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ORIGINAL RESEARCH

Novel Nomograms Based on Gamma-Glutamyl Transpeptidase-to-Lymphocyte Ratio Predict Prognosis of Hepatocellular Carcinoma Patients After Hepatectomy

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Background: The prediction of prognosis of hepatocellular carcinoma (HCC) is of great significance in improving disease outcome and optimizing clinical management, while reliable prognostic indicators are lacking. This study was conducted to develop readily-to-use nomograms for prognosis prediction of HCC after hepatectomy.

Materials and Methods: Data of eligible patients were collected and analyzed retrospectively. Independent prognostic factors were identified by Cox regression, and nomograms for the prediction of disease-free survival (DFS) and overall survival (OS) were developed. The performance of the nomograms was evaluated by receiver operating characteristics (ROC) curves, C-indexes and calibration curves and was verified by the validation cohort. The predictive value of the nomograms was also compared with the 8th edition of American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) and the Barcelona Clinic Liver Cancer (BCLC) staging systems.

Results: In total, 599 patients were enrolled in the analysis: 420 in the training cohort and 179 in the validation cohort. The optimal cut-off value of Gamma-Glutamyl Transpeptidase-to-Lymphocyte Ratio (GLR) was 19.5. GLR contributed significantly to the nomograms with good predictive power. In ROC analyses, the areas under curve (AUCs) of the nomograms for 1-, 3- and 5-year DFS and OS prediction were 0.758, 0.756, 0.734 and 0.810, 0.799, 0.758, respectively. The C-indexes of the DFS nomogram were 0.697 (95% CI 0.665–0.729) in the training cohort and 0.710 (95% CI 0.664–0.756) in the validation cohort. For OS prediction, the C-indexes were 0.741 (95% CI 0.704–0.778) and 0.758 (95% CI 0.705–0.811) in the training and validation cohorts, respectively. The calibration curves demonstrated satisfactory agreement between nomogram predictions and actual observations. The nomograms demonstrated superior predictive performance to the TNM and the BCLC staging systems.

Conclusion: Our novel nomograms showed adequate performance in the prediction of HCC prognosis after hepatectomy, which may facilitate the risk stratification and individualized management of HCC patients.

Keywords: hepatocellular carcinoma, nomogram, gamma-glutamyl transferase, lymphocyte, hepatectomy

Introduction

Liver cancer ranks the sixth in the most prevalent cancers and is the third leading cause of cancer-related death around the world.[1] Hepatocellular carcinoma (HCC) represents the most common histological type, comprising 75–85% of liver cancer cases.[1,2] As a leading high-risk area of HCC, China takes about half of the disease burden worldwide and Jiangsu, a province in Eastern China, is one of the regions with the highest incidence of HCC in China.[3] To date, surgical

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resection of HCC has become a safe treatment with a low mortality rate.[4] Despite recent improvement of diagnosis and management of HCC, the prognosis after hepatectomy remains unsatisfactory due to high incidence of recurrence and metastasis.[5]

The Tumor-Node-Metastasis (TNM) staging and the Barcelona Clinic Liver Cancer (BCLC) classification are the most widely used systems for predicting the prognosis of HCC. However, the TNM system only depends on pathological factors and does not perform well in survival prediction.[6] In tertiary centers, up to 50% of patients present deviations from BCLC therapeutic recommendations.[7] For laboratory parameters, serum α-fetoprotein (AFP) is the most widely used and readily available method for the diagnosis and monitoring of HCC.[8] Unfortunately, AFP is not an optimal prognostic indicator of HCC, especially for small tumors.[9] Therefore, there is an urgent need for effective indicators of HCC prognosis.

Chronic inflammation is closely correlated with the occurrence and progression of HCC.[10] HCC features dysregulated inflammatory mediators, aberrant immune response[11] and altered peripheral blood cell counts with prognostic significance.[12] Based on this background, multiple immune-inflammation-based prognostic indicators, developed with economical and non-invasive blood cell counts and biochemical parameters, have been proposed to predict the prognosis of HCC. As a classic indicator of liver inflammation, gamma-glutamyl transpeptidase (GGT) is induced during the development of multiple tumors and is correlated with poor survival.[13,14] Lymphocytes play a central role in systemic and local immune-inflammatory response.[15] Lymphocytopenia indicates a state of diminished immune function and may contribute to adverse survival of HCC patients.[16] By combining GGT and lymphocyte count, GGT-to-lymphocyte ratio (GLR) is recently developed as an inflammation-based indicator with prognostic value in HCC patients and was validated in cohorts from Southern China.[17,18] By combining multiple independent factors, nomograms could provide readily-to-use tools for risk estimation and decision-making with improved predictive performance. In this study, we developed and validated novel prognostic nomograms with good predictive efficacy by incorporating GLR and other clinically available objective clinicopathological characteristics in HCC patients receiving hepatectomy.

