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eViralHepatitis Review
VOLUME 3, ISSUE 3

SHOULD THIS PATIENT BE TREATED? BEST PRACTICES IN IDENTIFYING CIRRHOSIS AND HCC IN PATIENTS INFECTED WITH HBV – ROLE OF PREDICTION MODELS

In this Issue...

The goal of antiviral treatment is to prevent progression to cirrhosis, liver failure, and hepatocellular carcinoma and can be achieved with sustained suppression of HBV replication and hepatic inflammation. Ability to predict the risk of disease progression leading to HCC can help to identify patients who need antiviral treatment or enhanced HCC surveillance.

In this issue we focus on recent investigations into predictive models for cirrhosis and HCC in patients with HBV, including reports on the utility of HBV surface antigen levels, host and virus profiles, noninvasive tests for fibrosis, and determining HCC risk scores for patients receiving antiviral therapy.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Identify which patients with chronic hepatitis B virus (HBV) infection are at high risk for cirrhosis and hepatocellular carcinoma (HCC)
- Outline the utility and limitations of prediction models for cirrhosis and HCC in patients with chronic HBV infection
- Describe how to incorporate predicted risk of HCC into decisions regarding hepatitis B treatment

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STATEMENT OF NEED

HCV

- Clinicians do not adequately identify which of their patients are at highest risk for HCV infection or effectively interpret testing results.
- Clinicians need to understand best practices in how to identify and manage HCV treatment-related side effects.
- Clinicians need improved awareness of how newly emerging therapies impact therapeutic decision-making in HCV infected and HIV/HCV co-infected patients.

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CME Info
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October 29, 2013

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- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HCV.

HBV

- Clinicians do not effectively identify their patients at risk for HBV.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

INTENDED AUDIENCE

The target audience (clinicians) for this initiative includes: OB/GYNs, NPs, PAs, hepatologists, gastroenterologists, infectious disease physicians, community gastroenterologists and others who care for patients of Asian and West African descent in areas of high HBV prevalence.

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- **Raymond T. Chung, MD,** discloses that he has served as a consultant for AbbVie, Inc. and Idenix and has received grant/research funding from Gilead and Mass Biologics.

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Suna Yapali, MD has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of her presentationn

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COMMENTARY

The goal of hepatitis B treatment is to prevent progression to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). As these endpoints take decades to evolve, suppression of HBV DNA to undetectable levels, hepatitis B e antigen (HBeAg) seroconversion to hepatitis B e antibody (anti-HBe), normalization of alanine aminotransferase (ALT) levels, hepatitis B surface antigen (HBsAg) loss, and improvement in histology have been used to determine the efficacy of treatment.

Currently, seven drugs have been approved for treating hepatitis B including two formulations of interferon alfa (IFN-α) [standard IFNα and pegylated (PEG)-IFNα], and 5 nucleos(t)ide analogues (NUCs): lamivudine, telbivudine, entecavir, adefovir dipivoxil, and tenofovir disoproxil fumarate. These therapies suppress but do not eradicate hepatitis B virus (HBV). Thus, most patients require long-term and often lifelong treatment to maintain viral suppression.

The decision to initiate treatment is simple when a patient presents with life-threatening HBV-related liver disease such as acute liver failure, decompensated cirrhosis, or severe exacerbation of chronic hepatitis B, as well as in patients with compensated cirrhosis and detectable HBV DNA. The decision when to start treatment in patients who have no evidence of cirrhosis is difficult because of the fluctuating course of chronic HBV infection.

