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ORIGINAL RESEARCH

Machine Learning-Based Model Used for Predicting the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

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Object: Currently, predictive models that effectively stratify the risk levels for hepatocellular carcinoma (HCC) are insufficient. Our study aimed to assess the 10-year cumulative risk of HCC among patients suffering from chronic hepatitis B (CHB) by employing an artificial neural network (ANN).

Methods: This research involved 1717 patients admitted to Beijing Ditan Hospital of Capital Medical University and the People's Liberation Army Fifth Medical Center. The training group included 1309 individuals from Beijing Ditan Hospital of Capital Medical University, whereas the validation group contained 408 individuals from the People's Liberation Army Fifth Medical Center. By performing a univariate analysis, we pinpointed factors that had an independent impact on the development of HCC, which were subsequently employed to create the ANN model. To evaluate the ANN model, we analyzed its predictive accuracy, discriminative performance, and clinical net benefit through measures including the area under the receiver operating characteristic curve (AUC), concordance index (C-index), and calibration curves.

Results: The cumulative incidence rates of HCC over a decade were observed to be 3.59% in the training cohort and 4.41% in the validation cohort. We incorporated nine distinct independent risk factors into the ANN model's development. Notably, in the training group, the area under the receiver operating characteristic (AUROC) curve for the ANN model was reported as 0.929 (95% CI 0.910–0.948), and the C-index was 0.917 (95% CI 0.907–0.927). These results were significantly superior to those of the mREACHE-B(0.700, 95% CI 0.639–0.761), mPAGE-B(0.800, 95% CI 0.757–0.844), HCC-RESCUE(0.787, 95% CI 0.732–0.837), CAMD(0.760, 95% CI 0.708–0.812), REAL-B(0.767, 95% CI 0.719–0.816), and PAGE-B(0.760, 95% CI 0.712–0.808) models ($p < 0.001$). The ANN model proficiently categorized patients into low-risk and high-risk groups based on their 10-year projections. In the training cohort, the positive predictive value (PPV) for the incidence of liver cancer in low-risk individuals was 92.5% (95% CI 0.921–0.939), whereas the negative predictive value (NPV) stood at 88.2% (95% CI 0.870–0.894). Among high-risk patients, the PPV reached 94.6% (95% CI 0.936–0.956) and the NPV was 90.2% (95% CI 0.897–0.917). These results were also confirmed in the independent validation cohort.

Conclusion: The model utilizing artificial neural networks demonstrates strong performance in personalized predictions and could assist in assessing the likelihood of a 10-year risk of HCC in patients suffering from CHB.

Keywords: machine learning-based model, hepatocellular carcinoma, risk, chronic hepatitis B

Introduction

Hepatocellular carcinoma (HCC) has emerged as the third most common cause of cancer-related deaths.[1] Hepatitis B virus (HBV) infection is a significant contributor to the development of liver cancer.[2,3] Antiviral treatment currently represents the primary therapeutic approach, as effective virus suppression can diminish the incidence of liver cirrhosis and potentially lower liver-related mortality rates.[4] Nevertheless, some patients continue to progress to liver cancer

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despite long-term antiviral treatment[5,6]. A 10-year follow-up study conducted in Europe revealed that new HCC cases can still arise even after more than 5 years of nucleos(t)ide analog (NA) therapy, with an incidence rate as high as 1.34%.[7,8] Consequently, it is crucial to implement appropriate liver cancer risk monitoring for patients with chronic hepatitis B. According to the guidelines established by the American Association for the Study of Liver Diseases, patients with chronic hepatitis B(CHB) should undergo screening every 6 months to detect the onset of liver cancer. It is noted that when the annual incidence of HCC exceeds 0.2%, such screening is deemed cost-effective.[9]

In recent years, numerous risk scores have been developed to predict the likelihood of liver cancer in patients with CHB undergoing antiviral treatment. These scores include mREACH-B, PAGE-B, mPAGE-B, CAMD, and REAL-B.[10–14] However, despite extensive validation, these models include genetic and specific biological markers, which makes them less convenient for clinical use. Besides, they exhibit a limited number of baseline parameters, moderate accuracy, and an inability to effectively stratify the HCC risk among chronic hepatitis B patients.

To address these challenges, machine learning (ML) can be employed to predict the risk of HCC. Recent comparisons of ML algorithms with traditional regression analysis for predicting HCC development have demonstrated that ML outperforms conventional models. In a cohort study involving 442 patients with cirrhosis, ML exhibited significantly superior risk stratification performance compared to other predictive models.[15] One of the advantages of ML algorithms is their ability to account for all potential interactions without relying on predefined hypotheses, thereby minimizing the risk of overlooking unexpected predictor variables. Furthermore, ML can integrate new clinical data, allowing for continuous updates and optimization of the algorithm with minimal supervision. Although traditional models share some of these characteristics, ML methods can incorporate a greater number of parameters, resulting in more accurate predictions than their traditional counterparts.[16] We developed an ML-based HCC prediction model specifically for patients with CHB undergoing treatment with entecavir (ETV) or tenofovir disoproxil fumarate (TDF), and we validated its performance in an independent cohort.

Materials and Methods

Patients

A total of 1309 CHB patients diagnosed and treated at Beijing Ditan Hospital between January 2013 and January 2014 were included in this study, which featured a follow-up period of 10 years. The study endpoint was defined as either the diagnosis of HCC or the final follow-up date of February 2024. Additionally, 408 CHB patients from the Fifth Medical Center of the Chinese People's Liberation Army were incorporated into the validation cohort (Figure 1). The Ethics Committee of Beijing Ditan Hospital approved this study; written informed consent was obtained from all patients. All records and information were anonymized and de-identified to protect patient privacy prior to analysis.

