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ORIGINAL RESEARCH

Incidence of Hepatocellular Carcinoma and Decompensated Liver Cirrhosis and Prognostic Accuracy of the PAGE-B HCC Risk Score in a Low Endemic Hepatitis B Virus Infected Population

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Purpose: We aimed to determine incidence of hepatocellular carcinoma (HCC) and decompensated liver cirrhosis in persons with chronic hepatitis B virus (HBV) infection in Denmark stratified by disease phase, liver cirrhosis, and treatment status at baseline. Additionally, we aimed to assess the prognostic value of the PAGE-B HCC risk score in a mainly non-cirrhotic population.

Patients and Methods: In this register-based cohort study, we included all individuals over the age of 18, with chronic HBV infection first registered between 2002 and 2016 in at least one of three nationwide registers. The study population was followed until HCC, decompensated liver cirrhosis, death, emigration, or December 31, 2017, which ever came first.

Results: Among 6016 individuals included in the study, 10 individuals with and 23 without baseline liver cirrhosis developed HCC during a median follow up of 7.3 years (range 0.0–15.5). This corresponded to five-year cumulative incidences of 7.1% (95% confidence interval (CI) 2.0–12.3) and 0.2% (95% CI 0.1–0.4) in persons with and without baseline liver cirrhosis. The five-year cumulative incidence of decompensated liver cirrhosis was 0.7% (95% CI 0.5–1.0). Among 2038 evaluated for liver events stratified by disease phase, incidence of HCC was low in all who were non-cirrhotic and untreated for HBV at baseline. PAGE-B score was evaluated in 1529 persons. The 5-year cumulative incidence of HCC was 0, 0.8 (95% CI 0.5–1.8), and 8.7 (95% CI 1.0–16.4) in persons scoring <10, 10–17 and >17, respectively (c-statistic 0.91 (95% CI 0.84–0.98)).

Conclusion: We found low incidence of HCC and decompensated liver cirrhosis in persons with chronic HBV infection in Denmark. Moreover, the PAGE-B score showed good accuracy for five-year risk of developing HCC in the population with chronic HBV infection in Denmark.

Keywords: hepatitis B virus, viral hepatitis, Scandinavia, morbidity, nationwide

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Introduction

In 2019, chronic hepatitis B virus (HBV) infection was estimated to be responsible for 820,000 deaths worldwide mainly due to hepatocellular carcinoma (HCC) and liver cirrhosis.[1] Chronic HBV infection is defined as hepatitis B surface antigen (HBsAg) in the blood for at least six months, and the natural history is variable. The risk of long-term complications depends on viral and host factors. To describe the natural history and stratify complication risk, chronic HBV infection is divided into four phases depending on Hepatitis e Antigen (HBeAg) status, HBV DNA, alanine aminotransferase (ALT) level in the blood, and degree of liver inflammation or fibrosis.[2–4] As there is no eradicating cure for chronic HBV infection, international as well as Danish national guidelines mainly recommend treatment for persons with active hepatitis.[2–5] However, even persons with inactive infection may transition to an active phase, and develop complications.[2–4] HCC surveillance is recommended in persons with cirrhosis and in individuals with increased risk of HCC. HCC incidence above 0.2% per year has been suggested as a threshold for HCC surveillance.[2,6] Updated data on complication risk in persons with chronic HBV infection are important for clinical decisions on frequency of disease monitoring, antiviral treatment, and HCC surveillance.

Several scoring systems for predicting HCC risk in chronic HBV infection have been developed. For some, accuracy seems to vary across populations. The score Platelet-Age-GEnder- hepatitis B (PAGE-B) has shown good accuracy for predicting five-year HCC risk in persons on anti-viral treatment in both Asian and European populations.[7,8]

Like the rest of Northern Europe, Denmark is a low endemic country with an estimated chronic HBV infection prevalence of 0.3%. Most persons with chronic HBV infection in Denmark have migrated from countries with higher prevalence. Consequently, the chronic HBV infection population in Denmark is heterogenous regarding both region of origin and HBV genotypes.[9] Previous studies from Asia and Europe have suggested regional differences in the incidence of HCC in people with chronic HBV infection.[10–12] Consequently, studies from southern Europe or South East Asia may not represent the chronic HBV population in Denmark well.

As both incidence of long-term complications and prognostic accuracy of risk scores have been found to vary across different populations, the objective of this study was to determine the incidence of HCC and compensated/decompensated liver cirrhosis in the chronic HBV population in Denmark, a diverse population in terms of country of origin as well as HBV genotypes. We aimed to assess the incidence and long-term complications stratified by disease phase, liver cirrhosis, and treatment status. Moreover, we aimed to assess the prognostic accuracy of PAGE-B in a mainly non-cirrhotic chronic HBV population.

