Research Article
Viral Hepatitis

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Hepatocellular carcinoma risk in sub-Saharan African and Afro-Surinamese individuals with chronic hepatitis B living in Europe

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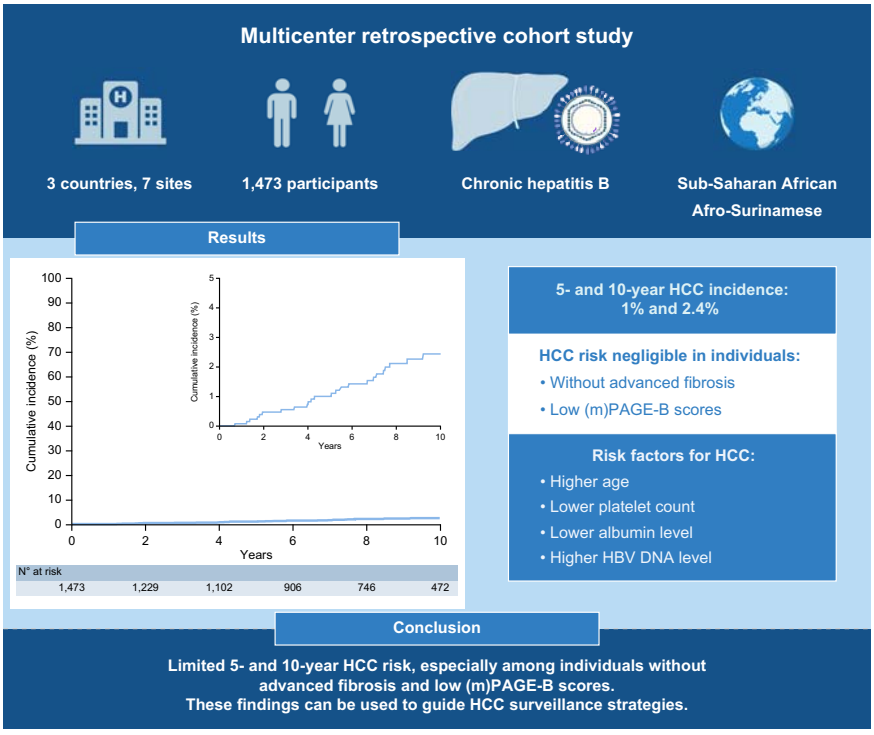
Graphical abstract



Highlights

- We found a 5- and 10-year cumulative HCC incidence of 1% and 2.4%.
- Older age, higher HBV DNA levels, lower platelet count, and lower albumin levels increased the risk of HCC.
- The 10-year HCC risk was negligible for individuals without advanced fibrosis at baseline.
- The 10-year HCC risk was negligible for individuals with low baseline (m)PAGE-B scores.
- These findings suggest opportunities for individualized HCC surveillance strategies.

Impact and implications

Sub-Saharan African ethnicity has been associated with a higher risk of hepatocellular carcinoma among individuals with chronic hepatitis B. In this international multicenter cohort study of sub-Saharan African and Afro-Surinamese individuals living with chronic hepatitis B in Europe, we observed 5- and 10-year cumulative incidences of hepatocellular carcinoma of 1% and 2.4%, respectively. The risk was negligible among individuals without advanced fibrosis and a low baseline (m)PAGE-B score. These findings can be used to guide HCC surveillance strategies in this population.

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Hepatocellular carcinoma risk in sub-Saharan African and Afro-Surinamese individuals with chronic hepatitis B living in Europe

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Background & Aims: Sub-Saharan African (SSA) ethnicity has been associated with a higher risk of hepatocellular carcinoma (HCC) among individuals with chronic hepatitis B in cross-sectional studies. However, the incidence of HCC and performance of HCC risk scores in this population are unknown.
Methods: We conducted an international multicenter retrospective cohort study of all consecutive HBV-monoinfected individuals of SSA or Afro-Surinamese (AS) ethnicity managed at sites in the Netherlands, the United Kingdom and Spain. We assessed the 5- and 10-year cumulative incidences of HCC in the overall study population, among different clinically relevant subgroups and across (m)PAGE-B subgroups. Next, we explored the different risk factors for HCC.
Results: During a median follow-up of 8 years, we analyzed 1,473 individuals of whom 34 developed HCC. The 5- and 10-year cumulative incidences of HCC were 1% and 2.4%. The 10-year cumulative incidence of HCC was 0.7% among individuals without advanced fibrosis at baseline, compared to 12.1% among individuals with advanced fibrosis (p <0.001). Higher age (adjusted hazard ratio [aHR] 1.05), lower platelet count (aHR 0.98), lower albumin level (aHR 0.90) and higher HBV DNA log10 (aHR 1.21) were significantly associated with HCC development. The 10-year cumulative incidence of HCC was 0.5% among individuals with a low PAGE-B score, compared to 2.9% in the intermediate- and 15.9% in the high-risk groups (p <0.001).
Conclusions: In this unique international multicenter cohort of SSA and AS individuals with chronic hepatitis B, we observed 5- and 10-year cumulative HCC risks of 1% and 2.4%, respectively. The risk of HCC was negligible for individuals without advanced fibrosis at baseline, and among individuals with low baseline (m)PAGE-B scores. These findings can be used to guide HCC surveillance strategies.

