Clinical Outcomes in Adults with Chronic Hepatitis B in Association with Patient and Viral Characteristics: A Systematic Review of Evidence

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We systematically reviewed the literature on the extent to which population characteristics or clinical features predict groups of individuals likely to develop advanced liver disease or die from chronic infection with hepatitis B virus (HBV). We searched Medline to include studies with reported cirrhosis, liver failure, liver cancer, or death outcomes after at least 1 year of follow-up from the measurement of predictive factors (age, age at infection, geographic location, race/ethnicity, sex, positive family history, presence of coinfections, HBV viral level, change in hepatitis B e antigen [HBeAg] status, genotype, HBV mutations, nonalcoholic fatty liver disease, alcohol consumption, liver enzymes, and liver biopsy finding). Evidence from 41 included articles suggested that cirrhosis, higher HBV viral level, and male sex were consistently associated with significantly increased risk of death and liver cancer. Evidence about the role of HBV genotype, HBeAg status, age and duration of infection, coinfections with hepatitis C virus, human immunodeficiency virus, hepatitis delta virus, and alanine aminotransferase levels were limited and inconsistent, but were deemed promising to identify patients at higher risk of clinical outcomes. Adults with chronic hepatitis B had increased risk for poorer health outcomes compared to the general population; however, the magnitude of risk varied greatly depending on baseline patient and disease characteristics, and typically clinical outcomes required many years to become manifest. Many adults with chronic hepatitis B had low absolute risks of clinical outcomes and likely would not benefit from immediate treatment. Baseline patient and disease characteristics provide important information about the risk of clinical outcomes and should be incorporated into monitoring or treatment decisions. (HEPATOLOGY 2009;49:S85-S95.)

Introduction

This systematic review analyzed the evidence about specific population characteristics (age, age at infection, geographic location, race/ethnicity, sex, positive family history) or clinical and virological features of chronic hepatitis B virus (HBV) infection in adults (presence of coinfections, HBV viral load, change in hepatitis B e antigen [HBeAg] status, HBV genotype, HBV mutations, nonalcoholic fatty liver disease, alcohol consumption, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] level, liver biopsy finding) that might be predictive of serious clinical outcomes including hepatocellular carcinoma (HCC), liver failure, cirrhosis, liver-related death, and all-cause mortality. This review was conducted under a contract from the Agency for Healthcare Research and Quality.

Methods

We searched Medline up to June 2008 using the search string found in Table 1, and also hand-searched and evaluated articles suggested by our Technical Expert Panel. In
the final review, we included all English-language articles if they were: original research articles; reported at least one of the following outcomes: HCC, liver failure, cirrhosis, or death; had at least 1 year of follow-up for an outcome of interest; and reported results for a population with hepatitis B only. All studies meeting the previous criteria were included if the study reported results from a U.S. population. Only studies with large sample sizes (at least 1000 participants) in populations outside the United States were included.

For each population characteristic and each clinical feature, we assessed both the magnitude of effect observed in the included studies for each outcome as well as the level of confidence in the estimate. Magnitude of relative risk (RR) increase due to each factor for each outcome was assigned according to the following ranges: “Small” (RR > 1-2), “Moderate” (RR > 2-5), and “Large” (RR > 5). Ratings for the level of evidence included: “Inconclusive” (evidence insufficient to permit estimation of effect), “Low” (further research is likely to change the magnitude and/or direction of the estimate), “Medium” (further research may change the magnitude and/or direction of the estimate), “High” (further research is very unlikely to change the estimate). The level of confidence in the estimates was based on quality, quantity, and consistency of evidence for the estimate of the relative risk magnitude. Consistent findings from multiple large and well-characterized cohort studies would likely receive a rating of “High”, whereas findings inconsistently reported from poorly characterized or small populations, or only reported in one population, would likely receive a rating of “Low”. Pooling and meta-analytical methods were not used in this review due to the heterogeneity of the populations and the heterogeneity of the results reported.

Results

Description of Study Characteristics. A total of 41 articles met inclusion criteria (Fig. 1). Studies from the United States were intentionally over-represented; although the majority of research was conducted outside the United States. Our review included 14 publications representing eight unique populations within the United States. Table 2 provides the descriptive characteristics in terms of country, study design, number of patients, participant characteristics, length of follow-up, and outcomes assessed for each of the included articles.

Population Characteristics and Outcomes. Table 3 provides a summary of the key risk factors and outcomes assessed, a semiquantitative estimate of risk magnitude, and a statement regarding our confidence in the effect based on strength of evidence. Narrative summaries of the evidence are provided in the following subsections, and more detailed descriptions of the evidence for each category are available in the full report (http://www.ahrq.gov/clinic/epcindex.htm).

