Original Article

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The prognostic nutritional index and tumor pathological characteristics predict the prognosis of elderly patients with early-stage hepatocellular carcinoma after surgery

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SUMMARY The elderly comprises over one-third of hepatocellular carcinoma (HCC) patients, however, they are not adequately represented in prognostic studies. The study aims to determine the prognostic significance of the preoperative prognostic nutritional index (PNI) and develop nomograms for predicting their recurrence-free and overall survival (RFS and OS). The study consisted of 282 elderly patients (aged ≥ 65 years) with early-stage HCC (China Liver Cancer Staging System: I-IIA) after curative resection (R0). They were randomly divided into a training (n = 197) and a test cohort (n = 85). The patients were stratified into two groups: PNI-low (PNI ≤ 49.05) and PNI-high (PNI > 49.05) based on a cut-off value. Most patients' demographics and perioperative outcomes were comparable, while patients in the PNI-high group were younger (P = 0.002), heavier (P < 0.001), and had lower comorbidity rates (P = 0.003). Although the tumor stages were earlier in the PNI-low group (P < 0.001), patients' OS (5-year OS: 48.9% *vs*. 93.1%) and RFS (5-year RFS: 27.3% *vs*. 75.7%) were significantly worse compared to the PNI-high group (both P < 0.0001). Patients' OS and RFS nomograms were developed by incorporating independent survival predictors including chronic obstructive pulmonary disease (COPD), age ≥ 75 years, PNI-low, tumor presence of satellite nodules, capsule, and microvascular invasion. The nomograms showed good calibration and discrimination, with all C-indexes ≥ 0.75 and calibration plots essentially coinciding with the diagonal. In conclusion, for elderly HCC patients, COPD, age ≥ 75 years, PNI-low, and tumor presence of satellite nodules, capsule, and microvascular invasion were independent prognostic factors. The nomogram could accurately predict the prognosis of these patients.

Keywords prognostic nutritional index, hepatocellular carcinoma, Recurrence-free survival, overall survival

1. Introduction

As the world's population ages, older hepatocellular carcinoma (HCC) patients will become a growing group (*1-4*). Current studies found surgery resection is still the first choice for elderly patients with HCC. Although current staging systems have identified important prognostic factors in HCC patients, most are based on radiological findings and do not sufficiently consider the basic demographic characteristics of the HCC patients, including age or comorbidities. These ignored factors may significantly influence HCC patients' long-term prognosis, especially in the elderly (*5-7*). As they usually tend to have more severe liver cirrhosis and higher co-morbidities rates such as hypertension (HBP), diabetes mellitus (DB), and chronic obstructive pulmonary disease (COPD), in comparison to younger HCC patients (*8-16*). Thus, the current clinical management and prognostic model for elderly HCC patients may be more complicated and different.

Nutrition and immune biomarkers have shown promising prognostic value for HCC patients. These factors may be of particular concern in elderly HCC patients, given that malnutrition and weakened immunity are more common in the elderly population. The prognostic nutritional index (PNI) based on patients' total lymphocyte count and serum albumin concentration integrates immune and nutrition indicators and has shown great research value (*9-12*). Pinato *et al*. (*13*) and Wang *et al*. (*14*) reported a low PNI was an independent predictor of poor survival in patients with HCC. Unfortunately, not all patients underwent surgical resection in the study by Pinato *et al*. (*13*). In the study by Wang *et al*. (*14*), the mean age of patients included in the study was only 50.41 years. Thus, the prognostic value of PNI in the elderly HCC population after surgical

resection is not well established.

Therefore, in this study, we aimed to determine the value of the preoperative prognostic nutritional index (PNI) and establish nomograms to help predict recurrence-free and overall survival (RFS and OS) for elderly patients (≥ 65 years) with early-stage (China Liver Cancer Staging System, CNLC: I-IIA) after curative resection (R0).

