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**Risk prediction of hepatitis B virus-related hepatocellular carcinoma in the era of antiviral therapy**

Wong GLH *et al*. Predict HBV-related HCC

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**Abstract**

Chronic hepatitis B (CHB) related hepatocellular carcinoma (HCC) is a major health problem in Asian-Pacific regions. Antiviral therapy reduces but not eliminates the risk of HCC. It would be a heavy financial burden to most of low and middle economic countries if all CHB patients receive antiviral therapy and HCC surveillance. This urges the need of accurate risk prediction to assist prognostication, decisions on the need of antiviral therapy and HCC surveillance. A few well-established risk factors of HCC, namely advanced age, male gender, high viral load, cirrhosis *etc.*, are the core components of three HCC risk scores: CU-HCC, GAG-HCC and REACH-B scores. These 3 scores were confirmed to be accurate to predict HCC up to 10 years in treatment-naïve patients. Their validity and applicability have been recently demonstrated in a large real-life cohort of entecavir-treated patients. Decrease in risk scores after antiviral therapy is translated to a lower risk of HCC. These findings support applying HCC risk scores to all CHB patients. Different levels of care and different intensities of HCC surveillance should be offered according to the risk profile of patients. Patients at risk of HCC should receive regular HCC surveillance even when they are receiving antiviral treatment.

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**Key words:** Antiviral therapy; Cirrhosis; Hepatitis B virus DNA; Hepatocellular carcinoma; Risk prediction score; Transient elastography

**Core tip:** CU-HCC, GAG-HCC and REACH-B scores accurately predict subsequent hepatocellular carcinoma (HCC) development in both treatment-naïve patients and those receiving antiviral therapy. At the recommended cutoff values, baseline CU-HCC and REACH-B scores had high sensitivity, while GAG-HCC score had high specificity to predict HCC. Patients persistently in the low-risk category have the lowest risk of HCC; those “downgraded” in risk category would have significantly lower yet a small risk of HCC compared to those remained in high-risk category. Patients at high-risk category either at baseline or after treatment should receive HCC surveillance.

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Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer deaths in men worldwide[[1](#_ENREF_1)] . Chronic hepatitis B virus (HBV) infection is one of the major causes of HCC, as it is estimated that over 350 million people are chronically infected with HBV worldwide[[2](#_ENREF_2)]. Globally, HBV accounts for 53% of all cases of HCC[[3](#_ENREF_3)]. Due to the high prevalence of HBV infection, the incidences of HCC in Eastern Asia and Southeast Asia are highest around the world[[4](#_ENREF_4)].

In the last two decades, the development of antiviral therapy was a major breakthrough in the management of chronic hepatitis B (CHB), which modifies the natural history of the disease and reduces the risk of HCC[[5-7](#_ENREF_5)]. Nonetheless, there is still a low yet clinically relevant risk of HCC in patients receiving antiviral therapy. It would be a heavy financial burden, in particular to low and middle economic countries, if all CHB patients receive antiviral therapy and HCC surveillance. This urges the need of accurate risk prediction to assist prognostication, decisions on the need of antiviral therapy and HCC surveillance.

**RISK FACTORS OF HBV-RELATED HCC**

***Treatment-naïve patients***

A handful of factors have been repeatedly shown to increase the risk of HCC when studying the natural history of chronic HBV infection. In general the risk factors can be categorized into host factors, liver factors and viral factors (Table 1). Host factors include advanced age[[8-10](#_ENREF_8)], male gender[[9](#_ENREF_9),[10](#_ENREF_10)], family history of HCC[[11](#_ENREF_11)], and possibly single-nucleotide polymorphisms at different human genomic loci [*e.g.*, chromosome 1p36.22, chromosome 6 of human leukocyte antigen (HLA)-DP and HLA-DQ loci, and chromosome 8p12][[12](#_ENREF_12),[13](#_ENREF_13)]. Immunosuppressed conditions like human immunodeficiency virus co-infection is another risk factor[[14](#_ENREF_14)]. Liver factors consist of advanced fibrosis and cirrhosis[[11](#_ENREF_11)]; poor liver function as evidenced by hypoalbuminemia and hyperbilirubinemia[[8](#_ENREF_8)]; active hepatitis as evidence by high alanine aminotransferase (ALT) and active necroinflammation demonstrated in liver biopsy[[9](#_ENREF_9)]; and other committant liver diseases like co-infection with hepatitis C virus or hepatitis delta virus, alcoholic liver disease, nonalcoholic fatty liver disease[[11](#_ENREF_11)]. Viral factors are high serum HBV DNA level[[8](#_ENREF_8), [15](#_ENREF_15)], hepatitis B virus e antigen (HBeAg) seropositivity[[16](#_ENREF_16)], HBV genotype C[[17](#_ENREF_17)] and subgenotype Ce[[18](#_ENREF_18)], core promoter mutations[[10](#_ENREF_10)] and probably high serum hepatitis B surface antigen (HBsAg) level[[19](#_ENREF_19)].