Age and Age at Infection. Individuals with earlier age of infection were more likely to develop chronic HBV infection and less likely to experience spontaneous hepatitis B surface antigen (HBsAg) loss. However, for any one individual the likelihood for events such as HCC, cirrhosis, liver failure, and death increased with age. So, ideally two pieces of information should be used to calculate risk: current age and age at onset of infection. Unfortunately, most studies were unable to identify the age of partici-

Table 1. Search Terms

| Database: Ovid MEDLINE Medical Subject Heading Terms |
|-----------------------------------------------------|
| 1. Exp Hepatitis B, chronic/ or exp Hepatitis B/ or exp Hepatitis B virus/ |
| 2. Exp hepatocellular carcinoma |
| 3. Exp liver failure |
| 4. Liver cirrhosis.mp. or exp liver cirrhosis/ |
| 5. Exp Death/ or death.mp |
| 6. Exp Survival/ or survival.mp. or exp survival rate |
| 7. or/2-7 |
| 8. Natural history/ or cohort studies/ or prospective studies/ or longitudinal studies/ or cohort.mp. or prospective.mp. or longitudinal.mp. |
| 9. 1 and 8 and 9 |
| 10. Limit 10 to (humans and English language) |

Fig. 1. Flow Chart Literature Search
### Table 2. Description of Study Characteristics