2. Patients and Methods

2.1. Patients

Consecutive HCC patients treated with curative surgical resection from 1st January 2010 to 2022 were retrospectively identified from the databases of West China Hospital, Sichuan University. All included patients were histologically confirmed HCC and obtained negative resection margins. We selected 65 years old at diagnosis as the cut-off value for elderly HCC patients (≥ 65 years old) (*5*). Pretreatment demographics and clinical laboratory data were retrieved through electronic medical records review. Patients excluded from the present study fit the following criteria: *i)* with cancers metastasis to the liver such as colorectal carcinoma liver metastasis or with other types of liver cancer including mixed hepatocellular-cholangiocarcinoma and intrahepatic cholangiocarcinoma; *ii)* diagnosed below 65 years (< 65y), with advanced stages of HCC (CNLC ≥ IIB) or after non-R0 resection (n =338); *iii)* with missing or uncomprehensive demographics, pathological, or survival data were also excluded from the study (n = 15). Finally, the cohort comprised 282 elderly patients (≥ 65y) with early-stage HCC (CNLC I-IIA) after R0 resection for further analysis.

The detailed CNLC criteria are presented in supplementary material Figure S1 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=169*). This study was approved by the institutional review committee of West China Hospital, Sichuan University. Since our analysis was retrospective, the need for informed consent was waived by our ethics committee.

2.2. Data Collection

Medical records were reviewed for smoking, alcohol history, body mass index (BMI, kg/m^2), comorbidity (DB, HBP, and COPD), HBV, and HCV infection history. Other clinicopathological factors were also collected: Sex, age at diagnosis, tumor size, number, differentiation grade (poor, moderate, or high differentiation), microvascular invasion (MVI), tumor satellite formation, tumor capsule invasion, liver fibrosis stage (ISHAK) and perioperative outcomes (operative blood loss, operative time, postoperative complication rate, ICU admission, and hospital stay). There are various staging systems for HCC, such as the Barcelona Clinic Liver Cancer (BCLC) system, the Japan Society of Hepatology (JSH) consensus statements and recommendations, and the Asian Pacific Association for the Study of the Liver (APASL). The China Liver Cancer Staging System (CNLC), which is the most used staging system for HCC patients in China, was adopted in our study. All patients were treated according to CNLC staging and after comprehensive multidisciplinary consultation.

Postoperative follow-up included physical examination, laboratory tests, and abdominal CT or MRI to assess the surgical effect and check for recurrence every 3 months in the first 2 years and every 6 months in the subsequent years. Telephone surveys were employed for patients who could not attend follow-up appointments.

2.3. Definitions

All patients' follow-up duration was defined from the diagnosis to the last examination date or lost follow-up. RFS was the duration between curative surgical resection and the first recurrence or death from any other cause. OS was defined as being from the time of surgery to the date of death or most recent follow-up. Obstructive jaundice was defined as serum total bilirubin (TB) concentration above 34.1 umol/L (TB ≥ 34.1 umol/L). The liver fibrosis diagnosis is based on an invasive pathological biopsy approach. The ISHAK classification (ISHAK0–6) was used to classify the severity of liver fibrosis. We classify fibrosis according to scores defined by the American Joint Committee on Cancer (AJCC), the Ishak score ranging from 0 to 4 (undetectable to moderate fibrosis), defined as "F0", and 5 to 6 (severe fibrosis or cirrhosis), defined as "F1". The Clavien–Dindo classification system was used to categorize all postoperative complications. Pre-operative baseline alpha-fetoprotein (AFP) was confirmed as continuous and dichotomous. Patients were grouped into AFP ≥ 400 ng/mL *vs.* < 400 ng/mL. Cancer antigen 19-9 (CA 19-9; also known as carbohydrate antigen 19-9) is used to help differentiate between cancer of the pancreas and other conditions, as well as to monitor treatment response and recurrence. The normal range of CA 19-9 is between 0 and 37 U/mL (units/milliliter). In our study, patients were grouped into CA 19-9 ≥ 37.0 U/mL *vs.* <37.0 U/mL. Infection with hepatitis B and C virus (HBV and HCV) was diagnosed according to blood test outcomes, liver biopsy, or medical records. Clavien-Dindo classification is used for postoperative complication evaluation. Anatomical resection (AR) was defined as the complete removal of a hepatic segment/section. Histopathologic findings of resected HCC specimens included the presence of a capsule and tumor invasion onto the capsule and the presence of microvascular emboli in the surrounding liver parenchyma, these factors were defined as tumor invasion onto the capsule and MVI.

