Review Article

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Risk Predictive Models for Hepatitis B Virus-Related Hepatocellular Carcinoma in Patients Receiving Entecavir or Tenofovir: A Narrative Review

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Hepatocellular carcinoma (HCC) is a major complication of chronic hepatitis B (CHB). In the era of antiviral therapy, host factors such as age, sex, and liver cirrhosis status remain key risk factors for HCC occurrence, whereas baseline virological factors such as hepatitis B e antigen (HBeAg) status and level of viremia, which were major determinants of HCC risk in untreated patients, are found to be non-predictive when long-term virus control has been achieved. To date, there have been at least eight risk scoring models proposed to predict HCC for CHB patients receiving long-term entecavir (ETV) and tenofovir disoproxil fumarate (TDF), which are the current first-line regimens for CHB patients. Most models consist of similar component variables with slightly different weights for each variable. Among these models, three were derived from the same Caucasian cohort whereas the others were derived from Asian populations. Furthermore, three of the existing scores have been externally validated and compared in subsequent extraneous studies with independent patient populations. In order to attain a more accurate risk prediction, further research may investigate to include presumably critical factors not covered in current models, such as genetic compositions, environmental exposures, and lifestyle factors; exploration of novel biomarkers is also warranted. Finally, efforts are required to prove that the validated risk models can inform clinical practice toward the goal of personalized medicine.

Key words: chronic hepatitis B, hepatocellular carcinoma, predictive model

Introduction

Hepatitis B virus (HBV) infection is a global health problem that affects approximately 240 million people and causes over 686,000 deaths a year,[1] and hepatocellular carcinoma (HCC) is a major complication of chronic hepatitis B (CHB) virus infection.[2] Natural history studies have demonstrated that

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a high HBV viral load is associated with an increased HCC risk.[3] Furthermore, viral markers (e.g., viral load and hepatitis B e-antigen [HBeAg] status) have been shown to be major determinants in risk formulas to predict HCC occurrence among CHB patients without treatment.[4-8]

In the era of antiviral therapy, long-term viral suppression with a nucleos(t)ide analog (NA) has been demonstrated to reduce but not eliminate the risk of HBV-related HCC.[9-16] Baseline virological factors that were identified as risk determinants in untreated patients were not predictive in patients who received NA treatment. Host factors, such as age, sex, cirrhosis, platelet count, and diabetes, remain residual key factors, which have thus been incorporated into new models to predict HCC risk in CHB patients undergoing antiviral therapy.[17-25] Nowadays, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) were first recommended antivirals for CHB patients according to international guidelines.[1,20,26,27] Because of the lack of long-term clinical outcome for TAF, which is the latest approved, we will discuss these HCC risk models and summarize their performance and generalizability in CHB patients under long-term ETV or TDF.

Current risk models of HBV-related HCC for patients undergoing ETV or TDF

The key risk factors for HBV-related HCC could be classified as viral factors including viral load, e-antigen status, and genotype, or host factors including age, sex, liver condition (fibrosis status and hepatitis activity), and metabolic factors. These factors are included in traditional risk formulas for untreated patients.[28,29] In the era of antiviral therapy when long-term viral suppression has been achieved, host factors remain the key determinants, which are collaborated to predictive models of HBV related HCC in patients who received antiviral therapy.[17-25]

Currently, 8 risk formulas have been derived from patients with CHB undergoing long-term ETV or TDF (Table 1).[17-22,24] The SAGE-B and CAGE-B models, proposed in one article, were derived from the same European cohort as PAGE-B, with longer follow-up durations (> 5 years). The PAGE-B cohort comprised only Caucasian patients, and the other models were derived from Asian countries.[19,22] CAMD was derived from population-based setting while other scores were developed from hospital-based cohorts.[20] CAGE-B and SAGE-B estimate HCC occurrence after 5 years of antiviral therapy whereas the other models evaluate the risk of HCC from the beginning of ETV or TDF.[19] These risk models consist of similar variables including age, sex, cirrhosis status, and fibrosis-related markers (platelet count, albumin, and liver stiffness measurement) with different weights for each variable. Diabetes was incorporated in CAMD as prediction formula.[20]