| Author/Country | Design Description | Subject Characteristics | Average Follow-Up/Outcomes |
|----------------|--------------------|-------------------------|-----------------------------|
| **A. American Studies** | | | |
| **Alaska Native Studies** | | | |
| Livingston (2007) | From a cohort of Alaska Native people with chronic hepatitis B virus (HBV) infection, 47 patients with hepatocellular carcinoma (HCC) and 1129 patients without HCC were genotyped. | N=1176. Alaska Native population with HBV genotype F. | 21 years HCC; HBV genotypes |
| Mcmahon (2001) | Population based cohort study of HBV carriers observed prospectively for 12.3 years (median) as part of an active surveillance program to detect carriers with HCC. | N=1536. Median age of first HBsAg-positive test 20 years (range 1-87). Men 59%. | 12.3 years (median) HCC; liver disease mortality; end-stage liver disease |
| Mcmahon (2000) | Prospective 16-year, population-based cohort study to determine the impact of screening for HCC in 1487 hepatitis-B surface antigen (HBsAg)-positive Alaska Native carriers with alpha-fetoprotein (AFP) determinations every 6 months. | N=1487. Men and nonpregnant women with an elevated AFP level. Men 59%. | 17 years HCC; mortality |
| Mcmahon (1990) | A total of 1400 hepatitis B surface antigen-positive Alaska Natives were followed up prospectively over a period of 7815 carrier-years for the development of sequelae related to chronic HBV infection. | N=1400 | 5.6 years Cirrhosis; HCC; mortality |
| **U.S. Studies by Tong** | | | |
| Tong (2007) | 101 hepatitis B surface antigen-positive patients with HCC. Baseline basal core promoter (BCP) T1762/A1764 mutants, precore (PC) A1896 mutants, HBV genotypes and HBV DNA in patients with HCC were compared with HBV genotypes and 67 chronic carriers prospectively. | N=168. Chronic carriers (n=67): Mean age 45.4 ± 12.3 years. Men 29 (43.3%) Asian = 58 (86.6%) Patients with HCC (n=101) Mean age 53.3 ± 13.5 years. Men 84 (83.2%) Asian = 91 (90.1%) | 9.3 years HCC |
| Tong (2006) | A long-term follow-up of 400 patients with chronic hepatitis B in order to identify hepatitis B viral factors associated with complications of liver disease or development of HCC. | N=400. Mean age 48.4 years. Men 70.5% HBsAg at baseline; positive = 197 (49.9%) negative = 198 (50.1%) | 7 years HCC; mortality |
| Tong (2006) | The long-term follow-up of 400 patients who presented to our clinic with chronic hepatitis B is described. | N=400. Mean age 48.4 years. Men 70.5% Asian = 314 (78.5%) patients born in Asia = 70% patients born in North America = 24% | 7 years HCC; mortality |
| Tong (2001) | 7-year prospective surveillance study to detect HCC. | N=602. Mean age 51 years. Men 59% | 7 years HCC |
| Schiodt (2003) | A retrospective analysis of HBsAg-positive patients enrolled in a US Acute Liver Failure (ALF) registry. | N=26. Mean age 43 years. Men 54%, Ethnicity: white race 50%. | Survival rate |
| Thio (2002) | Multicenter, prospective cohort study classified 5293 men who had sex with men, according to their HIV-1 antibody status, ascertained semiannually, and their HBsAg status, which we ascertained at baseline. | N=326. Homosexual, HIV-positive men. | 10.5 years Liver disease mortality |
| Abiad (2001) | Retrospective cohort study was conducted on 231 hepatitis B virus carriers, 65 of whom were also infected with hepatitis D virus, at 13 Illinois state facilities for the developmentally disabled. | N=231 Men 74.9% Mean age 33 years HBV-HDV patients N= 65 Mean age 37 years Male = 48 (74%) Caucasian = 51 (79%) HBeAg positive = 13 (20%) HBV only patients N=166 Mean age 31.4 Male = 125 (75%) Caucasian = 128 (77%) HBeAg positive = 41 (25%) | 10-12 years Overall mortality, mortality from hepatic disease, and risk of developing chronic hepatitis and cirrhosis |
| Nomura (1996) | Cohort of 5924 Japanese American men was examined for HCC. | N=5924. Men 100%. Ethnicity: Asian race 100%. | 25 years HCC |
| Norman (1993) | Large-scale serological and epidemiological follow-up study of the epidemic of hepatitis in the US Army in 1942. | N=69,988. White males | 37 years HCC; mortality; liver disease mortality |
| Weissberg (1984) | Survival data from 379 patients with chronic hepatitis B were analyzed to determine life expectancy for the patient from time of first contact. | N=379. Chronic persistent hepatitis (n=121) Male (n) = 100 Age (yr) = 35 ± 1 Chronic active hepatitis (n=128) Male (n) = 112 Age (yr) = 39 ± 1 Chronic active hep w/ cirrhosis (n=130) Male (n) = 121 Age (yr) = 43 ± 1 | 2.4 years Mortality |
| Author/Country            | Design Description                                                                 | Subject Characteristics | Average Follow-Up/Outcomes |
|--------------------------|-------------------------------------------------------------------------------------|-------------------------|----------------------------|
| **Sherman (1995)**       | Prospective cohort study of chronic carriers of hepatitis B virus, to determine the prevalence and annual incidence of HCC. | N=1069. Mean age 39 years. Men 65%. | 2.2 years HCC; mortality   |
| **B. European/Western nations Studies** |                                                                              |                          |                            |
| **Amin (2006)**          | The data from a cohort of 39,109 HBV, 75,834 HCV and 2604 HBV/HCV coinfected persons notified to the State health department, 1990-2002, were linked to the Cancer Registry and retrospectively analyzed. | N=41,713. Mean age 35 years. Men 55% | 12 years HCC, other cancers |
| **Konopnicki (2005)**    | A prospective, observational cohort study of 9802 patients with HIV-1 in 72 centers across Europe, including centers in Argentina and Israel. Coinfections with HBV and hepatitis C virus (HBC). | N=5728 (tested for HBsAg) Mean age 36. Men 78% HBsAg-negative 5230 (91.3%) HBsAg-positive 498 (8.7%) | 7 years Mortality; liver disease mortality |
| **Ribes (2006)**         | A nested case-control study to determine the role of other risk factors in the mortality from liver disease in HBsAg-positive subjects | N=2352. Mean age 34 years. Men 70%. | 21 years HCC; mortality; liver disease mortality; cirrhosis |
| **Crook (2003)**         | A prospective cohort study of HBsAg-positive blood donors comparing mortality rates in the cohort with the general population. | N=3658. Median age at entry: Men 29 (17-64); Women 29 (17-65). Men 73%. Subjects born in India/Southeast Asia 8%. | 22 years Mortality; liver disease mortality |
| **B. East Asian Studies**|                                                                                   |                          |                            |
| **Chan (2008)**          | A prospective cohort of patients infected with chronic HBV in a surveillance program for HCC was studied. Ultrasound and alpha-fetoprotein evaluation were regularly performed to detect HCC. Risk factors for HCC and the relationship between HBV DNA and HBV | N=1006. Mean age 48. Men 68%. | 7.7 years HCC |
| **Chen (2007)**          | Male cohort of 5,581 hepatitis B surface antigen carriers in Qidong, People’s Republic of China, who were recruited starting in 1989. | N=5581. Age range 30-65 years. Men 100% | 14 years HCC; mortality |
| **Haimen City Cohort Study** | A prospective cohort study with 11 year follow-up which assessed the relationship between past HBV viral load and mortality. | N=2763. Mean age 42 years. Men 61%. History of clinical hepatitis 30%. HBeAg+ at baseline 44%. | 11 years HCC; mortality |
| **Chen (2005)**          | Analyzed all-cause mortality related to HBV infection, focusing on the deaths not related to liver disease in a prospective cohort of adults living in Haimen City, China, who were followed from 1992 to 2002. | N=83,794. Age range 25-64 years. Men 70%. Male HBeAg+ 15% (n=8768) Female HBeAg+ 11% (n =2711) | 10 years Mortality |
| **Evans (2003)**         | 8-year follow-up of a prospective cohort study in Haimen City, China, identifying HCC risk factors in addition to HBV infection. Two cohorts of adults between ages 25 and 64 years at study entry were followed | N=83,885. Age range 25-64 years. Men 70%. 1. Male (n=58454) 2. Female (n=25340). Age (years) 25-34 24%; 35-44 39%; 45-54 25%; 55-64 12%. | 10 years HCC |
| **London (1995)**        | Nested case-control study of 183 patients (of 60,984 enrolled) who died from HCC | N=183. Age range 30-64 years. | 2.5 years HCC; mortality |
| **Chen (2006)**          | A prospective cohort study with 11 year follow-up; assessed the relationship between past HBV viral load and mortality. Surviving cohort members were evaluated for current liver disease. | N=3653. Age range 30-65 years. Men 62%. | 11 years HCC; mortality |
| **Iloeje (2006)**        | A population-based prospective cohort study of 3582 untreated HBV patients established in Taiwan from 1991-1992. | N=3582. Mean age 45. Men 61%. | 11 years Mortality; cirrhosis |
| **Taiwan Liver Unit of Chang-Gung Hospital based Studies** |                                                                                |                          |                            |
| **Chou (2008)**          | A nested case control from a cohort of 4841 male chronic carriers of HBV surface antigen aged 30-65 years who were free of diagnosed HCC was recruited from the Government Employee Central Clinics and the Liver Unit of Chang-Gung Memorial Hospital in Taiwan from 1988-1992 | HCC cases, n=132 Controls, n=204 | 16 years HCC |
### Table 2. Continued