Diagnostic Criteria

CHB is characterized by the presence of HBsAg and/or HBV-DNA for more than six months, accompanied by persistently or repeatedly elevated ALT levels, or the presence of liver histological lesions.[17] HCC is diagnosed based on (1) a positive histological examination; (2) the identification of typical vascular characteristics of HCC, such as arterial phase vascular proliferation, in nodules greater than 1 cm in diameter, as observed through CT or dynamic MRI.[18]

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Individuals aged over 18 years and under 75 years; (2) Patients diagnosed with CHB following the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2022 Edition);[17] (3) Patients who have previously received antiviral treatment or have not received it but have been on regular antiviral therapy since the baseline date; (4) A follow-up duration of 10 years. Exclusion criteria: (1) Patients with liver cirrhosis, HCC, or other malignant tumors; (2) Patients co-infected with other hepatitis viruses or HIV; (3) Patients with autoimmune hepatitis, drug-induced liver injury, alcoholic liver disease, or other liver disorders; (4) Pregnant or lactating individuals; (5) Patients with incomplete clinical data.

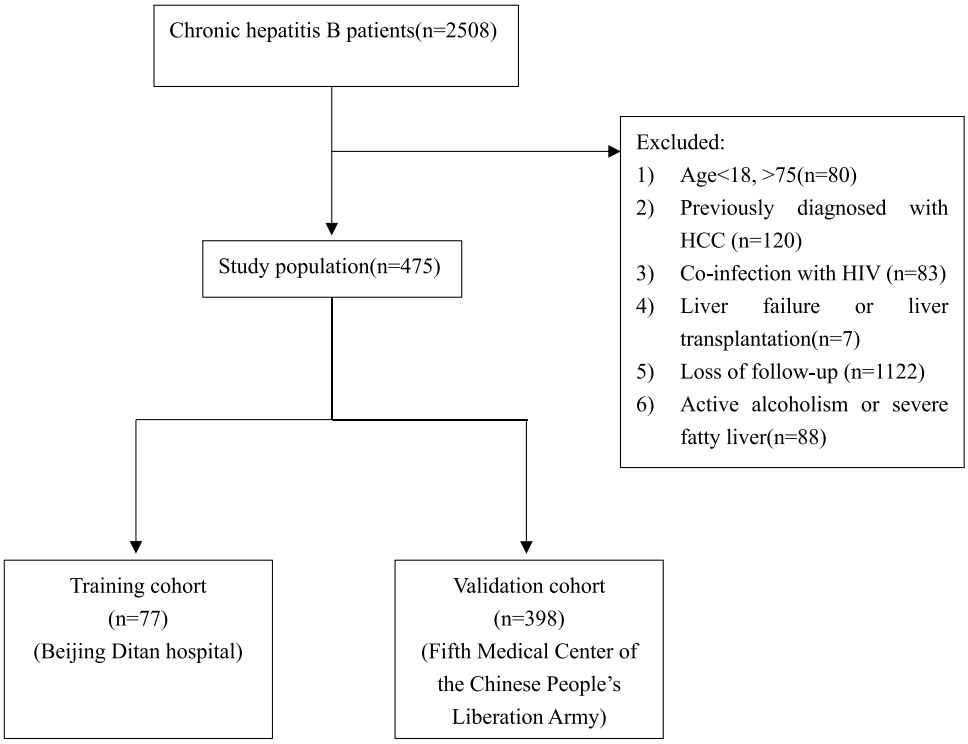

Figure 1 Outline of the recruitment and grouping of Hepatitis B-related cirrhosis cohort study.

Follow-up

All patients underwent CT, MRI, ultrasound, or serum AFP examinations every six months. When a patient's serum AFP level increased, or new intrahepatic nodules were detected via ultrasound, dynamic CT or MRI was employed to ascertain the occurrence of HCC. The endpoint of the study was defined as the first diagnosis of HCC or the conclusion of the 10-year follow-up period. Clinical data collected included demographic information (age, gender, and family history of HCC) as well as the presence or absence of comorbidities such as hypertension and diabetes. The biochemical parameters analyzed in this study encompassed alanine aminotransferase (ALT), aspartate aminotransferase(AST), total bilirubin, albumin, gamma-glutamyl transpeptidase(γ-GGT), leukocyte count, neutrophil count, lymphocyte count, platelet count, creatinine, prothrombin time, international normalized ratio(INR), alpha-fetoprotein(AFP), and hepatitis B virus DNA. To monitor changes over time, regular laboratory tests were conducted every six months, including assessments of AFP levels and radiological examinations.

Statistical Methods

Data analysis was conducted using SPSS version 22.0 and R version 3.3.2 (R Core Development Team, 2010). Data presentation was performed as median (range) or n (%), depending on the nature of the data. The statistical significance of differences among continuous and categorical variables was assessed using Student's *t*-test (or Mann–Whitney test, as appropriate) or a chi-squared test (or Fisher's exact test, as appropriate). We presented hazard ratios (HRs) with their 95% confidence intervals (CIs), along with the corresponding p values. To construct the artificial neural networks (ANNs) model, we utilized Mathematica version 11.1.1 for Microsoft Windows (64-bit) and considered factors related to the 10-year development of HCC in patients with HBV infection. To assess discrimination performance, we employed receiver operating characteristic (ROC) curves and computed the area under the ROC (AUROC) curve, which generated Harrell's c-index. Additionally, we compared the performance of the ANN model with well-established scores such as mPAGE-B, PAGE-B, FIB-4, and THRI scores using ROC curves. These scores were calculated using a previously published scoring formula. For graphical evaluation of the agreement between the predicted 10-year probability of HCC-free status and the observed probability, we employed a calibration plot. In all statistical tests, a P value of less than 0.05 was considered indicative of a statistically significant difference.

