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medLow Incidence of Adverse Outcomes in Adults with Chronic Hepatitis B Virus Infection in the Era of Antiviral Therapy

Short title: Clinical outcomes of CHB in era of antivirals

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Abbreviations:

ALT: alanine aminotransferase, APRI: AST to platelet ratio index, AST: aspartate aminotransferase, FIB-4: Fibrosis 4 markers, HBeAg: hepatitis B e antigen, HBRN: hepatitis B research network, HBsAg: hepatitis B surface antigen, HCC: hepatocellular carcinoma, NA: nucleos(t)ide analogue, PY: person-year, ULN: upper limit of normal

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Abstract (272/275 words)

Background and Aims:

Outcomes of persons with chronic HBV infection in the era of antiviral therapy are not well characterized. We determined the incidence and factors associated with clinical outcomes in a multiethnic, North American cohort of adults with chronic HBV infection, who were not on antiviral therapy at enrollment.

Methods:

Adults with chronic HBV infection, not receiving antiviral therapy, and without a history of decompensation, HCC or OLT were prospectively followed. Participants with known HIV, HCV or HDV coinfection were excluded. During follow-up, treatment could be initiated per standard of care. Clinical outcomes included: incident cirrhosis, decompensation, HCC, OLT and HBV-related death.

Results:

Among 1418 participants analyzed, 51.5% were women, median age 41.1 years, 75% Asian, 10% white, 13% black, 24% HBeAg(+), and 1.5% cirrhosis at baseline. During the study, 274 started treatment, 83 had an ALT flare, 118/330 initially HBeAg(+) became HBeAg(-), and 90/1329 became HBsAg(-). After 6641 person-years follow-up, 8 participants (4/21 with baseline cirrhosis) had 12 clinical outcomes (2 decompensation, 5 HCC, 2 OLT, 3 HBV-related deaths) and 19/1397 had incident cirrhosis. 21/26 participants had first outcome before treatment, none had become HBsAg(-) while 5/9 HBeAg(+) had become HBeAg(-) at time of first outcome. Cumulative percentage of clinical outcomes was 16% at year 4 in participants with baseline cirrhosis, and 2% (including incident cirrhosis) at year 7 in those without.

Conclusions:

Incidence of adverse outcomes was low in this closely monitored large cohort of North American adults with predominantly inactive, non-cirrhotic chronic HBV. Our data highlight the benefits of HBsAg loss and the importance of early diagnosis and treatment to prevent cirrhosis and other complications of chronic HBV infection.

Key words: Cirrhosis, hepatocellular carcinoma, liver transplant, hepatitis B surface antigen, nucleos(t)ide analogues

Introduction:

Chronic hepatitis B virus (HBV) infection is uncommon in the United States with an estimated population prevalence of 0.35% based on the National Health and Nutrition Examination Survey, corresponding to 840,000 persons. However, this may be an under-estimation of the true prevalence as persons at increased risk of infection, such as those who are homeless or incarcerated were not included, and until 2011, Asians, who have the highest prevalence of HBV infection were under-represented.

The majority of natural history studies in untreated chronic HBV infection have originated from Asia or Europe.[2-6] These studies have shown varying rates of cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality. While some of the discrepancies may be due to differences in study design, other factors, notably age at infection and HBV genotypes, may have contributed to the variable results.[2-8] Apart from the studies in Alaskan natives, there are limited data on the natural history of chronic HBV infection in adults living in North America.[9, 10]

The course of chronic HBV infection is dynamic, characterized by fluctuations in HBV replication and liver inflammation, and patients with inactive liver disease at presentation may progress to active disease or experience progressive disease during follow-up. Indeed, several studies have reported high rates of hepatic decompensation, HCC and liver-related mortality in patients who did not meet criteria for antiviral therapy at presentation and who did not receive treatment during follow-up.[3, 10, 11]

The availability of safe and potent antiviral therapy, in particular nucleos(t)ide analogues (NAs), in the last two decades has dramatically changed the outcomes of chronic HBV infection.

Antiviral therapy has been shown to be effective not only in suppressing HBV replication and decreasing liver inflammation but also in reversing liver fibrosis and in preventing cirrhosis, liver failure, HCC and liver-related mortality.[12-18] However, currently available therapies do not eradicate the virus and rarely result in clearance of hepatitis B surface antigen (HBsAg). Thus, professional society guidelines recommend treatment only in patients with cirrhosis or those with active disease at risk of progressive liver injury, and monitoring of patients who do not meet criteria for treatment.[19-21]

The Hepatitis B Research Network (HBRN) was funded by the National Institute of Diabetes and Digestive and Kidney Diseases in 2008 to investigate clinical, virological, and immunological characteristics of patients with HBV infection in the US and Canada. The HBRN cohort study enrolled persons with chronic HBV infection who were not receiving antiviral therapy and followed them prospectively per standard of care which included initiating antiviral treatment during follow-up if necessary. We analyzed data from the HBRN Adult Cohort Study to determine the incidence and factors associated with clinical outcomes in this large and diverse population of persons with chronic HBV infection.

Methods

Study design

The HBRN comprises 21 adult and 7 pediatric liver centers in the US and in Toronto, Canada. Details of the HBRN Adult Cohort Study protocol have been described.[22] In brief, consecutive, consenting, HBsAg positive patients, seen in outpatient clinics, who were not receiving antiviral therapy unless pregnant or were coinfected with HDV, and did not have a history of hepatic decompensation, HCC, liver transplant or known HIV or HCV infection were enrolled.

The baseline evaluation included detailed medical history, physical examination, health surveys, and blood tests. Recommended laboratory tests included complete blood count, liver panel, creatinine, international normalized ratio, alpha fetoprotein, HBV DNA level, HBV serologies (HBsAg, antibody against HBsAg, hepatitis B e antigen (HBeAg), and antibody against HBeAg),

and antibodies against HIV, HCV, and HDV. In addition, relevant clinical, laboratory, radiological, and histological data were extracted from past medical records. Participants were reassessed at week 12, 24 and then every 24 weeks, and additionally when participants experienced a flare in alanine aminotransferase (ALT), became HBeAg or HBsAg negative or became pregnant.

The protocol recommended testing for quantitative HBV DNA and qualitative HBeAg (for those who were HBeAg positive at enrollment) every 24 weeks and qualitative HBsAg every 48 weeks, and testing for hepatitis B e antibody and hepatitis B surface antibody among participants who cleared HBeAg or HBsAg. The protocol also recommended HCC surveillance per American Association for Study of Liver Diseases Guidelines on Hepatitis B. Standard of care tests were done at the local laboratories. Standardized cutoff values were chosen to define the upper limit of normal (ULN) for ALT: 30 U/L for men and 20 U/L for women. Research blood samples were collected at each visit, processed and stored at -70C at each site, and shipped in batches to a central repository for subsequent transfer to central testing laboratories. Follow-up ended with liver transplant or death.

Baseline cirrhosis was based on histology if available, and in the absence of biopsy by presence of 2 of the following 3 criteria: splenomegaly or nodular liver on radiological imaging, or platelet count <120,000/mm^3. Vibration-controlled transient elastography had not been approved for clinical care in the United States at the start of HBRN studies. Participants meeting these criteria within 24 weeks after enrollment were considered to have baseline cirrhosis after adjudication by an HBRN panel of investigators.

During follow-up, antiviral treatment could be initiated if a participant was enrolled in a HBRN treatment trial or if the physician initiated antiviral therapy per standard of care. There were two HBRN treatment trials: one for participants in the immune tolerant phase[23] and one for participants in either the HBeAg positive or HBeAg negative immune active phase.[24]

The protocol was approved by the institutional review boards or ethics committee of each participating institution and by a Data and Safety Monitoring Board appointed by NIDDK to oversee the HBRN studies. All participants gave written, informed consent. All authors had access to study data and reviewed and approved the final manuscript.