| Author/Country | Design Description | Subject Characteristics | Average Follow-Up/Outcomes |
|----------------|--------------------|-------------------------|---------------------------|
| **Wu (2008)**<sup>41</sup> Taiwan | A nested case control from a cohort of 4841 male chronic carriers of HBV surface antigen aged 30-65 years who were free of diagnosed HCC was recruited from the Government Employee Central Clinics and the Liver Unit of Chang-Gung Memorial Hospital in Taiwan from 1988-1992 | HCC cases, n=112 Controls, n=1031 |  |
| **Yu (2005)**<sup>37</sup> Taiwan | Baseline blood samples were collected from 4841 Taiwanese men who were HBV carriers but had not been diagnosed with HCC. | N=4841. Men 100%. | 14 years HCC |
| **Yu (1999)**<sup>36</sup> Taiwan | A cohort of 4841 male chronic carriers of HBV surface antigen aged 30-65 years who were free of diagnosed HCC was recruited from the Government Employee Central Clinics and the Liver Unit of Chang-Gung Memorial Hospital in Taiwan from 1988-1992 | N=4841. Age range 30-65 years. Men 100%. | 9 years HCC |
| **Yu (1997)**<sup>35</sup> Taiwan | A cohort of 1506 male chronic carriers of HBV surface antigen from Liver Unit of Chang-Gung Memorial Hospital in Taiwan from 1980-1990. HBsAg carriers were enrolled in the study to investigate prospectively for liver cirrhosis and HCC at 6-month intervals by means of ultrasonography and clinical assessment. | N=1506. Men 100%. | 7.1 years HCC; cirrhosis |
| **Taiwan Study by Wang/Yang** | | | |
| **Wang (2003)**<sup>32</sup> Taiwan | Prospective community-based cohort study. HBsAg and antibody to HCV in serum were determined | N=11,837. Age range 30-64 years. Men 100%. Other data provided | 7.7 years HCC |
| **Yang (2002)**<sup>34</sup> Taiwan | Prospective community-based cohort study of 11,837 without evidence of HCC from seven townships in Taiwan. | N=11,837. Age range 30-65 years. Men 100%. Other data provided | 7.8 years HCC |
| **Other East Asian Studies** | | | |
| **Yuen (2005)**<sup>38</sup> China | A total of 3233 Chinese chronic HBV patients were monitored for liver biochemistry, viral serology, HBV DNA levels, acute exacerbation, HBeAg seroconversion, and development of cirrhotic complications. | N=3233. Mean age 38 years (range 1-85). Men 66%. | 3.9 years HCC; mortality |
| **Jee (2004)**<sup>32</sup> Korea | A prospective cohort study of liver cancer in Korea to assess the independent effects and interactions of smoking, alcohol consumption, and hepatitis B on risk of mortality from HCC. | N=605,844. Men 79%. | 9 years liver disease mortality |
| **Lam (2004)**<sup>14</sup> Hong Kong | | N=1863 | Mortality |
| **Tanaka (2004)**<sup>25</sup> Japan | A community-based prospective study was conducted for over 8 years by record linkage to the Osaka Cancer Registry. The subjects were 1927 individuals who were positive for antiHCV through screening for second generation HCV antibody in voluntary blood donors. The risk factors for HCC and interaction between HCV and hepatitis B virus (HBV) infection were evaluated by including additional blood donors: 2519 individuals positive for hepatitis B virus surface antigen (HBsAg) alone, 25 positive for both antiHCV and HBsAg | N=2544 Mean age 48 years. Men 61%. | 9 years HCC |
| **Mori (2000)**<sup>20</sup> Japan | A community-based prospective study examined the effects of viral infections and lifestyle habits on HCC risk in Japan. | N=3052. Mean age 58 years. Men 32%. Age <54, 37%; 55-69, 43%; ≥70, 21%. HBsAg-negative 97%. History of habitual alcohol consumption: no 65%; yes 35.0% Presence of chronic hepatitis: no 97%; yes 3% | 5 years HCC |
| **Tokudome (1987)**<sup>27</sup> Japan | This prospective study investigated whether female Japanese hepatitis B surface antigen positive blood donors were at high risk for HCC. | N=3769. Women 100%. | 8 years HCC; mortality; liver disease mortality |
| **Beasley (1981)**<sup>3</sup> Taiwan | Prospective population study of Chinese men (government employees) in Taiwan. | N=22,707. Age range 40-59 years 82%. Men 100%. HBsAg positive subjects 15% | 3.3 years HCC; mortality; liver disease mortality |
pants’ exposure clearly, and few reported any information on duration of exposure. Therefore, the results were likely confounded by unmeasured or unreported age at exposure and duration of exposure.