Results

Baseline Characteristics of Patients

As shown in Table 1, we retrospectively included 1,309 CHB patients from Ditan Hospital. The average age of the cohort was 37 years, with a predominance of women (n = 981, 74.94%). The mean HBV DNA level was 5.71 log10 IU/mL, and the positive rate of hepatitis B e antigen (HBeAg) was 73%. The average levels of AST and ALT were 165.3 and 297.4 IU/L, respectively. Additionally, the mean values for platelet count, neutrophil-to-lymphocyte ratio (NLR), prothrombin time(PT), INR, and blood urea nitrogen were 166 × 10^9/μL, 1.78, 1.04, and 4.63 mg/dL, respectively. The average level of AFP was 39.2 ng/mL. Concurrently, we retrospectively included 408 CHB patients from the Fifth Medical Center of the Chinese People's Liberation Army Hospital as the validation set. In comparison to the training set, patients in the

Table 1 Basic Clinical Characteristics of Patients with HBV-Related Cirrhosis

Variable	Total (n = 1717)	Training Cohort (n = 1309)	Validation Cohort (n = 408)	P
Sex (%)				0.502
Female	1280 (74.55)	981 (74.94)	299 (73.28)	
Male	437 (25.45)	328 (25.06)	109 (26.72)	
Age	38±11	37±10	50±12	<0.001
Drink (%)				<0.001
No	1316 (76.65)	994 (75.94)	322 (78.92)	
Yes	401 (23.35)	315 (24.06)	86 (21.08)	
HCC History (%)				0.470
No	1616 (94.12)	1235 (94.35)	381 (93.38)	
Yes	101 (5.88)	74 (5.65)	27 (6.62)	
Hypertension (%)				0.072
No	1614 (94)	1238 (94.58)	376 (92.16)	
Yes	103 (6)	71 (5.42)	32 (7.84)	
Diabetes (%)				0.402
No	1610 (93.77)	1231 (94.04)	379 (92.89)	
Yes	107 (6.23)	78 (5.96)	29 (7.11)	
Smoke (%)				0.101
No	1356 (78.97)	1022 (78.07)	334 (81.86)	
Yes	361 (21.03)	287 (21.93)	74 (18.14)	
HBeAg	0.72 ± 0.55	0.73 ± 0.45	0.71 ± 0.81	0.717
HBV-DNA (log)	5.61 ± 1.92	5.71 ± 1.85	5.32 ± 2.11	<0.001
ALT	288.09 ± 373.21	297.40 ± 379.15	258.21 ± 352.30	0.064
AST	161.30 ± 224.92	165.30 ± 226.96	148.47± 218.00	0.187
Total Bilirubin	32.32 ± 54.03	33.23 ± 55.72	29.40 ± 48.14	0.211
Albumin	42.87 ± 11.86	42.50 ± 5.02	44.05 ± 22.60	0.168
γ-GGT	87.23 ± 91.08	87.91 ± 91.82	84.97 ± 88.64	0.586
Blood urea nitrogen	4.91 ± 4.80	4.63 ± 1.29	5.81 ± 9.61	0.021
Creatinine	67.94 ± 14.13	67.92 ± 13.46	67.99 ± 16.16	0.945
Leukocyte	5.14 ± 1.44	5.23 ± 1.42	4.83 ± 1.47	<0.001
Neutrophil	3.19 ± 1.41	2.87 ± 1.09	4.38 ± 1.75	<0.001
Lymphocyte	1.97 ± 0.81	1.81 ± 0.61	2.47 ± 1.11	<0.001
NLR	2.31 ± 9.01	1.78 ± 1.15	4.28 ± 19.24	0.015
Platelet	167.67 ± 56.06	166.77 ± 54.11	170.57 ± 61.92	0.267
INR	1.09 ± 1.00	1.04 ± 0.12	1.25 ± 2.13	0.075
AFP	39.80 ± 151.64	39.20 ± 108.61	41.76 ± 244.52	0.777
HCC (%)				0.448
No	1652 (96.21)	1262 (96.41)	390 (95.59)	
Yes	65 (3.79)	47 (3.59)	18 (4.41)	

(*Continued*)

Table 1 (Continued).

Variable	Total (n = 1717)	Training Cohort (n = 1309)	Validation Cohort (n = 408)	P
mREACHE-B	6.17±2.04	6.11±1.90	6.38±2.44	0.042
mPAGE-B	8.67±4.69	8.379.62±7.623.23	9.62±7.62	0.001
HCC-RESCUE	49.25±12.64	48.94±11.86	50.26±14.85	0.100
CAMD	4.15±3.47	4.01±3.36	4.62±3.78	0.004
REAL-B	3.92±1.87	3.89±1.83	4.02±1.99	0.210
PAGE-B	12.01±5.00	12.01±4.91	12.03±5.27	0.946

Abbreviations: HCC, Hepatocellular carcinoma; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; γ-GGT, γ-glutamyl transferase; NLR, Neutrophil-lymphocyte ratio; INR, International ratio; CTP, Child-Turcotte-Pugh; MELD, Model for end-stage liver disease.

validation set were older, exhibited a higher positive rate of HBeAg, and presented with elevated levels of blood urea nitrogen and NLR, while demonstrating lower viral quantification and leukocyte counts (all $P < 0.05$) (Table 1). Throughout the 10-year follow-up period, a diagnosis of HCC was made in 47 patients (3.59% of the training cohort) and 18 patients (4.41% of the validation cohort). The differences in baseline characteristics between the two groups may be attributed to variations in inclusion times and patient types.

