Journal of the Formosan Medical Association 122 (2023) 1238–1246

Available online at www.sciencedirect.com

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Review Article

Prediction model of hepatitis B virus-related hepatocellular carcinoma in patients receiving antiviral therapy

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Received 1 December 2022; received in revised form 15 May 2023; accepted 24 May 2023

KEYWORDS
Hepatitis B virus;
Hepatocellular carcinoma;
Prediction;
Model

Chronic hepatitis B virus (HBV) infection, which ultimately leads to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC), remains a significant disease burden worldwide. Despite the use of antiviral therapy (AVT) using oral nucleos(t)ide analogs (NUCs) with high genetic barriers, the risk of HCC development cannot be completely eliminated. Therefore, bi-annual surveillance of HCC using abdominal ultrasonography with or without tumor markers is recommended for at-risk populations. For a more precise assessment of future HCC risk at the individual level, many HCC prediction models have been proposed in the era of potent AVT with promising results. It allows prognostication according to the risk of HCC development, for example, low-vs. intermediate-vs. high-risk groups. Most of these models have the advantage of high negative predictive values for HCC development, allowing exemption from biannual HCC screening. Recently, non-invasive surrogate markers for liver fibrosis, such as vibration-controlled transient elastography, have been introduced as integral components of the equations, providing better predictive performance in general. Furthermore, beyond the conventional statistical methods that primarily depend on multi-variable Cox regression analyses based on the previous literature, newer techniques using artificial intelligence have also been applied in the design of HCC prediction models. Here, we aimed to review the HCC risk prediction models that were developed in the era of potent AVT and validated among independent cohorts to address the clinical unmet needs, as well as comment on future direction to establish the individual HCC risk more precisely.

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https://doi.org/10.1016/j.jfma.2023.05.029

Introduction

Chronic hepatitis B virus (HBV) infection is the main global cause of liver disease, progressing to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[1–4] HBV-related hepatocarcinogenesis had a very complex pathogenesis.[5] Among the various factors associated with liver disease progression in patients with chronic HBV infection, a high serum HBV- DNA level, as a surrogate of active viral replication, has been known as an independent risk factor.[1,2] Therefore, suppression of HBV replication with potent antiviral therapy (AVT) could reduce the risk of developing HCC substantially, but such a risk cannot be completely eliminated.[6–10] Furthermore, despite the availability of novel systemic chemotherapeutic regimens against HCC,[11] it remains the third leading cause of cancer-induced mortality. Therefore, early detection that allows for curative treatment is a critical factor in determining disease prognosis.[12–17] This is the reason why bi-annual surveillance for HCC screening using abdominal ultrasonography with or without tumor markers is still required even in patients with complete virological response through long-term AVT.

Meanwhile, in the era of potent AVT using oral nucleos(t)ide analogs (NUCs) with high genetic barriers, such as entecavir, tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF), complete virological and biochemical responses might be easily achieved.[3,18–25] Hence, the clinical importance of conventional factors associated with viral activity, such as serum HBV-DNA, hepatitis B e antigen, and alanine transaminase (ALT) levels, might be substantially offset, especially for patients undergoing regular follow-up with long-term AVT.[26,27] This is the reason why many prediction models for HCC development that were developed before the era of potent AVT have shown suboptimal predictive performance.[28,29]

Among patients receiving oral NUCs, the most important predictor of HCC is primarily the degree of liver fibrosis.[30–32] Cirrhosis, the so-called last stage of liver fibrosis progression, has been adopted as a key factor in almost all HCC prediction models with the highest weight in an integer scoring system. Therefore, it is important to evaluate the degree of fibrosis progression accurately. In clinical practice, gross imaging modalities, such as ultrasonography and/or clinical diagnosis based on laboratory results, symptoms, and signs, are used as surrogate markers for histological results. To compensate for this, other non-invasive tests that can indirectly predict advanced fibrosis or cirrhosis, such as vibration-controlled transient elastography (VCTE; Fibroscan, Echosens, Paris, France), shear-wave elastography, Fibrotest (Biopredictive, Paris, France), and Enhanced Liver Fibrosis test (ELF test; Siemens Healthcare Diagnostics Inc., Tarrytown, NY). They can assess fibrotic burden indirectly and have been introduced as variables for predicting HCC development, but more validation studies are needed to confirm the usefulness of these models.[31]

In this review, we aimed to summarize the prediction models to date, for HBV-related HCC development, and introduce new methods for the development of models.