In studies that controlled for other potential confounders such as disease severity, age was often found to increase the risk of poor outcomes among adults with HBV. In one U.S. case-control study of HCC in HBsAg-positive individuals (70% born in Asia), each 1-year increase in age was associated with a 5% increase in odds of developing HCC (95% confidence interval [CI] = 2%, 8%).

Similarly, among Alaska Native people, each

| Table 3. Factors Associated with Increased Risk of Selected Outcomes in Adults with Chronic Hepatitis B |
|---------------------------------------------------------------|
| **Risk Factor** | **All-Cause Mortality** | **Liver Mortality** | **Hepatocellular Carcinoma** | **Cirrhosis** |
|------------------|-------------------------|---------------------|-----------------------------|---------------|
| Increased Age (≥10 years) | 3 articles (14,33,38) | 1 article (30) | 6 articles (4,5,29,31,35) | 2 articles (11,35) |
| Modest alcohol consumption (drinkers average 1 or fewer drinks per day) | 4 articles (6,29,30,38) | 4 articles (6,9,23,29) | 8 articles (2,4,6,12,24,28,31) | 1 article (11) |
| Geographic location and Asian race/ethnicity, early age of infection | | | 3 articles (17,30,31) | Inconclusive |
| Family history of hepatocellular carcinoma | | | 3 articles (10,16,36) | Low confidence Moderate effect |
| Nonalcoholic fatty liver disease | | | 5 articles (5,10,12,32,35) | Low confidence Small effect |
| Heavy alcohol consumption | | | 1 article (11) | Inconclusive |
| Liver Histology Score | 1 article (29) | 2 articles (29,30) | 5 articles (4,5,28,30,35) | N/A |
| Various types of detection | High confidence Moderate effect | Medium confidence | High confidence Large effect | High confidence Large effect |
| Genotype C (vs. other [mostly A, B, D]) | 6 articles (4,15,31,37,39,41) | 1 article (15) | 4 articles (15,30,31,42) | Inconclusive |
| Precore mutation (A1896) | 1 article (39) | 3 articles (7,30,40) | 6 articles (4,5,31,34,41,44) | 1 article (11) |
| Basal core promoter mutation (T1762/A1764) | 1 article (8) | Low confidence Small to moderate effect | Low confidence Moderate effect | Medium confidence Large effect |
| High HBV DNA load (>10^5 copies mL vs. <10^5) | 1 article (39) | Low confidence Small to moderate effect | 3 articles (7,30,40) | High confidence Large effect |
| HBeAg-positive status | 8 articles (5,19,30,34,35,37,39,41) | Medium confidence Moderate effect | 2 articles (11,35) | Medium confidence Small effect |
| Coinfection with HCV | 2 articles (1,13) | Low confidence Small effect | 2 articles (1,13,26) | Low confidence Moderate effect |
| Coinfection with HIV | 3 articles (1,13,26) | Low confidence Large effect | Medium confidence Large effect | Medium confidence Small effect |
| Elevated ALT level (>45 U/L) | 2 articles (1,13) | Low confidence Moderate effect | Medium confidence Small effect | Medium confidence Small effect |

Studies with references providing data for each outcome according to risk factor; level of confidence in estimate based on quality, quantity and consistency of evidence for the estimate of the relative risk magnitude is rated as “Inconclusive” (evidence insufficient to permit estimation of effect), “Low” (further research is likely to change the estimate), “Medium” (further research may change the estimate), “High” (further research is very unlikely to change the estimate); blank cells indicate no evidence available or does not apply. Magnitude of relative risk increase (RR) due to each factor for each outcome is estimated according to ranges from studies as “Small” (RR = 1-2), “Moderate” (RR = 2-5), and “Large” (RR = 5 or greater).
1-year increase in age increased the rate of HCC by 4% (95% CI = 0%, 7%). Some of the largest and best-characterized non-U.S. studies have confirmed the finding of a relation between age and poor outcomes, particularly for HCC. \(^4,5,11\)

Overall, there was inconclusive evidence regarding the extent to which the association between age and clinical outcomes was explained by duration of infection, age of infection, comorbidities in older individuals, and other factors that tended to be different between older and younger patients.

**Sex.** Males were much more likely to develop chronic HBV infection than females. Among those with HBV, the rate of clinical outcomes in terms of HCC, \(^2,4,6,7,12\) cirrhosis, \(^11\) and death \(^6,9,23,30,38\) were consistently several-fold higher in males than females. Actual magnitudes of effect ranged from 1.5 to 7.6 times higher rates of outcomes in men than in women, with most studies reporting at least two-fold to three-fold differences, even after adjusting for important potential confounders such as age, severity of liver disease, and other health-related factors. Results tended to be somewhat stronger for HCC than overall mortality.