Introduction

Hepatocellular carcinoma (HCC) is a severe complication of chronic hepatitis B (CHB). Worldwide over 296 million people are chronically infected with hepatitis B and are therefore at risk for HCC development.[1] Ethnicity has been identified as an important risk factor for HCC, with birth in sub-Saharan Africa (SSA) being associated with an increased risk of (early onset) HCC.[2] The increased risk of HCC development may be due to genetic predisposition, HBV-related factors such as viral load and HBV genotype, or co-existing liver disease due to iron overload or alcohol-related liver disease, alone or in combination with metabolic dysfunction-associated fatty liver disease, which is increasingly prevalent.[3,4] Moreover, aflatoxin exposure is a specific risk factor for HCC development in the SSA region, the effect of which might be attenuated among individuals currently residing in Europe where exposure is absent. Aflatoxins are primarily produced by Aspergillus species which colonize a wide variety of foods such as nuts and dried fruits. Aflatoxin exposure is linked to a specific mutation in the tumor suppressor gene p53 which may promote carcinogenesis.[5] There is evidence suggesting that the frequency of the p53 249^{ser} mutation in HCC correlates with the level of exposure to aflatoxin.[6]

Based on the excess HCC risk reported in previous (case-control) studies, enrolment in HCC surveillance is widely advocated. Unfortunately, there is no clear consensus on which (non-cirrhotic) individuals should undergo surveillance. For

Keywords: Sub-Sahara Africa; Suriname; CHB; HCC; PAGE-B score; modified PAGE-B score; surveillance; advanced fibrosis.
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example, AASLD (the American Association for the Study of Liver Diseases) recommends starting HCC surveillance at the age of 40 years for African-Americans with CHB, APASL (the Asian Pacific Association for the Study of the Liver) recommends initiation of HCC surveillance from age 20 for CHB individuals born in SSA, while the EASL-EORTC (European Association for the Study of the Liver – European Organisation for Research and Treatment of Cancer) guideline notes the increased HCC risk in this population but does not specify how to approach surveillance.[7–10] Dutch guidelines also suggest HCC surveilance from age 20 for individuals from SSA which also includes the Afro-Surinamese (AS), a large ethnic group in the Netherlands with a SSA background.[10] Recently, several groups have used various combinations of patient characteristics and biomarkers to stratify HCC risk among Caucasian and Asian individuals. The most commonly used risk score for predicting HCC is the PAGE-B score which is based on platelet count, age and sex.[11] Subsequently, a modified PAGE-B risk score was proposed by adding albumin.[12] The performance of these risk scores among patients with CHB born in SSA is unknown, and stratification of HCC risk in this population is a major unmet clinical need.[13]

Therefore, this study aimed to investigate the incidence of HCC in SSA and AS individuals with CHB residing in Europe. Secondly, we investigated the risk factors for HCC development and the performance of the PAGE-B and modified PAGE-B risk scores in this population.

Patients and methods

Study design

We conducted an international multicenter retrospective cohort study enrolling all consecutive HBV-monoinfected adults born in SSA or born in Suriname and of AS ethnicity. We collected historical data from 1988 to 2021 from five sites in the Netherlands, King's College Hospital in London (United Kingdom) and Hospital Universitario Vall d'Hebron Barcelona (Spain) and combined the cohorts for further analysis.

We excluded individuals in case of (past) viral co-infections (HDV, HCV, HIV) or presence or development of other known chronic liver diseases (documented alcohol-related liver disease/alcohol misuse, Wilson's disease, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis and hemochromatosis). Individuals diagnosed with HCC within 3 months of their first visit date were excluded.

Data collection, HCC risk score calculation and outcome definitions

Clinical records were individually reviewed by the investigators. Baseline date was set on the first visit to the outpatient department after a positive HBsAg test. Data were collected on demographics (age, sex, country of birth), antiviral treatment, liver biochemistry and virology. Biochemistry and virology were obtained within 6 months of baseline. Information on presence of fibrosis and/or cirrhosis was obtained from ultrasound reports, liver stiffness measurement (LSM) using FibroScan and/or liver histology whenever available. Presence of advanced fibrosis was based on liver biopsy showing METAVIR F3 or F4 or a LSM >9.0 kPa.[14,15] In individuals without available data on histology and LSM, cirrhosis could be ruled in based on ultrasound findings compatible with cirrhosis and/or portal hypertension. HCC diagnosis was based on typical radiological findings and/or histology. The PAGE-B score, which is calculated using baseline age, sex and platelet count, is an index that can be used to stratify the risk of HCC in Caucasians and Asian individuals with CHB.[11] The modified PAGE-B score adds baseline albumin levels to the PAGE-B score for the prediction of HCC in Asians with CHB.[12] The PAGE-B and mPAGE-B scores were calculated as reported in the original articles by Papatheodoridis *et al.* and Kim *et al.* and individuals were classified as low, intermediate and high risk based on previously reported cut-offs (<10, 10-17, >17 for PAGE-B and <9, 9-12, >12 for mPAGE-B).[11,12]