HCC risk prediction models developed in the era of potent AVT using conventional methods

According to the recent guidelines from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and The Asian Pacific Association for the Study of the Liver, ETV, and TDF are recommended as the first-line treatment, and most patients with chronic HBV infection are usually treated with ETV or TDF in real-world practice. Consequently, many of the HCC risk prediction models for patients with chronic HBV infection treated with antivirals enrolled patients who used first-line medications (ETV or TDF). However, even in cases receiving oral NUCs with low-genetic barrier (e.g. lamivudine, adefovir, and telbivudine) their final prognosis might be comparable, provided that patients received appropriate rescue therapy in case of virologic breakthrough or resistance mutations.[33] Therefore, the predictive performances of certain risk prediction models were unlikely to vary according to the types of antiviral regimens. Nevertheless, in most HCC prediction models, the authors explored candidate variables from previously known risk factors such as age, sex, family history, laboratory parameters for liver function or viral status, and imaging parameters, and assessed their independent statistical significance for prognostication using multi-variable Cox regression analyses.

The representative HCC risk prediction models that were developed in the era of potent AVT and then externally validated among the independent cohort included the PAGE B, modified PAGE-B (mPAGE-B), CAMD, REAL-B, HCC-RESCUE, and AASL-HCC, as well as the modified REACH-B (mREACH-B) scores (Table 1).[34–40] In contrast to other models, many of which were generally developed from Asian populations, the PAGE-B score was derived from Caucasians, using the variables of age, sex, and platelets, and has acceptable predictive performance (c-index 0.82). By the PAGE-B score, patients were stratified into low- ($\leq$9), medium- (10–17), and high-risk ($\geq$18) groups; the 5-year cumulative HCC incidence among low-, medium-, and high-risk groups were 0%, 3%, and 17%, respectively. In the validation cohort, the negative predictive value of HCC within 5 years approached 100%, based on a 10-point cut-off.

In line with the PAGE-B score, the mPAGE B score was developed by incorporating serum albumin into the equation, along with three variables of the PAGE-B score, primarily based on a total of 3001 South Korean patients. Its predictive performance was also acceptable, with an area under the receiver operating characteristic curve [AUROC] of 0.82, and the 5-year cumulative probabilities of HCC development among the low- ($\leq$8), intermediate- (9–12), and high-risk ($\geq$13) groups were 0.7%, 5.1%, and 18.4%, respectively.

The CAMD (cirrhosis, age, male sex, and diabetes) score was developed in a study conducted in Hong Kong and Taiwan, with 23,851 patients with chronic HBV infection who were receiving either ETV or TDF, showing promising results with c indices of 0.83, 0.82, and 0.82 at 1-, 2-, and 3-years of AVT for the HCC development cohort, respectively.

Table 1 Summary of the HCC prediction models designed in the era of potent AVT.