Materials and Methods

Data Collection

We performed a nationwide register-based cohort study by combining data from several national administrative registries and nationwide clinical databases. Data was linked using the ten-digit personal identification number (PIN) provided all residents in Denmark. The data collection for this study has been described previously.[13]

Persons with chronic HBV infection were identified in the nationwide Danish Database for Hepatitis B and C (DANHEP), the laboratory database DANVIR and the National Patient Register (NPR). DANHEP has since 2002 enrolled patients from all Danish hospital departments specialized in infectious diseases or gastroenterology. Patients are eligible for inclusion if they are at least 16 years of age and have chronic hepatitis B or C. DANHEP includes demographic, clinical and laboratory data which is updated annually.[14] DANVIR is a laboratory database which has recorded hepatitis B and C antigen, antibody and virus DNA/RNA results since 2000.[15] The NPR is a hospital database which has registered dates, procedures and ICD diagnoses from all in- and outpatient visits in hospitals in Denmark since 1977 and 1995, respectively.[16] Information on HCC, liver cirrhosis, decompensated liver cirrhosis and comorbidities was retrieved from the NPR, the Danish Cancer Register (DCR), the Danish Register of Causes of Death (DRCD) and the Danish National Pathology Database (patobank). The DCR was established in 1943 and records all dates and ICD codes of cancer diagnoses given in Denmark.[17] The DRCD has recorded primary and secondary causes of death in Denmark since 1943, using the ICD classification system.[18] Patobank has recorded all pathology diagnoses in Denmark since 1997

using the SNOMED classification system.[19] Finally, we linked data with the civil registration system (CRS) to retrieve information on date of birth, sex, country of origin and, if relevant, date of death or emigration.[20]

Selection of Study Population

We included all individuals with chronic HBV infection in DANHEP, DANVIR or NPR first registered between 2002 and 2016. Chronic HBV infection was defined as inclusion in DANHEP and a positive HBsAg, ICD10 codes B18.0 or B18.1 in the NPR or one of the following criteria met in DANVIR: 1) Positive HBsAg twice at least 6 months apart, 2) positive HBsAg and negative HBc-IgM, or 3) positive HBsAg, no HBc-IgM measured and a country of origin where HBV is endemic. We wanted to assess the rate of HCC and decompensated liver cirrhosis in persons with chronic HBV mono-infection. Therefore, persons with hepatitis C virus (HCV) (ICD8: 07004, 07005 or ICD10: B18.2) infection or human immunodeficiency virus (HIV) (IDC8: 07983 or ICD10: B20.0–24.9) at baseline were excluded. Moreover, excessive alcohol use is a major risk factor for liver disease. To separate the effects of alcohol and chronic HBV infection, individuals with excessive alcohol use (defined as any alcohol-related diagnosis in NPR except acute intoxication ICD8: 29109, 29119, 29120, 29129, 29139, 29199, 30309, 30319, 30320, 30328, 30329, 30391, 30399, 57109, 57110, 57710 or ICD10: F10.1-9, G31.2, K70.0-9) were likewise excluded. Persons with HCC prior to index date were excluded from HCC analyses, while persons with decompensated liver cirrhosis prior to index date were excluded from analyses in which decompensated liver cirrhosis was the outcome. For the description of outcomes by disease phase, persons registered in DANHEP with baseline HBV DNA, ALT, and HBeAg available were selected. For evaluation of PAGE-B score the subset of this study population that were registered in DANHEP and had platelet count registered at baseline was selected.

Definitions of Outcomes and Risk Factors

The majority of the study population did not attend specialized care. Thus, most were not routinely assessed for liver fibrosis. Consequently, liver cirrhosis was likely underdiagnosed in this population. Because of this we chose to look at the incidence of decompensated liver cirrhosis in the analysis including the entire population, as decompensation is symptomatic and therefore likely less underdiagnosed. Decompensated liver cirrhosis was defined as oesophageal variceal haemorrhage (ICD10: I85.0, ICD8: 45601), spontaneous bacterial peritonitis (ICD10: K658I), hepatic encephalopathy (ICD10:K72.1+9, ICD8: 57300), hepatorenal syndrome (ICD10: K76.7) or ascites (ICD10: R18.0 + R18.9, ICD8: 78539) in the NPR or DRCD, and no diagnosis of acute liver failure in the NPR at the same time (ICD10 K71.2, K72.0, B15-17). HCC was defined as ICD10 codes C22.0, C22.9 or ICD8 code 15509 in the NPR, DCR or DRCD or SNOMED codes M81700, M81703, M81713 or M81803 in patobank. Region of origin was defined as the birth country of the mother or citizenship of the mother if she was born in Denmark. Information on antiviral treatment was retrieved from DANHEP. Antivirals used for chronic HBV infection treatment in Denmark are only dispensed by hospital departments. As data on liver biopsies and transient elastography were sparse, disease phases in this study were defined based on HBeAg status, ALT, and HBV DNA levels. Table 1 shows the definitions of disease phases. Those who were on antiviral treatment and/or had liver cirrhosis at baseline, were considered separately, and therefore not included in