Study endpoints

The primary aim of the study was assessment of the cumulative incidence of HCC during follow-up in the overall population and across clinically relevant subgroups. Secondary aims were identification of baseline predictors of HCC, and the cumulative HCC incidence across (m)PAGE-B risk strata.

Statistical analysis

Continuous variables are presented as median (IQR) and categorical variables as n (%). The follow-up time for each individual was calculated from baseline date until HCC date or last visit date or last visit date at the time of data collection.

The cumulative incidence of HCC was assessed using life-table methods and the Kaplan-Meier estimator. Analyses were performed in the overall study population and stratified by SSA/AS, presence of advanced fibrosis, and HBV genotype. Next, we assessed independent baseline predictors of HCC by entering potential predictors with a p <0.1 in univariable analysis into a multivariable Cox regression model. Finally, we compared the cumulative incidence of HCC across (m)PAGE-B risk groups by the log-rank test and analyses were repeated after excluding individuals with low HBV DNA levels.

To confirm the robustness of our results, we performed additional sensitivity analyses across enrolment era's, across different age groups and baseline HBV DNA levels and after excluding individuals with short or incomplete follow-up. Differences between the two groups were described using the Mann-Whitney U test for non-normally distributed continuous data and the Chi-square test for categorical data.

Differences were considered statistically significant when p <0.05. Statistical analyses were performed using SPSS 28.0.1.0 (IBM).

Ethics and consent

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was primarily reviewed by the Erasmus MC Medical Ethical Committee (MEC-2021-0782). The requirement for informed consent was waived, and the institutional review boards of participating sites gave necessary approval whenever required.

Results

Baseline characteristics

Data were collected on 1,486 individuals diagnosed with CHB, 13 of whom were excluded from the analysis because of HCC diagnosis within 3 months.

We therefore analyzed 1,473 individuals; the majority of whom were male (59.7%) with a median age of 37 years (IQR 29, 46) at enrolment; 1,351 (91.7%) individuals were of SSA and 122 (8.3%) were of AS ethnicity. Only 9.2% of the individuals were hepatitis B e antigen (HBeAg)-positive at enrolment. The predominant HBV genotypes were E (49.6%) and A (13.7%); for 34.8% of the individuals the HBV genotype was not available. Of the 187 individuals (12.7%) with advanced fibrosis (METAVIR F3 or F4) at baseline, 133 (71.1%) cases were based on biopsy, 49 (26.2%) on LSM and only five cases (2.7%) were based on ultrasound findings compatible with cirrhosis. During follow-up, 617 (41.9%) individuals received antiviral therapy with a nucleo(s)tide analogues (NUCs). All baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics.

	N = 1,473
Age, years	37 (29, 46)
Male sex	879 (59.7)
Region of origin	
Sub-Saharan African	1,351 (91.7)
Afro-Surinamese	122 (8.3)
Platelets, x10^9/L	221 (68)
ALT, U/L	31 (21, 50)
Albumin, g/L	47 (45, 48)
Total bilirubin, μmol/L	8 (6, 12)
HBeAg-positive	136 (9.2)
HBV DNA, log_{10} IU/ml	3.3 (2.6, 4.6)
HBV genotype	
A	202 (13.7)
B	11 (0.7)
D	18 (1.2)
E	730 (49.5)
Unknown	512 (34.8)
Advanced fibrosis	187 (12.7)
HCC	34 (2.3)
Antiviral therapy with any NUC during follow-up	617 (41.9)
Type of antiviral during follow-up, n*	
LAM or ADV	66
ETV	252
TDF or TAF	338
PAGE-B risk groups	
Low	771 (52.3)
Intermediate	569 (38.6)
High	85 (5.8)
Missing	48 (3.3)
mPAGE-B risk groups	
Low	824 (55.9)
Intermediate	336 (22.8)
High	67 (4.5)
Missing	246 (16.7)

ADV, adefovir; ALT, alanine aminotransferase; ETV, entecavir; HCC, hepatocellular carcinoma; LAM, lamivudine; mPAGE, modified PAGE; NUC, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDV, tenofovir disoproxil fumarate.
Data are presented as mean (SD) for normally distributed data, as median (IQR) for non-normally distributed data and as n(%) for categorical variables. *Some patients have received multiple types of antiviral therapy.