Professional guidelines from the American, European, and Asian Pacific Liver Associations (AASLD, EASL, APASL) recommend initiation of treatment in noncirrhotic patients with serum HBV DNA > 20,000 IU/mL and ALT > 2X upper limit of normal (ULN) or histologic evidence of moderate to severe inflammation or fibrosis, with lower thresholds in older patients and patients with family history of HCC.[1-3]

It has been argued that these treatment criteria do not identify all patients who are at risk of cirrhosis or HCC.[4, 5] Availability of prediction models for cirrhosis and HCC could help in deciding which patients should receive antiviral treatment. The best known models were

derived from the REVEAL-HBV Study.[6] The initial model for predicting HCC included age, gender, family history of HCC, alcohol consumption, ALT level, HBeAg status, HBV DNA level, and HBV genotype.[7] The correlation coefficients between the observed HCC risk and the predicted risk were greater than 0.90 in all model derivation and validation sets. In the study by Yang et al reviewed in this issue, this model was later simplified and validated in three external cohorts of hospital-based patients in Hong Kong and South Korea. The new model, REACH-B score, included sex, age, HBeAg status, ALT level, and HBV DNA level, and the predicted risk correlated well with the observed HCC risk.

Recently, HBsAg level has been shown to reflect immune control of chronic HBV infection. Two studies by Tseng et al found that HBsAg level was an independent predictor of HCC in patients negative for HBeAg with low or intermediate viral load (HBV DNA < 20,000 IU/mL) but not in HBeAg-positive patients or patients negative for HBeAg with high viral load.[8, 9] In the subset of patients who were HBeAg-negative with low viral load (HBV DNA < 2,000 IU/mL) and normal ALT, HBsAg level was a better predictor of HCC than HBV DNA level, a finding likely related to the narrow range of HBV DNA levels in these patients. Furthermore, HBsAg level was a predictor of HBeAg-negative hepatitis, ALT flares and cirrhosis (Tseng and colleagues, reviewed in this issue). These results led to the incorporation of HBsAg level in prediction models of disease progression and HCC for patients negative for HBeAg with low viremia, as pointed out in the reviewed study by Lee et al.

A key question is whether these models can help determine which patients with chronic HBV infection and no evidence of cirrhosis at presentation should be started on antiviral therapy based on predicted risk of cirrhosis and HCC. Although the models described above were derived from large cohorts of patients followed for more than 10 years, they focused on patients at low risk — HBeAg-negative with normal ALT and low viral load. One can argue that prediction models for the patients at highest risk — HBeAg positive or negative with elevated ALT and high viral load — are unnecessary because they should receive antiviral treatment anyway. It would, however, be extremely valuable to have accurate prediction models for patients positive for HBeAg in the immune tolerance phase (high viral load but normal ALT) and for patients negative for HBeAg in the gray zone (moderate viral load and normal or minimally elevated ALT).

These models have other limitations. They were derived from data in Asian patients with predominantly genotype B or C infection, so their applicability to patients in western countries (most of whom acquired HBV infection in adult life and are infected with other HBV genotypes) is unknown. Even among Asian patients, these models do not apply to those younger than 30 or older than 65 and have limited applicability to patients positive for HBeAg. The majority of the prediction models have focused on baseline values; however, given the fluctuating nature of chronic HBV infection, models that incorporate changes during follow-up would be helpful.

The study by Wong et al discussed herein attempted to apply prediction models of patients with HCC currently receiving antiviral therapy. Surprisingly, the risk score at the start of entecavir therapy was more accurate in predicting the risk of HCC than the risk score after two years of entecavir; however, this finding may be limited by the heterogeneity of the patients (some were switched from other treatment to entecavir), short duration of treatment, and small number of events.

In summary, models that can accurately predict the risk of cirrhosis and HCC will be of immense help in deciding which patients who have no immediate indications for treatment should be started on antiviral therapy. The proliferation of models in recent years is an important first step, but most of these models have limitations, and further validation is needed before they can be applied in clinical practice or incorporated into treatment guidelines.

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UTILIZATION OF MODELS FOR PREDICTING THE RISK OF HBV-RELATED HCC

Yang HI, Yuen MF, Chan HLY, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011;12(6):568-574.