**Geographic Location, Race/Ethnicity.** HBV infection is endemic in several locations around the world, including portions of Asia, Africa, and also among Alaskan Natives in the United States. Although geographic location is important in terms of exposure to HBV infection, we identified only three studies that attempted to address this issue and found little evidence that would allow us to accurately separate out the effects of geographic location of birth from race/ethnicity.

In one underpowered U.S. case-control study, Asians did not have a significantly increased rate of HCC compared to non-Asians (odds ratio [OR] = 1.6; 95% CI = 0.6, 4.2). Results were not adjusted for known differences in age at onset of infection, country of birth, or other key characteristics. \(^31\) However, significant geographic/ethnic differences in HCC have been reported in two studies in Alaska Native populations. \(^17,19\)

**Positive Family History.** Few studies reported information about the effect of positive family history on outcomes such as HCC, cirrhosis, and liver-related death. It was not possible to sort out any independent effects for family history outside of the effects already mentioned based on age of infection and patient’s geographic location or race/ethnicity.

A study from Haimen City, China, reported 2.3-fold (P < 0.001) greater odds of positive family history of HCC among cases with HCC compared to controls without HCC. \(^10,16\) Another study from Taiwan found that HCC cases were at 2.8-fold greater odds of having a family history of HCC compared to controls. \(^36\) Neither study was able to adequately control for shared environmental factors between family members, but both studies suggested that propensity for HCC may have a familial component.

**Presence of Coinfections.** Coinfection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis delta virus (HDV) was associated with poorer clinical outcomes. However, the number of studies reporting any one type of coinfection was small, and associations between different types of coinfections and risk of outcomes measures were not consistent. \(^1,13,25,26\)

Among patients infected with HIV, HBV coinfection increased all-cause and liver-related death rates by 1.5 (95% CI = 1.2, 1.9) and 3.6 (95% CI = 2.1, 6.2) times, respectively, compared with rates among patients infected with HIV without HBV coinfection. \(^13\) A large U.S. study found HIV coinfection increased the rate of liver-related mortality 10-fold to a rate of 14.2 per 1000 person years in men positive for HBsAg. \(^26\) However, these rates were not adjusted for disease severity.

Among Japanese blood donors positive for HBsAg, those with coinfection with HCV had a three-fold increase in HCC independent of age, sex, and ALT level. \(^25\) However, a study from Australia found similar rates of HCC in individuals with both HBV and HCV infection compared to those with HBV alone. \(^2\)

HDV coinfection was assessed in one U.S. study of 231 patients who were HBsAg-positive, developmentally disabled, and living in institutional facilities, of whom 65 were also HDV-positive. \(^1\) In multivariable analysis, patients positive for HDV were nearly 12 times (95% CI = 1.4, 97.8) more likely to die from liver-related causes, but all-cause mortality was not significantly increased. The evidence for this association was weak because there were only eight liver-related deaths, and it is uncertain how generalizable the results from a population with institutional confinement are to other populations.

**HBV Viral Level.** Higher HBV viral levels have been consistently associated with poorer clinical outcomes, particularly when the levels of HBV DNA were above 10\(^5\) copies/mL relative to very low or undetectable levels. However, having low or undetectable DNA did not eliminate the risk of clinical outcomes. \(^34\) Furthermore, much less is known about the extent to which spontaneous or drug-induced reductions in viral level lead to improvements in clinical outcomes.

The Taiwan REVEAL-HBV (Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV) Study found that in multivariable models adjusted for age, sex, smoking, alcohol use, HBeAg status, ALT level, and cirrhosis, the risk of HCC increased slightly for
people with >10^4 copies/mL and the risk was approximately six times higher for people with viral levels above 10^5 as compared to those with undetectable viral levels. This same study reported a similar association between viral level and risk of cirrhosis. Additional reports from this study have also shown a large increase in rate of liver-related mortality and a modest (approximately two-fold) increase in all-cause mortality in people with HBV DNA levels ≥10^5 compared to those with levels <10^5 copies/mL. There was no significant increase in risk of death from causes unrelated to the liver in those with elevated HBV DNA levels.

Mortality from HCC and other chronic liver disease has also been reported in a study from China with a similar trend. Results from the United States were consistent with the results from Asian countries, showing an increased rate of HCC and liver-related death across a gradient of HBV viral level. Among 400 patients with chronic hepatitis B, high baseline HBV DNA viral level significantly increased the odds of non-HCC related liver death by nearly five times (OR = 4.7; 95% CI 1.2, 20.4) after adjustment for age and sex.

**HBV Genotype.** Evidence for the impact of HBV genotypes on clinical outcomes for HBV was limited. It was clear that the prevalence of different genotypes varies substantially by geographic location, but more research is needed to determine the extent to which HBV genotype modifies the natural history of HBV-related outcomes. Available evidence indicated that U.S. adults with HBV genotype C have a four-fold greater odds of HCC compared to patients with other genotypes (genotypes A, B, and D). This association remained strong, but was not statistically significant, after accounting for age, sex, and basal core and precore mutations. A large study from Taiwan found similar associations of three-fold to six-fold increased risk of HCC among people with HBV genotype C compared to people with other genotypes (genotypes A, B, and D). This association remained strong, but was not statistically significant, after accounting for age, sex, and basal core and precore mutations. Finally, in a study among Alaska Native people, the odds of HCC were 4.7 times greater in adults with genotype A (95% CI = 1.4, 16.0) and 11.7 times greater in adults with genotype F (95% CI = 5.4, 25.4) compared to those with genotype D.