Table 1 Definitions of Disease Phases in Chronic Hepatitis B Virus Infection

HBeAg positive infection	Positive HBeAg, and HBV DNA >10^7 IU/mL, and ALT ≤ ULN*
HBeAg positive hepatitis	Positive HBeAg, and HBV DNA 10^4–10^7 IU/mL, and ALT > ULN
HBeAg negative infection	Negative HBeAg, and HBV DNA < 2000 IU/mL, and ALT ≤ ULN
HBeAg negative hepatitis	Negative HBeAg, and HBV DNA > 2000 IU/mL, and ALT > ULN
Indeterminate	Does not match one of the definitions above.

Notes: * ALT upper limit of normal was ≤ 35 U/L for men and ≤ 25 U/L for women.
Abbreviations: HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus DNA; ALT, alanine aminotransferase; ULN, upper limit of normal.

a disease phase group. We defined normal ALT levels as ≤35 U/L for men and ≤25 U/L for women as studies in healthy populations have found normal ranges close to this.[2,21–23]

Statistical Analysis

The study population was followed from six months after chronic HBV infection diagnosis until HCC/decompensated liver cirrhosis, emigration, death, or December 31, 2017, which ever came first. Individuals with an outcome within six months of diagnosis were excluded from analyses of the outcome in question. Baseline characteristics were described with frequency and percentage for categorical variables and median with interquartile range (IQR) for continuous variables. Cumulative incidence was calculated using cumulative incidence functions with death from a non-liver-related cause as competing risk. Chronic HBV infection diagnoses in the NPR have previously proven to have low positive predictive value.[24] Therefore, we chose to calculate incidence rate (IR) of HCC and decompensated liver cirrhosis both with and without chronic HBV infection cases only registered in the NPR. In an additional sensitivity analysis, we only accepted cases of decompensated liver cirrhosis with a liver cirrhosis diagnosis before or at the time of decompensation.

To evaluate the prognostic value of the PAGE-B score for HCC in this population, we calculated the score for the subset of persons who were registered in DANHEP and had platelets quantified. The score was categorized into the risk-groups low (score <10), intermediate (score 10–17), or high (score >17).[25] We calculated Harrell's c-statistic based on a Cox regression model. Cumulative incidence functions were used to calculate five-year cumulative incidence with six months after first platelet count in DANHEP as index date. Moreover, we calculated time-dependent sensitivity, specificity, positive and negative predictive values for various PAGE-B cutoffs.[26]

A two-sided alpha of 0.05 was considered significant in all analyses. Data management and statistical analysis were performed using STATA IC 16[27] and R studio 3.6.3.[28] The study was approved by the Danish Data Protection Agency as required by Danish law (P-2019-829).

Results

A total of 7040 persons over the age of 18 years had chronic HBV infection diagnosed between 2002 and 2017. Of them, 52 were excluded as they died within 6 months of follow up, 578 were excluded due to HIV and/or HCV co-infection at baseline and 394 were excluded due to excessive alcohol use. Figure 1 shows the selection of the study population. Compared with those included, individuals excluded were older (median age 46 years interquartile range (IQR) 37–55), more were men (70%), more had cirrhosis at baseline (23%) and more had Denmark as their country of origin (72%).

