favour of bio-clinical characteristics. However, many of the latter are not routinely collected. We developed two easy-to-use HCC predictive scores for people with chronic HBV infection, taking into account alcohol use, tobacco smoking, and soft drink consumption. Their performance is similar to existing scores. While further validation on other datasets is needed, these novel predictive scores can be implemented in multiple settings, including primary care and decentralised areas, and may facilitate follow-up of people with chronic HBV infection at risk of HCC.

Author Contributions

M.B., P.C., C.R.: conceptualisation. C.R., P.C., M.B., C.P.: methodology. P.C., M.B., C.P., F.M.: validation. V.D.B.: data curation. C.R.: formal analysis. F.C., L.P., T.A., M.B., and the ANRS/AFEF HEPATHER study group: investigation. F.C., T.A.: project administration and funding acquisition. C.R., M.B. and P.C.: writing of the first draft of the manuscript. All authors reviewed the paper. All authors approved the final version of the manuscript, including the authorship list.

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Ethics Statement

The study protocol (ClinicalTrials.gov: NCT01953458) was developed in accordance with the Declaration of Helsinki and the French law for biomedical research. It was approved by the 'CPP Ile de France 3' ethics committee (Paris, France) and the French National Agency for the Safety of Medicines and Health Products (ANSM).

Consent

Written informed consent was obtained from each participant before enrollment into the cohort.

Conflicts of Interest

L.P. reports non-financial support from Gilead Sciences, Abbvie, Novo Nordisk, and MSD, not related to this study. T.A. is a speaker and investigator for Antios Therapeutics, AbbVie, Eiger Bio-Pharmaceuticals, Enyo Pharma, Gilead Sciences, GSK, Janssen, Vir Biotechnology, and Roche. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available upon request from the scientific committee of the ANRS CO22 HEPATHER cohort (contact: fabrice.carrat@iplesp.upmc.fr). The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix

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