Models	Equations	Specific comments
PAGE-B	Age (years): <30 (−4 points), 30−39 (−2 points), 40−49 (0 point), 50−59 (2 points), 60−69 (4 points), ≥70 (6 points) Male sex: 5 points Platelets (mm^3): ≥200 × 10^3 (0 point), 100 × 10^3 to <200 × 10^3 (6 points), <100 × 10^3 (11 points) Sum of each score	It was developed from the Caucasian population and also validated in the Asian population
mPAGE-B	Age (years); 30−39 (3 points), 40−49 (5 points), 50−59 (7 points), 60−69 (9 points), ≥70 (11 points) Male sex: 2 points Platelets (× 10^9/L): ≥250 (0 point), 200−250 (2 points), 150−200 (3 points), 100−150 (4 points), <100 (5 points) Albumin (g/L): <3 (3 points), 3−3.5 (2 points), 3.5−4 (1 point), ≥4 (0 point) Sum of each score	It was developed from the Asian population. Further validation should be required among the other population.
CAMD	Age (years): <40 (0 point), 40−49 (5 points), 50−59 (8 points), ≥60 (10 points) Male sex: 2 points Diabetes: presence (1 point) Cirrhosis with age <40 years (10 points), ≥40 years (6 points) Sum of each score	It was developed from the Asian population and incorporated diabetes as a significant variable. Further validation should be required among the other population.
REAL-B	Male sex: 1 point Age (years): 30−39 (1 point), 40−49 (2 points), 50−59 (3 points), 60−69 (4 points), 70−79 (5 points), ≥80 (6 points) Alcohol use: 1 point Diabetes: 1 point Cirrhosis: 2 points Platelet count (× 10^9/L): <150 (1 point) AFP: ≥10 (1 point) Sum of each score	It was developed among the international cohorts from the Asia and the United States.
HCC-RESCUE	Age +15 × gender (female = 0; male = 1) + 23 × cirrhosis (absence = 0; presence = 1)	It was developed from the Asian population. Further validation should be required among the other population.
AASL-HCC	Age (years): <30 (0 point), 30−39 (2 points), 40−49 (4 points), 50−59 (6 points), 60−69 (8 points), ≥70 (10 points) Male sex: 3 points Albumin (g/L): <2.8 (5 points), 2.8−3.4 (3 points), ≥3.5 (0 point) Cirrhosis: presence (11 points) Sum of each score	It was developed from the Asian population. Further validation should be required among the other population.
mREACH-B	Male sex: 2 points Age: 1 point for every 5 years from 35 to 65 years of age (0−6 points) ALT (IU/L):15 to <45 (1 point), ≥45 (2 points) Positive HBeAg: 2 points LS value (kPa): <8.0 (0 point), 8−13 kPa (2 point), >13 (4 point) Sum of each score	It was developed from the Asian population based upon the REACH-B score. The prognostic significance of HBeAg might be suboptimal in the era of potent AVT.

Abbreviations: HCC, hepatocellular carcinoma; AVT, antiviral therapy; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen.

In this study, two cut-off points, 8 and 13, were set to stratify patients into low-, medium-, or high-risk subgroups. The 3-year cumulative incidences of HCC in patients with CAMD scores of <8, 8−13, and >13 points were 0.3%, 2.4%, and 10.8%, respectively. The CAMD score was externally validated with an acceptable predictive performance, with an integrated area under the curve (iAUC) of 0.790 among 3277 South Korean patients.

Another study proposing the AASL-HCC (age, albumin, sex, cirrhosis) score was performed in 1243 South Korean patients with chronic HBV infection receiving ETV or TDF, with an overall similar predictive performance compared to that of previous models, with a c-index of 0.802 for prediction of HCC development at 5 years. The AASL model classified the risk of HCC into low- (≤5), intermediate- (6−19), and high-risk (≥20) groups, with the 10-year

cumulative HCC incidence rate being almost zero in the low-risk group. Therefore, the 5-year cumulative incidence rates of HCC in the low-, intermediate-, and high-risk groups were 0%, 4.2%, and 17.6%, respectively. Likewise, the HCC-RESCUE score was developed from 2061 South Korean patients with chronic HBV infection receiving entecavir, based on three variables: age, sex, and cirrhosis. AUROCs for HCC development at 1-, 2-, 3-, 4-, and 5-years were 0.798, 0.789, 0.788, 0.786, and 0.817, respectively. The categorization of the risk groups using the HCC-RESCUE scores was as follows: low-risk, ≤64 points; intermediate-risk group, 65–84 points; high-risk, ≥85 points. A significant difference in HCC development in each risk group was determined using the 5-year HCC risk score in the training cohort (low-risk group: 0.5%; intermediate-risk group: 14.4%; high-risk group: 37.1%, $p < 0.001$). Yang et al.[37] proposed the REAL-B score, which includes seven variables (male sex, age, alcohol use, diabetes, baseline cirrhosis, platelet count, and alpha fetoprotein). Notably, this study enrolled a population from 6 to 19 centers in the United States and Asia–Pacific regions (Mainland China, New Zealand, South Korea, Hong Kong, Japan, and Taiwan), respectively. The AUROC for the prediction of HCC at 3, 5, and 10 years was 0.81, 0.80, and 0.80, respectively. The authors determined cutoffs based on the estimated 3-year risk as < 1% (0–3 points), 1%–5% (4–7 points), and >5% (8–13 points) for the low-, intermediate-, and high-risk groups, respectively. The REAL-B score was externally validated with time-dependent ROCs of 0.720, 0.739, and 0.695 for HCC development at 1-, 3-, and 5-years, respectively,[41] Chang et al.[42] compared the predictive performances of the AASL, RESCUE-B, PAGE-B, and mPAGE-B scores among 3171 South Korean patients with chronic HBV infection receiving both ETV and TDF and found that the predictive performance of the AASL score was the highest for 3- and 5-year HCC development (AUC: 0.818 and 0.816, respectively), followed by the HCC-RESCUE, PAGE-B, and mPAGE-B scores (AUC: 0.780–0.815 and 0.769–0.814, respectively).