Construction of ANN Model

To investigate the risk factors associated with the development of HCC in patients with CHB, we performed both univariate and multivariate COX regression analyses. Our findings indicate that hypertension (HR = 4.90, 95% CI 2.44–9.85, $P < 0.01$), type 2 diabetes (HR = 3.51, 95% CI 1.64–7.51, $P = 0.001$), HBV-DNA levels (HR = 1.36, 95% CI 1.14–2.45, $P < 0.001$), age (HR = 1.09, 95% CI 1.06–1.11, $P < 0.001$), and blood urea nitrogen (HR = 1.38, 95% CI 1.13–1.68, $P = 0.002$) emerged as independent risk factors for the occurrence of HCC (Table 2). Conversely, ALT (HR = 0.99, 95% CI 0.99–0.99, $P = 0.003$), AST (HR = 0.99, 95% CI 0.99–0.99, $P = 0.047$), and PLT (HR = 0.99, 95% CI 0.98–0.995, $P < 0.001$) were identified as

Table 2 COX Regression for Factors Associated with Prediction Incidence of 10-year HCC

Variables	*P*	HR (95% CI)
Sex		
Female		1.00 (Reference)
Male	0.590	0.83 (0.41 ~ 1.66)
HCC history		
No		1.00 (Reference)
Yes	0.684	1.03 (0.98 ~ 1.06)
Hypertension		
No		1.00 (Reference)
Yes	<0.001	4.90 (2.44 ~ 9.85)
Diabetes		
No		1.00 (Reference)
Yes	0.001	3.51 (1.64 ~ 7.51)
Smoke		
No		1.00 (Reference)
Yes	0.282	1.41 (0.75 ~ 2.64)
Drink		
No		1.00 (Reference)
Yes	0.261	1.42 (0.77 ~ 2.63)

(*Continued*)

Table 2 (Continued).

Variables	*P*	HR (95% CI)
HBeAg	0.108	0.61 (0.34 ~ 1.11)
HBV-DNA	<0.001	1.36 (1.14~2.45)
Age	<0.001	1.09 (1.06 ~ 1.11)
ALT	0.003	0.99 (0.99 ~ 0.99)
AST	0.047	0.99 (0.99 ~ 0.99)
Total Bilirubin	0.555	1.00 (0.99 ~ 1.00)
Albumin	0.295	0.97 (0.92 ~ 1.03)
γ-GGT	0.596	1.00 (1.00 ~ 1.00)
Blood urea nitrogen	0.002	1.38 (1.13 ~ 1.68)
Creatinine	0.519	1.01 (0.99 ~ 1.03)
Leukocyte	0.164	0.86 (0.69 ~ 1.06)
Neutrophil	0.098	0.78 (0.58 ~ 1.05)
Lymphocyte	0.534	0.85 (0.52 ~ 1.40)
NLR	0.740	0.95 (0.72 ~ 1.27)
Platelet	<0.001	0.99 (0.98 ~ 0.99)
INR	0.886	1.20 (0.10 ~14.21)
AFP	0.746	1.00 (1.00 ~ 1.00)

Abbreviations: HCC, Hepatocellular carcinoma; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; γ-GGT, γ-glutamyl transferase; NLR, Neutrophil-lymphocyte ratio; INR, International ratio; CTP, Child-Turcotte-Pugh; MELD, Model for end-stage liver disease.

protective factors against the development of HCC (Table 2). These factors were also incorporated in constructing the ANN model (https://houyixin.me/annmodel/myg-v4/). The most commonly used structure for ANN is the multilayer perceptron (MLP), which consists of input, hidden, and output layers. The input layer comprises clinical and biochemical parameters, while the output layer includes corresponding prognosis outcomes. The ANN model for predicting the 10-year risk of HCC development in patients with CHB is provided (https://houyixin.me/annmodel/myg-v4/).

Application of the ANN Model for Risk Stratification

As illustrated in Figure 2, we incorporated factors associated with the incidence of liver cancer into the COX multivariate regression and developed an ANN model. Using the cutoff value derived from the ANN model score, we categorized all CHB patients into two risk groups: Stratum 1, which represents low-risk patients, and Stratum 2, which represents high-risk patients. In the training cohort, the positive predictive value (PPV) for liver cancer occurrence among low-risk patients was 92.5% (95% CI 0.921–0.939), while the negative predictive value (NPV) was 88.2% (95% CI 0.870–0.894). In the validation cohort, the ANN model also performed equally well (Table 3).

In this study, we utilized patient information within the ANN model to evaluate the 10-year risk of cancer development. In the training set, 987 patients (75.4%) were classified as low-risk, while 322 patients (24.6%) were categorized as high-risk. The cumulative probabilities of developing HCC within 10 years for the low and high ANN model groups were 0.1% and 14.3%, respectively (this can be calculated independently) ($P < 0.0001$; Figure 3). Similarly, in the validation set, the cumulative probabilities of HCC development within 10 years for the high ANN model group were 0.9% and 16.5%, respectively ($P < 0.0001$; Figure 3). Previous literature indicates that PLT, HBV-DNA levels, and age are closely associated with the incidence of liver cancer. Consequently, we performed Kaplan-Meier curve analyses to assess the probability of HCC occurrence in CHB patients across different risk levels and varying HBV-DNA, PLT, and age strata. As illustrated in Figure 4, the incidence rate of HCC in high-risk CHB patients was significantly greater than that in the low-risk group, irrespective of HBV-DNA, PLT, or age group ($P < 0.05$).