Validation cohorts have indicated that the discriminative ability levels of current risk models are acceptable, with discrimination of 0.81 – 0.83 for 3 – 10-year HCC incidence. Notably, cirrhosis is a significant risk factor for HCC in the PAGE-B score. However, it was not included in the formula because its inclusion did not considerably improve discrimination (c-indices of the formulas with and without cirrhosis are 0.84 and 0.82, respectively, in the development group).[22] Furthermore, CAMD score includes an assessment of diabetes, a gradually valued risk factor, into their formulas.[20] CAMD and HCC-RESCUE are the only two models that use clinical data (age, sex, cirrhosis, and diabetes) without a blood test.[25]

External validation results for HCC risk models

Although the discriminative ability of current risk scores is acceptable in their valida-

Table 1. Summary of HCC risk models among patients with CHB under long-term ETV or TDF.

Risk Model	Ethnicity	Population‡	Number‡	Age‡	Male‡	Cirrhosis‡	Formula variables	Discrimination$ (95% CI)	Independent validation#	Duration of prediction
CAGE-B* Papatheodoridis[19] 2020	Caucasian	Hospital base	1427	52.1¶	69.5%	25.9%	Age (5 year after NA) LSM (5 year after NA)† Cirrhosis†	0.81	No	5 – 10 years after treat
SAGE-B* Papatheodoridis[19] 2020	Caucasian	Hospital base	1427	52.1¶	69.5%	25.9%	Age (5 years after NA) LSM (5 years after NA)	0.81	No	5 – 10 years after treat
AASL-HCC Yu[18] 2019	Asian	Hospital base	944	50‡	62.1%	39.3%	Age, Sex, Cirrhosis Albumin	0.80 (0.72 – 0.89)	No	5 years
CAMD Hsu & Yip[20] 2018	Asian	Population base	23851	47.5‡	74.0%	26.5%	Age, Sex, Cirrhosis Diabetes	0.82 (0.80 – 0.83)	Yes	5 years
mPAGE-B Kim[21] 2018	Asian	Hospital base	1211	50.3¶	59.8%	45.9%	Age, Sex, Platelet Albumin	0.82 (0.78 – 0.86)	Yes	5 years
HCC-RESCUE Sohn[17] 2017	Asian	Hospital base	990	47.4¶	65.0%	39%	Age, Sex, Cirrhosis	0.82 (0.72 – 0.82)	No	5 years
APA-B Chen[24] 2016	Asian	Hospital base	883	50¶	71.9%	35.9%	Age (1 year after NA) Platelet (1 year after NA) AFP (1 year after NA)	0.83 (0.77 – 0.88)	No	5 years (10 years)§
PAGE-B* Papatheodoridis[22] 2020	Caucasian	Hospital base	1325	52¶	70.0%	20%	Age, Sex, Platelet	0.82	Yes	5 years

* CAGE-B and SAGE-B came from the same cohort of PAGE-B with longer follow-up duration. † the baseline cirrhosis in relation to LSM at 5 years of treatment. § APA-B cohort was originally derived from a 5-year follow-up cohort[24]; the author validated this score at the 10-year follow-up[31]. # validated by subsequent studies using independent patient populations outside the derivation cohort. ¶ mean. ‡ median. ‡ from score developing cohort. $ the longest follow-up with 95% confidence interval (if available).
AFP: alpha-fetal protein; CHB: chronic hepatitis B; HCC: hepatocellular carcinoma; ETV: entecavir; PLT: platelet; TDF: Tenofovir disoproxil fumarate.