2.4. Statistical analysis

Data on the tumor parameters and patients' demographics are expressed as mean (SD) values for parametric continuous data and as median (range) values for data with the nonparametric distribution. Categorical data are expressed as percentage frequencies (N, %). The distribution of variables was analyzed using the Kolmogorov– Smirnov test. Chi-square, Mann–Whitney *U* test or Fisher's exact tests were used to make comparisons between groups as appropriate. Serum albumin and lymphocyte counts were measured and calculated before surgery and were used to calculate the pre-operative PNI. The index was calculated with the following formula: 10 × serum-albumin (g/dL) + 0.005 × total lymphocyte count in peripheral blood/mm^3. Patients were classified into 'PNI-low' and 'PNI-high' groups according to the optimal cut-point outcomes after maximally selected rank statistics for OS. The optimal cut point for PNI was determined using the maximally selected rank statistics from the 'maxstat' R package. This outcome-oriented method provides a value of a cut point that corresponds to the most significant relationship with the outcome. We also performed univariable, and multivariable Cox regression models to investigate variables associated with survival. The receiver operating characteristic (ROC) curve, area under the ROC curve (AUC), and Harrell's concordance index (C-index) were used to assess discrimination of the model, while the calibration plot was used to graphically evaluate the calibration of the nomogram in both training and validation cohorts.

All analyses were conducted using R software (version 3.6.3; R Foundation for Statistical Computing), and a two-tailed *p*-value < 0.05 was set for statistical significance.

3. Results

3.1. Baseline features of the study population

A total of 282 elderly HCC patients after R0 resection and met all inclusion criteria were included. The study flow diagram is shown in Figure 1. Among them, 197 (70%) and 85 (30%) patients were randomly segregated into the training and or test cohorts. The optimal PNI cutoff values were analyzed according to the survival data of the included HCC patients. The ideal cutoff value of preoperative PNI in our study was 49.05 (supplementary material Figure S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=169*), then we divided patients into the PNI-low (PNI ≤ 49.05) and PNI-high (PNI > 49.05) groups according to the canulated cutoff values. We also searched published studies and found comparable cut-off values of PNI in other types of cancers.

3.2. Prognostic value of PNI

Most of the clinicopathologic features of the patients in the PNI-low (n = 180) and PNI-high (n = 102) cohorts were comparable except for patients in the PNI-high group were younger (P = 0.002) and had higher BMI (P < 0.001), and leukocyte count (P < 0.001), meanwhile, shorter smoking years (P = 0.046) and less COPD rates (P = 0.003) were also noticed. While patients in the PNI-

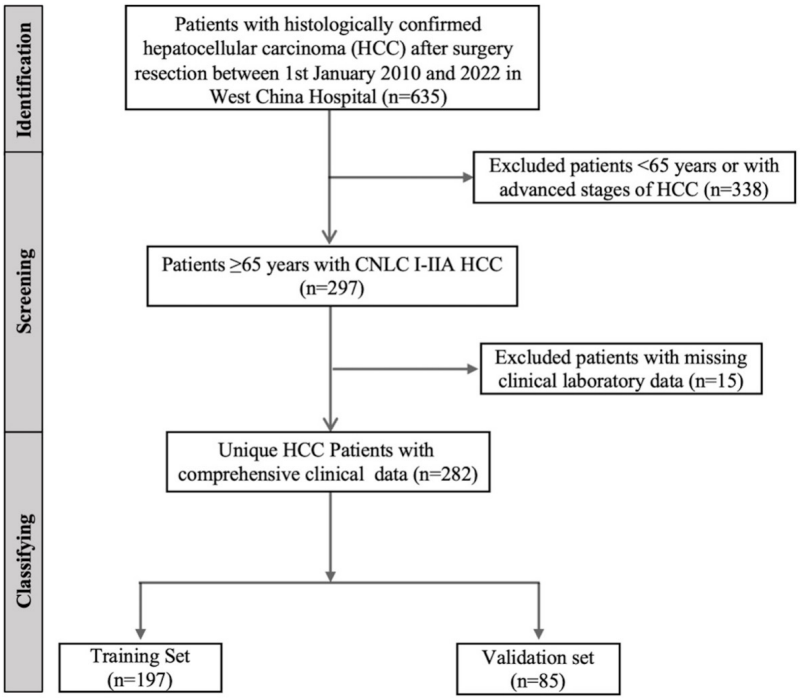

Figure 1. Flow chart of patient inclusion.