From the viewpoint of identifying a subgroup where universal biannual HCC surveillance based upon ultrasonography with or without tumor markers might be safely exempt in terms of the cost-effectiveness, the so called "low-risk" group defined by the PAGE B (≤9), mPAGE-B (≤8), CAMD (<8), AASL-HCC (≤5), HCC-RESCUE (≤64), and REAL-B (≤3) consistently showed the negligible risk of HCC development. So, how to apply such results effectively in the real-world practice should be studied in the further studies.

Meanwhile, VCTE, as a non-invasive surrogate marker for liver fibrosis, has been used to estimate liver stiffness (LS), and its prognostic role among patients with chronic HBV infection has been widely validated.[31,43] Since the mREACH-B score was developed in 192 patients with chronic HBV infection, who achieved complete virological response (defined as HBV DNA <20 IU/mL) through entecavir therapy, Lee et al.[40] incorporated the LS value into the REACH-B scoring model instead of serum HBV-DNA level, resulting in a better predictive performance with an AUROC of 0.814 (vs. 0.629). The mREACH-B score was validated in 1308 South Korean patients with chronic HBV infection, with reproducible predictive performance.[44] Moreover, Seo et al.[45] enrolled 1241 South Korean patients with chronic HBV infection during a 10-year follow-up and found that the mREACH-B score showed higher performance in predicting HCC than that of the PAGE-B score at 3 years (AUC: 0.824 vs. 0.715, respectively), 5 years (AUC: 0.750 vs. 0.719, respectively), and 7 years (AUC: 0.770 vs. 0.714, respectively). Further studies with external validation concerning the prognostic role of the surrogate markers other than LS by VCTE, i.e. either imaging (shear wave elastography or magnetic resonance elastography) or serology (Fibrotest®, ELF test, or mac-2-binding protein glycosylation isomer) based markers, as potential constituents in the equations are necessary.[46–55]

The clinical relevance of viral factors as the prognostic markers

Whether viral factors still serve as a predictor to assess the future risk of HCC development in the era of potent AVT remains controversial. Actually, from the studies where patients were enrolled prior to the era of potent AVT or did not receive AVT, those prediction models, e.g. GAG-HCC, CU-HCC, REACH-B, and LSM-HCC scores, had generally incorporated pre-treatment HBV-DNA as a prognostic variable.[56–59] In contrast, the most prediction models established from patients receiving AVT did not incorporate pre-treatment HBV-DNA as a prognostic predictor. Furthermore, there has been no study regarding the HCC prediction model incorporating a rapid decline of serum HBV-DNA as the favorable prognostic factor. However, given that the proportions of complete virological response after 1 year of ETV vs. TDF have become comparable, a decline rate of serum HBV-DNA during the AVT among treatment-naïve patients is not likely to have affected the final prognosis.[24,60]

On the other hands, hepatitis B core-related antigen (HBcrAg), as a reliable surrogate marker for intrahepatic covalently closed circular DNA activity which is responsible for viral persistence and disease progression, might be a promising biomarker to predicting HBV-related HCC development, based upon the reports that the positive correlation between the titer of HBcrAg and the risk of HCC development.[61–64] Further studies with external validation concerning the prognostic role of the serolocial viral markers are necessary.