tion cohorts, only PAGE-B, mPAGE-B, and CAMD scores have been externally validated using independent studies, which demonstrated various but acceptable discrimination (c-index for PAGE-B: 0.70 – 0.97,[18,20,21,23-25,30-37] mPAGE-B: 0.73 – 0.80,[32,33,35,37] CAMD: 0.79).[37] PAGE-B[22] is the only formula that has been externally validated in Caucasian populations,30 Asian populations,[18,20,21,23-25,31-33,35-37] and population with mixed ethnicities;[34] the other formulas, which are all derived from Asian populations, have not been validated in Caucasian patients. The 3 risk scores derived from CHB populations receiving antiviral therapy within 5 years (PAGE-B and mPAGE-B: 5 years; CAMD: 3 years) and the predictivity models for population over a 5-year follow-up have also been demonstrated to be acceptable in external validation studies on patients with CHB with a follow-up of over 5 years (c-index for PAGE-B: 0.71-0.83,[23,30-32,35,37] mPAGE-B: 0.73 – 0.77,[30,32,35,37] CAMD: 0.79).[37]

External comparison results for HCC risk models

Numerous risk models have been developed. However, the optimal models overall and under specific conditions have not been identified. Furthermore, the "time point of prediction" should be considered. Most of the formulas predict HCC probability within 5 years and were derived from cohorts with a 5-year follow-up, except for CAGE-B and SAGE-B (after 5 years of antiviral therapy),[19] Furthermore, the ease of clinical application is a crucial consideration. For example, CAGE-B and SAGE-B include a measure of liver stiffness, which cannot be obtained in every institution.[19] CAMD and HCC-RESCUE only use clinical information, including age, sex, cirrhosis status, and diabetes (for CAMD) and thus do not require laboratory tests, which may facilitate clinical application.[17,20] Currently, 4 external independent studies have compared PAGE-B, mPAGE-B, and CAMD in Asia (Table 2). These studies have reported acceptable predictability in all 3 models. However, the comparative results revealed differences in the risk scores.[32,33,35,37] Yip and colleagues concluded that mPAGE-B predicts the 5-year HCC incidence more accurately than PAGE-B (c-index: 0.80 vs. 0.77).[33] Lee and colleagues reported similar predictions of HCC incidence by using mPAGE-B and PAGE-B within 108 months of follow-up (c-index: 0.77 vs. 0.74).[35] Kirino and colleagues reported that PAGE-B provided slightly more accurate predictions than mPAGE-B for the 3-year and 7-year HCC incidence (c-index: 3-year: 0.79 vs. 0.77; 7-year: 0.74 vs. 0.73).[32] Kim and colleagues suggested that the CAMD results are similar to the mPAGE results, and are superior to the PAGE-B predictions within 100 months of follow-up (c-index: 0.79 vs. 0.77 vs. 0.76).[37]

How to link risk formulas to clinical practice

An accurate risk score may inform clinical practice. First, it can be used to determine the intensity of surveillance required. For example, the low-risk population (HCC annual incidence < 0.2%) could be exempted from HCC surveillance; the follow-up duration could be reduced or ultrasonography could be replaced with more sensitive modalities, such as computed tomography (CT) or magnetic resonance imaging, as screening tools for high-risk populations. Furthermore, high-risk patients may require additional strategies for HCC risk reduction.

Current evidence for adjusting surveillance intensity based on different risks remain limited. International guidelines have suggested that the threshold for surveillance is 0.2% of HCC annual incidence.[2,38] Thus far, only European guidelines have suggested that non-cirrhotic CHB patients who have PAGE-B scores of over 10 should receive HCC screening, with low evidence level and weak recommendation.[2] Yip and colleagues validated

Table 2. Independent studies comparing different risk scores of HCC under long-term TDF/ETV.