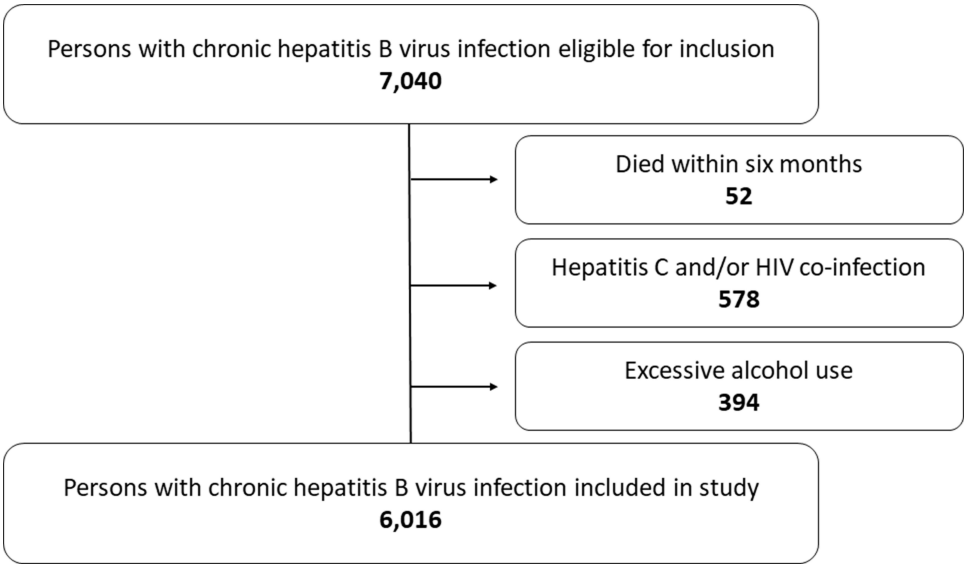

Figure 1 Selection of the study population.

Among the individuals who were excluded there were 26 cases of HCC and 67 cases of decompensated liver cirrhosis during follow up. Overall, 6016 were included in the study.

Baseline characteristics of the study population are summarized in Table 2. The included population was young with a median age of 34 years (IQR 27–45) and heterogenous in terms of region of origin. At baseline, 112 (2%) individuals had cirrhosis. Just over half of all included persons were registered in DANHEP, meaning that they had at least one visit at a clinic in Denmark specializing in management of chronic HBV infection. We did not have information on hepatitis D virus (HDV) co-infection for the entire population. Consequently, we were unable to account for the impact of this in our analyses. Of 1102 individuals in our study population that were tested for HDV, 42 (4%) had positive HDV RNA. During follow up, 489 (8%) received antiviral treatment, 144 (2%) started treatment at baseline.

There were 24 persons who were excluded from HCC analysis as they were diagnosed with HCC before or within 6 months of the chronic HBV diagnosis. This corresponded to 41% of all HCC events. There were 52 (42% of events) who had decompensated liver cirrhosis prior to or within 6 months of their chronic HBV infection diagnosis. The median follow-up was 7.3 years (range 0.0–15.5). During this time 72 (1%) persons developed decompensated cirrhosis and 33 (0.5%) developed HCC. Among those with HCC, 23 (70%) had a liver cirrhosis diagnosis prior to or less than two months after the HCC diagnosis while 10 (30%) had no liver cirrhosis registered. The median age at HCC was 59 years (range 35–77). The crude IR of HCC in the entire study population was 0.07 per 100 person-years (PY) (95% confidence interval (CI) 0.05–0.1), 0.1 per 100 PYs (95% CI 0.08–0.2) in those over the age of 40 years, and 1.4 per 100 PYs (CI 0.7–2.7) in those with liver cirrhosis at baseline. The five-year cumulative HCC incidence in persons with and without cirrhosis at baseline was 7.1% (95% confidence interval (CI) 2.0–12.3) and 0.2% (95% CI 0.1–0.4), respectively. In the analysis excluding 1146 chronic HBV cases only registered in the NPR, the IR of HCC was 0.08 per 100 PYs (95% CI 0.05–0.1).

We found that 0.2 per 100 PYs (95% CI 0.1–0.2) developed decompensated liver cirrhosis and the five-year cumulative incidence was 0.7% (95% CI 0.5–1.0). Among those with liver cirrhosis at baseline the rate of

Table 2 Baseline Characteristics of Individuals with Chronic Hepatitis B Virus Infection in Denmark

N	6016
Male sex (%)	3017 (50)
Median age (Interquartile range)	34 (27–45)
Region (%)	
Denmark	1684 (28)
Europe	731 (12)
Northern Africa and Western Asia	975 (16)
Sub-Saharan Africa	922 (15)
South-East and Central Asia	1596 (27)
Other/unknown	108 (2)
Cirrhosis (%)	122 (2)
Registered in DANHEP (%)	3171 (53)
HBeAg status (%)	
Positive	568 (9)
Negative	2491 (41)
Unknown	2957 (49)
Antiviral treatment (%)	144 (2)
Started antiviral treatment during follow up	345 (6)
Decompensated cirrhosis	72 (1)
Person years (decompensated cirrhosis)	44,489
Hepatocellular carcinoma	33 (1)
Person years (hepatocellular carcinoma)	44,818

Abbreviation: HBeAg, hepatitis B e antigen.

decompensation was 4.0 (95% CI 2.2–6.6) per 100 PYs. The median age at decompensation was 59 years (range 35–77). In the analysis excluding chronic HBV cases only registered in the NPR the overall IR of decompensated liver cirrhosis was 0.2 per 100 PYs (95% CI 0.1–0.2). In the analysis only accepting cases with a prior or concurrent liver cirrhosis diagnosis at decompensation the IR was 0.2 per 100 PYs (95% CI 0.1–0.2). Figures 2 and 3 show cumulative incidence curves for HCC and decompensated liver cirrhosis.