Materials and Methods

Study Population and Data Collection

The data of patients who underwent hepatectomy with curative intention at the Department of Hepatobiliary Surgery, Drum Tower Clinical College of Nanjing Medical University between July 2004 and August 2016 were retrieved from electronic medical record system and were analyzed retrospectively. To avoid potential bias brought by short follow-up period, patients who underwent surgery in a relatively early period (>5 years before the analysis) with complete follow-up data were included.[19–21] Patients eligible for the following criteria were included in this study: (1) >18 years old; (2) with pathologically confirmed diagnosis of HCC; (3) underwent curative hepatectomy; (4) with complete laboratory, pathological and follow-up data. The exclusion criteria included (1) <18 years old; (2) cholangiocarcinoma, metastatic tumor and recurrent HCC; (3) resections with residual tumor; (4) incomplete laboratory, pathological or follow-up data; (5) perioperative mortality; (6) patients with diseases of blood, immune or lymphatic system; (7) evidence of infectious or inflammatory diseases. Data were collected by two independent investigators (MC and CY) and were cross-checked by the third investigator (ZG). The clinical parameters collected included general information (age, gender, history of diabetes and hypertension and history of tobacco or alcohol consumption), preoperative laboratory test results (blood cell counts, biochemical tests, hepatitis virus antigen and antibody tests and serum AFP levels), preoperative radiological and ultrasound data (location of tumor, size and number of tumor, signs of cirrhosis and ascites), operative information (portal occlusion, intraoperative bleeding and intraoperative blood transfusion) and histopathological data (tumor size and number, differentiation, vascular invasion, status of resection margin). The TNM stage was determined by the American Joint Committee on Cancer (AJCC) staging manual (8th edition). The BCLC stage was determined as previously described.[22] The status of vascular invasion was subcategorized into microvascular invasion (MVI) and macrovascular invasion (MaVI). The definition of MVI was the presence of cancer cell nests with >50 cells in the endothelial vascular lumen under microscopy.[23] Tumor invading the main trunk or large branches of hepatic vein or portal vein was considered as macrovascular invasion. GLR was calculated as value of serum GGT (U/L)/lymphocyte count (10^9/L).[17,18] The study was approved by institutional ethics committee of the Drum Tower Clinical College of Nanjing Medical University and was in accordance with the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. The identities of patients included in this study were kept anonymous to the researchers by computer-generated ID numbers, and therefore consent from the patients was waived.

Follow-Up

Postoperative follow-up was carried out by regular examination in the outpatient clinic and was supplemented by telephone communication when needed. Blood cell count, biochemical test, serum AFP and abdominal ultrasonography or contrast-enhanced computed tomography were performed during the follow-up in outpatient clinic visits. The tests were performed monthly during the first three months after surgery and every three months in the first two years. After that, patients were followed up every six months during the third to fifth years. Afterwards, the follow-up was carried out annually. The diagnosis of recurrence was established based on imaging and laboratory tests and was confirmed pathologically when possible. Disease-free survival (DFS) was calculated as the time between surgery and the date of cancer recurrence, metastasis or the last follow-up, while overall survival was determined by the interval between surgery and death or the last follow-up.

Statistical Analysis

Statistical analyses were performed by SPSS v25.0 (IBM Corporation, Armonk, NY, USA) and R software v3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics were compared by chi square test or Fisher's exact test when applicable. Univariate analyses were performed by the Cox proportional hazard model. Factors with P value <0.1 were entered as candidate variables into multivariate Cox regression analyses to identify independent prognostic factors. Nomograms were formulated based on the results of the multivariate Cox proportional hazards regression analysis. Receiver operating characteristic (ROC) curves were generated, and areas under curve (AUCs) were calculated to evaluate the predictive characteristics of the model. The concordance indexes (C-indexes) were calculated to assess the accuracy of nomograms, and the calibration curves were used to determine the consistency of the models. Time-dependent ROC curves were drawn to compare the efficacy of different staging systems. The optimal cut-off value of the GLR was obtained by X-tile software v3.6.1 (Yale University School of Medicine, New Haven, CT, USA).[24] P-values <0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 599 patients with pathologically diagnosed HCC were included in this study. The patients were randomly divided into training cohort (n = 420) and validation cohort (n = 179) by the ratio of 7:3. This ratio was repeatedly employed in the previous similar nomogram-related studies because this ratio provided enough sample size for both model establishment and validation. Also, the random selection method also avoided potential bias from dividing the groups by time or other factors.[25–27] The baseline demographics, clinicopathological and operative characteristics of both the training and validation cohorts are shown in Table 1. According to the follow-up data, 384 (64.1%) of the patients developed recurrent HCC and 237 (39.6%) of them died of HCC. The DFS rate at 1-, 3- and 5-year, were 63.2%, 43.3% and 32.6%, respectively. The OS rate at 1-, 3- and 5-year were 85.2%, 74.0% and 54.5%, respectively. The optimal cut-off value of GLR with the best discriminative efficacy of survival was determined by X-tile software as 19.5 (Chi-square value = 23.39, P < 0.0001, Figure 1).

Identification of Prognostic Factors for DFS and OS

To identify the prognostic factors for DFS and OS, univariate and multivariate Cox proportional hazard regression analyses were performed. The results showed that elevated serum-positive HBeAg (HR 1.453, 95% CI 1.081–1.951, P = 0.013), AFP level (HR = 1.287, 95% CI 1.004–1.649, P = 0.047), larger tumor size (5–10 cm, HR = 1.690, 95% CI 1.119–2.552, P = 0.013; >10 cm, HR = 3.211, 95% CI 1.941–5.312, P < 0.001), multiple tumors (HR = 1.820, 95%

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Table 1 Baseline Characteristics of Patients

Characteristic	Training Cohort n = 420 (%)	Validation Cohort n = 179 (%)	P value
Gender			
Male	339 (80.7)	150 (83.8)	0.372
Female	81 (19.3)	29 (16.2)	
Age			
≤50	138 (32.9)	61 (34.1)	0.771
>50	282 (67.1)	118 (65.9)	
Hypertension			
No	324 (77.1)	138 (77.1)	0.990
Yes	96 (22.9)	41 (22.9)	
Diabetes			
No	369 (87.9)	160 (89.4)	0.594
Yes	51 (12.1)	19 (10.6)	
Smoking			
No	350 (83.3)	141 (78.8)	0.184
Yes	70 (16.7)	38 (21.2)	
Alcohol consumption			
No	369 (87.9)	157 (87.7)	0.960
Yes	51 (12.1)	22 (12.3)	
HBsAg			
Negative	83 (19.8)	42 (23.5)	0.307
Positive	337 (80.2)	137 (76.5)	
HBeAg			
Negative	330 (78.6)	138 (77.1)	0.689
Positive	90 (21.4)	41 (22.9)	
HCVAb			
Negative	413 (98.3)	176 (98.3)	0.616
Positive	7 (1.7)	3 (1.7)	
AFP			
≤200 ng/mL	241 (57.4)	107 (59.8)	0.586
>200 ng/mL	179 (42.6)	72 (40.2)	
Portal occlusion			
No	138 (32.9)	49 (27.4)	0.185
Yes	282 (67.1)	130 (72.6)	
Blood loss			
≤500 mL	267 (63.6)	112 (62.6)	0.816
>500 mL	153 (36.4)	67 (37.4)	
Transfusion			
No	299 (71.2)	129 (72.1)	0.828
Yes	121 (28.8)	50 (27.9)	
Cirrhosis			
No	97 (23.1)	47 (26.3)	0.407
Yes	323 (76.9)	132 (73.7)	
Tumor size			
≤5 cm	76 (18.1)	42 (23.5)	0.230
5–10 cm	294 (70.0)	113 (63.1)	
>10 cm	50 (11.9)	24 (13.4)	
Tumor number			
Single	308 (73.3)	135 (75.4)	0.594
Multiple	112 (26.7)	44 (24.6)	