***Patients receiving antiviral therapy***

The natural history of chronic HBV infection is altered by antiviral therapy. Therefore the risk factors of HCC may be different in treated patients compared to untreated patients. The landmark Asian lamivudine trial did not specifically look into the risk factors of HCC, while baseline Child–Pugh and Ishak fibrosis score, as well as genotypic resistance *YMDD* mutation were the risk factors of disease progression[[6](#_ENREF_6)]. The drug-resistant mutant did not increase the risk of HCC (both 4% in patients with or without *YMDD* mutation detected). Nonetheless, the significance of *YMDD* mutation might be masked by the short follow-up duration (study prematurely terminated at 32 mo) and the unspecified interval between emergence of drug resistance and HCC development.

In a retrospective study of total 2795 Japanese CHB patients (657 lamivudine-treated *vs* 2138 untreated patients), absence of treatment, male gender, family history of HBV carriage, age above 40 years, fibrosis of over grade 2 of 4, albumin level of below 40 g/L, and platelet count of < 150000/mm3 were the independent risk factors of HCC[[20](#_ENREF_20)]. The risk factors identified from this study appeared no different from those identified from studies of natural history, probably because more than three-fourths of patients were untreated.

In a nationwide study from Greece retrospectively analyzing 818 HBeAg-negative patients treated with lamivudine, advanced age and cirrhosis were the risk factors of HCC[[21](#_ENREF_21)]. On-therapy virologic remission (*i.e.,* undetectable on-treatment serum HBV DNA level) did not significantly affect the incidence of HCC (though there was a trend for lower risk of HCC in the absence of cirrhosis). As all patients with on-therapy virologic remission who developed HCC (8 of 228; 3.6%) happened within 30 mo of lamivudine treatment, some of these tumors might be in fact pre-existing HCC.

A recent large-scale real-life cohort study of 1531 entecavir-treated CHB patients demonstrated the importance of maintained virologic response[[22](#_ENREF_22)]. Old age, cirrhosis, and virologic remission for 24 mo or more were independent factors associated with HCC in the entire cohort; whereas advanced age and hypoalbuminemia were predictors in non-cirrhotic patients. Though maintained virologic response was important, 30 out of 47 patients (64%) who achieved this virologic target still developed HCC. This can be explained by early integration of HBV into the host genome and the presence of cirrhosis, such that even with very effective suppression of viral replication with antiviral agents, HCC may continue to develop[[23](#_ENREF_23)].

Summarizing the findings of these studies, advanced age and cirrhosis are the two major risk factors consistently demonstrated in patients receiving antiviral therapy. While maintained virologic response is likely a protective factor, baseline HBV DNA level is no longer important in these treated patients as it is usually much reduced after the treatment. Theoretically HBsAg level, which reflects the amount and transcriptional activity of covalently closed circular DNA inside the liver, might have a role to predict HCC in treated patients when serum HBV DNA is no longer detectable[[24](#_ENREF_24)]. However, this was not confirmed in patients receiving entecavir[[22](#_ENREF_22)]. The probable reason is that these patients had active disease to start with; those having lower HBsAg level were more likely to be cirrhotic. In other words, there were no “inactive HBV carriers” at very low risk of HCC as in untreated natural history cohorts[[19](#_ENREF_19)]**.**

**APPROACHES TO DEVELOP RISK SCORES**

There are different approaches to develop a risk score for HCC, but the first common step is to identify important independent factors associated with HCC in a training cohort. After statistical analysis, scores are assigned to different parameters in the equation to make up the final score. In order to demonstrate the applicability and reproducibility of the score, it should be validated in an independent cohort. If this independent cohort is not available, the leave-one-out cross-validation can be applied to assess the performance of the score in new data[[25](#_ENREF_25)]. This validation involves using a single observation from the original sample as the validation data, and the remaining observations as the training data. This is repeated such that each observation in the sample is used once as the validation data.