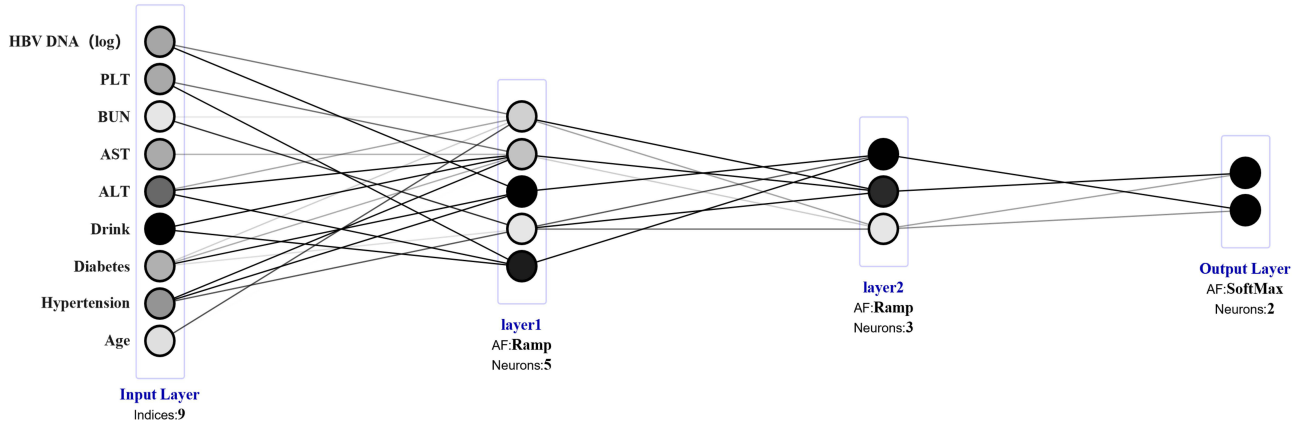

Figure 2 Artificial neural network model page design according to different condition of patients.

Discrimination and Calibration of the ANN Model

Compared to other models in the training and validation cohorts, the ANN model exhibited superior performance in predicting the occurrence of HCC. In the training cohort, the AUROC curve value for the ANN model was 0.929 (95% CI 0.910–0.948), while the C-index value was 0.917 (95% CI 0.907–0.927). These values were significantly higher than those of the mREACHE-B, mPAGE-B, HCC-RESCUE, CAMD, REAL-B, and PAGE-B models ($P < 0.001$) (Table 4, Figure 5). Similarly, in the validation cohort, the ANN model demonstrated strong predictive ability, with an AUROC curve value of 0.977 (95% CI 0.962–0.992) and a C-index value of 0.887 (95% CI 0.861–0.913), both significantly exceeding those of the mREACHE-B, mPAGE-B, HCC-RESCUE, CAMD, REAL-B, and PAGE-B models ($P < 0.001$) (Table 4, Figure 5). Furthermore, the ANN model displayed significant net benefits over the mREACHE-B, mPAGE-B, HCC-RESCUE, CAMD, REAL-B, and PAGE-B models in both the training and validation cohorts (Figure 6). The calibration curve of the ANN model indicated a strong consistency between the predicted probability of no HCC and the observed probability over a 10-year period in both the training (Figure 7A) and validation (Figure 7B) cohorts. This finding underscores the clinical utility of the artificial neural network model relative to other models.

Discussion

In this study, we developed a novel ANN model utilizing machine learning to predict the risk of HCC in patients with chronic hepatitis B over a 10-year period. This model was trained on a substantial cohort from our hospital (n = 1309), while validation was performed using independent data from an external hospital (n = 408). Both cohorts demonstrated high prediction accuracy, underscoring the model's reliability. The ANN model integrates various factors, including patient demographics, underlying diseases, and laboratory markers, such as age, hypertension, type 2 diabetes, HBV-DNA, ALT, AST, blood urea nitrogen, and PLT. It classifies patients into low- and high-risk groups based on the estimated risk of HCC. Compared to previous models, the implementation of the HCC monitoring strategy informed by our model's risk estimation offers greater overall benefits.

Table 3 Positive Predictive and Negative Predictive Values

Cohort	Models	10-Year Risk of HCC	
		Positive(%)(95% CI)	Negative(%) (95% CI)
Training	ANN (low)	0.925(0.921–0.939)	0.882(0.870–0.894)
	ANN (high)	0.946(0.936–0.956)	0.902(0.897–0.917)
Validation	ANN (low)	0.882(0.869–0.895)	0.864(0.843–0.885)
	ANN(high)	0.916(0.893–0.939)	0.875(0.847–0.903)

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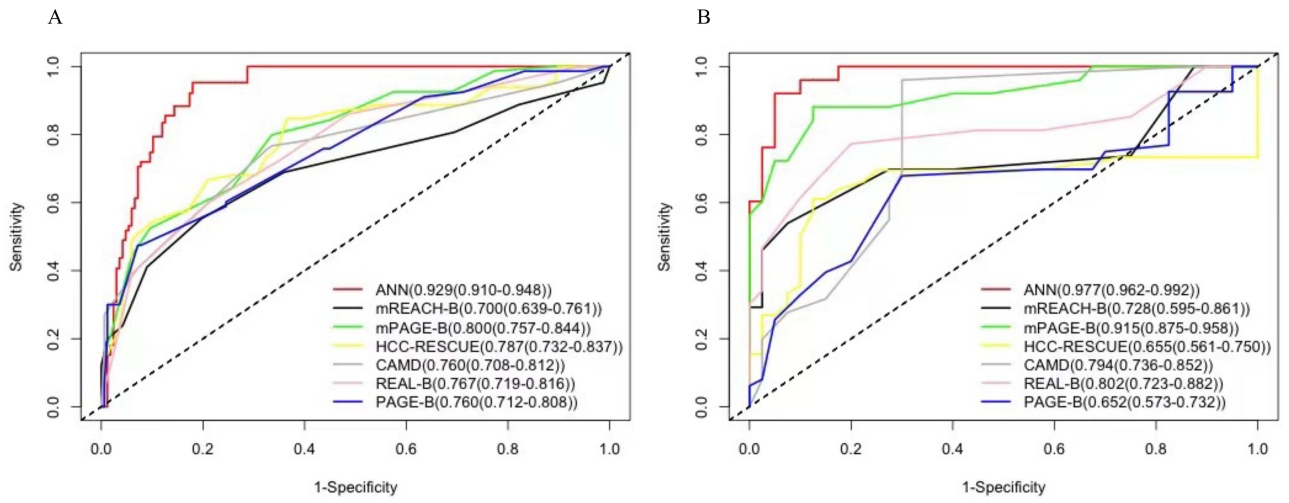

Figure 3 The ROC of 10-year HCC in training cohort (**A**), and validation cohort (**B**).