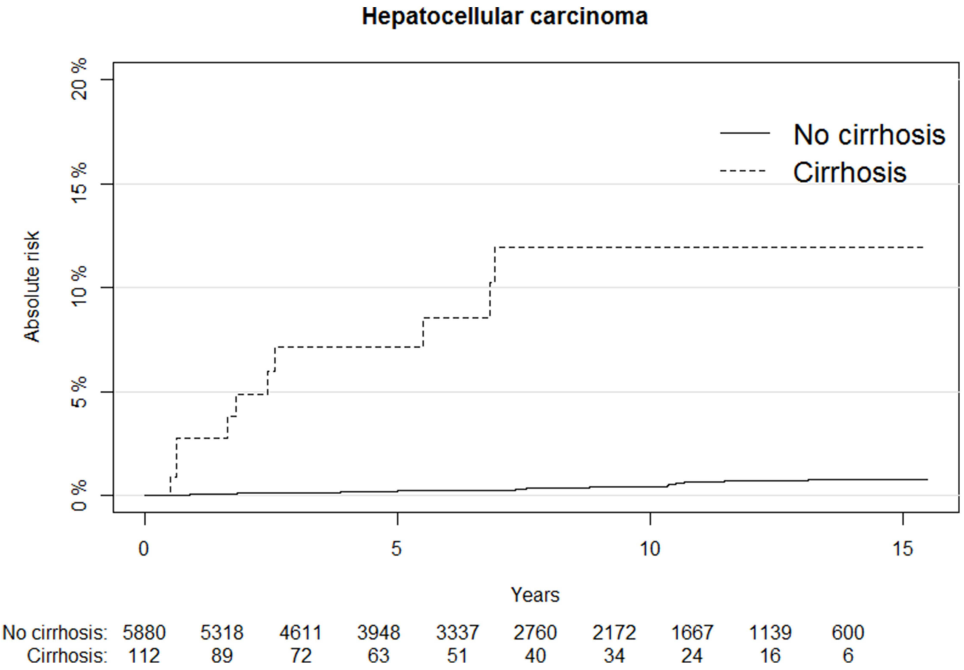

Figure 2 Cumulative incidence of hepatocellular carcinoma in individuals with chronic hepatitis B virus infection in Denmark stratified by baseline liver cirrhosis status.

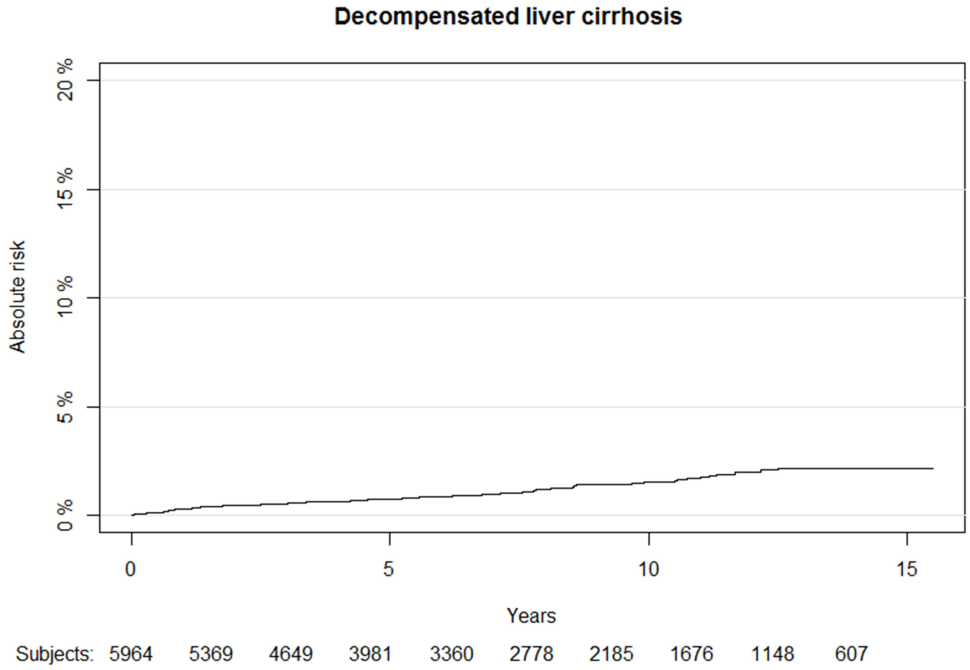

Figure 3 Cumulative incidence of decompensated liver cirrhosis in individuals with chronic hepatitis B virus infection in Denmark.