Take CU-HCC score as the example, significant variables were first identified in the multivariable Cox proportional hazards model[[8](#_ENREF_8)]. A score was attributed to each variable according to its relative contribution in the model, as determined by the *χ*2 score. Furthermore, different cutoff values of the score were determined to categorize patients into different levels of risk (*i.e.,* low-, medium-, and high-risk categories). The performance of the cutoff can be assessed in terms of discriminatory ability and monotonicity by linear trend *χ*2 test[[26](#_ENREF_26)].

Validation of the score usually involves two steps: discrimination and calibration. Discrimination can be assessed with the receiver operating characteristic (ROC) curve, *i.e.,* area under ROC (AUROC) curves, sensitivity, and specificity. Calibration is evaluated by estimating the observed HCC risk with the Kaplan-Meier method with the same cumulative risk scores. Combination of neighboring groups of cumulative risk scores will be done if the observed HCC risk in a group with the same cumulative risk score is sparse[[9](#_ENREF_9)].

**EXISTING PREDICTION SCORES FOR HCC**

The three most commonly applied HCC risk scores are described here (Tables 2 and 3).

***CU-HCC score***

CU-HCC score[[8](#_ENREF_8)] was first derived from a cohort 1005 Chinese CHB patients from a prospective study on the surveillance of HCC in chronic HBV carriers from The Chinese University of Hong Kong (abbreviated as CU in the name of the score)[[18](#_ENREF_18)]. It was validated in an independent cohort of 424 Chinese CHB patients[[27](#_ENREF_27)]. Both cohorts came from tertiary referral clinics. While all patients were treatment-naïve at baseline, 15.1% and 25.0% of patients from the training and validation cohort respectively received antiviral therapy during the long-term follow up to 10 years. CU-HCC score is composed of 5 parameters: age, albumin, bilirubin, HBV DNA, and cirrhosis; it ranges from 0 to 44.5 (Table 2). The investigators identified two cutoff values (5 and 20) best discriminating HCC risk into three categories. The 5-year HCC-free survival rates were 98.3%, 90.5%, and 78.9% in the low-, medium-, and high-risk groups, respectively. By applying the lower cutoff value, this score has high negative predictive value of 97.8% to exclude future HCC development.

***GAG-HCC score***

GAG-HCC score[[10](#_ENREF_10)] was first developed from a cohort 820 Chinese CHB patients from tertiary referral clinics. The name was abbreviated from ‘‘Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis”. All patients were treatment-naïve at baseline and censored at the time of initiation of antiviral therapy. As an independent cohort was not included, the investigators adopted the leave-one-out cross-validation mentioned above[[25](#_ENREF_25)]. There are two versions of the score. The original version is composed of gender, age, core promoter mutations, HBV DNA level and cirrhosis. There is a simplified version by omitting core promoter mutations, as they may not be easily available in some centers. The score ranges widely to above 100 as age (in years) is one of the components in the formula. A cutoff value of 101 was found to have good sensitivity and specificity of 84.1% and 76.2% for 5-year prediction, and 88.0% and 78.7% for 10-year prediction respectively. The negative predictive values were as high as 98.3% to 100% to exclude future HCC development.

***REACH-B score***

REACH-B score[[9](#_ENREF_9)] was first derived from a cohort 3584 Chinese CHB patients from the community-based prospective Taiwanese REVEAL-HBV study[[15](#_ENREF_15)], and then validated in a cohort of 1505 patients from three hospitals in Hong Kong and South Korea tertiary referral clinics. The name was the abbreviation of “Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B”. All patients of the training cohort did not have cirrhosis according to ultrasonography at the time of recruitment, and remained treatment-naïve throughout the follow-up period for as long as 12 years. In contrast, 18.4% (277/1505) of patients in the validation cohort had cirrhosis. REACH-B score consists of 5 parameters: gender, age, ALT level, HBeAg status and HBV DNA level. The score ranges from 0 to 17 and is primarily designed for patients without cirrhosis. The authors did not categorize patients into different risk levels, instead the 3-, 5- and 10-year risk of HCC was presented to each particular risk score. The HCC risk ranged from 0% to 23.6% at 3 years, 0% to 47.4% at 5 years, and 0% to 81.6% at 10 years for patients with the lowest (0 point) and highest HCC risk (17 points), respectively. As the risk increased more dramatically starting from 8 points, it could be used as an arbitrary cutoff value to categorize patients into different level of risks.