**HBeAg Status.** Among chronic carriers of HBV, absence of HBeAg is likely to indicate the inactive carrier status if ALT levels are normal and HBV viral levels are low. However, some patients without HBeAg have an active form of the infection and have high levels of HBV DNA and ALT. Therefore, it is difficult to interpret the association between HBeAg status and clinical outcomes without adjusting for ALT and HBV DNA levels and classifying patients into immune tolerant, inactive carrier, or HBeAg-negative but active carrier status. Because it is well known that inactive carriers have lower rates of clinical outcomes than those with chronic active hepatitis regardless of HBeAg status, the most interesting research questions may be to determine the impact of HBeAg status in people with active hepatitis and the effect of HBeAg reversion on clinical outcomes. We found few studies that classified people into groups of inactive and active chronic hepatitis and then examined the effect of HBeAg within those groups.

Although several studies have reported a consistently higher rate of outcomes among individuals who are HBeAg-positive compared to HBeAg-negative, we were unable to assess the effect of the HBeAg independent of its role as a marker of active versus inactive chronic hepatitis. One study in Taiwan found the incidence of HCC was 3.6 times higher in individuals who were HBsAg-positive who were also HBeAg-positive compared to those who were HBsAg-positive but HBeAg-negative. From the REVEAL-HBV study in Taiwan, this increased risk of HCC (hazard ratio = 2.6; 95% CI = 1.6, 4.2) and cirrhosis (RR = 1.7; 95% CI = 1.3, 2.9) for HBeAg-positive adults persisted following adjustment for age, sex, HBV viral level, and ALT level. A third large Taiwanese study also reported a two-fold to three-fold increased risk of HCC among adults with HBeAg-positive chronic hepatitis B. One U.S. study that classified patients into “inactive carriers,” “chronic hepatitis,” or “cirrhotic” groups found that adults positive for HBeAg at baseline had similar rates of HCC and all-cause death as adults with anti-HBe at baseline.

The effect of change in HBeAg status has been rarely reported. Among Alaska Native people, reversion to HBeAg-positivity or multiple switches in HBeAg status was associated with increased risk for HCC (HR = 2.6; 95% CI = 1.3, 5.4), after adjustment for potential confounders.

**Basal Core Promoter or Precore Mutation.** Only a few studies have examined the extent to which basal core promoter (BCP) mutations and precore (PC) mutations in the HBV genome impact clinical outcomes, and the results have been inconsistent, especially for PC mutations. Among Alaska Native people, there was no significant association between PC mutations and rates of HCC. However, there was a negative association between the presence of BCP mutation and HCC in those infected with genotype F but, as in other studies, a positive association between BCP in HCC in Alaska Native individuals infected with genotypes A, C, or D. In a U.S. case-control study of HCC in HBsAg-positive individuals, the G1896A PC mutation was associated with a nearly four-fold increase in HCC risk, and
the A1762T/G1764A double BCP mutation was associated with an 11-fold increase in HCC compared to wild types for both of these factors, independent of age, sex, race, and HBV genotype.\(^3\) In a U.S. cohort study of 400 patients with chronic HBsAg, the odds of developing HCC were 2.9 times greater (95% CI = 1.2, 7.6) for those with the BCP mutation and 4.2 times greater (95% CI = 1.5, 19.6) for those with the G1896A PC mutation compared to those with wild-type BCP and PC mutations, respectively.\(^30\) In a large Chinese study, the HCC death rate was 1.40 (95% CI = 1.06, 1.85) times greater in those with A1762T/G1764A BCP mutations compared to other HBsAg-positive subjects.\(^8\) Finally, in a recent publication, the REVEAL-HBV study from Taiwan found a 1.7-fold (95% CI = 1.1, 2.7) increased risk of HCC associated with the BCP mutations, but contrary to other studies found a reduced risk of HCC associated with the G1896A PC mutation (RR = 0.34; 95% CI = 0.21, 0.57).\(^42\)

**Liver Histology–Cirrhosis.** No studies reported on the association between liver histology scores and clinical outcomes. Few large studies had biopsy results from all participants and most relied instead on ultrasound to detect cirrhosis which still strongly predicted increased rates of clinical outcomes.

Cirrhosis has been shown to be a consistently strong predictor of HCC development and death in many studies. It has been reported for decades that survival is greatly reduced in adults with cirrhosis compared to adults without cirrhosis.\(^29,33\) As early as 1984, Weissberg and colleagues reported that the 5-year survival rate among adults with chronic hepatitis was 97% in adults without cirrhosis compared to only 55% in adults with chronic active hepatitis and cirrhosis.\(^33\) In a recent U.S. study, biopsy-determined cirrhosis was associated with a 3.6-fold (95% CI = 1.6, 8.9) increased odds of developing HCC.\(^29\) In the same study, the independent association was even stronger for all-cause death and non-HCC liver-related death (OR = 14.2 and 7.3, respectively).