Incidence of HCC in the overall cohort, and stratified by fibrosis stage

During a median follow-up period of 8 years (IQR 3.9, 11.4), 34 individuals developed HCC. The incidence rate was 2.83 cases per 1,000 person-years. The 5- and 10-year cumulative incidences of HCC were 1% (95% CI 0.99-1.01) and 2.4% (95% CI 2.39-2.41) in the overall study cohort (Fig. 1). This was similar for SSA (1% and 2.4%) and AS individuals (1% and 2.4%, p = 0.238). Findings were consistent in the subset of individuals with a follow-up time of at least 5 years (n = 984). Within this subset, we observed a 5- and 10-year cumulative incidence of HCC of 1.2% and 2.7%.

Six (12.6%) individuals were younger than 40 years when diagnosed with HCC. The characteristics of the individuals who developed HCC during study follow-up are shown in Table 2. The majority had advanced fibrosis at baseline, and no individual without advanced fibrosis at baseline developed HCC within the first 5 years of follow-up. The 5- and 10-year cumulative incidences of HCC were 0% and 0.7% among individuals without advanced fibrosis at baseline, compared to 7.1% and 12.1% among individuals with advanced fibrosis (p <0.001; Fig. 2A).

The 5- and 10-year cumulative HCC incidences were 0.7% and 1% for individuals with a baseline HBV DNA <2,000 IU/ml compared to 1.3% and 3.6% among individuals with HBV DNA at baseline >2,000 (Fig. 2B, p = 0.031).

Risk factors for HCC: multivariable analysis

In univariable analysis, higher age (HR 1.068; 95% CI 1.04–1.10, p <0.001), male sex (HR 2.587; 95% CI 1.13–5.94, p = 0.025), lower platelet count (HR 0.987; 95% CI 0.97–0.98, p <0.001), lower albumin level (HR 0.885; 95% CI 0.83–0.94, p <0.001) and higher HBV DNA log_{10} (HR 1.4; 95% CI 1.16–1.60, p <0.001) at baseline were significantly associated with HCC development (Table 3). Almost all individuals who developed HCC were on antiviral therapy, therefore antiviral therapy was not included in the analysis.

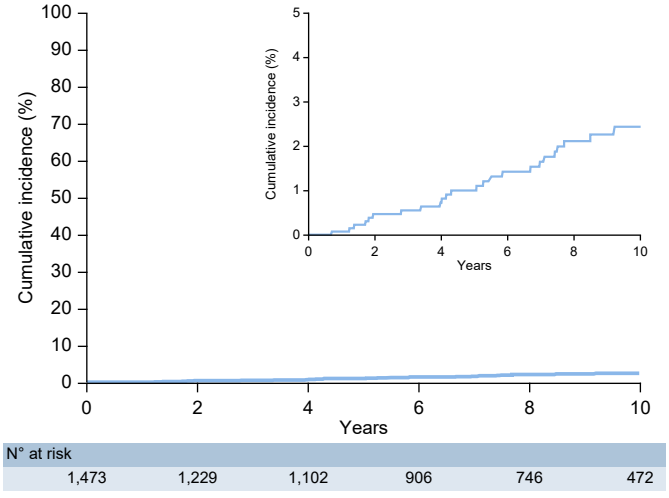

Fig 1. Kaplan-Meier curve of cumulative incidence of HCC in the overall study population. HCC, hepatocellular carcinoma.

Table 2. Baseline characteristics of individuals with a diagnosis of HCC.

	HCC, n = 34
Age at enrolment, years	48 (40, 58)
Age at HCC diagnosis, years	53.5 (44, 65)
Male sex	27 (79.4)
Ethnicity	
Sub-Saharan African	28 (82.4)
Afro-Surinamese	6 (17.6)
Platelets, x10^9/L	119 (78, 172)
ALT, U/L	70 (47, 101)
Albumin, g/L	46 (43, 47)
Total bilirubin, μmol/L	9 (7, 16)
HBeAg-positive	10 (29.4)
HBV DNA, log_{10} IU/ml	5.7 (3.5, 7.2)
Advanced fibrosis	26 (76.5)
PAGE-B risk groups	
Low	5 (14.7)
Intermediate	16 (47.1)
High	13 (38.2)
Missing	0
mPAGE-B risk groups	
Low	7 (20.6)
Intermediate	18 (52.9)
High	9 (26.5)
Missing	0

ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; mPAGE, modified PAGE. Data are presented as mean (SD) for normally distributed data, as median (IQR) for non-normally distributed data and as n (%) for categorical variables. *Some patients have received multiple types of antiviral therapy.