**IMPACT OF ANTIVIRAL THERAPY ON RISK PREDICTION**

Most of the patients involved in the development of the risk scores did not receive antiviral therapy. This raised the concern of their validity and applicability to patients receiving treatment. This is particularly relevant to those at risks of HCC as they are most often put on antiviral therapy. Antiviral therapy modifies the natural history of CHB by decreasing the serum HBV DNA levels, and altering other laboratory parameters (*e.g.,* lowering ALT, raising albumin and lowering bilirubin level). This leads to another question on the clinical significance of dynamic changes in the risk scores during longitudinal follow-up.

These importance concerns have been addressed in a recent real-life cohort study of 1531 entecavir-treated CHB patients followed up for 42 ± 13 mo[[22](#_ENREF_22)]. All of them received entecavir 0.5 mg daily for at least 12 mo. The importance of maintained viral suppression was emphasized in this study as virologic remission for 24 mo or more, together with advanced age and cirrhosis, were the independent factors associated with HCC in this cohort. All the CU-HCC, GAG-HCC and REACH-B scores were found accurate to predict HCC in 3 years and 5 years. Among them CU-HCC score had the highest AUROC at baseline (0.80 *vs* 0.76 and 0.71 respectively). At the recommended cutoff values, baseline CU-HCC and REACH-B scores had high sensitivity (93.6% and 95.2% respectively), while GAG-HCC score had high specificity (78.9%) to predict HCC.

After antiviral therapy, the risk scores would change because of decreased in viral load (*i.e.,* lower HBV DNA) and even HBeAg-seroconversion, improvement in liver function (high albumin, lower bilirubin) and necroinflammation (lower ALT). Therefore a significant proportion of patients would have decreased risk scores with treatment. From this real-life cohort study, 14.0%, 8.2% and 38.3% of patients had their risk category changed from high risk to low risk as defined by CU-HCC, GAG-HCC and REACH-B score respectively after 2 years of entecavir[[22](#_ENREF_22)]. One unresolved issue is the regression of cirrhosis, which may happen after long-term antiviral therapy[[28](#_ENREF_28),[29](#_ENREF_29)]. However, as this regression take years to happen, its effect on the dynamic change in risk level can only be evaluated in a study with at least 8 to 10 years of follow up.

The dynamic changes of risk scores after antiviral therapy posed significant meaning on HCC risk. For all the three risk scores, patients persistently in the low-risk category had the lowest risk of HCC; those “downgraded” in risk category would have significantly lower risk of HCC compared to those remained in high-risk category (Table 4)[[22](#_ENREF_22)]. Only 0.4% of patients who remained at low risk at baseline and 2 years according to CU-HCC score would develop HCC in 5 years; the corresponding figures were 2.1% and 12.9% in those changed from high risk to low risk, and those remained at high risk at both time points, respectively. For GAG-HCC score, 1.4%, 5.1% and 26.4% of patients who remained at low risk, changed from high to low risk, and remained at high risk respectively developed HCC in 5 years. The results from both CU-HCC and GAG-HCC score showed that the downgrading of risk score reduces but does not eliminate the risk of HCC (Figure 1).

