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MINIREVIEWS

Prediction models of hepatocellular carcinoma development in chronic hepatitis B patients

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Abstract

Chronic hepatitis B virus (HBV) infection is a major cause of cirrhosis and hepatocellular carcinoma (HCC). Applying the same strategies for antiviral therapy and HCC surveillance to all chronic hepatitis B (CHB) patients would be a burden worldwide. To properly manage CHB patients, it is necessary to identify and classify the risk for HCC development in such patients. Several HCC risk scores based on risk factors such as cirrhosis, age, male gender, and high viral load have been used, and have negative predictive values of $\geqslant$ 95%. Most of these have been derived from, and internally validated in, treatment-naïve Asian CHB patients. Herein, we summarized various HCC prediction models, including IPM (Individual Prediction Model), CU-HCC (Chinese University-HCC), GAG-HCC (Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC), NGM-HCC (Nomogram-HCC), REACH-B (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B), and Page-B score. To develop a noninvasive test of liver fibrosis, we also introduced a new scoring system that uses liver stiffness values from transient elastography, including an LSM (Liver Stiffness Measurement)-based model, LSM-HCC, and mREACH-B (modified REACH-B).

Key words: Chronic hepatitis B; Hepatocellular carcinoma; Development; Prediction models

Core tip: This is the summary about prediction models of hepatocellular carcinoma development in chronic hepatitis B patients.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is the main cause of cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC) globally[1]. Of chronic HBV carriers, approximately 15%-40% develop chronic hepatitis B (CHB)[2]. Around 90% of CHB patients undergo seroconversion of HBeAg to anti-HBe and become inactive carriers. However, approximately 10% of CHB patients have chronic active hepatitis and develop liver cirrhosis at a rate of 2% per year. Because progression of liver disease in CHB patients is closely associated with active viral replication, a high level of HBV DNA has been known as an independent risk factor for disease progression. Therefore, suppression of HBV with antiviral therapy could reduce the risk of developing cirrhosis and HCC.

The development of potent antiviral drugs has an important role in the management of patients with CHB. The natural course of the disease could be modified by HBV therapy and risk for HCC could be reduced[3-5]. Antiviral therapy reduces, but does not completely eliminate risk for HCC[6,7]. The annual incidence of HCC range from 0.01% to 5.4% in CHB patients treated with entecavir or tenofovir[8]. Therefore, applying a standardized policy for antiviral therapy and HCC surveillance to all CHB patients may not be cost-effective[9]. Thus, stratification of the risk for HCC development is important for the management of CHB patients.

This review summarizes the prediction models of HCC development in CHB patients.

RISK FACTORS FOR HBV-RELATED HCC

Risk factors for disease progression in CHB can be classified into three categories: host factors, viral factors and liver factors[4,10,11]. Host factors include older age, male gender, family history of HCC, obesity, genetic susceptibility such as single-nucleotide polymorphisms, cirrhosis, smoking, alcohol, diabetes mellitus and immune status[11-16]. Viral factors include a high level of HBV DNA, positive hepatitis B virus e antigen (HBeAg), HBV genotype, HBV mutants, and a high serum level of hepatitis B surface antigen (HBsAg)[16-22]. Particularly, an increasing viral load is a strong predictor of the risk for HCC independent of HBeAg, aminotransferase, and cirrhosis[12,13,18,23]. Liver factors consist of advance fibrosis and cirrhosis, poor liver function, active hepatitis, and other concomitant liver diseases such as co-infection with hepatitis C virus or, alcoholic and nonalcoholic fatty liver diseases[11-13,24-26].