	Comparison	Validation cohort				Discrimination	Remark
		Number	Age	Male	Cirrhosis		
Yip[33] 2020	mPAGE-B vs. mAGE-B	32150	53*	2086 (64.9%)	4625 (14.4%)	5 year: 0.80 vs. 0.77 ($p < 0.001$)	PAGE-B is better than mPAGE-B
Kirino[32] 2020	mPAGE-B vs. PAGE-B	443	51*	282 (63%)	82 (18.5%)	3 years: 0.77 vs. 0.79 5 years: 0.73 vs. 0.74	PAGE-B is similar with mPAGE-B
Kim[37] 2019	CAMD vs. mPAGE-B vs. PAGE-B	3227	48.7*	2053 (62.6%)	1061 (32.4%)	0.79 vs. 0.77 vs. 0.76†	CAMD is similar with mPAGE-B CAMD is better than PAGE-B mPAGE-B ins similar with PABE-B
Lee[35] 2019	mPAGE-B vs. PAGE-B	1330	48.1*	821 (61.7%)	611 (45.9%)	0.77 vs 0.74 ($p > 0.05$)†	mPAGE-B is similar with PAGE-B

* mean. †during the study period.
ETV: Entecavir; HCC: Hepatocellular carcinoma; TDF: Tenofovir Disoproxil Fumarate.

PAGE-B and mPAGE-B by using a large database from the Hong Kong population, which revealed that 29.7% population would be classified as a low-risk group with 5-year HCC accumulative incidence of approximately 0.6% (95% CI, 0.4% – 0.8%), achieving a negative predictive value of 99.5% (95% CI, 99.4% – 99.7%). These patients may be exempted from HCC surveillance.[33] This approach could reduce the health care burden. However, further evidence is needed to validate the feasibility and cost effectiveness. In their retrospective study, Kim and colleagues reported that alternating ultrasonography with CT every 6 months detected more very-early-stage HCCs than regular 6-month ultrasonography among high-risk patients (PAGE-B ≥ 18) but not among intermediate-risk patients (PAGE-B = 10 – 17).[39] Furthermore, this approach was associated with higher overall survival in patients with cirrhosis.[40] However, prospective studies are required to clarify whether a more intensive surveillance strategy would improve patients' outcome rather than just enabling early detection and to determine how different strategies can be applied based on the risk stratification.

Providing different risk reduction strategies according to risk stratification is a crucial purpose of the risk model; for example, suggesting statin usage or more aggressive control for metabolic risk factors, such as obesity, for high-risk patients to reduce the HCC occurrence.[41,42] However, additional studies are required to prove or refute these hypotheses.

Limitations of HCC risk models and future directions

Although the risk formulas of HCC prediction have been developed for CHB patients receiving long-term NA treatment, several aspects warrant further study. First, most of the risk models use single-point data to predict HCC occurrence, which does not account for dynamic changes during antiviral therapy. For example, the degree of liver fibrosis changes under long-term virus suppression is reasonably correlated with HCC risk. This concept was somewhat applied to the CAGE-B model. Second, most formulas, which were derived from CHB populations receiving 3 – 5 years of ETV or TDF treatment, predict HCC prob-

ability within 5 years. The exceptions were CAGE-B and SAGE-B (5 – 10 years after NA). Further data are needed to validate the accuracy of risk scores for patients undergoing longer-term virus suppression (longer than 5 – 10 years of treatment). Third, except for alcohol consumption and alpha-fetal protein, which were incorporated in some models, current formulas focus on host factors, such as age, sex, diabetes, and markers related to liver fibrosis (e.g., albumin, platelet, and cirrhosis). Certain well-documented risk factors, such as smoking, obesity, and nonalcoholic steatohepatitis, which could potentially improve the predictability, were not incorporated into current formulas.[41] Notably, patient education in daily practices could be used to reduce these factors. Furthermore, novel predictors, including genetic, circulatory, or imaging biomarkers, and algorithmic approaches based on machine learning could be used to produce more accurate models.[43,44] For example, hepatitis B core-related antigen and Mac-2 binding protein glycan isomer have displayed promising initial results for the prediction of HCC occurrence. Further investigation is warranted to facilitate personalized risk stratification.[45-47] Fourth, the fundamental question for current risk formulas is when and how they can be applied in daily practice to improve outcomes on a balance of cost and effectiveness. Additional studies are warranted to clarify whether these scores can guide the surveillance intensity or provide recommendations based on risk stratification. Ideally, risk reduction strategies would be based on different HCC risks.