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The goal of treatment of hepatitis B is to prevent cirrhosis and hepatocellular carcinoma (HCC). For patients who do not have cirrhosis, practice guidelines recommend antiviral treatment based on hepatitis B virus (HBV) DNA and alanine aminotransferase (ALT) levels; however, other factors contribute to the risk of HCC. Yang et al developed several prediction models for HCC with data obtained from the Risk Evaluation of Viral Load Elevation and Associated Liver disease/Cancer-HBV (REVEAL-HBV) study.[1,2] In this community-based study in Taiwan, 3653 hepatitis B surface antigen (HBsAg)-positive persons aged 30-65 years were followed for a median of 12 years. At enrollment, 94% had normal ALT, 85% were negative for hepatitis B e antigen (HBeAg), and 2% had cirrhosis. Factors associated with HCC included: sex, age, alcohol consumption, family history of HCC, HBeAg status, HBV DNA level, ALT level, and HBV genotype.

The authors developed three regression models to predict HCC. The correlation coefficients between the observed HCC risk and the nomogram-predicted risk were greater than 0.90 in all model derivation and validation sets. In this study, the authors developed a simplified model using objective, readily available data from a derivation cohort of 3584 persons without cirrhosis in the REVEAL study. This REACH-B (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B) risk score has a range of 0-17 and comprised gender, age, ALT, HBeAg status, and HBV DNA level. The predicted HCC risk at three, five, and 10 years was 0-23.6%, 0-47.4%, and 0-81.6% for persons with the lowest and highest risks, respectively. This model was validated in an external cohort of 1505 patients from three hospitals in Hong Kong and South Korea. The area under receiving operating characteristic (AUROC) curves for predicting HCC risk in the validation cohort at three, five, and 10 years was 0.811 (95% confidence interval [CI], 0.790-0.831), 0.796 (95% CI, 0.775-0.816), and 0.769 (95% CI, 0.747-0.790), respectively. Because the validation cohort included a higher percentage (19.4%) with cirrhosis, analysis was repeated after excluding patients with cirrhosis, and AUROC for predicting HCC was slightly higher.

The REACH-B score is a simple-to-use model, but its utility in determining which patients should undergo enhanced HCC surveillance or receive antiviral treatment is unclear. The REACH-B model has several limitations. It was derived from and validated in Asian patients, and its accuracy in patients with different genetic background, HBV genotypes

other than B and C, or adult-acquired infection remains to be confirmed. Even among Asian patients, this model cannot be applied to people younger than 30 years or older than 65 years.

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CAN HEPATITIS B SURFACE ANTIGEN LEVELS PREDICT RISK OF DISEASE PROGRESSION AND HCC?

Tseng CT, Liu CJ, Yang HC, et al. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. *Hepatology* 2013;57:441-450.

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A high level of HBV DNA (> 2,000 IU/mL) had been shown to be an independent predictor of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality in the Risk Evaluation of Viral Load Elevation and Associated Liver disease/Cancer-HBV (REVEAL-HBV) study, which included predominantly hepatitis B e antigen (HBeAg) negative persons. Tseng et al investigated the association between levels of hepatitis B surface antigen (HBsAg), HBV DNA, and alanine aminotransferase (ALT) with the risk of HCC in a retrospective cohort of 2688 patients followed for a mean of 14.7 years in the Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers (ERADICATE-B) Study.1 In this hospital-based cohort, 60.8% of the patients were men, 29.1% had ALT >= 40 U/L, 19.5% were positive for hepatitis B e antigen (HBeAg), 59.7% had HBV DNA level ≥ 2,000 IU/mL, and 59.1% had HBsAg level ≥ 1000 IU/mL. All the patients had a minimum follow-up of three years.