HBV testing

Quantitative HBV DNA, HBeAg, and HBsAg were performed at a central laboratory (University of Washington, Seattle, WA). HBV DNA levels were determined using a real-time PCR assay (COBAS Ampliprep/COBAS TaqMan HBV Test, v2.0; Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of detection of 10 IU/mL and lower limit of quantification of 20 IU/mL. Quantitative HBsAg and HBeAg were tested using the Roche Diagnostics Elecsys platform with lower limit of detection for HBsAg and HBeAg of 0.05 IU/mL and 0.3 IU/mL, respectively. Qualitative assays for HBsAg and HBeAg were also performed locally using commercially available enzyme immunoassays. HBV genotype was determined based on mass spectrometry, at the Molecular Epidemiology and Bioinformatics Laboratory in the Division of Viral Hepatitis at the Centers for Disease Control and Prevention.[25]

Central laboratory results were used when available and supplemented by local laboratory results when missing.

Study population

HBsAg positive patients ≥18 years old, enrolled in the HBRN Adult Cohort Study were included in this analysis unless they met one of the following exclusion criteria: acute HBV infection, HIV, HCV or HDV coinfection at enrollment; or had all labs while on treatment or within 24 weeks of stopping treatment for those who received treatment prior to enrollment, or while pregnant or within 24 weeks of end of pregnancy. Chronic HBV infection was defined by presence of HBsAg or HBV DNA for at least 6 months. Participants who either transferred from the HBRN Pediatric Cohort Study, who entered an HBRN treatment trial concurrently with the Adult Cohort Study, who did not have at least 1 follow-up visit >24 weeks after enrollment or who started antiviral

treatment that lasted ≥24 weeks within 24 weeks after enrollment were also excluded (**Figure 1**).

Baseline date was the date of enrollment into the HBRN Adult Cohort study. Values of HBsAg, HBeAg, HBV DNA, aspartate aminotransferase (AST), ALT, and platelets on the same day or closest to each other during the period from 24 weeks before to 18 weeks after enrollment were used as baseline labs. Baseline HBV clinical phenotypes were determined based on a combination of HBeAg status, HBV DNA level and ALT level as previously described.[26] AST to platelet ratio index (APRI) and Fibrosis 4 marker (FIB-4) were calculated as previously described.[27, 28] If there were multiple results for any component lab test within a study visit window, then the results closest to each other were used to calculate APRI and FIB-4.

Follow-up ended on January 28, 2019 or at the last date data were collected. For this analysis, follow-up data from participants at or after new diagnosis of HIV or HCV infection were excluded. Data from 111 participants (median 2 years follow-up prior to enrollment in the trial) after enrollment into an HBRN clinical trial were excluded from all analyses. Data from participants who started treatment per standard of care were included in all analyses except for analysis of ALT flare, and changes in APRI and FIB-4, where data after start of treatment were excluded.

Outcomes

The clinical outcomes analyzed were: hepatic decompensation, HCC, liver transplant, or HBV-related death. Given the low occurrence of individual outcomes, they were grouped and termed major clinical outcomes (**Supplementary Table 1**)*.* Among participants without baseline cirrhosis, incident (new diagnosis) cirrhosis was also determined. Other outcomes analyzed were non-HBV deaths, incident ALT flare (ALT ≥10 x ULN), initiation of antiviral therapy, ever becoming HBeAg negative for participants who were HBeAg positive at baseline, and ever becoming HBsAg negative. Initiation of antiviral therapy per standard of care was considered as an outcome because treatment might have averted a clinical outcome. In this study, only

treatment lasting ≥24 weeks was considered as an outcome, because shorter courses of treatment, most commonly prescribed in highly viremic pregnant women to prevent mother-to-child transmission, were not expected to impact clinical outcomes. Fibrosis progression was assessed based on changes in APRI (≤0.5, 0.5-2.0, >2.0) and FIB-4 (<1.45, 1.45-3.25, >3.25) categories. All outcomes were pre-defined and the occurrence and timing of the major clinical outcomes including incident cirrhosis and ALT flares were adjudicated by a committee of HBRN clinical investigators to determine if criteria for these outcomes were met (**Supplementary Table 1**).

Statistical analyses

Descriptive statistics are reported as medians (25th and 75th percentiles) for continuous variables and frequencies (percentages) for categorical variables. Distributions of baseline characteristics of participants with versus those without cirrhosis at baseline were compared using exact Pearson chi-square or Kruskal-Wallis tests as appropriate.

For each outcome, rates per 100 person-years (PY) and corresponding confidence intervals (CI) assuming a Poisson distribution are reported overall and by baseline characteristics and laboratory measures. Univariate associations between each outcome and each baseline measure were assessed from Poisson regression models. Exact CIs were calculated if the number of events in a category was <5 and p-values were exact if the number of events in any one category of a baseline measure was <5. Otherwise, asymptotic Wald statistics were used. The Kaplan-Meier method was used to estimate the cumulative probability of each outcome over time. For major clinical outcomes, time to first event was recorded. For incident hepatitis flare, follow-up ended when treatment was initiated. All outcomes were conditional on participants having more than 24 weeks of follow-up. The follow-up for incident cirrhosis, liver transplant, deaths and treatment initiation was reduced by 24 weeks since, by design, none of these events could occur within the first 24 weeks after enrollment. For APRI and FIB-4, the change in category from first result to last result, if at least 24 weeks after first, within each duration category (<96, 96-192, >192 weeks) prior to initiating treatment was summarized.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of participants

A total of 2032 participants were enrolled between January 2011 and Janurary 2018; of these, 614 were excluded (**Figure 1**). Among the 1418 participants included in this study, median age was 41.1 years, 51.5% were female, and most were Asian (74.6%), followed by blacks (12.7%), whites (10.0%), and other/mixed races (2.8%) (**Table 1**). Roughly one quarter (24.0%) were HBeAg positive, median HBV DNA was 3.6 $\log_{10}$ IU/mL, and median HBsAg was 3.4 $\log_{10}$ IU/mL. Genotypes B (40.2%) and C (33.4%) were most common followed by genotypes A (16.8%), D (6.7%), E (2.5%), and others (0.4%). Only 21 (1.5%) participants were considered to have cirrhosis at baseline. This was corroborated by a low percentage with APRI >2.0 (1.8%) or FIB-4 >3.25 (1.7%). Participants with baseline cirrhosis were older, more likely to be men, white, diabetic, had higher AST and lower platelet count. The most common phenotype was indeterminant (37.0%), followed by inactive carriers (24.2%), and HBeAg negative (17.4%) and HBeAg positive (17.2%) chronic hepatitis.

Incidence of major clinical outcomes and incident cirrhosis and associated baseline factors

After 6641 person-years of follow-up, 26 participants had a total of 31 clinical outcomes including incident cirrhosis (**Figure 2**). Among the 21 participants with baseline cirrhosis, 4 had major clinical outcomes including 3 HCC (2 followed by liver transplant and 1 followed by HBV-related death) and 1 HBV-related death. Of the 1397 participants without baseline cirrhosis, 22 had major clinical outcomes or incident cirrhosis: 18 with incident cirrhosis only, 1 incident cirrhosis at the same time as decompensation followed by HBV-related death, 2 HCC, and 1 hepatic decompensation.

The incidence rate per 100 PY for each individual outcome was low, hepatic decompensation (0.03), HCC (0.08), liver transplant (0.03), HBV-related death (0.05), and incident cirrhosis (0.32)

(**Table 2**). Eight participants (4 with and 4 without baseline cirrhosis) had major clinical outcomes with incidence of 0.12 per 100 PY (95% CI = 0.06, 0.24). Cumulative percentages of major clinical outcomes at Years 4 and 7 were 0.5% and 1%, respectively for the overall cohort. The incidence rate of major clinical outcomes was 4.79 per 100 PY (95% CI = 1.80, 12.75) and the cumulative percentage at Year 4 was 16% for those with baseline cirrhosis; while the incidence rate was 0.06 per 100 PY (95% CI = 0.02, 0.16) and the cumulative percentages were 0.2% at Year 4 and 0.5% at Year 7 for those without baseline cirrhosis (**Figure 3A**).