Conclusions

In the era of antiviral therapy, baseline virological factors no longer play a critical role in the prediction of HCC occurrence, whereas host factors remain key predictors. To date, there have been at least 8 models (5 from Asia and 3 from Europe with the same cohort) developed to determine HCC risk among CHB patients undergoing long-term viral control. These formulas share similar variables and have displayed acceptable predictability. Future studies may consider to investigate new risk factors, biomarkers, and algorithmic approaches based on machine learning to improve accuracy of the risk prediction. Finally, efforts are warranted to validate risk models into clinical practice toward the goal of personalized medicine.

Author Contributions

Study design: CHT, YCH; Data extraction: THC, CHT; Data analysis and interpretation: THC, CHT, YCH.

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Conflicts of Interest

YCH: Research support: Gilead Sciences, and served as an advisory committee member for Gilead Sciences; Speaker: Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Novartis. CHT: Speaker: Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme.

References

1. European Association for the Study of the Liver: EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98. doi: 10.1016/j.jhep.2017.03.021.
2. European Association for the Study of the Liver: EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236. doi: 10.1016/j.jhep.2018.03.019.
3. Chen CJ, Yang HI, Su J, et al: Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73. doi: 10.1001/jama.295.1.65.
4. Lee MH, Yang HI, Liu J, et al: Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. Hepatology 2013;58:546-54. doi: 10.1002/hep.26385.
5. Wong VW, Chan SL, Mo F, et al: Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol 2010;28:1660-5. doi: 10.1200/JCO.2009.26.2675.
6. Wong GL, Chan HL, Wong CK, et al: Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. J Hepatol 2014;60:339-45. doi: 10.1016/j.jhep.2013.09.029.
7. Yuen MF, Tanaka Y, Fong DY, et al: Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol 2009;50:80-8. doi: 10.1016/j.jhep.2008.07.023.
8. Yang HI, Yuen MF, Chan HL, et al: Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011;12:568-74. doi: 10.1016/S1470-2045(11)70077-8.
9. Singal AK, Salameh H, Kuo YF, et al: Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. Aliment Pharmacol Ther 2013;38:98-106. doi: 10.1111/apt.12344.
10. Lok AS, McMahon BJ, Brown RS Jr, et al: Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology 2016;63:284-306. doi: 10.1002/hep.28280.
11. Ahn J, Lim JK, Lee HM, et al: Lower observed hepatocellular carcinoma incidence in chronic hepatitis B patients treated with entecavir: results of the ENUMERATE study. Am J Gastroenterol 2016;111:1297-304. doi: 10.1038/ajg.2016.257.
12. Kim WR, Loomba R, Berg T, et al: Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. Cancer 2015;121:3631-8. doi: 10.1002/cncr.29537.
13. Hosaka T, Suzuki F, Kobayashi M, et al: Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013;58:98-107. doi: 10.1002/hep.26180.
14. Wong GL, Chan HL, Mak CW, et al: Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. Hepatology 2013;58:1537-47. doi: 10.1002/hep.26301.
15. Nguyen MH, Yang HI, Le A, et al: Reduced incidence of hepatocellular carcinoma in cirrhotic and noncirrhotic patients with chronic hepatitis B treated with tenofovir - a propensity score-matched study. J Infect Dis 2019;219:10-8. doi: 10.1093/infdis/jiy391.
16. Su TH, Hu TH, Chen CY, et al: Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755-64. doi: 10.1111/liv.13253.
17. Sohn W, Cho JY, Kim JH, et al: Risk score model for the development of hepatocellular carcinoma in treatment-naïve patients receiving oral antiviral treatment for chronic hepatitis B. Clin Mol Hepatol 2017;23:170-8. doi: 10.3350/cmh.2016.0086.
18. Yu JH, Suh YJ, Jin YJ, et al: Prediction model for hepatocellular carcinoma risk in treatment-naive chronic hepatitis B patients receiving entecavir/tenofovir. Eur J Gastroenterol Hepatol 2019;31:865-72. doi: 10.1097/MEG.0000000000001357.
19. Papatheodoridis GV, Sypsa V, Dalekos GN, et al: Hepatocellular carcinoma prediction beyond year 5 of oral therapy in a large cohort of Caucasian patients with chronic hepatitis B. J Hepatol 2020;72:1088-96. doi: 10.1016/j.jhep.2020.01.007.
20. Hsu YC, Yip TC, Ho HJ, et al: Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B. J Hepatol 2018;69:278-85. doi: 10.1016/j.jhep.2018.02.032.
21. Kim JH, Kim YD, Lee M, et al: Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy. J Hepatol 2018;69:1066-73. doi: 10.1016/j.jhep.2018.07.018.
22. Papatheodoridis G, Dalekos G, Sypsa V, et al: PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800-6. doi: 10.1016/j.jhep.2015.11.035.
23. Lee HW, Park SY, Lee M, et al: An optimized hepatocellular carcinoma prediction model for chronic hepatitis B with well-controlled viremia. Liver Int 2020;40:1736-43. doi: 10.1111/liv.14451.
24. Chen CH, Lee CM, Lai HC, et al: Prediction model of hepatocellular carcinoma risk in Asian patients with chronic hepatitis B treated with entecavir. Oncotarget 2017;8:92431-41. doi: 10.18632/oncotarget.21369.
25. Yang HI, Yeh ML, Wong GL, et al: Real-world