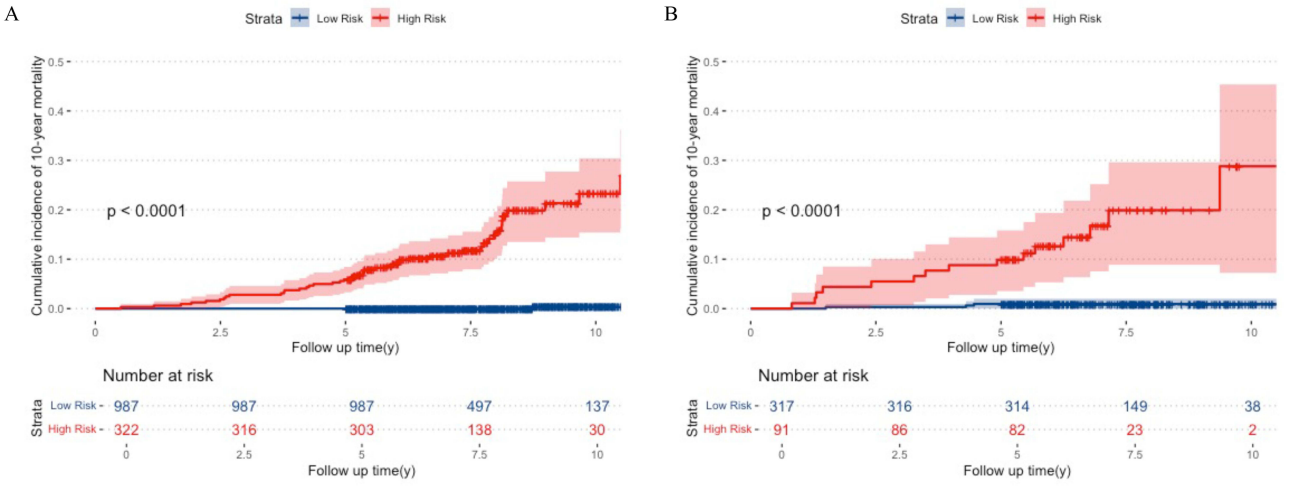

Figure 4 The Kaplan-Meier incidence of 10-year HCC in training cohort (**A**), and validation cohort (**B**). According to the artificial neural network model, the patient training and validation sets are divided into two risk layers as follows: high (Stratum1), and low (Stratum2).

The performance of the ANN model in predicting 10-year HCC development in patients with chronic hepatitis B is commendable, as reflected by the high AUC value of 0.929 obtained from the training and calibration curves. In comparison to other models, such as mPAGE-B (which includes age, gender, albumin, and platelet count) and PAGE (which includes age, gender, and platelet count), our ANN model demonstrates superior predictive performance in patients infected with HBV(all $P < 0.001$). The ANN model possesses several advantages. Firstly, unlike traditional logistic regression or Cox regression models that can only accommodate variables with linear relationships to the outcome, the ANN model is capable of handling nonlinear data. Secondly, the ANN model can learn from the data, adjusting the connections between variables and iteratively training on factors related to the outcome. This iterative process enables the ANN model to achieve higher prediction accuracy. While the PAGE score, based on age, gender, and platelet count, can predict the occurrence of cancer within 5 years, its predictive performance requires enhancement. In contrast, the modified mPAGE-B score, which combines albumin, age, gender, and weighted platelet count, demonstrates limited accuracy, with an AUROC of only 0.800, which is lower than our ANN model's AUC of 0.929, indicating its capability to accurately predict HCC incidence within 10 years.

Table 4 Comparison of Performance and Discriminative Ability Among the Current Model and Other Models

Cohort	Models	10-Year Risk of HCC			
		AUROC (95% CI)	*P* value	C-index (95% CI)	*P* value
Training	ANN	0.929(0.910–0.948)		0.917(0.907–0.927)	
	mREACHE-B	0.700(0.639–0.761)	<0.001	0.721(0.679–0.763)	<0.001
	mPAGE-B	0.800(0.757–0.844)	<0.001	0.764(0.732–0.796)	<0.001
	HCC-RESCUE	0.787(0.732–0.837)	<0.001	0.784(0.751–0.817)	<0.001
	CAMD	0.760(0.708–0.812)	<0.001	0.773(0.740–0.806)	<0.001
	REAL-B	0.767(0.719–0.816)	<0.001	0.759(0.727–0.791)	<0.001
	PAGE-B	0.760(0.712–0.808)	<0.001	0.728(0.690–0.766)	<0.001
Validation	ANN	0.977(0.962–0.992)		0.887(0.861–0.913)	
	mREACHE-B	0.728(0.595–0.861)	<0.001	0.843(0.795–0.891)	<0.001
	mPAGE-B	0.915(0.875–0.958)	0.045	0.839(0.790–0.888)	<0.001
	HCC-RESCUE	0.655(0.561–0.750)	<0.001	0.628(0.533–0.723)	<0.001
	CAMD	0.794(0.736–0.852)	0.001	0.755(0.729–0.821)	<0.001
	REAL-B	0.802(0.723–0.882)	0.021	0.748(0.679–0.817)	<0.001
	PAGE-B	0.652(0.573–0.732)	<0.001	0.583(0.499–0.667)	<0.001