The authors found that HBV DNA and ALT levels were better predictors of HCC than HBsAg level in the overall cohort. In the subset of patients negative for HBeAg who had HBV DNA < 2,000 IU/mL, HBsAg level but not HBV DNA level predicted HCC development. The adjusted hazard ratio (HR) of HCC was 13.7 (95% CI 4.8-39.3) for those with HBsAg level ≥ 1,000 IU/mL vs those with level < 1,000 IU/mL. Subsequently, they examined whether HBsAg level was related to hepatitis activity, hepatitis flares, and cirrhosis in 1068 patients negative for HBeAg who had baseline HBV DNA levels < 2,000 IU/mL. The authors found that the incidence of HBeAg-negative hepatitis was 2.0%/year, and there was an association between HBeAg-negative hepatitis and cirrhosis. Patients who developed HBeAg-negative hepatitis were older, more likely to be male, and more likely to have higher baseline ALT levels. After adjustment for age, sex, ALT, and HBV DNA levels, HBsAg ≥ 1,000 IU/mL was an independent predictor for HBeAg-negative hepatitis, hepatitis flare, and cirrhosis, with HR of 1.7 (95% CI, 1.3-2.3), 2.3 (95% CI, 1.5-3.5), and 4.1 (95% CI, 2.0-8.3), respectively.

The authors concluded that HBeAg-negative patients with HBV DNA < 2,000 IU/mL, ALT < 40 U/L and HBsAg < 1,000 IU/mL had minimal risk of disease progression, which may explain their lower risk of HCC. They further suggested that the monitoring interval for these patients might be increased to 12 months. However, the data were solely obtained from Chinese patients with genotype B and C infection, and the results should be validated in patients infected with other HBV genotypes. In this study, the authors did not investigate whether HBsAg level can further stratify the risk of progressive disease among patients negative for HBeAg who have HBV DNA 2,000 to 20,000 IU/mL. However, in another study,[2] they found that HBsAg levels help stratify risk of HCC in patients negative for HBeAg who have intermediate levels of HBV DNA.

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1. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology.* 2012;142:1140-1149.
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THE INTEGRATION OF HOST AND VIRUS PROFILES IN PREDICTION MODELS OF CIRRHOSIS AND HCC

Lee MH, Yang HI, Liu J, et al. Prediction models of long-term cirrhosis and HCC risk in chronic hepatitis B patients: Risk scores integrating host and virus profiles. Hepatology. 2013; Aug;58(2):546-554

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The Risk Evaluation of Viral Load Elevation and Associated Liver disease/Cancer-HBV (REVEAL-HBV) study had been used to generate prediction models for hepatocellular carcinoma development.[1,2] The REACH-B model included sex, age, alanine aminotransferase, hepatitis B e antigen status, and HBV DNA level.[3] Recent studies showed that hepatitis B surface antigen (HBsAg) level is an indicator of immune control of HBV infection and an independent predictor of HCC as well as disease progression in patients negative for HBeAg who had low viremia (HBV DNA < 2,000 IU/mL).[4-6] In this study, Lee et al used the REVEAL-HBV data to develop predictive models for cirrhosis. In addition, they developed a revised model incorporating HBsAg level to predict HCC.

A total of 3342 persons were included. Patients were randomly divided in a ratio of 2:1 to derivation and validation sets. Diagnosis of cirrhosis was determined by a quantitative scoring system based on ultrasound findings.[7] After 39,016 person-years of follow-up, 327 persons developed cirrhosis. Persons who developed cirrhosis were more likely to be older than age 50, male, alcohol consumers, positive for HBeAg, infected with HBV genotype C, and to have higher ALT, HBV DNA > 10,000 copies/mL, and HBsAg > 100 IU/mL. One hundred-sixty-four incident HCC cases were observed. In addition to the risk factors for cirrhosis, family history of HCC was predictive of HCC development. The multivariate-adjusted HR of cirrhosis was 1.68 (95% CI, 1.12-2.54) and 2.20 (95% CI, 1.48-3.27) for serum HBsAg levels 100-999 and ≥ 1000 IU/mL, compared to those with HBsAg < 100 IU/mL. Multivariate adjusted HR of HCC was 2.83 (95% CI, 1.55-5.18) and 4.06 (95% CI, 2.24-7.36) for HBsAg levels 100-999 and ≥ 1000 IU/mL. HBsAg levels were significantly associated with risk of cirrhosis and HCC in the subset of patients negative for HBeAg, particularly those who had HBV DNA levels < 6 log10 copies/mL but not in the subset of those positive for HBeAg.