HCC risk prediction models considering dynamic change of parameters during long-term AVT

As long-term AVT can lead to regression of surrogate markers for hepatic fibrosis, for example, FIB-4, APRI, and LS by TE, it might be clinically useful to track their dynamic changes during follow-up. However, most studies to date have been based on the parameters assessed once at the start of AVT. Lee et al.[65] reported the prognostic value of on-treatment liver stiffness (LS) for the prediction of HCC development among 880 patients receiving ETV or TDF for ≥2 years, suggesting that the achievement of an on-treatment LS value less than 6.4 kPa should be a key determinant for HCC prediction, regardless of the baseline LS value. In line with this concept, Lee et al.[66] proposed an optimized HCC prediction model for patients with well-

controlled HBV viremia during long-term AVT, which is called the CAMPAS score, using variables at the time of confirmed virological response (serum HBV DNA <2000 IU/mL), providing a c-index of 0.874.

More recently, based on on-therapy changes in non-invasive fibrosis marker (NFM) as an independent indicator of HCC risk, Nam et al.[67] proposed the Fibrosis marker response, Sex, Age, and Cirrhosis (FSAC) score, where the response of NFM was assessed using changes in the APRI or FIB-4 index. The FSAC score showed higher C-index values than the PAGE-B and modified PAGE-B (0.84 vs 0.77 and 0.80, respectively; both $P < 0.005$). The better predictive performance of the FSAC score, compared to the mPAGE-B, mREACH-B, and CAMD scores, were also reported in an independent cohort.[68] Further studies are required concerning the clinical utility of on-treatment dynamic changes of other NFMs; e.g. LS by TE, shear wave elastography, or magnetic resonance elastography, as well as Fibrotest®, ELF test, or other serological biomarkers.

HCC risk prediction using artificial intelligence (AI)

Recently, AI has been widely used in medical research and practice, including in the field of liver disease. It might improve the full spectrum of HCC clinical care, that is, not only HCC risk prediction, but also its diagnosis and prognostication. AI approaches include computational search algorithms, machine learning (ML), and deep-learning (DL) models. ML involves a computer running repeated iterations of models to progressively improve the performance of a specific task, such as classifying an outcome. DL models are a subtype of ML, based on neural network structures that are inspired by the neuroanatomy of the human brain. A growing body of recent data applied DL models to diverse data sources, including electronic health records, imaging modalities, histopathology, and molecular biomarkers, to improve the accuracy of HCC risk prediction. Recently, Kim et al.[69] proposed a prediction model based on AI, in which an optimal model was constructed using the gradient-boosting machine learning method among 6051 South Korean patients with chronic HBV infection. Notably, the validation was performed on South Koreans and Caucasians, showing that the predictive power of HCC is better than that of previously reported models, such as the PAGE-B and REACH-B models.[69]

However, although an HCC prediction model will become more precise through the application of AI, AI-based HCC prediction models so far did not show the overwhelming performances, when compared to the conventional ones. To overcome this issue, one of the viable options is to identify the novel biomarkers other than routine tests performed in the real-world practice. They might include serological markers as well as data from radiomics, genomics, or metabolomics. In addition, future research is still needed to standardize AI data, to improve both the