(*Continued*)

Table 1 (Continued).

Characteristic	Training Cohort n = 420 (%)	Validation Cohort n = 179 (%)	P value
MVI			
No	252 (60.0)	116 (64.8)	0.269
Yes	168 (40.0)	63 (35.2)	
MaVI			
No	349 (83.1)	151 (84.4)	0.703
Yes	71 (16.9)	28 (15.6)	
Differentiation			
Well	64 (15.2)	36 (20.1)	0.007
Moderate	216 (51.4)	106 (59.2)	
Poor	140 (33.3)	37 (20.7)	
Surgical margin			
>1 cm	246 (58.6)	116 (64.8)	0.153
≤1 cm	174 (41.4)	63 (35.2)	
GLR			
≤19.5	102 (24.3)	44 (24.6)	0.939
>19.5	318 (75.7)	135 (75.4)	
TNM stage			
I/II	277 (66.0)	123 (68.7)	0.408
III/IV	143 (34.0)	56 (31.3)	
BCLC stage			
0/A	268 (63.8)	120 (67.0)	0.747
B	81 (19.3)	31 (17.3)	
C	71 (16.9)	28 (15.7)	

CI 1.389–2.384, P < 0.001), the presence of MVI (HR = 1.506, 95% CI 1.169–1.939, P = 0.002), tumor differentiation (moderate differentiation, HR = 1.958, 95% CI 1.293–2.968, P = 0.002; poor differentiation, HR = 2.562, 95% CI 1.670–3.930, P < 0.001) and high GLR (GLR >19.5, HR = 1.560, 95% CI 1.118–2.177, P = 0.009) were independent prognostic factors for DFS (Table 2).

For OS, the independent prognostic factors (Table 3) included elevated AFP (HR = 1.711, 95% CI 1.225–2.390, P = 0.002), larger tumor size (>10 cm, HR = 2.271, 95% CI 1.180–4.373, P = 0.014), multiple tumors (HR = 1.976, 95% CI 1.420–2.749, P < 0.001), the presence of MVI (HR = 1.587, 95% CI 1.146–2.197, P = 0.005), MaVI

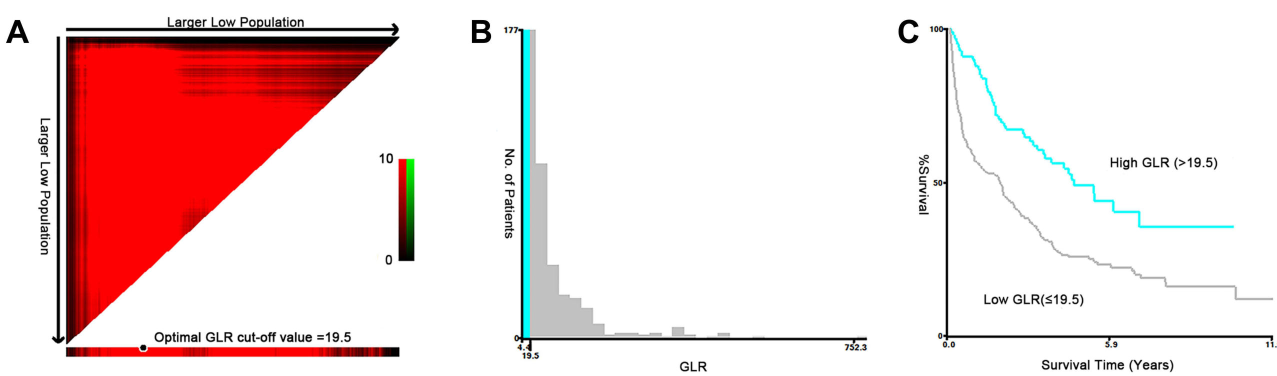

Figure 1 Determination of the optimal cut-off value of GLR by X-tile analysis. (**A**) X-tile plot generated by GLR and survival data of the patients. The black point on the horizontal bar highlighted the optimal outcome-based cut-off value. (**B**) The histogram of the cohort. The cohort was divided into two groups based on the GLR cut-off value. (**C**) Kaplan–Meier curve displayed the difference of survival between high GLR and low GLR groups.
Abbreviation: GLR, gamma-glutamyl transpeptidase-to-lymphocyte ratio.