Among the participants without cirrhosis at baseline, incident cirrhosis was assessed in addition to major clinical outcomes. Incident cirrhosis or major clinical outcomes occurred in 22 participants with incidence rate of 0.34 per 100 PY (95% CI = 0.22, 0.51) and the cumulative percentages were 2% at both Year 4 and Year 7 (**Figure 3B**).

Among the 21 participants with baseline cirrhosis, the four participants who developed major clinical outcomes were older, more likely to be white, had lower baseline HBV DNA, quantitative HBsAg and platelet count than the other 17 who did not develop major clinical outcomes.

Among the 1397 participants without baseline cirrhosis, the 22 participants who met a criterion for major clinical outcomes or incident cirrhosis were older, more likely to be men, had higher APRI, and lower platelet counts at baseline compared to those who did not meet criteria for these outcomes (**Table 3**).

Characteristics of participants with major clinical outcomes or incident cirrhosis
Of the 26 participants who had a major clinical outcome or incident cirrhosis, 5 had started antiviral therapy, none had become HBsAg negative, and 5 of 9 HBeAg positive participants had become HBeAg negative prior to their first outcome.

Eight participants (7 men, median age 57 years, 4 white, 1 black, 3 Asians) had a total of 12 major clinical outcomes (**Figure 2 and Table 4**). Of these, 4 had one outcome each and 4 had two outcomes each. Two participants had started antiviral treatment prior to and 2 others after their first outcome, while 4 (including 2 with persistently undetectable HBV DNA) never received treatment. None of the 8 participants with major clinical outcomes had experienced ALT flares. All 8 were still HBsAg positive at the time of first outcome. Of the two participants who were initially HBeAg positive, one had become negative and the other remained HBeAg positive at the time of first outcome.

Hepatocellular carcinoma

Of the five participants with HCC (nos. 112, 933, 1157, 1287, and 1432), 3 had cirrhosis at baseline including 2 with persistently undetectable HBV DNA and did not receive antiviral treatment and the third started treatment but HCC was diagnosed nearly a year later despite having undetectable HBV DNA (**Table 4**). The other 2 participants with HCC had no evidence of cirrhosis at baseline or throughout the study; one of these two started treatment, but despite suppression of HBV DNA to undetectable level was diagnosed to have HCC 2.6 years later.

Hepatic decompensation

Two participants (no. 113 and 729) without baseline cirrhosis developed hepatic decompensation, one was found to have cirrhosis at the time of decompensation, but despite starting treatment immediately after decompensation had an HBV-related death 1.6 years later.

HBV-related death

Three participants were considered to have HBV-related deaths, 1 following hepatic decompensation (no. 729), 1 after HCC (no. 1157), and 1 following sepsis attributed to cirrhosis (no. 134). One participant started antiviral therapy upon diagnosis of hepatic decompensation while the other two had not been treated.

Incident cirrhosis

Eighteen participants met criteria for incident cirrhosis only (15 men, median age 49 years, 3 white, 5 black, 10 Asian) a median of 1.4 years after enrollment with no major clinical outcomes during median subsequent follow-up of 3.5 years. Three participants had started treatment before and 5 others started treatment after the finding of incident cirrhosis. Ten participants did not start treatment; of these, 1 had undetectable HBV DNA and 2 had HBV DNA <3 log10 IU/mL throughout the study and the remaining 7 had HBV DNA ≥3 log10 IU/mL. Of these 18 participants, 2 had an ALT flare 40 and 16 weeks before cirrhosis diagnosis, 3 of 7 initially HBeAg positive remained HBeAg positive, and all remained HBsAg positive at the time of cirrhosis diagnosis.

Deaths

A total of 16 participants were known to have died during the study, 3 were adjudicated to be HBV-related (2 in those with and 1 in those without baseline cirrhosis). Cumulative probabilities of HBV-related and all-cause mortality at Year 7 were 0.4% and 2.0%, respectively.

Incidence of other outcomes and associated baseline factors

Treatment initiation per standard of care

During the study, 274 participants initiated antiviral therapy (13 with baseline cirrhosis and 8 with incident cirrhosis) per standard of care that lasted at least 24 weeks. Of these, only one received pegylated interferon and the remainder NA therapy. The incidence rate of treatment initiation was 5.45 per 100 PY and cumulative percentage by Year 7 was 27% (**Table 2 and Figure 3C**). These participants were more likely to be Asian, HBeAg-positive, and to have cirrhosis, HBV genotype C, higher HBV DNA, HBsAg, ALT and APRI, and lower platelet counts at baseline than those who did not start treatment (**Supplementary Table 2**).

Serum ALT flare ≥10 x ULN

Eighty-three participants had at least one incident ALT flare (incidence = 1.51 per 100 PY) yielding cumulative percentage at Year 7 of 8% (**Table 2 and Figure 4**). These participants were

younger, more likely to be HBeAg positive, and to have cirrhosis, higher HBV DNA, HBsAg, ALT and APRI but lower platelet count at baseline than those who did not have ALT flare (**Supplementary Table 3**). The vast majority (96%, 80 of 83) did not have any clinical outcome or incident cirrhosis after the flare, though 33 started treatment after the flare.

Transition to HBeAg or HBsAg negative status

Of the 330 participants who were HBeAg positive at enrollment and had follow-up HBeAg testing, 118 became HBeAg negative (incidence = 11.69 per 100 PY) with cumulative percentage by Year 7 of 55% (**Table 2 and Supplementary Figure 1A**). Rates of clinical outcomes were similar in those who became HBeAg negative as those who remained positive. The participants who became HBeAg negative were older, more likely to have genotype A infection, and to have lower HBV DNA and HBsAg levels at baseline than those who remained HBeAg positive. Of the 118 participants who became HBeAg negative, 82 did so spontaneously and the other 36 a median of 1.7 years after treatment initiation.

Ninety of the 1329 participants with follow-up HBsAg tests became HBsAg negative (incidence = 1.52 per 100 PY) with cumulative percentage by Year 7 of 12% (**Table 2 and Supplementary Figure 1B**). None of the participants who became HBsAg negative subsequently experienced any clinical outcome. The participants who became HBsAg negative were older, more likely to be men, non-Asian, HBeAg negative, and to have lower HBV DNA and HBsAg levels and normal AST and ALT at baseline than those who remained HBsAg positive. Of the 90 participants who became HBsAg negative, 86 did so spontaneously and the other 4 a median of 3.1 years after treatment initiation.

Changes in APRI or FIB-4 categories

Liver fibrosis remained largely unchanged with 80-88% participants remaining in the same APRI or FIB-4 category during follow-up and similar proportions moved either up or down 1 category, and ≤1% moved 2 categories.

Discussion

The large number of participants in the HBRN Adult Cohort Study with diverse race and HBV genotypes and a median follow-up of 5 years (maximum 8 years) provided a unique opportunity to examine the outcomes of mostly untreated patients with inactive chronic HBV infection residing in North America.

We found a very low rate (2% at 7 years) of clinical outcomes (incident cirrhosis, hepatic decompensation, HCC, liver transplant, or HBV-related deaths) in this contemporary cohort followed at liver centers in the US and in Toronto, Canada. This contrasts with reports in the 1980s and 1990s prior to the availability of antiviral therapy where combined rates of cirrhosis and HCC development among patients with chronic hepatitis B were 10 to 20% after 5 year follow-up with evolution to cirrhosis being more common in European studies and HCC more common in Asian studies.[4, 5, 29] Our results also differ from the more recent REVEAL study in Taiwan which enrolled 3653 untreated persons with chronic HBV infection enrolled from the community between 1991 and 1992, in which 10.2%, 4.5%, and 4.5% participants had incident cirrhosis, HCC, and liver-related mortality after a median follow-up of 11-12.5 years.[3, 30-32]

There are several reasons why the outcomes of our study were more favorable, foremost being the exclusion of patients that were receiving antiviral therapy at the time of enrollment. Given that guidelines recommend patients with advanced fibrosis or cirrhosis and those with active liver disease should receive antiviral therapy, the HBRN Adult Cohort Study by design targeted patients with less active and/or less advanced liver disease for enrollment. Indeed, only 1.5% participants were deemed to have baseline cirrhosis and only 35% were classified as having HBeAg positive or HBeAg negative chronic hepatitis. In fact, a third of the participants had normal baseline ALT using lower gender-based ULN, outcomes of which had not been reported in previous natural history studies.