The authors developed a risk score for cirrhosis comprising age, sex, ALT, and different combinations of HBeAg status/HBV DNA level/HBsAg level/HBV genotype, and a risk score for HCC comprising the same variables plus family history of HCC. The cirrhosis risk model predicted three, five, and 10-year risk of cirrhosis with area under receiving operating characteristic curve (AUROC) of 0.86, 0.86, and 0.83 in the derivation set, and 0.79, 0.80, and 0.82 in the validation set, respectively. The AUROC for prediction of HCC risk at five, 10, and 15 years was 0.89, 0.85 and 0.86 in the derivation set and 0.84, 0.86, 0.87 in the validation set.

This study confirmed that HBsAg level predicts HCC and disease progression; however, the authors did not show whether the current model for predicting HCC is superior to their previous models, which did not include HBsAg level, HBV genotype, and family history of HCC. The novelty of this study is the predictive model for cirrhosis, but the diagnosis of cirrhosis was based on ultrasonography (which is subjective and insensitive for making that diagnosis). The two models discussed in this paper have not been externally validated, and the inclusion of variables that are not widely available may limit their utility in clinical practice.

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THE PROGNOSTIC VALUE OF NON-INVASIVE TESTS FOR FIBROSIS AND LIVER STIFFNESS TO PREDICT OUTCOME IN PATIENTS WITH CHRONIC HBV INFECTION

de Lédinghen V, Vergniol J, Barthe C, et al. Non-invasive tests for fibrosis and liver stiffness predict 5-year survival of patients chronically infected with hepatitis B virus. *Aliment Pharmacol Ther*. 2013; 37: 979-88.

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Assessment of liver fibrosis is important in predicting the risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. Liver fibrosis may be assessed by histology or noninvasive tests based on quantification of serum biomarkers of fibrosis or by measurement of liver stiffness. While the accuracy of noninvasive tests in predicting fibrosis has been validated in patients with chronic hepatitis C, performing these tests in patients with chronic HBV infection is less well studied and maybe confounded by liver inflammation and HBV replication status. This investigation by de Lédinghen et al compared the prognostic value of liver stiffness measurement, FibroTest, aspartate aminotransferase (AST) to platelet ratio index (APRI), FIB-4 score, and liver biopsy in predicting five-year survival in patients with chronic hepatitis B infection. The authors prospectively enrolled 600 patients from a hospital-based cohort: 64% were men, mean age was 42.5 years, 16.3% were positive for hepatitis B e antigen (HBeAg), and 56.5% had normal alanine aminotransferase levels. Liver biopsy was available in 214 (35.7%) patients. During the course of the study, 24.7% of the patients received antiviral treatment.

Laboratory tests required for FibroTest, APRI, and FIB-4 scores were performed at the time of liver stiffness measurement. Study endpoint was defined as any cause of death, including liver transplantation. After a median of 49.7 months, 29 (4.8%) patients reached study endpoint, including 17 liver-related events and 12 deaths not liver-related. The five-year overall survival was 97.1% in patients with liver stiffness < 9 kPa and 61.5% in patients with liver stiffness > 20 kPa, and 96.8% for FibroTest ≤0.73, and 49.2% for FibroTest > 0.85. FibroTest and liver stiffness had higher prognostic values compared to liver histology, APRI, and FIB-4, even after adjustment for age, necro-inflammation assessed by ActiTest, HBV DNA level, and treatment status.