Table 2 Univariate and Multivariate Cox Proportional Hazard Regression Analyses of DFS

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (Male vs Female)	0.871	0.615–1.234	0.436			
Age (>50 vs ≤50)	0.939	0.700–1.260	0.675			
Hypertension (Yes vs No)	0.990	0.711–1.377	0.950			
Diabetes (Yes vs No)	1.245	0.840–1.845	0.275			
Smoking (Yes vs No)	0.913	0.628–1.327	0.632			
Alcohol consumption (Yes vs No)	1.351	0.866–2.108	0.184			
HBsAg (Positive vs Negative)	0.831	0.585–1.179	0.299			
HBeAg (Positive vs Negative)	1.505	1.094–2.072	0.012	1.453	1.081–1.951	0.013
HCVAb (Positive vs Negative)	1.425	0.578–3.513	0.441			
AFP, ng/mL (>200 vs ≤200)	1.306	0.994–1.716	0.055	1.287	1.004–1.649	0.047
Portal occlusion (Yes vs No)	1.007	0.763–1.328	0.962			
Blood loss, mL (>500 vs ≤500)	0.972	0.780–1.332	0.860			
Transfusion (Yes vs No)	1.107	0.797–1.537	0.545			
Cirrhosis (Yes vs No)	1.405	1.010–1.953	0.044	1.367	0.998–1.874	0.052
Tumor size, cm						
≤5 cm	Reference			Reference		
5–10 cm	1.676	1.099–2.555	0.016	1.690	1.119–2.552	0.013
>10 cm	3.295	1.937–5.607	<0.001	3.211	1.941–5.312	<0.001
Tumor number (Multiple vs Single)	1.765	1.339–2.326	<0.001	1.820	1.389–2.384	<0.001
MVI (Yes vs No)	1.446	1.110–1.883	0.006	1.506	1.169–1.939	0.002
MaVI (Yes vs No)	1.306	0.935–1.824	0.118			
Differentiation						
Well	Reference			Reference		
Moderate	1.899	1.245–2.897	0.003	1.958	1.293–2.968	0.002
Poor	2.555	1.650–3.957	<0.001	2.562	1.670–3.930	<0.001
Surgical margin, cm (≤1 vs >1)	1.245	0.963–1.612	0.094	1.231	0.962–1.583	0.098
GLR (>19.5 vs ≤19.5)	1.477	1.043–2.093	0.028	1.560	1.118–2.177	0.009

(HR = 1.775, 95% CI 1.224–2.575, P = 0.003), tumor differentiation (moderate differentiation, HR = 2.662, 95% CI 1.406–5.043, P = 0.003; poor differentiation, HR = 3.299, 95% CI 1.722–6.320, P < 0.001) and high GLR (GLR >19.5, HR = 2.012, 95% CI 1.246–3.248, P = 0.004).

Development and Validation of Nomograms for the Prediction of DFS and OS

Based on the results of Cox regression analyses, nomograms were developed to predict the probabilities of 1-, 3- and 5-year DFS (Figure 2A) and OS (Figure 2B). The risk points of each risk factor could be generated by drawing an upward line to the point axis. The probability of survival could be read by the corresponding position of the accumulated points on the total point axis.

To evaluate the performance of the nomograms, the ROC curves were generated and the areas under curve (AUCs) were calculated. As indicated in Figure 3A and B, the novel nomograms showed good predictive value on both DFS and OS. The AUCs for 1-, 3- and 5-year DFS prediction were 0.758, 0.756 and 0.734, respectively. For the prediction of 1-, 3- and 5-year OS prediction, the AUCs were 0.810, 0.799, and 0.758, respectively. To assess the predictive accuracy and consistency of the nomograms, C-indexes were calculated and calibration curves were generated. The C-index was 0.697 (95% CI 0.665–0.729) for DFS prediction while 0.741 (95% CI 0.704–0.778) for OS prediction. The calibration curves for both DFS and OS (Figure 3C and D) showed good agreement between nomogram predictions and the actual observation results.

The developed novel nomograms were further validated by an internal validation cohort. The ROC curves in the validation cohort are shown in Figure 4A and B. The AUCs were 0.784, 0.766 and 0.755 for 1-, 3- and 5-year DFS

Table 3 Univariate and Multivariate Cox Proportional Hazard Regression Analyses of OS

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (Male vs Female)	0.971	0.619–1.521	0.896			
Age (>50 vs ≤50)	1.433	0.970–2.116	0.071	1.297	0.913–1.843	0.146
Hypertension (Yes vs No)	0.947	0.615–1.460	0.806			
Diabetes (Yes vs No)	1.204	0.735–1.973	0.461			
Smoking (Yes vs No)	1.035	0.644–1.663	0.887			
Alcohol consumption (Yes vs No)	1.272	0.700–2.309	0.43			
HBsAg (Positive vs Negative)	0.874	0.563–1.356	0.548			
HBeAg (Positive vs Negative)	1.375	0.908–2.082	0.133			
HCVAb (Positive vs Negative)	2.499	0.934–6.689	0.068	1.858	0.736–4.691	0.19
AFP, ng/mL (>200 vs ≤200)	1.821	1.277–2.598	0.001	1.711	1.225–2.390	0.002
Portal occlusion (Yes vs No)	0.881	0.628–1.240	0.468			
Blood loss, mL (>500 vs ≤500)	1.363	0.903–2.059	0.141			
Transfusion (Yes vs No)	1.114	0.732–1.693	0.615			
Cirrhosis (Yes vs No)	1.275	0.821–1.978	0.279			
Tumor size, cm						
≤5 cm	Reference			Reference		
5–10 cm	1.368	0.780–2.397	0.274	1.446	0.841–2.487	0.183
>10 cm	2.07	1.054–4.061	0.034	2.271	1.180–4.373	0.014
Tumor number (Multiple vs Single)	1.834	1.302–2.584	0.001	1.976	1.420–2.749	<0.001
MVI (Yes vs No)	1.572	1.120–2.207	0.009	1.587	1.146–2.197	0.005
MaVI (Yes vs No)	1.593	1.074–2.364	0.021	1.775	1.224–2.575	0.003
Differentiation						
Well	Reference			Reference		
Moderate	2.529	1.320–4.845	0.005	2.662	1.406–5.043	0.003
Poor	3.204	1.648–6.230	0.001	3.299	1.722–6.320	<0.001
Surgical margin, cm (≤1 vs >1)	1.154	0.827–1.609	0.399			
GLR (>19.5 vs ≤19.5)	1.826	1.111–3.000	0.018	2.012	1.246–3.248	0.004

prediction and 0.810, 0.805 and 0.810 for 1-, 3- and 5-year OS prediction, respectively, which were in consistent with the results of the training cohort. The C-indexes of the nomograms for predicting DFS and OS were 0.710 (95% CI 0.664–0.756) and 0.758 (95% CI 0.705–0.811). Similar to the training cohort, the calibration curves plotted in the validation cohort also revealed a good consistency between nomogram predictions and actual observations (Figure 4C and D).