Outcomes by Disease Phase

The subgroup that was registered in DANHEP, and had HBV DNA, ALT and HBeAg status available at the time of the first HBV DNA measurement, counted 2038 persons and they were followed for a median of 4.8 years (range 0.0–15.5). Baseline was set to six months after first HBV DNA measurement. There were 791 persons with HBeAg negative infection, 16 with HBeAg positive infection, 134 with HBeAg positive hepatitis, 146 with HBeAg negative hepatitis and 779 who could not be determined based on their first measurements. Those with liver cirrhosis or antiviral therapy at baseline were not included in the disease phases but in separate categories. Persons with liver cirrhosis at baseline on antiviral treatment were included in the treatment category. There were 36 individuals with cirrhosis at the time of first HBV DNA measurement of whom 16 initiated antiviral treatment. Overall, 152 individuals started antiviral treatment within six months of the first HBV DNA measurement.

The median HBV DNA level at baseline was 1.2×10^8 IU/mL (IQR 10^8–1.7×10^8) in those with HBeAg positive infection, 3.15×10^5 IU/mL (IQR 1.1×10^5–10^6) in those with HBeAg positive hepatitis, 20 IU/mL (IQR 0.4–240) in those with HBeAg negative infection, 1.82×10^4 IU/mL (IQR 6×10^3-1.2 x 10^5) in those with HBeAg negative hepatitis, 212 IU/mL (IQR 5–3×10^3) in those of indeterminate phase, 2486 IU/mL (IQR 18–1.8×10^6) in individuals with liver cirrhosis at baseline, and 2×10^5 IU/mL (IQR 804–7.3×10^6) in those that started antiviral therapy within six months of follow up. During follow up 12 developed HCC and 28 developed liver cirrhosis. Table 3 shows incidence of HCC and liver cirrhosis stratified by disease phase at baseline. Among individuals who started antiviral treatment within six months of diagnosis that did not have liver cirrhosis the HCC IR was 0.4 per 100 PYs (0.08–1.2). All who developed HCC were men, over the age of 50 years, and mostly from Asia or Africa. Prior to the HCC diagnosis, seven developed liver cirrhosis and six started treatment. Of those who developed liver cirrhosis, 13 were women and the median age at cirrhosis was 48 years. There were 8 who developed liver cirrhosis and had HBeAg negative infection at baseline. All were over the age of 40 years. There were 12 among those with HBeAg negative infection who started treatment during follow up. Half were women – aged 24–42 years – who started treatment due to extrahepatic symptoms, pregnancy, or immunosuppressive treatment. The rest were men over the age of 45 at treatment initiation who started treatment due to fibrosis, active hepatitis or for unknown reasons.

PAGE-B Score

We were able to calculate PAGE-B score in 1529 persons who had platelet levels available at baseline. In this subset, the median age was 34 years (IQR 27–37), 753 (49%) were male, 31 (2%) had liver cirrhosis at baseline and 61 (4%) received antiviral treatment at baseline. Table 4 shows risk score and HCC distribution as well as the five-year

Table 3 Incidence of Decompensated Liver Cirrhosis and Hepatocellular Carcinoma in Individuals with Chronic Hepatitis B Virus Infection in Denmark Stratified by Disease Phase, Liver Cirrhosis and Antiviral Treatment at Baseline

	Liver Cirrhosis			Hepatocellular Carcinoma		
	N	**IR/100 PYs**	**95% CI**	**N**	**IR/100 PYs**	**95% CI**
HBeAg positive infection	0	–	–	0	–	–
HBeAg positive hepatitis	<5	0.4	0.1–1.0	0	–	–
HBeAg negative infection	8	0.2	0.1–0.4	<5	0.05	0.006–0.2
HBeAg negative hepatitis	7	1.1	0.5–2.1	0	–	–
Indeterminant	8	0.6	0.4–0.9	<5	0.08	0.02–0.3
Liver cirrhosis	–	–	–	<5	1.8	0.2–6.3
Antiviral treatment	9	1.1	0.5–2.2	5	0.6	0.2–1.4

Abbreviations: HBeAg, hepatitis B e antigen; IR, incidence rate; PY, persons year; CI, confidence interval.