Baseline alanine aminotransferase, total bilirubin and HBeAg status were not associated with HCC risk. Furthermore, there was again no difference by ethnicity (SSA *vs*. AS; HR 1.706; 95% CI 0.695–4.185 $p = 0.244$). HBV genotype was available for 961 individuals (65.2%) in the cohort, with the largest groups being genotype E (n = 730, 49.6%) and genotype A (n = 202, 13.7%). We observed no difference in 10-year cumulative HCC incidence between genotype E and A (2.2% vs. 2.9% $p = 0.784$; HR 0.89; 95% CI 0.38–2.08).

Multivariable Cox regression showed that higher age (adjusted hazard ratio [aHR] 1.052; 95% CI 1.023–1.083; $p < 0.001$), lower platelet count (aHR 0.981; 95% CI 0.974–0.987; $p < 0.001$), lower albumin level (aHR 0.898; 95% 0.840–0.961; $p = 0.002$) and higher HBV DNA log_{10} (aHR 1.208; 95% CI 1.016–1.437 $p = 0.033$) at baseline were independently associated with HCC development. Male sex was associated with an increased risk (aHR 2.073; CI 0.822–5.225), however this was not statistically significant ($p = 0.122$; Table 3). Time of enrolment (before or after 2010) was not associated with HCC development (aHR 0.77; $p = 0.527$).

Performances of HCC risk scores

Among 1,425 individuals with available data, the median PAGE-B risk score was 8 (IQR 4, 12), and 771 (52.3%), 569 (38.6%) and 85 (5.8%) individuals were classified as low, intermediate and high risk. The 5- and 10-year cumulative incidences of HCC in the low-risk PAGE-B group were 0% and 0.5%, compared to 0.6% and 2.9% in the intermediate-risk group and 11.6% and 15.9% in the high-risk group ($p < 0.001$ by log-rank test; Fig. 3A). In a sensitivity analysis, we also observed a negligible 5- and 10-year cumulative HCC risk in the low-risk PAGE-B group for SSA individuals (0% and 0.5%) and we observed no events in AS individuals with a low PAGE-B score. We also performed a separate sensitivity analysis focusing on individuals with HBV DNA levels below (<2,000 IU/ml) and above (>2,000 IU/ml) the treatment threshold at baseline. HCC risk was negligible among individuals with a low PAGE-B score and among individuals with baseline HBV DNA levels <2,000 IU/ml (0% at 10 years) and among individuals with baseline HBV DNA >2,000 IU/ml (0.9% at 10 years). Consistent results were obtained in the subset of individuals with a follow-up of at least 5 years. The 5- and 10-year cumulative incidences of HCC in the low-risk PAGE-B group were 0% and 0.5%, compared to 1% and 3% in the intermediate-risk group and 12.5% and 16.7% in the high-risk group.

Findings were consistent when we applied the mPAGE-B score. Among 1,205 individuals with available data to calculate the score, the median baseline mPAGE-B risk score was 7.0 (IQR 5, 9), and 824 (55.9%), 337 (22.8%) and 67 (4.5%) individuals were classified as low, intermediate and high risk. The 5- and 10-year cumulative incidences of HCC were 0% and 0.6% in the low-risk mPAGE-B group, compared to 1.6% and 5.5% in the intermediate- and 11.6% and 13.4% in the high-risk groups ($p < 0.001$ by log-rank test) (Fig. 3B).