Comparison of Predictive Performance Between the Nomograms and Conventional Staging Systems

The predictive value of the novel nomograms was compared with conventional staging systems including the TNM staging system (AJCC 8th edition) and the BCLC staging system. The comparison of C-indexes demonstrated that our current nomograms were superior to the conventional staging systems. Specifically, the C-indexes of the TNM staging and the BCLC staging for DFS prediction were 0.629 (95% CI 0.586–0.672) and 0.641 (95% CI 0.596–0.686), both of which were significantly smaller than the C-index of the nomogram. Similarly, the C-index of the nomogram for OS prediction also showed advantage over C-indexes of the TNM (0.650, 95% CI 0.595–0.705) and the BCLC staging (0.675, 95% CI 0.618–0.732).

Time-dependent ROC curves of the nomograms, the TNM and the BCLC staging system were generated for the comparison of prognostic values. As shown in Figure 5A and B, the time-dependent AUCs of the nomogram showed consistent superiority over both the TNM and the BCLC staging systems throughout the observation period, indicating the adequate discriminative efficacy and satisfactory stability of the novel nomograms for the prediction of both DFS and OS in HCC patients.

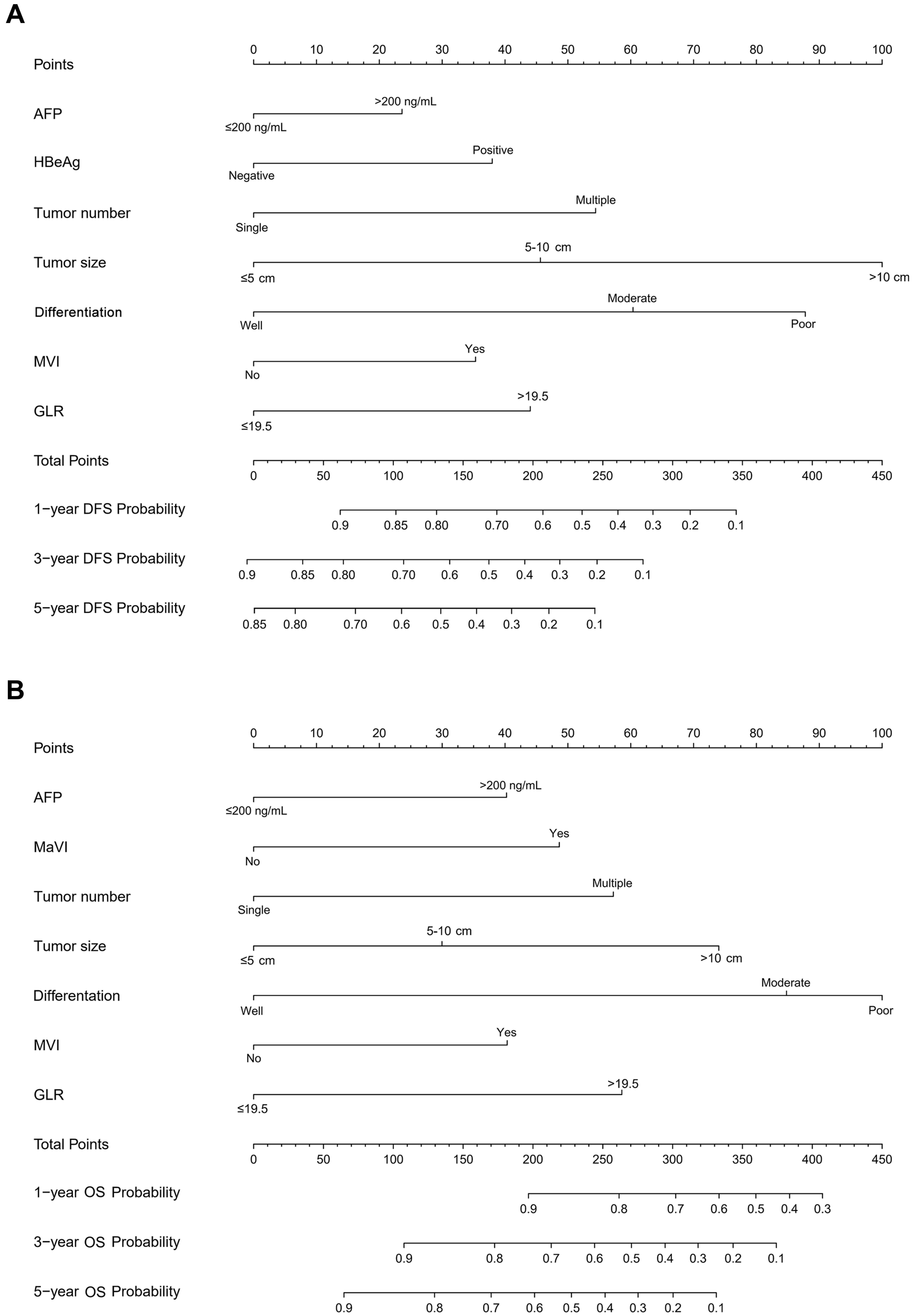

Figure 2 Nomograms for the prediction of 1-, 3- and 5-year DFS and OS. Each independent prognostic factor identified in the Cox regression was assigned a point. The total points could be obtained by calculating the sum of all factors. With the total points, the probabilities of 1-, 3- and 5-year DFS (**A**) and OS (**B**) could be predicted.
Abbreviations: AFP, serum α-fetoprotein; HBeAg, Hepatitis Be Antigen; MVI, microvascular invasion; MaVI, macrovascular invasion; GLR, gamma-glutamyl transpeptidase-to-lymphocyte ratio; DFS, disease-free survival; OS, overall survival.