**CLINICAL APPLICATION OF RISK SCORES**

The risk scores discussed above are simple to use as they combine a few widely available clinical variables for the estimation of HCC risk within a specific timeframe. However, the version of GAG-HCC score with core promoter mutations as a component may be less preferred by clinicians as tests of these mutations are not easily accessible in primary care setting and general practitioners taking care of most of the CHB patients. The simple calculations of the scores facilitate implementation of routine clinical use. But probably the complexity of calculation is now less a concern as web-based or smart phone apps of calculators of some of these scores are now available[[30](#_ENREF_30),[31](#_ENREF_31)]. The major limitation of these scores is that all studies only involved Asian (and mostly Chinese) patients, so that the validity and applicability in other ethnic groups remained uncertain. These risk scores can be potentially incorporated into a clinical risk-prediction instrument that could improve patient management through appropriate and timely intervention. Clinicians could use the scores to assess the risk of progression, and subsequently make evidence-based decisions about the clinical management of choice for these patients. A recent Japanese study showed that patients at high-risk categories according to these risk scores would benefit most from entecavir[[5](#_ENREF_5)]. Another long-term follow-up study of 641 patients receiving tenofovir for 6 years showed that the observed incidence of HCC was lowered compared to the predicted risk by REACH-B score[[32](#_ENREF_32)]. This would be indirect evidence that antiviral therapy reduces the risk of HCC.

We advocate estimating the risk scores for all CHB patients. For treatment-naïve patients, the results of these scores may guide the need of antiviral therapy complementary to the treatment guidelines. The scores should be monitored regularly every 1 to 2 years. Patients remaining at low risk are suitable for regularly monitoring at primary care setting. Those at high risk should be referred to specialist care and consider appropriate treatment.

For patients receiving antiviral therapy, the risk scores should be monitored yearly. Those respond well to treatment, *i.e.,* achieved maintained virologic remission, and remain at low-risk category have minimal risks of HCC. Therefore they may also be referred back to family physicians who are experienced in monitoring such patients. Patients have risk downgraded after treatment would have lower but yet 2% to 5% risk of HCC in 5 years. Therefore they should still receive regular HCC surveillance[[33](#_ENREF_33)]. Those remain at high-risk category despite antiviral therapy may need more intensive HCC surveillance, as the risk of HCC can be as high as 12.9% to 26.4% in 5 years (Table 3). On the other hand, patients who fail to achieve maintained viral suppression should consider alternative treatment regimes in order to reduce the risk of HCC[[34](#_ENREF_34)].

**FUTURE DIRECTION**

One potential problem of the risk scores is that heavy weighting is assigned to cirrhosis in CU-HCC and GAG-HCC. In the study of REACH-B, liver cirrhosis was excluded by ultrasonography. As early cirrhosis may be missed by ultrasonography, this limitation may lead to substantial prediction errors if the presence or absence of cirrhosis is misclassified[[35](#_ENREF_35)]. Transient elastography is one of the most widely validated non-invasive tools to detect early liver cirrhosis in various chronic liver diseases[[36](#_ENREF_36)]. Liver stiffness measurements (LSM) with this tool may be useful to refine the diagnosis of cirrhosis and substitute clinical cirrhosis as a component of the risk score to predict HCC. There has been evidence that LSM can predict HCC[[37](#_ENREF_37)], patient survival[[38](#_ENREF_38)] as well as complications after hepatic resection[[39](#_ENREF_39)]. Therefore, it is reasonable to believe that LSM would be an important parameter in a HCC risk score.

A recent Korean study of 1250 CHB patients developed a predictive model for HCC four clinical parameters, which include age, gender, HBV DNA and LSM value[[40](#_ENREF_40)]. The probability equals to 1 − *P*A; while A = exp (0.05306 × age + 1.106 × male gender + 0.04858 × LSM values + 0.50969 × HBV DNA ≥ 20000 IU/L). This model was found to have a moderately good discrimination capability, with an AUROC of 0.81. The predicted risk of HCC development correlated fairly well with the observed risk (*r* = 0.91). More data concerning the role of LSM in HCC risk score is now evolving[[41](#_ENREF_41)].

**CONCLUSION**

In conclusion, HCC risk scores can accurately predict subsequent HCC development in both treatment-naïve patients and those receiving antiviral therapy. Different levels of care and different intensities of HCC surveillance should be offered according to the risk profile of patients. Patients at high-risk category should be one of the indications of antiviral therapy, as well as appropriate HCC surveillance. For patients receiving antiviral therapy, maintained virologic response should be the treatment target, particularly in patients with cirrhosis. Patients at risk of HCC should receive regular HCC surveillance even when they are receiving antiviral treatment.