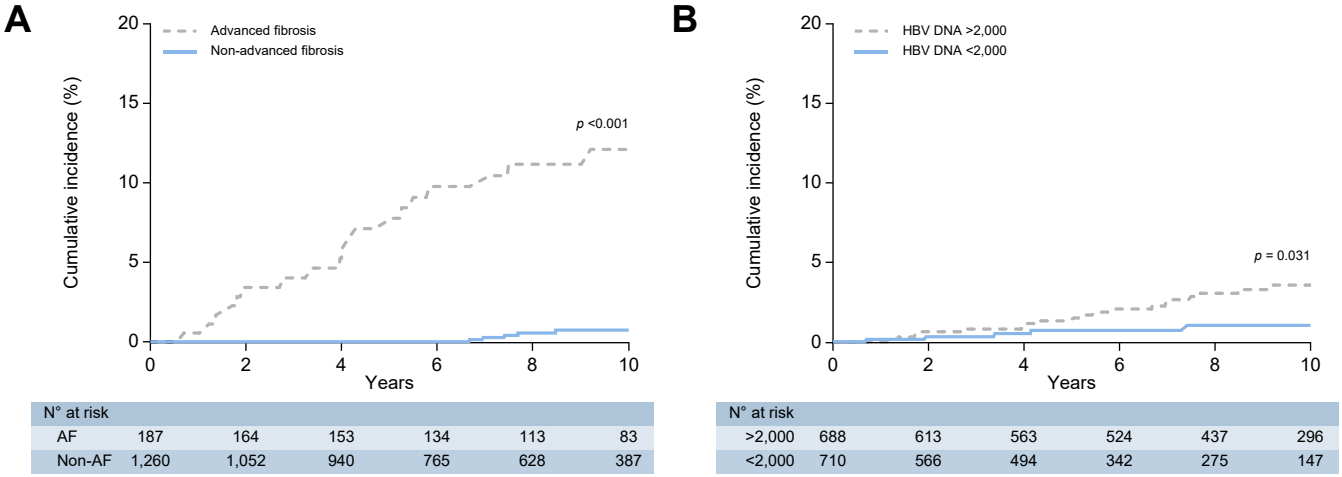

Fig 2. Kaplan-Meier curve of cumulative incidence of HCC stratified by fibrosis status and HBV DNA level at baseline. Kaplan-Meier curve of cumulative incidence of HCC in individuals with (A) advanced fibrosis or non-advanced fibrosis at baseline (B) HBV DNA <2,000 or HBV DNA >2,000 at baseline, $p = 0.031$ by log-rank test. HCC, hepatocellular carcinoma.

Table 3. Univariable and multivariable analysis.

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
Age at baseline	1.068	1.040–1.097	<0.001	1.052	1.023–1.083	<0.001
Male sex	2.587	1.126–5.944	0.025	2.073	0.822–5.225	0.122
Platelet count at baseline	0.987	0.973–0.984	<0.001	0.981	0.974–0.987	<0.001
Albumin at baseline	0.885	0.829–0.994	<0.001	0.898	0.840–0.961	0.002
HBV DNA $\log_{10}$ at baseline	1.400	1.163–1.596	<0.001	1.208	1.016–1.437	0.033

HR, hazard ratio. Results were obtained with Cox proportional hazard analysis.

Since age is a major factor in the calculation of (m)PAGE-B scores, we performed a sensitivity analysis among individuals aged ≥50 (n = 242). We observed no events in 10 years among individuals with a low PAGE-B score.

Discussion

This unique international multicenter cohort of 1,473 SSA and AS individuals with chronic hepatitis B showed 5- and 10-year cumulative HCC risks of 1% and 2.4%. The risk of HCC was negligible among individuals without advanced fibrosis at baseline, and among individuals with low baseline (m)PAGE-B scores. These findings can be used to guide HCC surveillance strategies in this population.

HCC is highly endemic in SSA[16,17] with CHB as one of the main risk factors. In a large registry study form the United States which included 59,907 individuals with HCC, the proportion of persons with very early (<40 years) and early (<50 years) onset HCC was the highest in those born in SSA.[2] However, this was a case-control study and no information on the etiology of the underlying liver disease was available. Another study from the United States found that the main risk factor of non-cirrhotic HCC in HBV individuals was African American ethnicity.[18]

Our study confirmed that HCC may occur at a young age in this population, with 6 (12.8%) of the HCC cases occurring under age 40. However, our median age at time of HCC diagnosis was 53.5 years whereas most studies reported a median age of 42 years.[19] This may be explained by the fact that all these studies included individuals still living in SSA without access to antiviral therapy, with potential HIV and HDV coinfection and with continued exposure to other risk factors such as aflatoxin. This hampers comparison with our study population. Despite the alarmingly young age at which HCC was diagnosed in some cases, our study also showed that the overall cumulative risk of HCC was relatively low (2.4% after 10 years of follow-up). This is an important finding because population-based estimates of HCC risk in the SSA/AS CHB population are largely lacking as these individuals have often been underrepresented or excluded from established cohorts that have assessed HCC risk in CHB. Importantly, presence of advanced fibrosis at baseline was the most important predictor of HCC incidence in our cohort; the 10-year cumulative incidence of HCC was 0.7% among individuals without advanced fibrosis, compared to 12.1% among those with advanced fibrosis. In a review by Papatheodoridis *et al.*, annual HCC incidence rates in individuals treated with entecavir or tenofovir ranged from 0.0% to 1.4% in non-cirrhotic Asians and from 0.1 to 1.0% in non-cirrhotic predominantly Caucasian populations. For individuals with cirrhosis treated with entecavir or tenofovir, annual HCC rates ranged from 0.9% to 5.4% in Asians and from 1.5% to 5.2% in Caucasians.[20] This is in line with our study findings and suggests that the commonly used practice of enrolling all SSA/AS individuals into surveillance programs regardless of fibrosis stage is unlikely to be cost-effective, and highlights the importance of individualized HCC surveillance strategies based on fibrosis stage and/or risk scores.