While this study showed that noninvasive tests of fibrosis may be used to predict survival of patients with chronic HBV infection, it has several limitations. First, the study endpoint

was a combination of liver and nonliver- related deaths, and liver-related deaths included both deaths and liver transplantation. Second, the short duration of follow-up limits the number of events and the accuracy of the prediction of the study endpoint. Third, the study focused on noninvasive tests of fibrosis and did not include other factors that had been shown to be predictive of HCC, such as gender, HBeAg status, and ALT level. Fourth, the study population was heterogeneous, with patients who had hepatic decompensation or HCC at baseline lumped together with inactive carriers. Fifth, 24.7% patients received antiviral therapy. Finally, although the authors claimed that Fibrotest and liver stiffness measurement had better prognostic value than liver biopsy, only 35.7% of patients had liver biopsies.

Determining the utility of noninvasive tests of fibrosis in predicting outcomes of patients with chronic HBV infection requires longer follow-up of a large cohort of patients with compensated liver disease and no HCC at enrollment. Other factors that influence disease progression such as ALT, HBeAg status, HBV DNA level, and HBsAg level should also be tested in the prediction models, and the potential impact of antiviral therapy must be accounted for in these models.

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SHOULD HCC RISK MODELS BE INCORPORATED INTO CLINICAL PRACTICE GUIDELINES?

Chen TM, Chang CC, Huang PT, et al. Performance of risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) score in classifying treatment eligibility under 2012 Asian Pacific Association for The Study of the Liver (APASL) guideline for chronic hepatitis B patients. *Aliment Pharmacol Ther*. 2013; 37:243-251.

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Current treatment guidelines for hepatitis B recommend antiviral therapy for patients with active or advanced liver disease and high serum HBV DNA levels. The decision about when to start treatment should also consider the predicted risk of cirrhosis and HCC. The REACH-B score that predicts the risk of HCC in patients with chronic HBV infection was derived from the community-based REVEAL-HBV Study.[1] Chen et al investigated the performance of REACH-B score in determining antiviral treatment eligibility according to the Asian Pacific Association for the Study of the Liver (APASL) 2012 treatment guideline.[2]

The investigators retrospectively reviewed the data from 4762 consecutive HBsAg-positive patients in the Bureau of National Health Insurance in Taiwan database between January 2006 and May 2012. A total of 904 patients between age 30-65 who did not have cirrhosis, HCC, or HCV coinfection at presentation and who had at least one HBV DNA test result were included. Of these, 438 patients, 71% of patients positive for HBeAg and 41.3% of patients negative for HBeAg met the APASL 2012 guideline criteria for treatment. REACH-B score was higher in the patients who met treatment criteria than those who did not [10.1 ± 1.9 vs 7.8 ± 2.9, 10.5 ± 1.8 vs 6.9 ± 2.6, respectively ($P < 0.001$)]. The minimum REACH-B score to meet the treatment criteria was 7 for patients positive for HBeAg and 6 for patients negative for HBeAg. Increase in REACH-B score predicted treatment eligibility in patients negative for HBeAg but not in patients positive for HBeAg. Using a cutoff score of 8 in patients positive for HBeAg age < 40 and patients negative for HBeAg age < 45, a cutoff score of 11 in patients positive for HBeAg age ≥ 40 and in patients negative for HBeAg age ≥ 45, the authors found that the sensitivity and specificity of REACH-B score in identifying patients meeting treatment criteria were more than 80% for patients negative for HBeAg. The sensitivity and specificity for patients positive for HBeAg < 40 years were 80% and 74.3%, respectively. For patients positive for HBeAg ≥ 40, the sensitivity was 78.4%, but the specificity of the REACH-B score was only 53.6%. The projected HCC risk estimated by REACH-B score for patients who met the treatment criteria of the APASL guideline at three, five, and 10 years was 0.9%, 2%, and 5.2%, respectively, and 0.2%, 0.5% and 1.2%, respectively for those who did not meet treatment criteria.