effectiveness from the Asia Pacific Rim Liver Consortium for HBV risk score for the prediction of hepatocellular carcinoma in chronic hepatitis B patients treated with oral antiviral therapy. J Infect Dis 2020;221:389-99. doi: 10.1093/infdis/jiz477.
26. Terrault NA, Lok ASF, McMahon BJ, et al: Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-99. doi: 10.1002/hep.29800.
27. Sarin SK, Kumar M, Lau GK, et al: Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98. doi: 10.1007/s12072-015-9675-4.
28. Voulgaris T, Papatheodoridi M, Lampertico P, et al: Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B. Liver Int 2020;40:484-95. doi: 10.1111/liv.14334.
29. Papatheodoridis GV, Voulgaris T, Papatheodoridi M, et al: Risk scores for hepatocellular carcinoma in chronic hepatitis B: a promise for precision medicine. Hepatology 2020;72:2197-205. doi: 10.1002/hep.31440.
30. Riveiro-Barciela M, Tabernero D, Calleja JL, et al: Effectiveness and safety of entecavir or tenofovir in a Spanish cohort of chronic hepatitis B patients: validation of the Page-B Score to predict hepatocellular carcinoma. Dig Dis Sci 2017;62:784-93. doi: 10.1007/s10620-017-4448-7.
31. Sou FM, Hu TH, Hung CH, et al: Incidence and predictors of hepatocellular carcinoma beyond year 5 of entecavir therapy in chronic hepatitis B patients. Hepatol Int 2020;14:513-20. doi: 10.1007/s12072-020-10031-3.
32. Kirino S, Tamaki N, Kaneko S, et al: Validation of hepatocellular carcinoma risk scores in Japanese chronic hepatitis B cohort receiving nucleot(s)ide analog. J Gastroenterol Hepatol 2020;35:1595-601. doi: 10.1111/jgh.14990.
33. Yip TC, Wong GL, Wong VW, et al: Reassessing the accuracy of PAGE-B-related scores to predict hepatocellular carcinoma development in patients with chronic hepatitis B. J Hepatol 2020;72:847-54. doi: 10.1016/j.jhep.2019.12.005.
34. Brouwer WP, van der Meer AJP, Boonstra A, et al: Prediction of long-term clinical outcome in a diverse chronic hepatitis B population: Role of the PAGE-B score. J Viral Hepat 2017;24:1023-31. doi: 10.1111/jvh.12727.
35. Lee HW, Kim SU, Park JY, et al: External validation of the modified PAGE-B score in Asian chronic hepatitis B patients receiving antiviral therapy. Liver Int 2019;39:1624-30. doi: 10.1111/liv.14129.
36. Kim MN, Hwang SG, Rim KS, et al: Validation of PAGE-B model in Asian chronic hepatitis B patients receiving entecavir or tenofovir. Liver Int 2017;37:1788-95. doi: 10.1111/liv.13450.