Although our cohort was not dissimilar to the REVEAL cohort in sex, age, preponderance of subjects being HBeAg negative, low percent with cirrhosis (1.5% vs. 2%) and not receiving antiviral therapy at baseline, there were major differences. All participants in the REVEAL cohort were Chinese who likely acquired HBV infection perinatally or during early childhood, and were infected with HBV genotypes B or C. Though the majority of our cohort were Asians with genotypes B and C, our cohort also included 10% whites and 13% blacks, and 26% were infected with HBV genotypes other than B or C. Another major difference was that our cohort began one decade later than the REVEAL cohort, when NA therapy was widely available. Indeed, 19% of participants in our study started antiviral therapy per standard of care, and treatment might have averted clinical outcomes in some of these participants. One additional difference was that duration of follow-up in our study was shorter than the REVEAL study.

Multiple studies have shown that antiviral therapy, particularly long-term NA therapy, decrease the risk of clinical outcomes but does not completely eliminate HCC risk.[13-18] One study of 1951 Caucasians with chronic hepatitis B including 27% with cirrhosis who had received either entecavir or tenofovir for >5 years found that risk factors for HCC after year 5 included age older than 50, and lower platelets at both baseline and year 5.[14] In our study, both participants who developed HCC while receiving NA therapy were older than 50.

As expected, we found a marked difference in clinical outcomes between participants with and those without baseline cirrhosis. Previous studies have shown that clinical outcomes are associated with male gender, older age, HBV genotype C, higher HBV DNA, higher ALT, and cirrhosis,[2-4, 6, 30, 33] and HCC is more common among Asians and blacks than whites.[34] While the low incidence of clinical outcomes in this study preclude meaningful analysis of baseline and longitudinal factors, among the 8 participants with major clinical outcomes, 7 were men and median age was 57 years. However, despite predominance of Asians, half (4 of 8) of the participants (2 of 5 with HCC) with major clinical outcomes were white. The significance of our finding is unclear given the small numbers.

Increasing attention has been given to whether or not patients with minimally elevated or normal ALT would benefit from antiviral therapy but the data are difficult to interpret because of the varied definition of normal ALT.[35-37] In our study, 18 participants who did not receive antiviral therapy before having first major clinical outcome or incident cirrhosis had detectable baseline HBV DNA. Of these, 8 (1 with and 7 without baseline cirrhosis) would have met AASLD guidelines (HBV DNA >20,000 IU/mL for HBeAg-positive and >2,000 IU/mL for HBeAg-negative patients and ALT >2x ULN) for treatment. However, not all 18 would have met criteria for treatment even if the criteria were expanded to include lower HBV DNA cutoff or ALT 1-2x ULN.

Severe hepatitis flares can precipitate hepatic decompensation in patients with advanced fibrosis or cirrhosis, and recurrent hepatitis flares may increase the risk of cirrhosis and HCC. In this study, 83 untreated participants had at least one incident ALT flare. None of the participants with major clinical outcomes had a documented ALT flare during follow-up while 2 of 18 participants with incident cirrhosis had transient ALT flare prior to diagnosis of incident cirrhosis. The other participants did not have any clinical outcomes following the flare, though 33 started treatment after the first flare which might have averted outcomes.

HBeAg clearance and HBsAg clearance have been shown to improve clinical outcomes.[2, 4 38-40] In this study, of the 26 participants with clinical outcomes, none had become HBsAg negative prior to the outcomes while 5 of 9 participants who were initially HBeAg positive became HBeAg negative prior to their first outcome. Of note, majority of participants who became HBeAg negative or HBsAg negative did so spontaneously.

The strengths of our study include the large number of participants of diverse race and HBV genotypes in contrast to studies in Asia which included only Asians with genotypes B and C and studies in Europe which included mostly Caucasians with genotypes A and D. In addition, we used central labs for HBV testing and adjudicated clinical outcomes. Nevertheless, our study has several limitations. First, it was clinic based and not population based; however, the enrollment of patients not receiving treatment more closely mimics patients in the community than those

seen in academic liver centers. Second, neither liver biopsy nor liver elastography measurements were routinely available to corroborate disease activity and extent of fibrosis but the low percentage of patients with baseline cirrhosis was corroborated by APRI and FIB-4. Another perceived limitation is that 19% of our participants started antiviral therapy during the study (additional 8% enrolled into HBRN clinical trials but data after enrollment into trials were excluded from analysis), which might have altered the clinical course. We however, view this as a strength since this represents the current standard of care.

In summary, we found a low incidence of adverse outcomes in this large cohort of racially diverse persons with chronic HBV infection living in North America. The majority of clinical outcomes occurred in patients with cirrhosis at baseline or during follow-up and none in participants who lost HBsAg, confirming the clinical benefits of HBsAg loss in the absence of cirrhosis – the definition of functional cure of hepatitis B. Our data support that early diagnosis, linkage to care, close monitoring, and treatment initiation when indicated, can prevent adverse outcomes and that treatment upon diagnosis may not be necessary for all patients.

Figure Legends

Figure 1: Flow Chart Showing Selection of HBRN Adult Participants for Analysis.

Figure 2: Clinical Outcomes by Baseline Cirrhosis. Outcomes of interest: decompensation, HCC, liver transplantation, HBV-related death, and incident cirrhosis shown in bolded boxes. 26 participants had outcomes of interest: 8 major clinical outcomes and 18 with incident cirrhosis and no further clinical outcomes. No. in parentheses indicate no. of outcomes that occurred after HBV treatment initiation.

Figure 3A: **Cumulative Probability of Major Clinical Outcomes by Baseline Cirrhosis.** *Major clinical outcomes* – first of decompensation, HCC, liver transplantation, or HBV-related death.

Figure 3B: **Cumulative Probability of Major Clinical Outcomes or Incident Cirrhosis among Participants without Baseline Cirrhosis.**

Figure 3C: **Cumulative Probability of Initiation of HBV Treatment.** Only treatment lasting ≥24 weeks was considered.

Figure 4: **Cumulative Probability of Incident ALT Flares**

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REFERENCES

1. Le MH, Yeo YH, Cheung R, et al. Chronic Hepatitis B Prevalence Among Foreign-Born and U.S.-Born Adults in the United States, 1999-2016. Hepatology 2020;71:431-443.

2. Liaw YF. Natural history of chronic hepatitis B virus infection and long-term outcome under treatment. Liver Int 2009;29 Suppl 1:100-7.

3. Iloeje UH, Yang HI, Chen CJ. Natural history of chronic hepatitis B: what exactly has REVEAL revealed? Liver Int 2012;32:1333-41.

4. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008;48:335-52.

5. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. J Hepatol 2001;34:306-13.

6.   Yu MW, Yeh SH, Chen PJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst 2005;97:265-72.

7.   Shimakawa Y, Lemoine M, Njai HF, et al. Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. Gut 2016;65:2007-2016.

8.   Ching LK, Gounder PP, Bulkow L, et al. Incidence of hepatocellular carcinoma according to hepatitis B virus genotype in Alaska Native people. Liver Int 2016;36:1507-15.

9.   McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49:S45-55.

10.   Tong MJ, Hsien C, Hsu L, et al. Treatment recommendations for chronic hepatitis B: an evaluation of current guidelines based on a natural history study in the United States. Hepatology 2008;48:1070-8.

11.   Aberra H, Desalegn H, Berhe N, et al. The WHO guidelines for chronic hepatitis B fail to detect half of the patients in need of treatment in Ethiopia. J Hepatol 2019;70:1065-1071.

12.   Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468-75.

13.   Wong GL, Chan HL, Mak CW, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. Hepatology 2013;58:1537-47.

14.   Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444-1453.

15.   Wu CY, Lin JT, Ho HJ, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology 2014;147:143-151 e5.

16.   Su TH, Hu TH, Chen CY, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755-1764.

17.   Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. J Hepatol 2018;68:1129-1136.