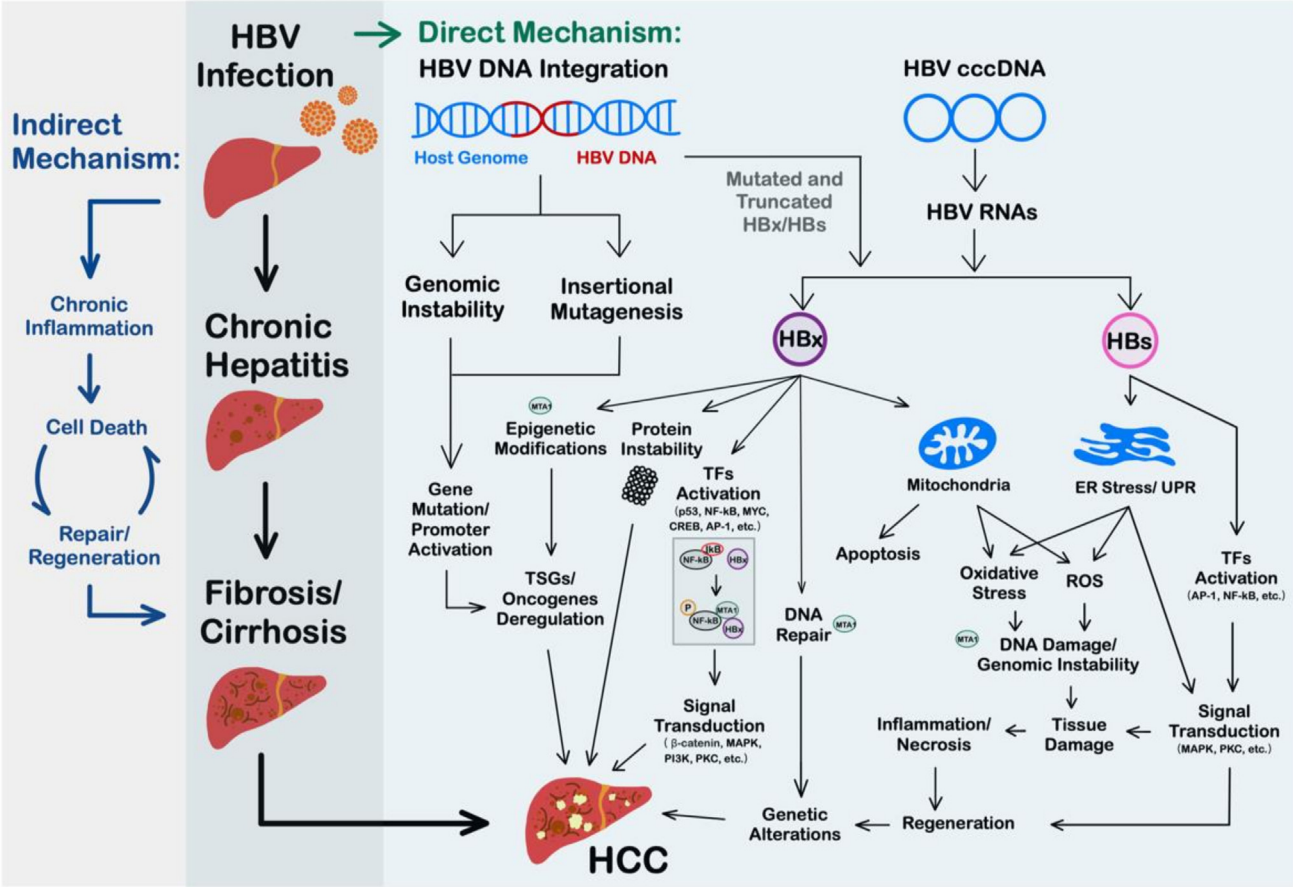

Figure 1 Hepatocarcinogenesis among patients with chronic HBV infection (cited from the article by Li et al.[5] with permission).