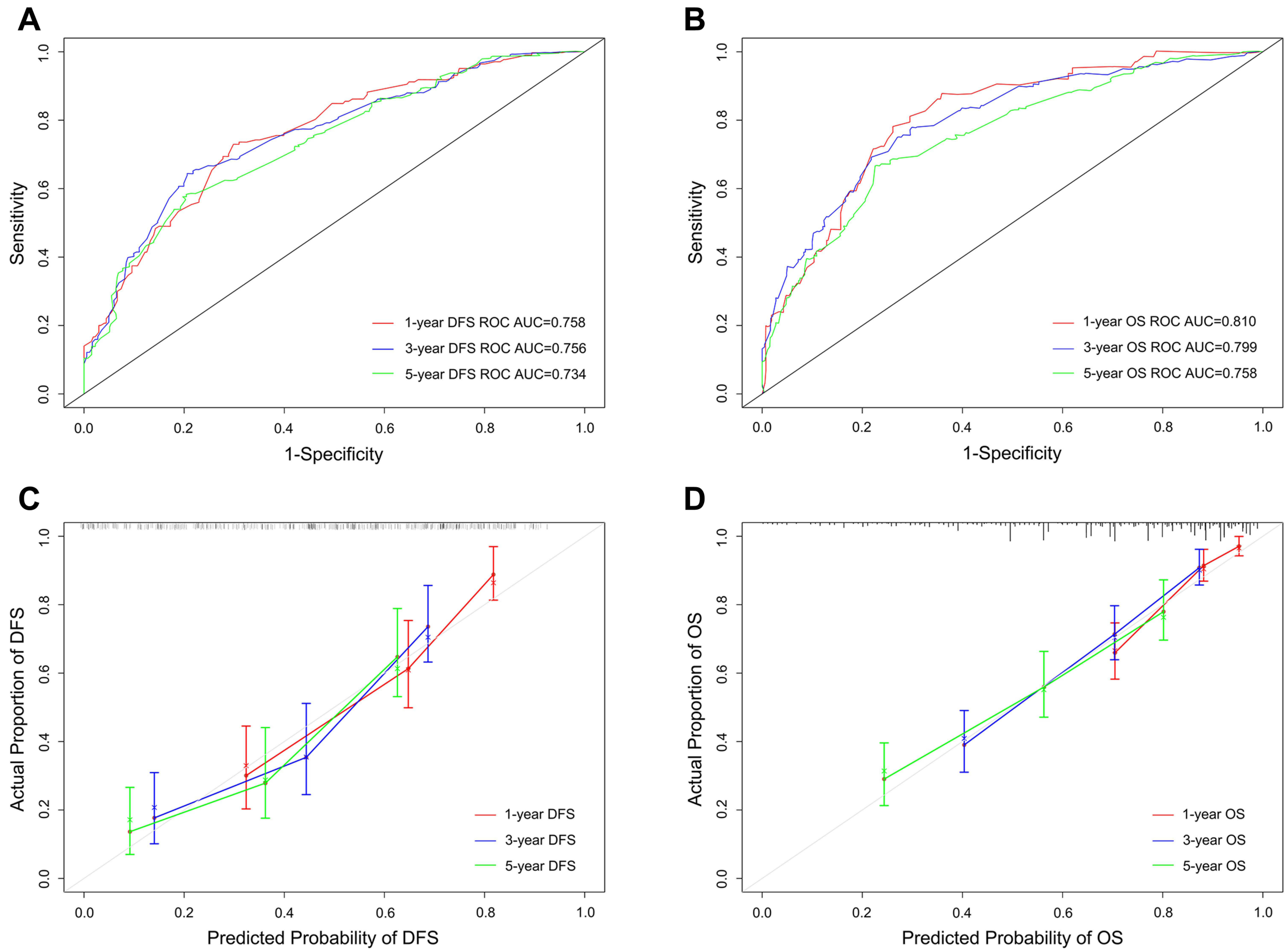

Figure 3 Evaluation of the performance of the nomograms in the training cohort. (**A**) ROC curves of the nomogram predicting 1-, 3- and 5-year DFS in the training cohort. (**B**) ROC curves of the nomogram predicting 1-, 3- and 5-year OS in the training cohort. (**C**) Calibration curves of the nomogram predicting 1-, 3- and 5-year DFS in the training cohort. (**D**) Calibration curves of the nomogram predicting 1-, 3- and 5-year OS in the training cohort.
Abbreviations: DFS, disease-free survival; OS, overall survival; ROC, receiver operating characteristic; AUCs, the areas under curve.

Discussion

For resectable HCC, hepatectomy remains the best treatment option. However, high incidence of postoperative recurrence limited the prognosis after surgery.[2] It is indicated that up to 70% of HCC patients developed recurrent disease after resection and only about 50–60% of them survived longer than 5 years.[2,28,29] In this study, 67.4% of the patients suffered from recurrence of HCC and about a half of them died in 5 years, which is similar with the reported data. Therefore, the prediction and stratification of postoperative prognosis are of great significance so that early intervention for high-risk patients could be applied. Currently, the 8th edition of AJCC-TNM and the BCLC systems are the most widely used staging tools for HCC. The TNM staging system relies solely on tumor pathological factors, which significantly limited its prognostic value. As another widely used system, the BCLC staging incorporated tumor burden, liver function and performance status to stratify HCC patients and to guide clinical management.[22] Unfortunately, the performance of BCLC system in prognosis stratification is also unsatisfactory and deviations from recommended treatment are common.[7,30–32] Therefore, novel tools with improved performance in the prediction of HCC prognosis are urgently needed.