Since estimates of hepatic fibrosis are not always easy to obtain in clinical practice, various scores have been developed

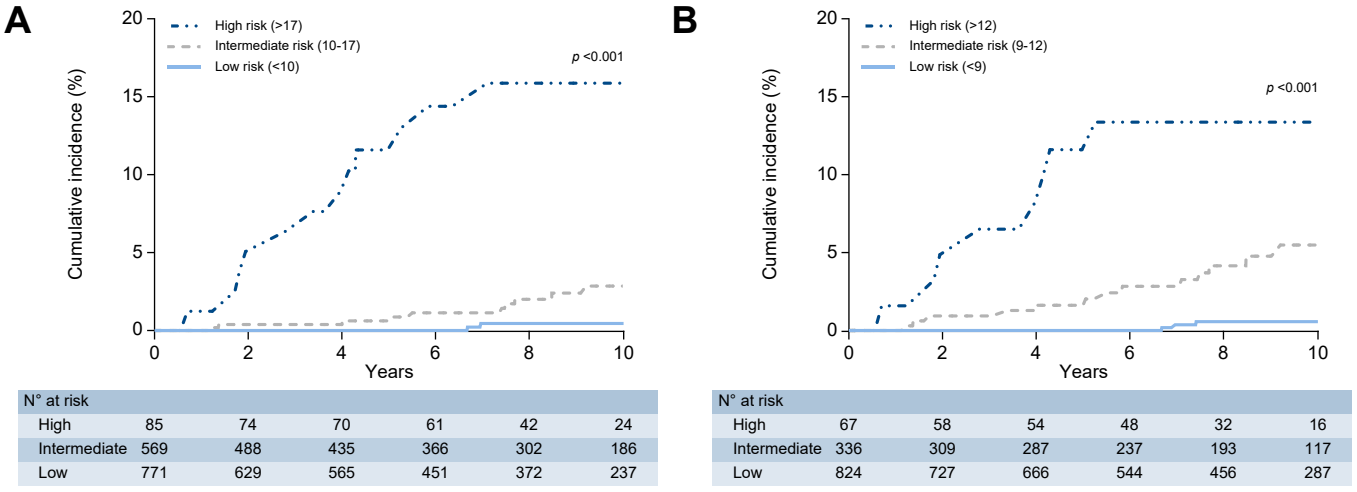

Fig 3. Kaplan-Meier curve of cumulative incidence of HCC stratified by (m)PAGE-B score. Kaplan-Meier curve of cumulative incidence of HCC in individuals with low risk, intermediate risk and high risk (A) PAGE-B score at baseline, *p* <0.001 by log-rank test (B) mPAGE-B score at baseline, *p* <0.001 by log-rank test. HCC, hepatocellular carcinoma; mPAGE, modified PAGE.

to stratify HCC risk among individuals with CHB. First of all, the current study supports previous data obtained in Asian cohorts that showed that elevated HBV DNA levels are an independent risk factor for HCC development.[21] This finding supports the use of HBV DNA as a tool to identify SSA/AS individuals most likely to benefit from antiviral therapy. In addition to HBV DNA, we identified sex, age, platelet count and albumin levels as potential risk factors for HCC. Interestingly, these factors were previously identified as risk factors in Caucasian and Asian populations, and are included in the existing (m)PAGE-B HCC score.[22] Importantly, SSA/AS individuals were either excluded or underrepresented in existing cohorts that derived and validated the PAGE-B risk scores, and the performance of these scores in the SSA/AS population is therefore unknown.[11,12,23] In the current study, we found that the risk of HCC varied significantly across (m)PAGE-B categories. The 10-year risk of HCC in the (m)PAGE-B low risk groups, which comprises 52-56% of the cohort, was negligible, and well below the 0.2%/year threshold that has been proposed to warrant HCC surveillance.[9] These findings support the use of (m)PAGE-B to stratify HCC risk in SSA/AS individuals with CHB. If individuals with a low (m)PAGE-B score are exempt from surveillance, this could potentially reduce the demand on healthcare resources and on individuals with CHB. The current study is a first step towards personalized HCC surveillance strategies in this population. Despite the excellent performance of a low PAGE-B score in identifying individuals at low risk of HCC, the majority of individuals identified as high risk will not develop HCC. We observed a 5-year cumulative incidence of 11.6% (or a time dependent 5-year positive predictive value of 10.9%). Further studies are therefore required to optimize risk stratification for this high-risk group, perhaps focusing on readily available (virological) biomarkers.

In this study, we included SSA and AS individuals because of their similar genetic background. This is in line with recommendations from the AASLD guideline which suggest HCC surveillance above 20 years for the Afro-American population.[10] Most importantly, we observed similar 5- and 10-year cumulative incidences of HCC for SSA (1% and 2.4%) and AS (1% and 2.4%, $p = 0.238$) individuals and no difference across subgroups in Cox regression analysis, supporting the pooling of these groups for further analysis.