The progression of liver disease in chronic HBV infection is mediated by active virus replication. The annual incidence of cirrhosis in the overall population with CHB is 2%-7%, depending on viral replication status[27]. In particular, disease progression is markedly accelerated in patients with active viral replication by up to 15%-20%. Currently, a complete virological response (CVR) can be achieved even in CHB patients using potent antiviral therapy. Thus, the prognostic value of the baseline level of HBV DNA, which was suggested by large-scale studies to be a robust prognostic indicator of the "natural" course of chronic HBV infection before the era of antiviral treatment, is limited[28]. In the era of antiviral therapy, the prognostic significance of serum levels of HBV DNA has substantially diminished, because most treated patients achieve a virological response[28]. More importantly, the risk for developing liver-related events cannot be completely eliminated even in those who achieve a complete virological response; thus, caution is required in so-called "high-risk" patients who may experience disease progression.

APPROACHES TO DEVELOPING RISK SCORES

Factors independently associated with HCC are first identified in a training or derivation cohort[4,16]. Second, scores are assigned to different parameters in the equation to generate the final score. This score is validated in a validation cohort to demonstrate its applicability and reproducibility. If no independent cohort is available, external validation can be applied to assess the performance of the score in new data. 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 is used as training and validation data.

Validation of the score usually includes discrimination and calibration. Discrimination can be assessed using a receiver operating characteristic (ROC) curve, sensitivity, and specificity[29,30]. Calibration is evaluated by estimating the observed HCC risk using the Kaplan-Meier method with the same cumulative risk scores. A combination of neighboring groups of cumulative risk scores will be performed if the observed HCC risk in a group with the same cumulative risk score is low[4,13].

HCC RISK SCORES

Until now, several HCC risk prediction scoring systems have been derived to estimate the risk for HCC development in CHB from baseline parameters[11-13,31]. Almost all the scores were derived from and internally validated in treatment-naïve Asian CHB patients[23]. Besides, external validation has been limited to Asian CHB patients or those undergoing treatment with entecavir. Studies including European Caucasian and American patients have shown the models to be somewhat less predictive; however, rates of HCC were very low, significantly limiting the conclusions[6,32].

Individual prediction model

Based on the risk factors of 4339 Korean patients, the individual prediction model (IPM) was developed by calculating the relative weights of risk factors, and a screening program for HCC was established[33]. Old age, male gender, initial serum AFP level, platelet count, serum albumin, severe liver parenchymal echogenic pattern in ultrasonography and heavy alcohol consumption were significant risk factors for HCC. Based on these risk factors, the IPM was calculated using the following formula: risk index (RI) for HCC = e^A, A = -6.2543 + (1.7219 × liver cirrhosis) + (1.3145 × old age over 40 years) + (1.2631 × chronic HCV infection) + (0.8257 × AFP > 20 ng/mL) + (0.7754 × chronic HBV infection) + (0.7339 × chronic hepatitis) + (0.5840 × heavy alcoholics) + (0.3 × man) + (0.2830 × ALT > 40 IU/L) + (0.221 × unknown alcohol history). Probability for HCC = RI/(1 + RI). The authors prospectively applied the screening program to 833 patients with chronic liver disease stratified into three groups [a low-risk group (< 5% probability), an intermediate group (5%-15% probability), and high-risk group (> 15% probability)] by IPM. The patients were followed, at intervals that varied according to the risk index. According to IPM, 2 of 324 patients in the low-risk group (0.62%), 20 of 413 patients in the intermediate-risk group (4.8%), and 22 of 96 patients in the high-risk group (22.9%) were diagnosed with HCC. Thus, the screening program based on IPM enabled cost-effective prediction of the risk of developing of HCC by focusing on the high-risk group.

CU-HCC score

The Chinese University (CU)-HCC score was first derived using a cohort of 1005 Chinese CHB patients that had undergone HCC surveillance at the Chinese University of Hong Kong[4,12,25]. It was validated in an independent cohort of 424 Chinese CHB patients[34]. All patients were treatment-naïve at baseline. Among the patients in the training and validation cohort, 15.1% and 25.0%, respectively, received antiviral therapy during the long-term follow-up. The CU-HCC score is composed of five factors: age, albumin, bilirubin, HBV DNA, and cirrhosis; it ranges from 0 to 44.5. Two cutoff values (5 and 20) discriminated HCC risk into three categories. In all, 105 (10.4%) patients in the training cohort and 45 (10.6%) patients in the validation cohort developed HCC during a median of 10 years of follow-up. The 5-year HCC-free survival rates were 98.3%, 90.5%, and 78.9% in the low-, medium-, and high-risk groups, respectively. Using the lower cutoff of 5 points, this score has a high negative predictive value (97.8%) for excluding future HCC development.