Nomograms provide illustrated and readily-to-use tools for personalized risk estimation and decision-making through integrating multiple prognostic factors. Recently, numerous nomograms with promising predictive values are developed in various cancers, including HCC.[33,34] In this study, we established prognostic nomograms based on a novel immune-inflammation-based indicator GLR with good performance in the prediction of prognosis in HCC patients receiving hepatectomy. The novel nomograms were developed based on seven independent risk factors identified in multivariate

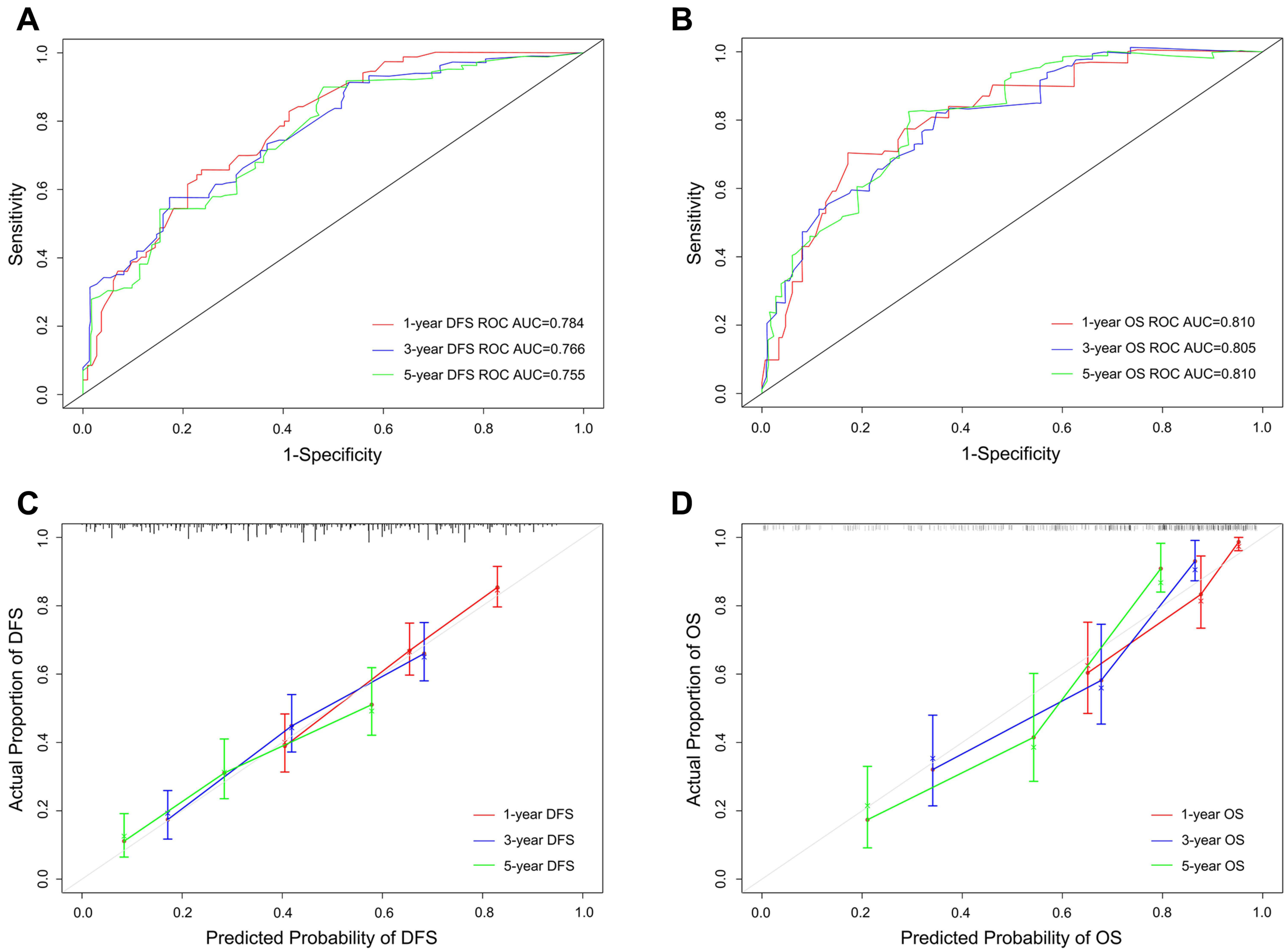

Figure 4 Performance of the nomograms in the validation cohort. (**A**) ROC curves of the nomogram predicting 1-, 3- and 5-year DFS in the validation cohort. (**B**) ROC curves of the nomogram predicting 1-, 3- and 5-year OS in the validation cohort. (**C**) Calibration curves of the nomogram predicting 1-, 3- and 5-year DFS in the validation cohort. (**D**) Calibration curves of the nomogram predicting 1-, 3- and 5-year OS in the validation cohort.

Abbreviations: DFS, disease-free survival; OS, overall survival; ROC, receiver operating characteristic; AUCs, the areas under curve.

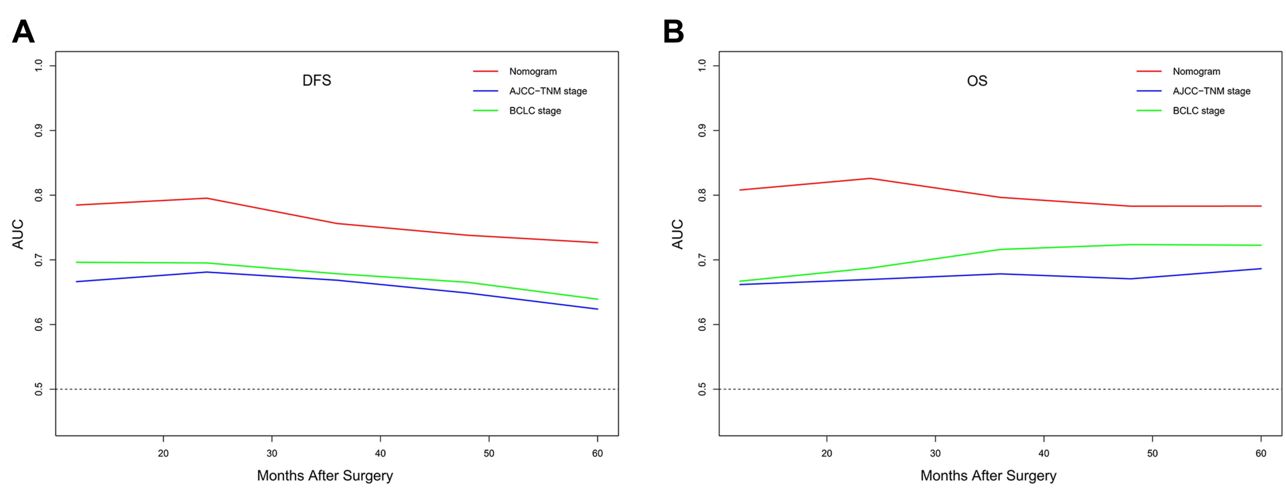

Figure 5 Time-dependent ROC curves of the nomograms, the TNM and the BCLC staging systems. (**A**) Time-dependent ROC curves of DFS predicting. (**B**) Time-dependent ROC curves of OS predicting.