The current study focusses on HCC as the primary outcome and given the relatively low number of eligible individuals per center and the low incidence of HCC, a prospective design was not feasible. Therefore, we opted for a retrospective design, which enabled a very long follow-up, but which is also associated with some potential limitations. First, management and follow-up practices will have varied over time and complete follow-up data was not available for all individuals. We performed sensitivity analyses to account for potential differences over time. We found no association between era of enrolment with outcome in multivariable analysis, and consistent performance of PAGE-B across the eras, also after exclusion of individuals with short follow-up. These findings consistently show that our findings are robust even if individuals with short follow-up are excluded. Furthermore, stratifying the cohort into individuals with complete follow-up data and without complete follow-up showed limited differences across these subgroups (Table S1). If anything, these comparisons showed that individuals retained in follow-up had slightly more severe liver disease, and it is therefore unlikely that loss to follow-up would result in any underestimation of HCC risk. Secondly, even though this is a large study conducted across multiple countries, we identified only 34 individuals who developed an HCC, which may limit statistical power. Third, not all potential risk factors for the development of HCC, such as route of transmission, duration of stay in Europe, presence of moderate alcohol consumption (individuals with alcohol misuse were excluded), *de novo* development of steatotic liver disease during follow-up, historical aflatoxin exposure, positive family history for HCC and other lifestyle factor, could be taken into account. However, failure to detect these risk factors in some individuals would in turn have resulted in an overestimation of HBV-attributed HCC risk in this analysis, which supports, rather than refutes, our conclusion that the risk of incident HCC is low in this population. Fourth, because histological information was unavailable for a proportion of the individuals, we relied on LSM to determine presence of cirrhosis in a subset of individuals. In this cohort, 70% of the cirrhosis cases were diagnosed based on biopsy and 30% on LSM. LSM has been well-validated in individuals with CHB and the diagnostic accuracy for ruling in cirrhosis is excellent.[15,24] Fifth, this cohort comprises both treated and untreated individuals. In the overall cohort, 617 (41.9%) individuals started with NUC therapy, of whom 231 received entecavir, 311 tenofovir and 63 lamivudine or adefovir. Of the 63 individuals who started lamivudine or adefovir, 25 changed to either entecavir or tenofovir during follow-up. The median treatment duration with a NUC was 7.8 years (IQR 3.8, 11.3). Previous studies have shown that antiviral therapy can effectively suppress serum HBV DNA and may reduce but not eliminate the risk of HCC.[25] In the current cohort, virtually all individuals who developed HCC were on antiviral therapy, precluding assessment of the influence of antiviral therapy on HCC development. We therefore assessed the HCC risk in individuals with low and high HBV DNA levels at baseline which mimics the antiviral therapy thresholds. We also performed a sensitivity analysis excluding individuals treated with only lamivudine or adefovir, which did not influence any of the findings. Lastly, the majority of the sites were referral centers which could potentially influence the external validity of our findings. However, the baseline characteristics show this is a mixed cohort with a large group of individuals with no advanced fibrosis and a median HBV DNA of 3.3 log IU/ml, suggesting this is not a cohort significantly enriched for individuals with severe disease. Moreover, this would have led to an overestimation of HCC risk rather than an underestimation, not influencing the main conclusions of our analysis.

In a recent review from Mitchell *et al.*,[13] the health inequalities in the management of individuals with CHB from SSA in high-income countries was underlined with a focus on the lack of evidence for treatment and surveillance regimens in this population. HCC surveillance practices have evolved over time and surveillance is currently advised for SSA males ≥40 years in the UK and for all SSA individuals aged ≥20 years in the Netherlands and Spain. Unfortunately, data on HCC surveillance enrolment and adherence was not available in this cohort, and is likely to have varied significantly over time. Nevertheless, it is important to note that HCC surveillance leads to early detection and suboptimal surveillance may therefore result in a slightly delayed diagnosis at a more advanced stage, rather than a missed

diagnosis of HCC. Nearly all HCCs in our study were detected on screening, highlighting that at-risk individuals appear to be enrolled in surveillance programs. Given that previous studies suggest that surveillance is associated with a lead time of around 7 months in the diagnosis of HCC, we feel that suboptimal surveillance is unlikely to significantly impact the HCC incidence in our study with a median follow-up of over 8 years.[26]

In conclusion, the current study showed that although HCC may develop at a young age in individuals from SSA/AS with CHB, the absolute 5- and 10-year risk of HCC is limited, particularly among individuals without advanced fibrosis and among individuals with low (m)PAGE-B scores. These findings suggest that the majority of these individuals can be safely exempt from HCC surveillance.

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Abbrievations

aHR, adjusted HR; AS, Afro-Surinamese; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; LSM, liver stiffness measurement; mPAGE, modified PAGE; NUC, nucleo(s)tide analogue; SSA, sub-Saharan Africa(n).

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Conflicts of interest

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Authors' contributions

Collection of data: LAP, KMAvE, MB, OMK, CS, IC.
Study design, writing of the manuscript and approval of final version: LAP, MJS.
Critical review of the manuscript and approval of final version: KMAvE, MB, OMK, RJdK, BH, HLAJ, KA, MvdV, FIL, MK, JdB, MAAC, CS, RAdM, RBT, IC.

Data availability statement

The data that support these findings are not publicly available, since they are subject to (inter)national data protection laws to ensure data privact of the study participants. The data can therefore not be shared.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.10.019.

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