GAG-HCC score

The Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis (GAG-HCC) score was developed from a cohort of 820 Chinese CHB patients from tertiary referral clinics[4,13]. All patients were treatment-naïve at baseline and followed-up for a median of 77 mo. There are two versions of the score. The original version is composed of five parameters: gender, age, core promoter mutations, levels of HBV DNA, and cirrhosis. Because the test for core promoter mutations may not be available in some centers, the score was simplified to omit such mutations. The score can be above 100, as age is one of the components. A cutoff value of 100 had a 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 for excluding future HCC development were 98.3%-100%.

NGM1-HCC and NGM2-HCC

The risk evaluation of viral load elevation and associated liver disease (REVEAL)-HBV investigators first suggested easy-to-use nomograms based on noninvasive clinical characteristics using data from 3653 patients[31]. Previously confirmed independent risk predictors were sex, age, family history of HCC, alcohol consumption habit, ALT level, HBeAg serostatus, levels of HBV DNA, and HBV genotype. Regression coefficients were rounded to integer risk scores, and the predicted risk over 5- and 10-year periods for each risk score was calculated and depicted as nomograms. Nomogram 1 and Nomogram 2 hepatocellular carcinoma (NGM1-HCC and NGM2-HCC) were used to calculate individual baseline risk scores for each patient[31]. The patients were categorized into low-, medium- and high-risk groups to facilitate comparison of the risk scores using the different prediction models, and to simplify their use in the clinical setting. The correlation coefficients between observed HCC risk and the nomogram-predicted risk were greater than 0.90.

REACH-B score

The risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) score was derived using 3584 Chinese CHB patients from the Taiwanese REVEAL cohort, and validated in a cohort of 1505 patients from

three tertiary referral clinics in Hong Kong and South Korea[4,11]. The patients in the training cohort did not have cirrhosis at the time of recruitment, and remained treatment-naïve throughout the 12-year follow-up period. Variables included in the risk score were sex, age, serum levels of alanine aminotransferase, HBeAg status, and levels of HBV DNA level. In all, 131 (3.7%) patients in the training cohort and 111 (7.4%) patients in the validation cohort were developed HCC. A 17-point risk score was developed and 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 and highest HCC risks, respectively. The score accurately estimated the risk for developing HCC at 3, 5, and 10 years in patients with CHB. A revised version of REACH-B that includes serum levels of qHBsAg is also available[35].

PAGE-B score

Previous risk scores have been developed mainly in Asians. Therefore, these scores may not be suitable for Caucasian patients with CHB. A new score named PAGE-B has recently been developed for Caucasian CHB patients[36]. A nine-center cohort study was performed in Caucasian CHB patients treated with oral antivirals[36]. They included 1815 adult CHB patients without baseline HCC who received entecavir or tenofovir for more than 1 year. The PAGE-B score was developed based on age, gender, and platelets. During a median of 50 months of follow-up, 51 (3.8%) patients in the derivation group and 34 (6.9%) patients in the validation group developed HCC. Patients with PAGE-B scores of $\leqslant$ 9, 10-17, and $\geqslant$ 18 had 5-year cumulative HCC incidences of 0%, 3% and 17%, respectively. In the validation cohort, the negative predictive value to exclude HCC using at a cut-off of 10 points approached 100%. This was the first study to develop an HCC risk score for Caucasian CHB patients and was the first score for patients treated with current first-line antiviral therapies.