Table 4 Liver Events in Individuals with Chronic Hepatitis B Virus Infection in Denmark Stratified by PAGE-B Score at Baseline

PAGE-B Score	<10	10–17	>17
N	911 (60%)	522 (34%)	96 (6%)
Hepatocellular carcinoma	0	< 5	6
5-year cumulated incidence % (95% CI)			
Hepatocellular carcinoma	0	0.8 (0.5–1.8)	8.7 (1.0–16.4)

Abbreviations: CI, confidence interval; PAGE-B, Platelet count, Age, Gender.

cumulative incidence of HCC in three strata (PAGE-B score <10, 10–17 and >17). Figure 4 shows cumulative incidence of HCC stratified by PAGE-B score. Overall, there were nine cases of HCC during follow up. There were no events in the group with PAGE-B score <10 at baseline. Five-year cumulative incidence of HCC increased from 0.8% (95% CI 0.5–1.8) for PAGE-B score 10–17 to 8.7% (95% CI 1.0–16.4) for PAGE-B score >17. Harrel's c-statistic for the discrimination of risk for HCC was 0.91 (95% CI 0.84–0.98). A PAGE-B cutoff of 10 yielded a sensitivity of 100%, a specificity of 73.3%, a positive predictive value of 3% and a negative predictive value of 100%. The PAGE-B cutoff with the highest combined specificity and sensitivity for HCC was 14 for which the sensitivity was 82.4%, the specificity was 89.4%, the positive predictive value was 5.9% and the negative predictive value was 99.8%. The five-year cumulative incidence of HCC was 0.2% (95% CI 0.1–0.4) for individuals with PAGE-B scores <14 at baseline and 5.8% (95% CI 1.0–10.6) for individuals with PAGE-B scores ≥14 at baseline.

Discussion

In this nationwide study, we found that the incidence of HCC and decompensated liver cirrhosis in the relatively young and heterogenous population with chronic HBV infection in Denmark was low. Moreover, we found that PAGE-B score was predictive for risk of HCC in a population in which the majority did not have liver cirrhosis.

The overall HCC incidence as well as the HCC incidence for persons over the age of 40 without cirrhosis was lower than the 0.2% per year which has been suggested as a threshold for HCC surveillance[2,6] This was in line with previous studies in similar populations in Sweden and the United States.[29,30] Other studies found HCC incidence rates ranging from 0.02 to 0.9 per 100 PYs.[12,31–41] The differences can be explained by differences in age, sex and liver disease stage,

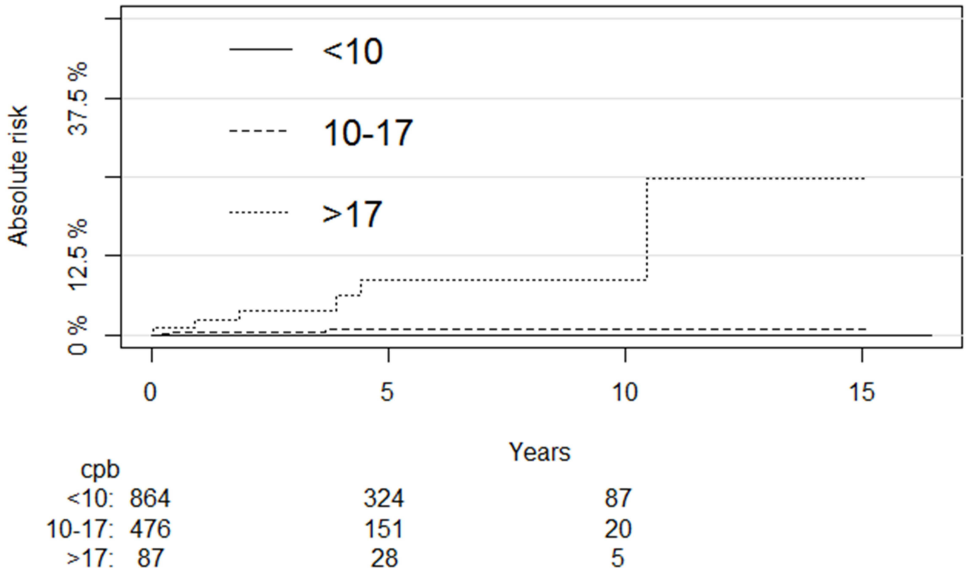

Figure 4 Cumulative incidence of hepatocellular carcinoma or liver events individuals with chronic hepatitis B virus infection in Denmark stratified by baseline PAGE-B score. PAGE-B score categories are <10, 10–17 and >17.

which was supported by the findings of Raffetti et al.[32] Likewise, lifestyle, genetics, HBV variants and importantly age at HBV infection are likely contributors.[12,37,39] Due to this, we would have preferred to provide IRs and risk estimates stratified by age, sex, region of origin and comorbidities such as diabetes, however with few events, estimates would have been too imprecise.

There were 41% of those who developed HCC, and 42% of those who developed decompensated liver cirrhosis that were excluded as they already had complications at baseline. This implies that a large part of the population with chronic HBV infection in Denmark is not diagnosed before symptomatic complications occur. This is in line with a previous finding that only 67% with chronic HBV infection in Denmark are diagnosed.[42] Both findings highlight the importance of screening high risk populations and monitoring liver disease in persons diagnosed with chronic HBV infection.