Current major international guidelines recommend that patients with chronic hepatitis B undergo related examinations, such as abdominal ultrasound and AFP testing, every six months to monitor the occurrence of HCC, regardless of their individual risk levels.[19–22] However, research indicates that not all patients are at equal risk for HCC. Consequently, the prevailing "one-size-fits-all" approach can often lead to both overestimation and underestimation of HCC risk for individuals.[23,24] To address this issue, a hierarchical management strategy may be implemented for patients with chronic hepatitis B. The ANN model can classify patients into two distinct risk categories based on their 10-year cumulative incidence rate of HCC. In the training cohort, the positive predictive value for the low-risk group is 92.5%, while for the high-risk group, it is 94.6%. In the validation cohort, these values are 88.2% and 91.6%, respectively. This demonstrates that the model effectively identifies the incidence rate of HCC, regardless of the individual's risk. By adopting a screening strategy informed by our predictive model, we have observed greater net benefits compared to other methods and models. According to the risk stratification provided by the ANN model, the annual incidence rate of HCC in the low-risk group is approximately 0.1%, allowing for a reduction in the frequency of monitoring for this group, thereby minimizing potentially harmful and costly diagnostic tests. Conversely, the incidence rate in the high-risk group is significantly elevated, with a cumulative incidence rate reaching 14.3% after 10 years of follow-up observation. Therefore, for the high-risk population, it is crucial to emphasize early monitoring and identification to maximize the effectiveness of early HCC screening, optimize the cost-effectiveness of medical interventions, and ensure the optimal allocation of limited medical resources.

We also acknowledge the limitations of this study. Firstly, this investigation is retrospective in nature, which introduces inherent selection bias. However, it benefits from comprehensive clinical data and a robust sample size. Additionally, the use of deep learning techniques and extensive training of artificial intelligence neural networks has resulted in the ANN model demonstrating exceptional predictive ability in assessing the risk of HCC. Nevertheless, it is essential to replicate these findings on a larger scale and consider the potential for prospective studies. Secondly, a significant number of our patients lack hepatitis B surface antigen levels and genetic studies, making it impossible to evaluate the potential role of these markers within the context of our research.

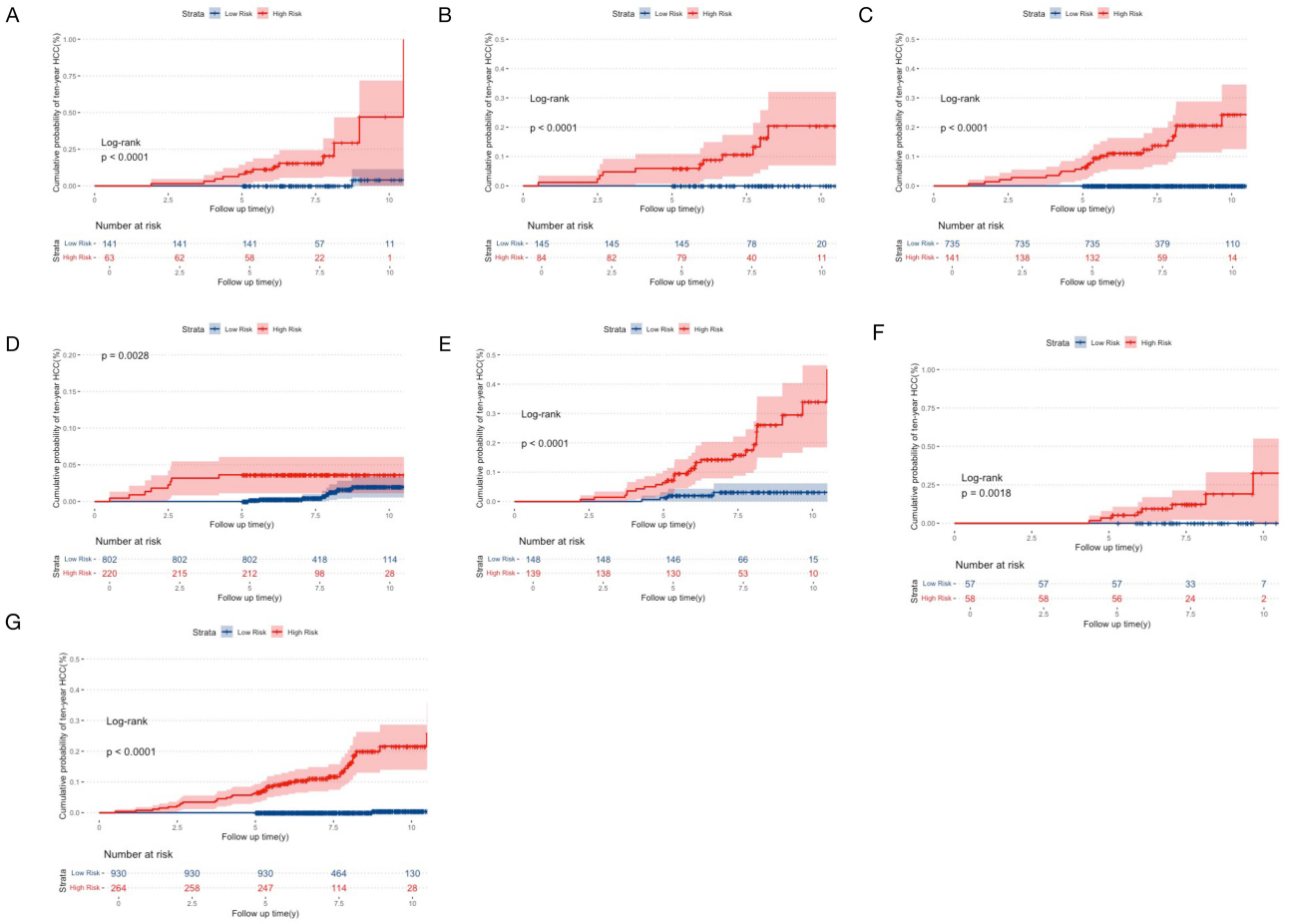

Figure 5 The Kaplan-Meier curves of incidence of 10-year HCC in training cohort and the patients are divided into different risk layers in HBV-DNA, age, PLT subgroups. In HBV-DNA subgroup, patients are divided into three risk groups as follow: HBV-DNA (log)<3 (**A**), 3≤HBV-DNA (log)≤5 (**B**) and HBV-DNA (log)>5 group (**C**); In age subgroup, patients are divided into two risk groups as follow:age≤46 (**D**) and age>46 (**E**). In PLT subgroup, patients are divided into two risk groups as follow: PLT<100 (**F**) and PLT≥100 (**G**).