LIVER STIFFNESS MEASUREMENT-BASED MODELS

The degree of liver fibrosis is significantly related to risk for HCC development[37,38]. To date, the gold standard for evaluating the degree of fibrosis is liver biopsy. However, liver biopsy cannot be performed in all CHB patients in a clinical setting due to its invasiveness and complications[39]. Transient elastography (TE, FibroScan®, Echosens, Paris, France) has been validated as a noninvasive method for assessing fibrosis in chronic liver disease[40]. The advantage of TE include its noninvasiveness, highly reproducibility, and accuracy. TE is used as a reliable surrogate for liver biopsy to detect early cirrhosis in patients with CHB[41].

For patients with ascites or high BMI, the use of XL probe could be helpful to check liver stiffness[42,43]. Especially, the presence of nonhepatic ascites does not affect underlying liver stiffness by TE[42]. A liver stiffness value > 12 kPa or 13 kPa by TE can be used to detect histologic cirrhosis in patients with CHB[44,45]. Furthermore, recent studies have reported TE can predict the development of portal hypertension-related complications and HCC[46-48].

Liver stiffness measurement-based Model

Stratified baseline liver stiffness values in patients with CHB are independent predictors of HCC development[38]. The 3-year cumulative incidence of HCC is significantly higher in patients with a higher liver stiffness value[38]. Kim *et al*[49] prospectively analyzed 1110 patients with CHB who received a transient elastography and were available for inclusion criteria from May 2005 to December 2007.

A previous multivariate analysis showed that age, male gender, and liver stiffness values independent predictors of HCC (all $P < 0.05$). In addition, HBV DNA levels $\geqslant$ 20000 IU/L showed borderline significance. Using these four variables, a predictive model was developed (AUROC 0.806, 95%CI: 0.738-0.874). The formula for a 3-year probability of HCC occurrence is as follows: Probability = 1 - P^A [A = exp (0.05306 × age + 1.106 × male gender + 0.04858 × liver stiffness values + 0.50969 × HBV DNA $\geqslant$ 20000 IU/L)]. In bootstrap analyses, the AUROC remained largely unchanged between iterations, with an average value of 0.802 (95%CI: 0.791-0.812). The predicted risk for HCC development calibrated well with the observed risk, with a correlation coefficient of 0.905 ($P < 0.001$).

LSM-HCC score

Wong *et al*[50] developed a new liver stiffness measurement (LSM)-HCC score composed of LSM, age, serum albumin, and levels of HBV DNA. Because diagnosis of cirrhosis based on ultrasonography may be incorrect, cirrhosis as a factor of CU-HCC score was substituted by LSM. Among 1555 CHB patients, 1035 and 520 were assigned to the training and validation cohort, respectively. During a mean of 69 months of follow-up, 38 (3.7%) patients in the training cohort and 17 (3.4%) patients in the validation cohort developed HCC. The LSM-HCC score ranged from 0 to 30. Using 11 as the cutoff value, 706 (68.2%) and 329 (31.8%) patients were in the low- and high-risk categories; 4 (0.6%), and 29 (8.8%) patients developed HCC over 5 years. The AUROCs of the LSM-HCC score were higher than those of the CU-HCC score (0.83-0.89 *vs* 0.75-0.81). The sensitivity for identifying HCC was 87.9% and the NPV was 99.4% at 5 years.

Modified REACH-B score

The REACH-B scoring system, which was developed and validated as a simple HCC prediction model prior to the era of antiviral therapy, showed suboptimal