high group had higher Cancer Antigen 19-9 (CA19-9) levels compared to patients in the PNI-low group ($P = 0.019$). For patients in the PNI-low group, the prothrombin time (PT) was longer ($P < 0.01$), and the alanine aminotransferase and aspartate aminotransferase level (ALT and AST) was higher ($P = 0.005$ and $P = 0.018$, respectively) when compared with PNI-high group. Although, in the PNI-low group, more patients had a single tumor ($P < 0.001$), and the CNLC stages of HCC were earlier ($P < 0.001$), improved tumor histopathological features resulted in the PNI-high group. In the PNI-high group, tumor of high/well differentiation degree was more common ($P = 0.011$), while in the PNI-low group, more patients had satellite nodules ($P = 0.002$). When we compared the PNI-high and PNI-low groups according to their perioperative outcomes, we found that there was a higher rate of anatomical resection (AR) and hemi-hepatectomy ($P = 0.016$) for the PNI-high group, in addition, the hospital stay ($P =0.002$) was also longer for patients in the PNI-high group (Table 1).

In the Kaplan–Meier analysis, the 1-, 3- and 5-year OS and 1, 3 and 5-year RFS of the entire cohort were 99.6%, 94.1 %, 69.1 %, and 99.3%, 65.8%, 48.7%, respectively (Figure 2A-B). Patients in the PNI-low group had a significantly shorter OS ($P <0.0001$) and RFS ($P < 0.0001$) than the PNI-high group. The 1-, 3- and 5-year OS rate in the PNI-low (PNI ≤ 49.05) and PNI-high (PNI > 49.05) group groups was 99.4%, 91.7%, 48.9% versus 100%, 98.0% and 93.1%, respectively. The 1-, 3- and 5-year RFS rate in the PNI-low group (PNI ≤ 49.05) was 98.9%, 54.3%, 27.3% versus 100%, 83.3 %, and 75.7%, respectively in the PNI-high (PNI > 49.5) group (Figure 2C-D).

3.3. Independent Predictors of OS and RFS

The baseline characteristics of the two cohorts (training and/or test cohorts) are shown in Table 2. Most of the variables were found to be similar between the two cohorts at baseline. To further identify the clinically significant factors for OS and RFS, univariate and multivariate analysis was performed in the training cohort. A multivariate Cox proportional hazards model was entered for all factors with a p-value < 0.05 in the univariate analysis. The outcome is presented in Table 3.

The univariate Cox regression analysis showed that PNI-high was a significant prognostic factor associated with both longer OS (hazard ratio (HR) = 0.16, 95% confidence interval (CI), (0.06-0.44), $P < 0.01$) and RFS (HR = 0.22, 95%CI (0.12-0.41), $P < 0.001$) in elderly patients with HCC. In multivariate analysis, we found that age ≥ 75 years (HR = 2.46, 95%CI (1.16-5.24), $P = 0.02$), PNI-high (HR = 0.16, 95%CI (0.06-0.44), $P < 0.01$), COPD (HR = 2.83, 95%CI (1.39-5.75), $P = 0.004$), tumor of moderate /high differentiation (HR = 0. 38, 95% CI (0.17-0.86), $P = 0.02$), capsular invasion (HR=2.68, 95% CI (1.17-6.12), $P = 0.02$) and satellite nodules (HR = 4.52, 95% CI (1.95-10.45), $P < 0.01$) were independent prognostic markers for OS. Apart from PNI (HR = 0.22, 95% CI (0.12-0.41), $P < 0.001$), we also found that tumor differentiation (moderate/high vs low) (HR = 0.22, 95% CI (0.12-0.41), $P = 0.025$) or microvascular invasion (HR = 0.22, 95% CI (0.12-0.41), $P < 0.001$) were independent prognostic factors for patients' postoperative RFS (Table 3).

3.4. Development and Validation of the prediction models

The nomogram prediction models for patients' OS (Figure 3A) and RFS (Figure 3B) were built by incorporating independent OS and RFS predictors, which included patients' age (≥ 75 years vs < 75 years), PNI (PNI-high *vs*. low), COPD diagnosis, tumor differentiation degree (moderate/high *vs*. low), presence of satellite nodules, tumor capsule invasion, and MVI. As we can see from the nomogram, PNI (PNI-high *vs*. low) had the greatest impact on OS, followed by MVI on RFS.