18.   Gordon SC, Lamerato LE, Rupp LB, et al. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. Clin Gastroenterol Hepatol 2014;12:885-93.

19.   Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.

20.   European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398.

21.   Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.

22.   Ghany MG, Perrillo R, Li R, et al. Characteristics of adults in the hepatitis B research network in North America reflect their country of origin and hepatitis B virus genotype. Clin Gastroenterol Hepatol 2015;13:183-92.

23.   Feld JJ, Terrault NA, Lin HS, et al. Entecavir and Peginterferon Alfa-2a in Adults With Hepatitis B e Antigen-Positive Immune-Tolerant Chronic Hepatitis B Virus Infection. Hepatology 2019;69:2338-2348.

24.   University of Pittsburgh NCfRR. HBRN Combination Therapy of Pegylated Interferon Alfa-2a and Tenofovir Versus Tenofovir Monotherapy in Chronic Hepatitis B (HBRN). Clinicaltrials.gov 2020.

25.   Ganova-Raeva L, Ramachandran S, Honisch C, et al. Robust hepatitis B virus genotyping by mass spectrometry. J Clin Microbiol 2010;48:4161-8.

26.   Di Bisceglie AM, Lombardero M, Teckman J, et al. Determination of hepatitis B phenotype using biochemical and serological markers. J Viral Hepat 2017;24:320-329.

27.   Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26.

28.   Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25.

29.   Yu MW, Hsu FC, Sheen IS, et al. Prospective study of hepatocellular carcinoma and liver cirrhosis in asymptomatic chronic hepatitis B virus carriers. Am J Epidemiol 1997;145:1039-47.

30.   Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.

31.   Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-86.

32.   Iloeje UH, Yang HI, Jen CL, et al. Risk and predictors of mortality associated with chronic hepatitis B infection. Clin Gastroenterol Hepatol 2007;5:921-31.

33. Yang HI, Yeh SH, Chen PJ, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J Natl Cancer Inst 2008;100:1134-43.

34. Yang JD, Altekruse SF, Nguyen MH, et al. Impact of country of birth on age at the time of diagnosis of hepatocellular carcinoma in the United States. Cancer 2017;123:81-89.

35. Hoang JK, Yang HI, Le A, et al. Lower liver cancer risk with antiviral therapy in chronic hepatitis B patients with normal to minimally elevated ALT and no cirrhosis. Medicine (Baltimore) 2016;95:e4433.

36. Shim JJ, Kim JW, Oh CH, et al. Serum alanine aminotransferase level and liver-related mortality in patients with chronic hepatitis B: A large national cohort study. Liver Int 2018;38:1751-1759.

37. Choi GH, Kim GA, Choi J, et al. High risk of clinical events in untreated HBeAg-negative chronic hepatitis B patients with high viral load and no significant ALT elevation. Aliment Pharmacol Ther 2019;50:215-226.

38. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002;35:1522-7.

39. Kim GA, Lim YS, An J, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 2014;63:1325-32.

40. Liu J, Yang HI, Lee MH, et al. Spontaneous seroclearance of hepatitis B seromarkers and subsequent risk of hepatocellular carcinoma. Gut 2014;63:1648-57.

Table 1: Baseline Characteristics of Participants with and without Cirrhosis

Characteristics	All n=1418	With Baseline Cirrhosis n=21	Without Baseline Cirrhosis n=1397
Age at Enrollment (Years)	**n=1418**	**n=21**	**n=1397**
Median (25th:75th)	41.1 (32.9 : 51.5)	50.7 (42.4 : 57.3)	41.0 (32.9 : 51.4)
Sex	**n=1418**	**n=21**	**n=1397**
Female	730 (51.5%)	6 (28.6%)	724 (51.8%)
Race	**n=1415**	**n=21**	**n=1394**
White	142 (10.0%)	5 (23.8%)	137 (9.8%)
Black	179 (12.7%)	3 (14.3%)	176 (12.6%)
Asian	1055 (74.6%)	11 (52.4%)	1044 (74.9%)

Characteristics	All n=1418	With Baseline Cirrhosis n=21	Without Baseline Cirrhosis n=1397
Other/Mixed	39 (2.8%)	2 (9.5%)	37 (2.7%)
Continent of Birth	**n=1414**	**n=21**	**n=1393**
Africa	139 (9.8%)	1 (4.8%)	138 (9.9%)
Asia	972 (68.7%)	11 (52.4%)	961 (69.0%)
Europe	43 (3.0%)	1 (4.8%)	42 (3.0%)
North America	249 (17.6%)	8 (38.1%)	241 (17.3%)
South America	8 (0.6%)	0 (0.0%)	8 (0.6%)
Australia	3 (0.2%)	0 (0.0%)	3 (0.2%)
HBeAg Status	**n=1379**	**n=20**	**n=1359**
Positive	331 (24.0%)	6 (30.0%)	325 (23.9%)
HBV DNA ($\log_{10}$ IU/mL)	**n=1417**	**n=21**	**n=1396**
Median (25th:75th)	3.6 (2.6 : 5.6)	3.7 (1.8 : 5.8)	3.6 (2.6 : 5.5)
Quant HBsAg ($\log_{10}$ IU/mL)	**n=1354**	**n=20**	**n=1334**
Median (25th:75th)	3.39 (2.67 : 4.11)	3.14 (2.45 : 3.92)	3.40 (2.67 : 4.11)
HBV Genotype	**n=1301**	**n=17**	**n=1284**
A	219 (16.8%)	4 (23.5%)	215 (16.7%)
B	523 (40.2%)	3 (17.6%)	520 (40.5%)
C	434 (33.4%)	7 (41.2%)	427 (33.3%)
D	87 (6.7%)	2 (11.8%)	85 (6.6%)
E	33 (2.5%)	1 (5.9%)	32 (2.5%)
Mixed/Other	5 (0.4%)	0 (0.0%)	5 (0.4%)
APRI	**n=1209**	**n=21**	**n=1188**
≤0.5	943 (78.0%)	3 (14.3%)	940 (79.1%)
>0.5 - 2	244 (20.2%)	15 (71.4%)	229 (19.3%)
>2	22 (1.8%)	3 (14.3%)	19 (1.6%)
FIB-4	**n=1209**	**n=21**	**n=1188**
<1.45	966 (79.9%)	6 (28.6%)	960 (80.8%)
1.45 - 3.25	222 (18.4%)	11 (52.4%)	211 (17.8%)
>3.25	21 (1.7%)	4 (19.0%)	17 (1.4%)

Characteristics	All	With Baseline Cirrhosis	Without Baseline Cirrhosis
	n=1418	**n=21**	**n=1397**
HBV Phenotype	**n=1337**	**n=20**	**n=1317**
Immune tolerant	55 (4.1%)	0 (0.0%)	55 (4.2%)
HBeAg+ CHB	230 (17.2%)	5 (25.0%)	225 (17.1%)
HBeAg- CHB	233 (17.4%)	3 (15.0%)	230 (17.5%)
Inactive carrier	324 (24.2%)	4 (20.0%)	320 (24.3%)
Indeterminant	495 (37.0%)	8 (40.0%)	487 (37.0%)
Platelets (x10³/mm³)	**n=1219**	**n=21**	**n=1198**
Median (25th:75th)	219.0 (182.0 : 256.0)	142.0 (106.0 : 181.0)	220.0 (183.0 : 257.0)
AST x ULN [a]	**n=1379**	**n=21**	**n=1358**
≤1 x ULN	1103 (80.0%)	8 (38.1%)	1095 (80.6%)
>1 - 2 x ULN	211 (15.3%)	9 (42.9%)	202 (14.9%)
>2 x ULN	65 (4.7%)	4 (19.0%)	61 (4.5%)
ALT x ULN [b]	**n=1401**	**n=21**	**n=1380**
≤1 x ULN	466 (33.3%)	4 (19.0%)	462 (33.5%)
>1 - 2 x ULN	622 (44.4%)	9 (42.9%)	613 (44.4%)
>2 x ULN	313 (22.3%)	8 (38.1%)	305 (22.1%)
Albumin (g/dL)	**n=1344**	**n=21**	**n=1323**
Median (25th:75th)	4.3 (4.1 : 4.6)	3.9 (3.8 : 4.3)	4.3 (4.1 : 4.6)
Total Bilirubin (mg/dL)	**n=1371**	**n=21**	**n=1350**
Median (25th:75th)	0.6 (0.4 : 0.8)	0.8 (0.6 : 1.0)	0.6 (0.4 : 0.8)
Ever received HBV Treatment	**n=1418**	**n=21**	**n=1397**
Yes	194 (13.7%)	2 (9.5%)	192 (13.7%)
BMI (kg/m²)	**n=1296**	**n=20**	**n=1276**
Median (25th:75th)	24.1 (21.6 : 27.0)	26.2 (24.6 : 31.1)	24.0 (21.6 : 27.0)
Diabetes	**n=1415**	**n=21**	**n=1394**
Yes	77 (5.4%)	5 (23.8%)	72 (5.2%)
NIAAA Alcohol Risk Level in Past 12 Months [c]	**n=1410**	**n=21**	**n=1389**
At-Risk	100 (7.1%)	2 (9.5%)	98 (7.1%)