Table 1 Summary of hepatocellular carcinoma prediction models

	IPM	CU-HCC	GAG-HCC	REACH-B	LSM-HCC	mREACH-B	PAGE-B
Full name	Individual Prediction Model	Chinese University-HCC	Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC	Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B	Liver Stiffness Measurement-HCC	Modified Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B	
Calculation	Risk Index (RI) for HCC = e^A, A = -6.2543 + (1.7219 × liver cirrhosis) + (1.3145 × old age over 40 yr) + (1.2631 × chronic HCV infection) + (0.8257 × AFP > 20 ng/mL) + (0.7754 × chronic HBV infection) + (0.7339 × chronic hepatitis) + (0.5840 × heavy alcoholics) + (0.3 × man) + (0.2830 × ALT > 40 IU/L) + (0.221 × unknown alcohol history)	Age (> 50 yr = 3; ≤ 50 = 0) + albumin (≤ 35 g/L = 20; > 35 = 0) + bilirubin (> 18 μmol/L = 1.5; ≤ 18 = 0) + HBV DNA (< 4 log copies/mL = 0; 4-6 = 1; > 6 = 4) + cirrhosis (yes = 15; no = 0)	14 × sex (male = 1; female = 0) + age (in years) + 3 × HBV DNA (log copies/mL) + 33 × cirrhosis presence = 1; absence = 0)	Male sex: 2 points Age: 1 point for every 5 yr from 35 to 65 yr of age (0-6 points) ALT (IU/L): 15-<45 (1 point), ≥ 45 (2 points) Positive HBeAg: 2 points HBV DNA (log copies/mL): 4-< 5 (3 points), 5-< 6 (5 points), ≥ 6 (4 points)	Age (> 50 yr = 10; ≤ 50 = 0) + albumin (≤ 35 g/L = 1; > 35 = 0) + HBV DNA (> 200000 IU/mL = 5; ≤ 200000 = 0) + liver stiffness (≤ 8.0 kPa = 0; < 8.0-12.0 = 8; > 12.0 = 14)	Male sex: 2 points Age: 1 point for every 5 yr from 35 to 65 yr of age (0-6 points) ALT (IU/L): 15-< 45 (1 point), ≥ 45 (2 points) Positive HBeAg: 2 points Liver stiffness values: < 8.0 kPa (0 point), 8.0-13.0 (2 points), > 13.0 kPa (4 points)	Age; < 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-< 200 × 10^3 (6 points), < 100 × 10^3 (11 points)

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

predictive performance. Therefore, an alternative predictor of long-term prognosis is required particularly in CHB patients who had achieved CVR from antiviral treatment, because levels of HBV DNA are no longer useful at the time of CVR.

In the modified REACH-B model (mREACH-B model), the serum levels of HBV DNA were substituted for the LS value, and had better predictive performance among patients who were at CVR following entecavir therapy[28]. The authors reassessed the scores at CVR, using LS values instead of suppressed HBV DNA. The AUROC value for risk at the 3-year follow-up was 0.805, compared to 0.629 using the original REACH-B scoring system, when 0, 1, and 2 points were assigned to LS values of < 8.0, 8.0-13.0, and > 13.0 kPa, respectively (referred to as the modified REACH-B I), and 0.814 (95%CI: 0.709-0.912) when 0, 2, and 4 points were assigned to LS values of < 8.0, 8.0-13.0, and > 13.0 kPa, respectively (referred to as the modified REACH-B II).

The performance of conventional HCC prediction models (CU-HCC, GAG-HCC, REACH-B, and LSM-HCC scores) and the mREACH-B score has been assessed[51]. During the follow-up (median, 75.3 mo), HCC developed in 125 (9.6%) of 1308 subjects. The mREACH-B score had a significantly higher AUROC for prediction of HCC development at 3/5 years (0.828/0.806), compared to the LSM-HCC (0.777/0.759), GAG-HCC (0.751/0.757), REACH-B (0.717/0.699), and CU-HCC (0.698/0.700) scores (all *P* values < 0.05 *vs* mREACH-B). Thus, the prognostic performance of the mREACH-B score was superior to that of the conventional models.

OTHER HCC RISK MODELS

Existing prediction models were mostly developed in Asia. There were limited data about HCC risk models for people at high risk in the United States or European countries. France group suggested *PNPLA3* rs738409 (GG) genotype had an effect on the occurrence of HCC[52]. They created the following model: age × 0.05085 - 1.88790 × female gender + BMI × 0.09712 + rs738409 (GG) × 0.78377.

When applied to 250 patients with alcoholic cirrhosis, scores ranged from 2.20-9.25. The cut-off values for calculated score were below 5, between 5 and 7, and above 7, respectively. 6-year incidence of HCC increased according to stratification of three risk groups.