37. Kim SU, Seo YS, Lee HA, et al: Validation of the CAMD score in patients with chronic hepatitis B virus infection receiving antiviral therapy. Clin Gastroenterol Hepatol 2020;18:693-9.e1. doi: 10.1016/j.cgh.2019.06.028.
38. Marrero JA, Kulik LM, Sirlin CB, et al: Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-50. doi: 10.1002/hep.29913.
39. Kim JH, Kang SH, Lee M, et al: Individualized surveillance of chronic hepatitis B patients according to hepatocellular carcinoma risk based on PAGE-B scores. Eur J Gastroenterol Hepatol 2021;33:1564-72. doi: 10.1097/MEG.0000000000001870.
40. Kim JH, Kang SH, Lee M, et al: Improved detection of hepatocellular carcinoma by dynamic computed tomography in cirrhotic patients with chronic hepatitis B: a multicenter study. J Gastroenterol Hepatol 2020;35:1795-803. doi: 10.1111/jgh.15046.
41. Li W, Deng R, Liu S, et al: Hepatitis B virus-related hepatocellular carcinoma in the era of antiviral therapy: the emerging role of non-viral risk factors. Liver Int 2020;40:2316-25. doi: 10.1111/liv.14607.
42. Simon TG, Duberg AS, Aleman S, et al: Lipophilic statins and risk for hepatocellular carcinoma and death in patients with chronic viral hepatitis: results from a nationwide Swedish population. Ann Intern Med 2019;171:318-27. doi: 10.7326/M18-2753.
43. Singal AG, Mukherjee A, Elmunzer BJ, et al: Machine learning algorithms outperform conventional regression models in predicting development of hepatocellular carcinoma. Am J Gastroenterol 2013;108:1723-30. doi: 10.1038/ajg.2013.332.
44. Audureau E, Carrat F, Layese R, et al: Personalized surveillance for hepatocellular carcinoma in cirrhosis - using machine learning adapted to HCV status. J Hepatol 2020;73:1434-45. doi: 10.1016/j.jhep.2020.05.052.
45. Hsu YC, Jun T, Huang YT, et al: Serum M2BPGi level and risk of hepatocellular carcinoma after oral anti-viral therapy in patients with chronic hepatitis B. Aliment Pharmacol Ther 2018;48:1128-37. doi: 10.1111/apt.15006.
46. Jun T, Hsu YC, Ogawa S, et al: Mac-2 binding protein glycosylation isomer as a hepatocellular carcinoma marker in patients with chronic hepatitis B or C infection. Hepatol Commun 2019;3:493-503. doi: 10.1002/hep4.1321.
47. Tseng TC, Liu CJ, Hsu CY, et al: High level of hepatitis B core-related antigen associated with increased risk of hepatocellular carcinoma in patients with chronic HBV infection of intermediate viral load. Gastroenterology 2019;157:1518-29.e3. doi: 10.1053/j.gastro.2019.08.028.