The C-index of OS in the training cohort and test cohort were 0.875 (95% CI: 0.842–0. 908) and 0.820 (95% CI: 0.714–0. 927), respectively, indicating that the model had good discriminatory power. The C-index of RFS in the training cohort and test cohort were 0.803 (95% CI: 0.765–0.842) and 0.800 (95% CI: 0.768–0.832), respectively, indicating that the model had good discriminatory ability. In the training cohort, the AUC of the predicted nomogram for OS and RFS was 0.851 and 0.877 (Figure 4A-B). In the test cohort, the AUC of the predicted nomogram for OS and RFS was 0.877 and 0.909 (Figure 4 C-D). The ROC curve and the AUC of the PNI of OS and RFS are additionally presented in Figure S3 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=169*). The calibration plots for training and test cohorts used to predict 3-year, 5-year OS, and 3-year, 5-year RFS showed good agreement between the actual observations and the model predictions (Figure 5A-H).

4. Discussion

We found significant differences in postoperative recurrence and long-term survival between patients in the PNI-low and PNI-high groups. More importantly, this difference persisted after univariate and multivariate analysis. Therefore, we found that the PNI has a role in predicting the prognosis of elderly HCC patients after surgical resection. In our analysis, we also found that the patient's age, diagnosis of COPD, whether the tumor infiltrated blood vessels, had satellite nodules, and whether it was a poorly differentiated type of tumor also had a significant impact on patient prognosis. Based on these results, we created a nomogram chart that can predict a patient's three-year and five-year survival prognosis. These nomograms are easy to calculate and

Table 1. Patients' demographics grouped by the cutoff value for PNI

Variable	PNI low (≤ 49.05) (*n* = 180)	PNI high (> 49.05) (*n* = 102)	*P* Value
AGE, years, (Median (IQR)	70.00 (67.00 to 75.00)	69.00 (67.00 to 71.00)	0.002
AGE group, *n* (%)			
< 75 years	130 (72.2%)	91 (89.2%)	0.001
≥ 75years	50 (27.8%)	11 (10.8%)	
SEX, *n* (%)			
Female	21 (11.7%)	18 (17.6%)	0.223
Male	159 (88.3%)	84 (82.4%)	
BMI, kg/m^2, median (IQR)	22.20 (20.31 to 24.67)	24.26 (21.67 to 25.95)	< 0.001
BMI group, *n* (%)			
< 18.5 (underweight)	9 (5%)	0 (0%)	< 0.001
≥ 18.5 ≤ 23.9 (normal)	114 (63.3%)	48 (47.1%)	
≥ 24 ≤ 27.9 (overweight)	45 (25%)	39 (38.2%)	
≥ 28 (obesity)	12 (6.7%)	15 (14.7%)	
Comorbidity, *n* (%)			
DB	75 (41.7%)	42 (41.2%)	1.000
HBP	90 (50%)	45 (44.1%)	0.409
COPD	57 (31.7%)	15 (14.7%)	0.003
Cardiovascular disease	63 (35%)	42 (41.2%)	0.367
Smoking and drinking history, *n* (%)			
Smoking ≥ 20 years	87 (48.3%)	36 (35.3%)	0.046
Drinking ≥ 20 years	45 (25%)	27 (26.5%)	0.897
Abdornimal surgery history, *n* (%)	18 (10%)	6 (5.9%)	0.333
HBV infection history, *n* (%)			
Presence	174 (96.7%)	99 (97.1%)	1.000
HCV infection history			
Presence	3 (1.7%)	0 (0%)	0.480
Ishak group, *n* (%)			
F0	63 (35%)	42 (41.2%)	0.367
F1	117 (65%)	60 (58.8%)	
PS score, *n* (%)			
0	33 (18.3%)	24 (23.5%)	0.195
1	81 (45%)	51 (50%)	
2	66 (36.7%)	27 (26.5%)	
Laboratory tests			
PLT,$10*^9$/L, Median (IQR)	112.50 (83.50 to 160.00)	128.00 (93.00 to 169.00)	0.283
WBC, $10*^9$/L, Median (IQR)	4.70 (3.92 to 5.94)	5.27 (4.81 to 6.40)	< 0.001
TB, umol/L, Median (IQR)	13.20 (10.35 to 17.15)	14.10 (10.30 to 18.00)	0.785
ALT, U/L, Median (IQR)	40.50 (26.00 to 59.00)	28.50 (24.00 to 48.00)	0.005
AST, U/L, Median (IQR)	47.00 (29.50 to 60.50)	36.50 (31.00 to 48.00)	0.018
ALP, U/L, Median (IQR)	99.50 (74.50 to 133.00)	99.50 (75.00 to 117.00)	0.662
PT, Seconds, Median (IQR)	12.00 (11.40 to 12.75)	11.30 (10.90 to 11.90)	< 0.001
AFP, ng/mL, Median (IQR)	22.72 (3.40 to 312.80)	12.21 (4.82 to 180.20)	0.601
AFP ≥ 400 ng/mL	51 (28.3%)	30 (29.4%)	0.956
CA19-9 (median [IQR])	21.52 (9.86 to 40.32)	26.74 (16.30 to 60.32)	0.019
CA19-9 ≥ 37.0 U/mL	45 (25%)	33 (32.4%)	0.235
CNLC stage, *n* (%)			
IA	84 (46.7%)	33 (32.4%)	< 0.001
IB	93 (51.7%)	48 (47.1%)	
IIA	3 (1.7%)	21 (20.6%)	
Differentiation, *n* (%)			
H	27 (15%)	24 (23.5%)	0.011
L	60 (33.3%)	18 (17.6%)	
M	93 (51.7%)	60 (58.8%)	
Tumor size (median [IQR])	5.00 (3.50 to 7.75)	5.25 (3.50 to 7.00)	0.259
Tumor number, *n* (%)			
1	171 (95%)	72 (70.6%)	< 0.001
2	8 (4.4%)	19 (18.6%)	
3	1 (0.6%)	11 (10.8%)	
Microvascular invasion, *n* (%)			
Presence	75 (41.7%)	36 (35.3%)	0.355
Tumor Invasion onto The Capsule, *n* (%)			
Presence	90 (50%)	51 (50%)	1.000