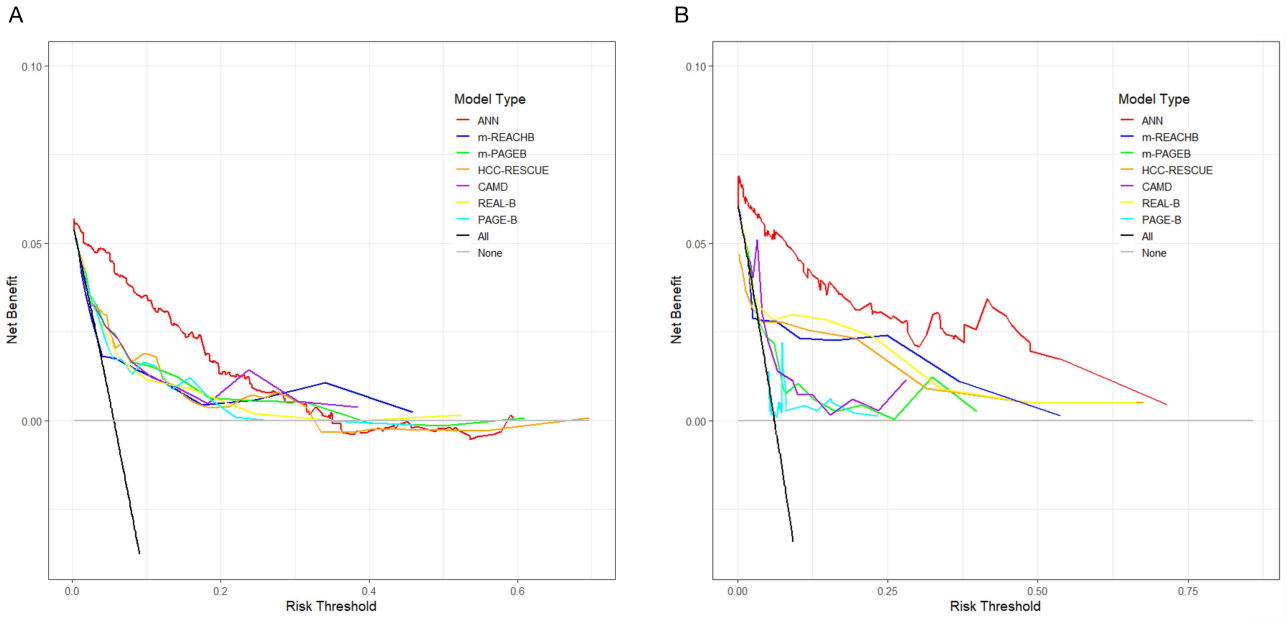

Figure 6 The calibration curve for predicting 10-year HCC in training cohort (**A**)and validation cohort (**B**).

 https://doi.org/10.2147/JHC.S498463

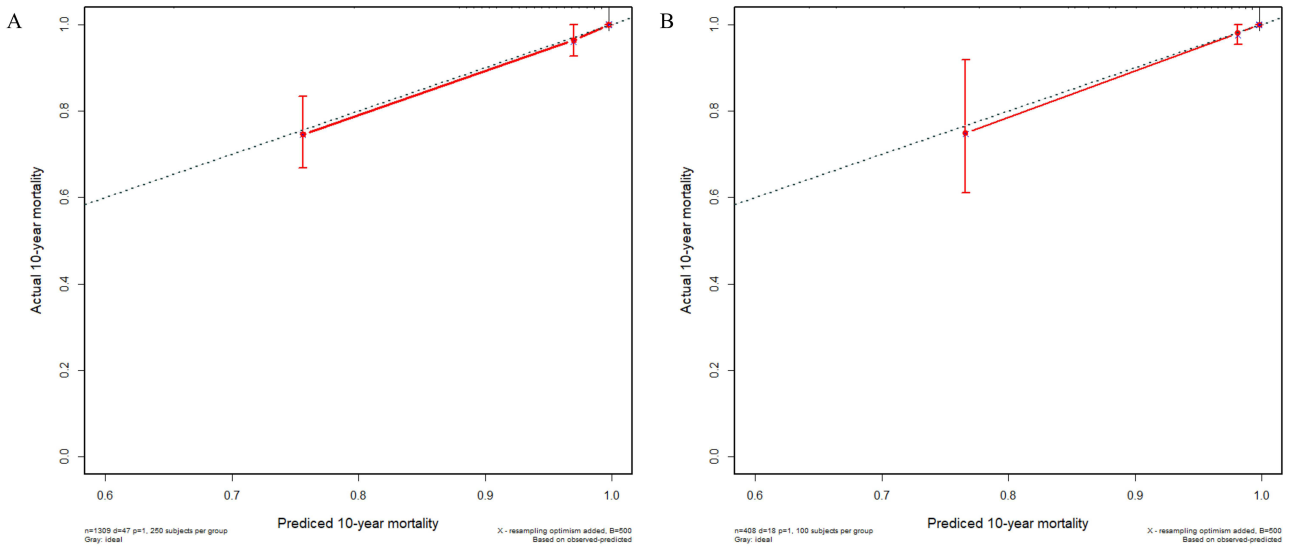

Figure 7 The cumulative probabilities of HCC of artificial neural network model at 10 years in the training cohort (**A**) and validation cohort (**B**) data sets.

Summary

In conclusion, our ANN model demonstrates superior performance compared to previous models in predicting the risk of HCC in patients with chronic hepatitis B. Future studies should leverage this new ANN model to develop a more cost-effective monitoring program for HCC.

Ethical Approval

The study was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. Written informed consent was obtained from each patient. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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Disclosure

The authors declare that they have no conflicts of interest regarding the publication of this research report.

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