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**P-Reviewers** Grasso A, Khattab MA, Malnick S **S-Editor** Gou SX  **L-Editor E-Editor**

**Figure 1 Risk of hepatocellular carcinoma in the next 3 years by risk scores.** Results adopted from Wong *et al*[[22](#_ENREF_22)].

**Table 1 Risk factors of hepatitis B virus-related hepatocellular carcinoma**

|  |  |  |
| --- | --- | --- |
| **Host factors** | **Liver factors** | **Viral factors** |
| Advanced age | Advanced fibrosis | High serum HBV DNA |
| Male gender | Cirrhosis | Positive HBeAg |
| Family history of HCC | Hypoalbuminemia | HBV genotype C |
| SNP at human genomic loci, *e.g.* | Hyperbilirubinemia | HBV subgenotype Ce |
| Chromosome 1p36.22 | High ALT | Core promoter mutations |
| Chromosome 6 of HLA-DP/Q loci | Active necroinflammation | High serum HBsAg level |
| Chromosome 8p12 | Concomitant liver diseases *e.g.* |  |
| Immunosuppressed condition, *e.g.* | Hepatitis C virus co-infection |  |
| Human immunodeficiency virus co-infection | Hepatitis delta virus co-infection |  |
|  | Alcoholic liver disease |  |
|  | Nonalcoholic fatty liver disease |  |

ALT: Alanine aminotransferase; HBeAg: Hepatitis B virus e antigen; HBsAg: Serum hepatitis B surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HLA: Human leukocyte antigen; SNP: Single-nucleotide polymorphisms.

**Table 2 Components of the risk scores**

|  |  |  |  |
| --- | --- | --- | --- |
| **Factor** | **Risk Score** | | |
|  | **CU-HCC** | **GAG-HCC** **(yr)** | **REACH-B** |
| Age (yr) | ≤ 50: 0  >50: 3 |  | 30-34: 0  35-39: 1 40-44: 2  45-49: 3 50-54: 4 55-59: 5  60-65: 6 |
| Sex | NA | Male: 16  Female: 0 | Male: 2  Female: 0 |
| Albumin (g/L) | ≤ 35: 20 > 35: 0 | NA | NA |
| Bilirubin (mmol/L) | ≤ 18: 0  > 18: 1.5 | NA | NA |
| ALT (U/L) | NA | NA | < 15: 0  15-44: 1  ≥ 45: 2 |
| HBeAg | NA | NA | Positive: 2  Negative: 0 |
| HBV DNA (copies/mL) | < 4 log: 0  4-6 log: 1  > 6 log: 4  (lack of maintained virologic suppression: 4) | 3 × in log | < 4 log: 0  4-5 log: 3 5-6 log: 5  ≥ 6 log: 4 (lack of maintained virologic suppression: 4) |
| Cirrhosis | Presence: 15 Absence: 0 | Presence: 33 Absence: 0 | NA |

ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; NA: Not applicable.

**Table 3 Comparison between CU-HCC, GAG-HCC and REACH-B score**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Score** | **Patients** | **Components** | **Cutoff value** | **Performance** |
| CU-HCC | Clinic patients:  1005 in training cohort, 424 in validation cohort | Age, albumin, bilirubin, HBV DNA, cirrhosis | 5 | 97% NPV at 10 years |
| GAG-HCC | 820 clinic patients (leave-one-out cross-validation method) | Age, gender, HBV DNA, cirrhosis | 101 | 99% NPV at 10 years |
| REACH-B | Non-cirrhotic patients:  3,584 in training cohort, 1,505 in validation cohort | Age, gender, ALT, HBV DNA, HBeAg | 8 | 98% NPV at 10 years |

ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; NPV: Negative predictive value.

**Table 4 Dynamic changes of risk scores and 5-year risk of hepatocellular carcinoma**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Risk score** | | **HCC in 5 years** | | |
| **Baseline** | **2 years** | **CU-HCC** | **GAG-HCC** | **REACH-B1** |
| Low | Low | 0.4% | 1.4% | 0% |
| Low | High | 0% | NA | 0% |
| High | Low | 2.1% | 5.1% | 0% |
| High | High | 12.9% | 26.4% | 2.1% |

1Only patients with no cirrhosis were analyzed for REACH-B score. Results adopted from Wong *et al*[[22](#_ENREF_22)]. HCC: Hepatocellular carcinoma; NA: Not available.