Outcome	No. of Participants with Outcome	Incidence/100 person-years (95% CI)

[a] Includes those with baseline cirrhosis

[b] First of decompensation, HCC, liver transplant or HBV-related death

[c] First of major clinical outcomes or incident cirrhosis

[d] Treatment only considered if lasted ≥24 weeks

Table 3: Incidence Rates of Major Clinical Outcomes or Incident Cirrhosis among 1397 Participants without Baseline Cirrhosis

Baseline Characteristic		No. of Participants	No. with Outcome	Total PY	Incidence/100 PY (95% CI) [a]
Age (Years)	<30	249	1	1080	0.09 (0.01, 0.66)
	30 - 50	752	10	3470	0.29 (0.16, 0.54)
	>50	396	11	1941	0.57 (0.31, 1.02)
Sex	Male	673	19	3063	0.62 (0.40, 0.97)
	Female	724	3	3429	0.09 (0.03, 0.27)
Race	White	137	4	689	0.58 (0.22, 1.55)
	Black	176	6	760	0.79 (0.35, 1.76)
	Asian	1044	12	4856	0.25 (0.14, 0.44)
	Other/Mixed	37	0	177	–
HBeAg Status	Negative	1034	12	4954	0.24 (0.14, 0.43)
	Positive	325	8	1366	0.59 (0.29, 1.17)
HBV DNA ($\log_{10}$ IU/mL)	<3	488	6	2296	0.26 (0.12, 0.58)

Baseline Characteristic		No. of Participants	No. with Outcome	Total PY	Incidence/100 PY (95% CI) [a]
	3 - 5	485	9	2404	0.37 (0.19, 0.72)
	>5	423	7	1788	0.39 (0.19, 0.82)
qHBsAg (log$_{10}$ IU/mL)	<3	459	5	2217	0.23 (0.09, 0.54)
	3 - 4	495	10	2361	0.42 (0.23, 0.79)
	>4	380	5	1627	0.31 (0.13, 0.74)
HBV Genotype	A	215	8	941	0.85 (0.43, 1.70)
	B	520	6	2425	0.25 (0.11, 0.55)
	C	427	6	1994	0.30 (0.14, 0.67)
	D	85	1	444	0.23 (0.03, 1.60)
	E	32	1	126	0.79 (0.11, 5.62)
	Mixed/Other	5	0	30	–
APRI	≤0.5	940	8	4580	0.17 (0.09, 0.35)
	>0.5 - 2	229	9	920	0.98 (0.51, 1.88)
	>2	19	2	82	2.43 (0.61, 9.72)
FIB-4	<1.45	960	3	4556	0.07 (0.02, 0.20)
	1.45 - 3.25	211	12	969	1.24 (0.70, 2.18)
	>3.25	17	4	58	6.91 (2.59, 18.40)
Platelets (x10^3/mm^3)	<150	94	6	371	1.62 (0.73, 3.60)
	≥150	1104	13	5266	0.25 (0.14, 0.43)
AST x ULN	≤1 x ULN	1095	10	5256	0.19 (0.10, 0.35)
	>1 - 2 x ULN	202	6	815	0.74 (0.33, 1.64)
	>2 x ULN	61	4	250	1.60 (0.60, 4.27)
ALT x ULN	≤1 x ULN	462	6	2177	0.28 (0.12, 0.61)

Baseline Characteristic		No. of Participants	No. with Outcome	Total PY	Incidence/100 PY (95% CI) [a]
	>1 - 2 x ULN	613	6	2971	0.20 (0.09, 0.45)
	>2 x ULN	305	9	1279	0.70 (0.37, 1.35)

[a] Confidence interval (CI) based on Wald

PY = person-years; APRI = AST-platelet ratio index; FIB-4 = Fibrosis 4 markers; ULN = upper limit of normal

Table 4: Characteristics of Participants with Clinical Outcomes[a]

ID	Sex Age	Race	Genotype	Cirrhosis at Wk 0	HBeAg at Wk 0	Outcomes (Timing, Wk)	HBV DNA, log$_{10}$ IU/mL Wk 0 / At first outcome	ALT xULN Wk 0 / At first outcome	Platelet x10^3/mm^3 Wk 0 / At first outcome	Treatment Start
113	M 48	B	B	No	Neg	Decomp (172), Other death (180)	3.1 / 2.2	0.5 / 1.5	175 / 195	No
729	M 55	W	A	No	Pos	Cirrh & decomp (173), HBV death (258)	8.5 / 8.4	2.1 / 5.3	248 / 138	Wk 174
112	M 64	W	A	Yes	Neg	HCC (75), LT (86)	UD / UD	1.0 / 1.6	67 / 81	No
933	F 54	A	C	Yes	Pos	HCC (76), LT (338)	5.8 / UD	2.5 / 1.9	136 / 86	Wk 28
1157	M 66	W	Unk	Yes	Neg	HCC (69), HBV death (103)	UD / UD	0.9 / 1.0	61 / 53	No
1287	M 59	A	B	No	Neg	HCC (252)	5.0 / UD	0.9 / 1.1	225 / 198	Wk 116
1432	M 65	A	C	No	Neg	HCC (259)	3.5 / 3.2	1.1 / 1.7	231 / 226	Wk 285

| 134 | M 35 | W | Unk | Yes | Unk | HBV death (257) | 1.5 / Unk | 1.4 / Unk | 93 / Unk | No |

[a] Hepatic decompensation, hepatocellular carcinoma (HCC), liver transplant (LT) or HBV-related death

M = male, F = female, B = black, W = white, A = Asian

UD = below lower limit of detection or lower limit of quantification

Unk = unknown

Wk = week

Author contributions:

Conceptualization: ASL, RP, CL, SB, MGG, MK, RKS, HLAJ

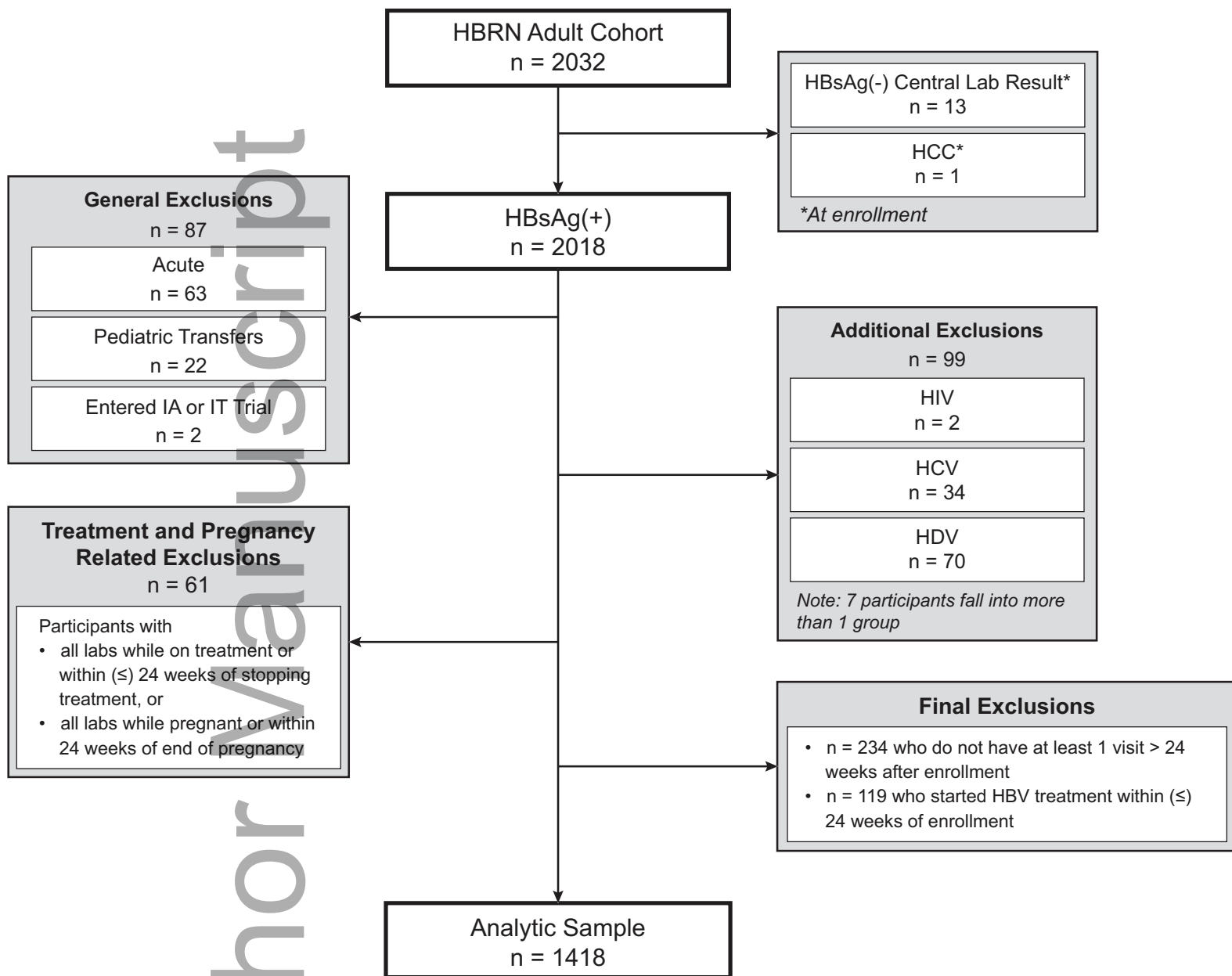Data curation: ASL, RP, CL, SB, MGG, MK, RKS, HLAJ

Formal analysis: CL, SB

Investigation: ASL, RP, MF, MGG, MK, RF, RKS, NT, JF, AD, DL, MS, MH, HLAJ

Writing original draft: ASL, RP, CL, SB, MGG, MK, RF, RKS, HLAJ
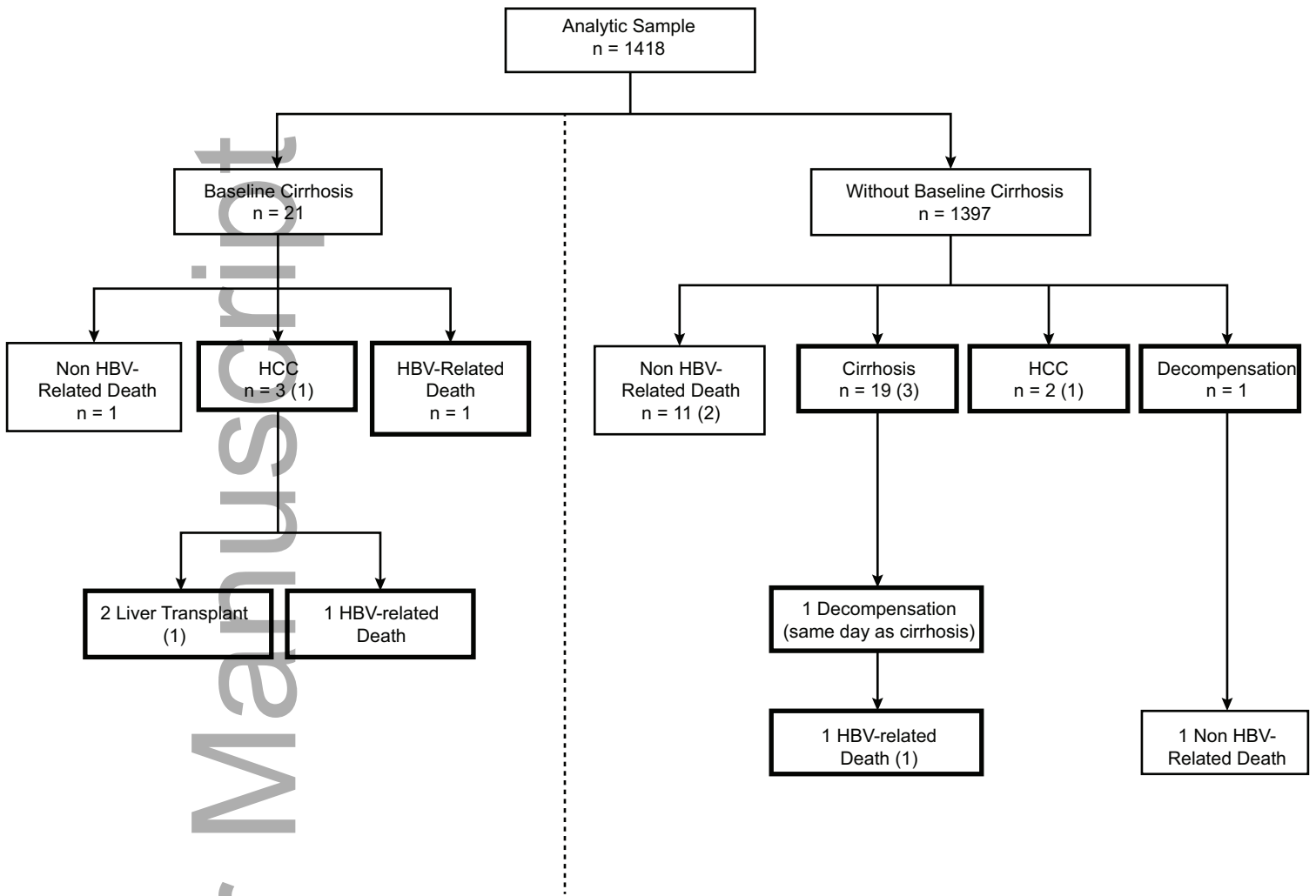
Writing – review & editing: ASL, RP, CL, MF, SB, MGG, MK, RF, RKS, NT, JF, AD, DL, MS, MH, HLAJ

Figure 1: Flow Chart Showing Selection of HBRN Adult Cohort Participants for Analysis
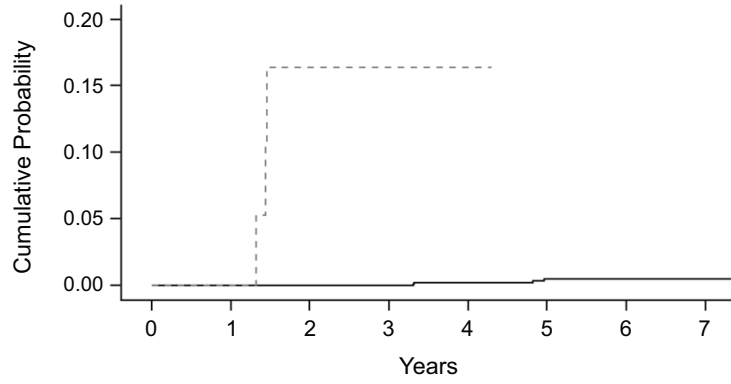