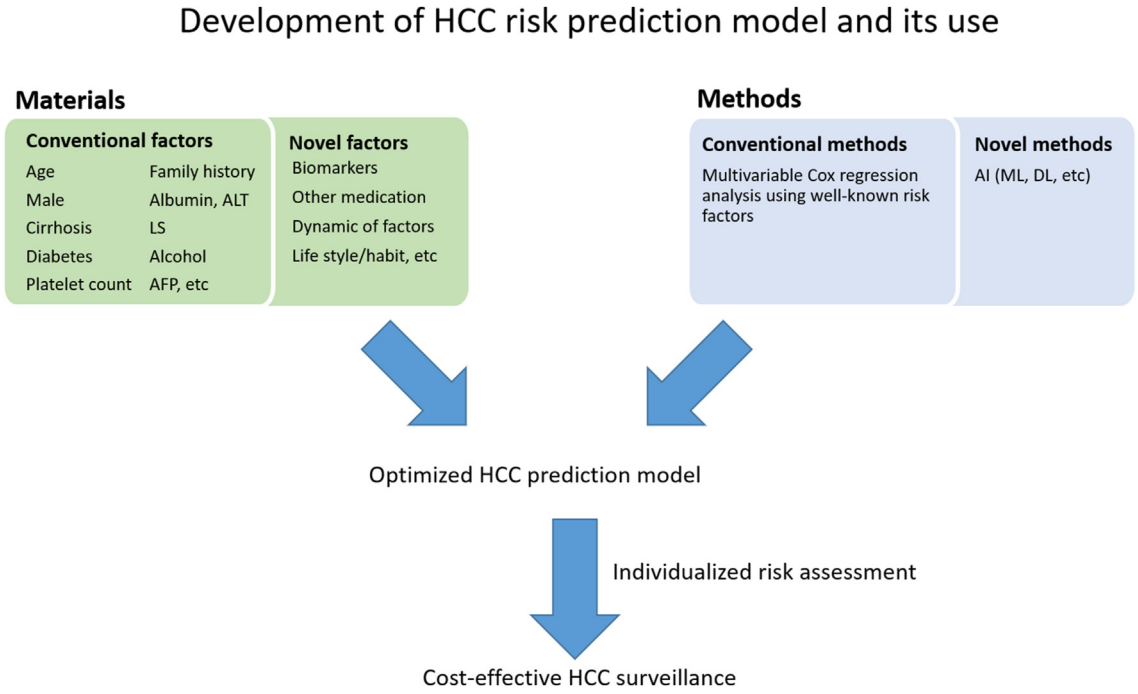

Figure 2 The scheme of developing HCC risk prediction model and its use.

generalizability and interpretability of results, and ultimately to overcome any errors from AI process.

Future perspectives

First, despite the substantial predictive performance of HCC prediction models in patients with chronic HBV infection, optimization of the surveillance strategy through model-based individual approaches remains to be determined. Many such models have the advantage of high negative predictive values, allowing for the exemption from bi-annual periodic HCC surveillance using abdominal ultrasonography, with or without tumor markers. However, when should the surveillance program begin remains another issue for such so-called "very-low risk group". Conversely, further studies are required to evaluate whether HCC surveillance protocols with shorter intervals and more sensitive tools, including liver dynamic computed tomography (CT) or magnetic resonance imaging (MRI) with or without contrast agents[70,71] might lead to longer overall survival among high-risk patients with chronic HBV infection. Ultimately, to adequately establish an HCC screening program in accordance with each country's epidemiological and socioeconomic backgrounds, a cost-effectiveness analysis of such individualized approaches using HCC prediction models is also required.

Second, despite the excellent predictive performances among overall population with chronic HBV infection, suboptimal predictive performances of the HCC prediction models were observed among patients without cirrhosis, ranging from 0.565 to 0.667 as c-indices.[72] This is most likely because the "cirrhosis" itself is the most essential variable for HCC development. However, given that some patients still develop HCC without advanced fibrosis or overt cirrhosis, further studies are required to overcome such a gap, considering the complex hepato-carcinogenesis among patients with chronic HBV infection (Fig. 1). So, identification and application of the novel biomarker for the HBV-specific carcinogenesis, e.g. quantitative hepatitis B surface antigen, hepatitis B core-related antigen (HBcrAg), pre-genomic (pg) RNA, intrahepatic HBV-DNA integration, HBV covalently closed circular DNA, and pre-S mutation, might in part complement the current suboptimal predictive performances among such a population.[73–78] Furthermore, non-viral factors such as co-morbidities (e.g. obesity, dyslipidemia, or metabolic associated fatty liver disease), life style/habit, and medication other than oral NUCs (e.g., aspirin, statin, and metformin) might be considered as disease modifiers in this setting.[79–84]

In summary, Fig. 2 summarizes the ideal approach for establishment of HCC risk prediction models and their use in the real-world practice among patients with chronic HBV infection.

Financial support

None.

Conflicts of interest

Nothing to declare for all authors.

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