There was another risk prediction model suggested from United States[53]. By Cox proportional hazards regression model, clinical and demographic data (including age, sex, smoking status, alkaline phosphatase level, and platelet count) and Epidermal Growth Factor Gene genotype (GG) was used to predict HCC risk. The cohort was stratified into three groups depending on the risk of HCC development.

CONCLUSION

This review summarizes prediction models of HCC development in CHB patients (Tables 1 and 2). HCC

Table 2 Comparisons of published hepatocellular carcinoma prediction models

	IPM	CU-HCC	GAG-HCC	REACH-B	LSM-HCC	mREACH-B	PAGE-B
Number of patients	994	1005	820	3584	1035	1308	1325
Place of development	South Korea	Hong Kong	Hong Kong	Taiwan	Hong Kong	South Korea	Europe
Race	Asian	Asian	Asian	Asian	Asian	Asian	Caucasian
Age (yr)		48	40.6	45.7	46	50	52
HBeAg-negative (%)			56.6	84.8	75	60.3	84
Cirrhosis (%)		38.1	15.1	0	32	17.8	20
Follow-up (yr)	2.7	9.94	5.62	12	5.8	6.3	3.6
Antiviral therapy (%)		15.1	0	0	38	64.8	100
HCC (%)	90 (0.1)	105 (10.4)	40 (4.9)	131 (3.7)	38 (3.7)	125 (9.6)	51 (3.8)
Components of the risk scores	Age Male Platelet Cirrhosis Albumin AFP Heavy alcoholics	Age Albumin Bilirubin Cirrhosis HBV DNA	Age Male BCP mutation Cirrhosis HBV DNA	Age Male ALT HBeAg-positive HBV DNA	Age Albumin HBV DNA LS value	Age Male ALT HBeAg-positive LS value	Age Male Platelet
Risk scores	Low (< 5) Intermediate (5-15) High (> 15)	Low (< 5) Intermediate (5-19) High (> 19)	Low (< 100) High (≥ 100)	Low (0-5) Intermediate (6-11) High (12-18)	Low (< 11) High (≥ 11)	Low (< 10) High (≥ 10)	Low (≤ 9) Intermediate (10-17) High (≥ 18)
NPV (%)		97% at 10 yr	99% at 10 yr	98% at 10 yr	99.4% at 5 yr	96.8% at 5 yr	100% 5 yr

HCC: Hepatocellular carcinoma; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; LS: Liver stiffness; AFP: α-fetoprotein; NPV: Negative predictive value.

risk scores can accurately predict subsequent HCC development in CHB patients. Different levels of care and different intensities of HCC surveillance should be offered according to the patient's risk profile. Patients in the high-risk category should be offered antiviral therapy, as well as appropriate HCC surveillance. Effective suppression of HBV replication by antiviral therapy can reduce risk for HCC development. However, antiviral therapy does not eliminate the HCC risk completely, because of the presence of virus integrated into the host genome. The HCC risk is higher in cirrhotic than non-cirrhotic patients. Antiviral therapy with no risk of resistance such as entecavir or tenofovir should be initiated before cirrhosis occurs.

HCC prediction models can help optimize antiviral therapy based on the level of HCC risk. It should be adjusted for patients who are already on treatment. Decisions regarding who needs treatment and regular surveillance should be individualized using HCC risk prediction models.

FUTURE PERSPECTIVES

In the future, a more accurate risk model that incorporates newly identified risk factors and somatic and inherited biomarkers (*e.g.*, single-nucleotide polymorphisms, proteomics) is required for more accurate estimation of risk. Various plasma proteins have been proposed as new biomarkers of genetic background to predict development of HCC. These biomarkers are expected to guide individual surveillance or treatment for CHB patients. However, further functional studies are needed to validate these biomarkers. In addition, simple, user-friendly models for primary care providers would facilitate referral of high-risk patients.

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