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Figure 2: Clinical Outcomes by Baseline Cirrhosis

Bolded boxes represent outcomes of interest
No. in parentheses indicate no. of outcomes that occurred after HBV treatment initiation

hep_31554_f2.eps

Figure 3A: Cumulative Probability of Major Clinical Outcomes by Baseline Cirrhosis

Cumulative Probability

0.20
0.15
0.10
0.05
0.00

0   1   2   3   4   5   6   7

Years

At Risk by Baseline Cirrhosis

	0	1	2	3	4	5	6	7
No (4)	1397	1282	1113	983	843	723	575	289
Yes (4)	21	19	14	13	11	7	5	2

Cumulative Probability by Baseline Cirrhosis

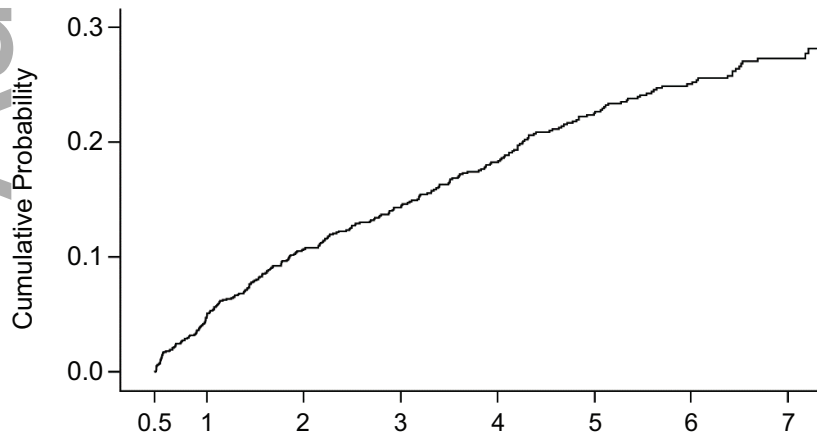|		1	2	3	4	5	6	7
No		0	0	0	0.002	0.005	0.005	0.005
Yes		0	0.16	0.16	0.16	.	.	.

Figure 3B: Cumulative Probability of Major Clinical Outcome or Incident Cirrhosis among Participants without Baseline Cirrhosis (22 events)

Cumulative Probability

0.20
0.15
0.10
0.05
0.00

0   1   2   3   4   5   6   7

Years
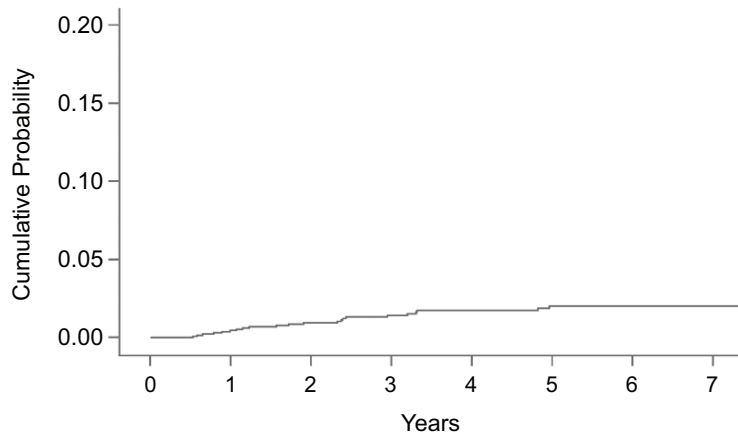
At Risk

1397	1276	1104	974	833	713	566	286

Cum. Prob. of Major Clinical Outcome or Incident Cirrhosis

0.005	0.01	0.01	0.02	0.02	0.02	0.02

Figure 3C: Cumulative Probability of Initiation of HBV Treatment Lasting ≥24 Weeks (274 events)

Cumulative Probability

0.3
0.2
0.1
0.0

0.5   1   2   3   4   5   6   7

Years

At Risk

1418	1235	995	832	683	549	425	206

Cumulative Probability of Treatment Initiation

Figure 4: Cumulative Probability of ALT Flare After Enrollment and Prior to Initiating HBV Treatment (83 events)
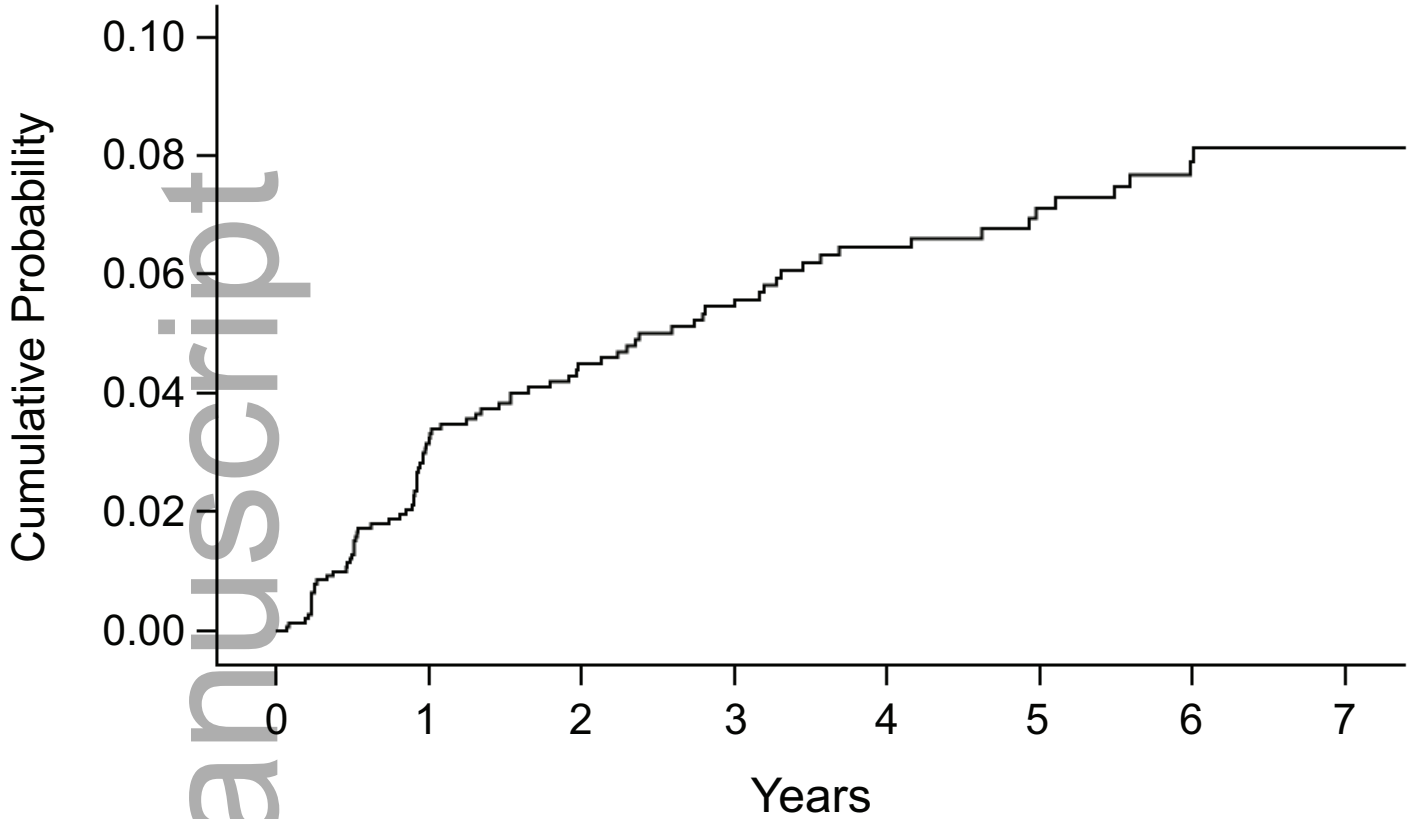
At Risk							
1415	1185	958	807	658	532	408	197

Cumulative Probability of ALT Flare							
	0.03	0.04	0.05	0.06	0.07	0.08	0.08

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