In the subgroup, that we were able to stratify by disease phase at baseline, we found the highest IRs of HCC in persons with liver cirrhosis and in those on antiviral treatment. Other studies have likewise found persisting increased risk of HCC the first years after treatment initiation.[43,44] All who developed HCC were men over the age of 50 years. Our findings support HCC surveillance in those with liver cirrhosis. Moreover, HCC surveillance may be needed in individuals who initiate antiviral treatment for chronic HBV infection if they have additional risk factors for HCC.[3] There were no cases of HCC in the group with HBeAg negative hepatitis. This may be due to a small number and that most with the true HBeAg negative hepatitis (continuously elevated HBV DNA and ALT and evidence of liver fibrosis or inflammation) started antiviral treatment. During follow up, 33% with HBeAg negative hepatitis started antiviral therapy. Likewise, there were no cases of HCC among those with HBeAg positive hepatitis. As expected, this group was younger (median age 27 years), and 29% initiated antiviral treatment during follow up, while 41% became HBeAg negative during follow up. Younger age, antiviral treatment and seroconversion are all factors that reduce risk of HCC. Like previous studies, we found low incidence of HCC liver-cirrhosis in persons with HBeAg negative disease.[12,29,32,38] Moreover, only men over the age of 45 initiated treatment due to liver disease progression. Current guidelines recommend monitoring every 3–12 months in this group.[2,3] Our results suggest that monitoring might not need to be that close in younger persons with stable HBeAg negative infection. However, studies in other populations have shown transition to active hepatitis also in younger persons with HBeAg negative disease.[12,45–47] Hence, this finding alone is not sufficient to cause a change in recommendations on monitoring frequency, but should be confirmed in other HBV populations resembling the one in Denmark.

The PAGE-B score was developed to assess HCC risk in Europeans with chronic HBV infection on antiviral therapy.[25] However, it has since been shown to offer good discrimination in both European and Asian populations.[48] Moreover, a Dutch study, including 557 treated and untreated persons, showed that PAGE-B discriminated risk for both HCC and any clinical event well.[8] Our study confirmed that PAGE-B discriminated well in a mainly non-cirrhotic population with chronic HBV infection, mixed ethnicity and low rate of HCC. Our study showed that persons with a PAGE-B score <10 have an extremely low risk of HCC and do not require surveillance.[3]

A major strength of the present study was the ability to use PINs to crosslink data between national registers and nationwide databases. This enabled us to include a large cohort gathered from several registers that represented not only those seen in specialized liver or infectious disease centers but also persons diagnosed, for instance, in general practice settings. Due to public registers, people were also only lost to follow up if they emigrated. Finally, we had clinical and laboratory data on a subset of the population which enabled us to determine incidence of liver events in different disease phases, and to calculate risk scores.

Limitations to this study include that we did not have power to estimate cumulative incidence of HCC stratified by age, sex, and region of origin, which are all important risk factors. We would also have preferred to stratify by HDV status. However, we did not have information about HDV co-infection for the majority of the study population. As a result, we were not able to point out all subgroups with high HCC incidence in whom HCC surveillance should be considered. A possible limitation was that the validity of the chronic HBV diagnosis in the NPR is low. However, we found similar IRs of HCC and decompensated cirrhosis when chronic HBV cases only registered in the NPR were excluded. Another limitation to our study is that we had to exclude a large portion of our study population in the evaluations stratified by disease phase and PAGE-B score due to missing baseline data. However, the median age, sex distribution, and overall IRs of HCC and decompensated liver cirrhosis were similar in all chronic HBV patients registered in DANHEP and those included in sub analyses. Our stratification by disease

phase was based on single baseline measurements and did not include an assessment of liver fibrosis. If liver fibrosis assessments had been available more might have been placed in the indeterminant group. Finally, the study population may not be representative of the entire chronic HBV population in Denmark. Those who are in contact with a doctor and thereby have the opportunity to be screened for HBV may differ from those who are not. Nonetheless, the study population does represent the chronic HBV patients seen in clinics in Denmark, for whom clinical decisions are made.

Conclusion

In conclusion, this study showed a low incidence of HCC and decompensated liver cirrhosis in persons with chronic HBV infection in Denmark. Moreover, our study showed that persons with liver cirrhosis, and those with a PAGE-B score ≥14, had an annual incidence of HCC above 0.2%, which has been suggested as a lower limit for offering HCC surveillance to persons with chronic HBV infection and no liver cirrhosis. Our data suggest that the PAGE-B score is useful for selecting patients with chronic HBV infection in Denmark for HCC surveillance.

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