Abbreviations: DFS, disease-free survival; OS, overall survival; AUCs, the areas under curve; AJCC, American Joint Committee on Cancer; TNM, tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer.

Cox regression analyses for DFS and OS, respectively. The combination of cancer-related biological markers with tumor characteristics is a practical strategy to improve prognosis prediction efficacy. Our nomograms incorporated well-established tumor characteristics with prognostic significance including multiple tumors, tumor size, tumor differentiation, MVI and MaVI with biological markers including AFP, HBeAg and GLR.[35–38]

To date, AFP remains the most widely used serum tumor marker for the diagnosis, surveillance and prognosis prediction of HCC.[39] The level of AFP may reflect the growth, differentiation, invasion and metastasis of HCC and could serve as an indicator of prognosis.[40,41] In this study, as expected, elevated AFP level was an independent risk factor for both DFS and OS and contributed to the construction of nomograms. Considering the fact that most Chinese HCC patients have viral hepatitis background,[3] markers of virus were also included in the analyses. Our study showed that positive HBeAg was an independent risk factor for DFS, which is consistent with previous reports.[42–44] This result further emphasized the importance of antiviral therapy since HBeAg was demonstrated to have a negative impact on prognosis and seroconversion of HBeAg may be beneficial for reducing recurrence of HCC.[43]

Dysregulation of inflammation and immune reaction are considered as the hallmarks of cancer.[45] For HCC, the disturbance of inflammation and immune response plays an especially critical role since it underlies both the tumor-promoting environment and the pathogenesis of background liver diseases. This led to the proposal of multiple immune-inflammation-based prognostic markers including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), gamma-glutamyl transpeptidase-to-platelet ratio (GPR), etc.[46–48] Derived from economical and readily available clinical blood and biochemical tests, these indicators provided useful tools for clinicians to predict the prognosis of HCC. Among the source parameters to derive the prognostic markers, GGT is a classic enzymatic marker of hepatic inflammation and is routinely tested for liver function evaluation. Elevation of GGT level reflects inflammation in liver microenvironment, which may contribute to the development and recurrence of HCC.[49] On the other hand, GGT expression could also facilitate tumor formation, progression, metastasis and drug resistance through multiple mechanisms.[50–52] Importantly, multiple studies revealed that elevated GGT correlated with poor prognosis of HCC, supporting the value of GGT as a prognostic indicator.[52–55] Lymphocyte plays an essential and central role in systemic and local immune-inflammatory reaction as well as anti-tumor response.[15,56] The level of tumor infiltrating lymphocyte correlated with the survival of HCC,[57] while lymphocytopenia predicted poor prognosis in HCC patients.[16,58] By combining GGT and lymphocyte, GLR was recently proposed to be a novel promising inflammation-based prognostic indicator in HCC.[17,18] In our HCC cohort from Eastern China, the optimal cut-off value of GLR was determined as 19.5 based on the outcome-based analysis by X-tile software. GLR exhibited adequate prognostic value in the following univariate and multivariate Cox regression and was incorporated in our nomograms as an independent predictive factor. As shown in the nomograms, GLR contributed significantly to the performance of the model with similar or even stronger power as the well-established risk factors including AFP, HBeAg, multiple tumors, MVI and MaVI.

The current nomograms demonstrated good predictive efficacy as indicated by ROC curves, C-indexes and calibration curves. The performance remained stable in an internal validation cohort. The nomograms also exhibited superior prognosis predictive ability to conventional tools including the TNM and the BCLC staging systems. These novel nomograms integrating tumor characteristics, viral and tumor biomarkers and immune-inflammation-based indicators, may contribute to the risk stratification after surgery and facilitate the individualized interventions in high-risk patients. Active interventions could include intensive postoperative surveillance; antiviral therapy for viral hepatitis;[43] adjuvant therapies for patients with tumor-related risk factors such as multiple tumors, large tumor size, poor differentiation and vascular invasions;[59] anti-inflammation and immune-regulatory interventions,[60,61] which might improve the prognosis of HCC after curative hepatectomy.

Nevertheless, limitations of this study should be noted. Although the nomograms were validated with an internal cohort and displayed stable performance, the results generated from our single-center data need further external or multicenter verification. The nomograms have been developed in a selected patient group of HCC and predict survivals of the patients treated by only surgical resection, so it is not applicable for all HCC patients. Due to the retrospective nature of the current study, future prospective investigations are also required to verify the predictive performance of the nomograms.

Conclusion

In this study, we developed novel nomograms incorporating tumor characteristics, viral and tumor biomarkers and immune-inflammation-based prognostic indicator GLR. The nomograms demonstrated adequate performance in the prediction of prognosis of HCC patients after curative hepatectomy and showed advantage over the traditional TNM and BCLC staging systems. These easy-accessible tools may contribute to the risk stratification after surgery and might facilitate the individualized interventions in high-risk patients.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the author Cheng Ma (Email: xzmacheng@163.com) upon reasonable request.

Ethics Statement

The study was approved by the institutional ethics committee of the Drum Tower Clinical College of Nanjing Medical University and was in accordance with the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. The identities of patients included in this study were kept anonymous to the researchers by computer-generated ID numbers, and therefore consent from the patients was waived.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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