This study showed that the majority of patients regardless of HBeAg status, below the age of 40 who are predicted to have a high risk of HCC based on REACH-B score would meet the APASL guideline treatment criteria, but nearly half of the patients positive for HBeAg ≥

40 years who are predicted to have high risk of HCC based on REACH-B score would be excluded from treatment (according to the APASL guideline). In this study, a large number of patients (66.5% of the entire cohort) were excluded because of the unavailability of a HBV DNA result. Further, the patients included in this study differed from the REACH-B cohort in that a higher percentage of patients were HBeAg positive and a higher percentage had elevated ALT. Another limitation of this study is that it did not consider histological evidence of significant fibrosis as a criterion for treatment (as recommended by the APASL guidelines) in patients who had ALT levels 1-2X ULN, particularly those above age 40.

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THE ACCURACY OF RISK SCORES FOR PATIENTS RECEIVING ENTECAVIR

Wong GL, Chan HL, Chan HY, et al. Accuracy of risk scores for patients with chronic hepatitis B receiving entecavir treatment. *Gastroenterology*. 2013;144:933-944.

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Most models developed to predict the risk of HCC in patients with chronic HBV infection have been based on patients who never received treatment or who were censored at the start of antiviral treatment. With the availability of safe and efficacious antiviral treatment, patients with moderate or high risk for HCC are expected to be receiving antiviral therapy. Antiviral therapy has been shown to decrease but not eliminate the risk of HCC; therefore, it is important to determine whether any of the previously published models are accurate in predicting HCC in patients receiving antiviral therapy.

In this study, Wong et al investigated the accuracy of HCC risk scores using values at baseline and during treatment, including a retrospective-prospective cohort of chronic hepatitis B patients who received entecavir 0.5 mg daily for at least 12 months. Patients with preexisting HCC and those whose HCC was diagnosed in the first year of entecavir treatment were excluded. The authors examined the performance of three HCC risk scores: CU-HCC score comprising age, albumin, bilirubin level, HBV DNA level, and cirrhosis; GAG-HCC score comprising sex, age, HBV DNA level, and cirrhosis; and REACH-B score consisting of sex, age, ALT level, HBeAg status, and HBV DNA level.[1-3] They applied the risk scores at the time of initiation of entecavir treatment and again at year 2 and assessed the three- and five-year HCC risk based on the reported cut-off values in treatment-naive patients.

Of 1531 patients, 47 (2.9%) patients developed HCC during a mean follow-up of 42 months. Overall cumulative incidence rates of HCC at three and five years were 2.9% (95% CI, 2.4% - 3.4%) and 4.3% (95% CI, 3.6% - 5.0%), respectively. Hypoalbuminemia, presence of cirrhosis, and duration of virologic remission less than 24 months were independent predictors of HCC. The sensitivity of CU-HCC, GAG-HCC, and REACH-B scores in predicting HCC was 93.6%, 55.3% and 95.2%, respectively; while the specificity was 47.8%, 78.9%, and 16.5%.

The authors concluded that CU-HCC was superior to the other two models. This is not surprising because there is partial overlap between the original cohort from which CU-HCC was derived and the current cohort. Patients who had risk scores above the cutoff values both at baseline and at year 2 had a higher risk of HCC than those with baseline scores below the cutoff values at both time points. Patients with high baseline CU-HCC score that declined at year 2 had lower risk of HCC than those with persistently high score, but the risk remained higher than for those with low baseline score.

This is the first study showing that HCC risk scores derived in untreated patients are also accurate in predicting risk of HCC in patients receiving antiviral treatment. It is surprising that risk scores derived from values when HBV DNA was suppressed were not more accurate in predicting HCC risk than scores derived from values at baseline. This may be related to the short duration of treatment and the heterogeneity of patients, with 31% having been on other antiviral therapy prior to the start of entecavir treatment. In these latter patients, baseline lab values were obtained after varying durations of treatment with the other antiviral therapy.

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Presented by JHUSOM and IJHN in collaboration with **DKBmed**.

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