The findings from U.S. studies were consistent with the large studies from Taiwan and China, which reported much higher rates of HCC and death in individuals with cirrhosis.\(^4,5,35\) Rates were often nearly 10-fold greater in adults with cirrhosis even after adjustment for other markers of disease severity such as elevated ALT or HBV viral levels.

**Nonalcoholic Fatty Liver Disease.** No studies were identified that reported the impact of nonalcoholic fatty liver disease on clinical outcomes in individuals with chronic HBV infection.

**Alcohol Consumption.** The association between alcohol consumption and clinical outcomes reported in the identified studies appeared modest at best with effect sizes of approximately a 1.5-fold increased risk of HCC. In a large Taiwanese study of more than 2000 people, alcohol consumption and duration of alcohol use were only weakly associated with HCC development. Compared to adults who never drank alcohol, those who drank for more than 20 years had a nonsignificant 1.33-fold increased risk of HCC (95% CI = 0.75, 2.43) after adjustment for age, family history of HCC, HCV status, baseline liver function, ethnicity, and education.\(^32\) Similar associations were reported in two other studies.\(^5,12\)

In the studies reporting alcohol consumption, average consumption was modest (about one drink per day). Overall, moderate alcohol consumption in people chronically infected with HBV appeared to be a weak predictor of increased risk for HCC. Little evidence exists regarding the association between heavy alcohol use and clinical outcomes in people with chronic HBV infection.

**AST and ALT Levels.** Few studies reported associations between elevated aminotransferase levels and clinical outcomes, and those that did tended to report increased risk of outcomes. This increased risk may be in part explained by other factors. Among a large Taiwanese study of asymptomatic carriers at baseline followed for an average of 7 years, those with either elevated AST or ALT levels had a 3.1-fold (95% CI = 1.0, 10.0) increased risk of HCC and a 3.7-fold (95% CI = 2.3, 6.0) increased rate of cirrhosis, independent of age, HBeAg status, and baseline cirrhosis for the HCC results.\(^35\) Another study from Taiwan found a similar association with HCC.\(^39\) Also from Taiwan, the REVEAL-HBV study reported an unadjusted four-fold increased risk of HCC with ALT levels >45 U/L, but after adjusting for age, sex, smoking, alcohol, HBeAg status, cirrhosis, and HBV viral level, the association was completely attenuated (HR = 1.1; 95% CI = 0.7, 1.7).\(^5\) In the same study, the association between elevated ALT levels and cirrhosis remained significant but only modest in strength after multiple adjustment (HR = 1.5; 95% CI = 1.1, 2.1).\(^11\)

**Discussion**

Evidence from observational studies suggests that cirrhosis, increased HBV viral level, and male sex were consistently associated with significantly increased risk of death and liver cancer. HBV genotype, age and duration of infection, coinfections (HCV, HIV, or HDV), and ALT levels were less consistently reported but also could be helpful for risk stratification of patients with hepatitis B. Several other factors, such as HBV DNA mutations and histological features potentially could be used for risk stratification of patients with HBV, but more research is needed.
Gaps in Evidence and Recommendations for Future Research. What remains to be addressed is the extent to which these predictors of disease progression represent clinically useful therapeutic targets or disease surrogates. Observational studies that report longitudinal measurements of these predictors and also collect outcome data could better identify whether change in predictor status leads to change in outcomes. Although there is strong evidence that cirrhosis is associated with significantly poorer clinical outcomes, there is little evidence available that provides information on the predictive ability of other indicators of liver histology (fibrosis grade, necroinflammatory score, presence of steatohepatitis). Large studies with baseline histological measurements would help to fill this gap. The vast majority of research on the natural history of chronic hepatitis B, even within the United States, is composed primarily of individuals with HBV infections acquired perinatally or early in childhood. Therefore, the evidence base for patients with HBV infection acquired later in life is much weaker and findings from other populations cannot necessarily be extrapolated to this group. Because recent clinical guidelines classify patients into diagnostic groups based on HBsAg status, serum HBV DNA, ALT/AST levels, and biopsy results, it is important that future observational studies at a minimum should measure these factors and analyze data that are controlled for or stratified by these variables.

Conclusions
Adults with chronic hepatitis B are at increased risk for poor health outcomes. However, the range of risk varies greatly depending in part on baseline patient and disease characteristics. Typically, clinical outcomes require many years to become manifest. Baseline patient and disease characteristics provide important information about the risk of clinical outcomes and should be considered when deciding how aggressively to monitor or treat patients with chronic hepatitis B.

Although there are several factors that are associated with increased relative risk of clinical outcomes, the absolute risk of clinical outcomes is relatively small for many people. Therefore, this absolute risk of clinical outcomes should be factored in when public health policy on intervention or treatment of chronic hepatitis B is being developed.

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