HBP: Hypertension, DB: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, PNI: Prognostic Nutritional Index, MVI: Microvascular Invasion, BMI: Body Mass Index, CNLC: China Liver Cancer Staging System, TB: Total Bilirubin, Cancer Antigen 19-9, AFP: Alpha-Fetoprotein, HBV And HCV: Hepatitis B And C Virus, CV: Clavien-Dindo Classification, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, AR: Anatomical Resection, PLT: Blood Platelet Count, WBC: White Blood Cell, N:No, Y: Yes, MVI: Microvascular Invasion.

Table 1. Patients' demographics grouped by the cutoff value for PNI (continued)

Variable	PNI low (≤ 49.05) (*n* = 180)	PNI high (> 49.05) (*n* = 102)	*P* Value
Satellite Nodules, *n* (%)			
Presence	45 (25%)	9 (8.8%)	0.002
Operation time, min, (median [IQR])	185.00 (145.00 to 240.00)	220.00 (135.00 to 260.00)	0.192
Hepatectomy Methods, *n* (%)			
Non-AR	81 (45%)	51 (50%)	0.016
Right hemi-hepatectomy	18 (10%)	9 (8.8%)	
Left hemi-hepatectomy	24 (13.3%)	3 (2.9%)	
AR	57 (31.7%)	39 (38.3%)	
Blood loss (ml) (median [IQR])	200.00 (200.00 to 400.00)	200.00 (150.00 to 400.00)	0.330
Post operative complication, *n* (%)			
Clavien–Dindo classification I	30 (1.7%)	24 (23.5%)	0.211
Clavien–Dindo classification II	150 (83.3%)	78 (76.5%)	
Hospital stays, day (median [IQR])	12.00 (10.00 to 15.00)	13.00 (12.00 to 15.00)	0.002

HBP: Hypertension, DB: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, PNI: Prognostic Nutritional Index, MVI: Microvascular Invasion, BMI: Body Mass Index, CNLC: China Liver Cancer Staging System, TB: Total Bilirubin, Cancer Antigen 19-9, AFP: Alpha-Fetoprotein, HBV And HCV: Hepatitis B And C Virus, CV: Clavien-Dindo Classification, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, AR: Anatomical Resection, PLT: Blood Platelet Count, WBC: White Blood Cell, N:No, Y: Yes, MVI: Microvascular Invasion.

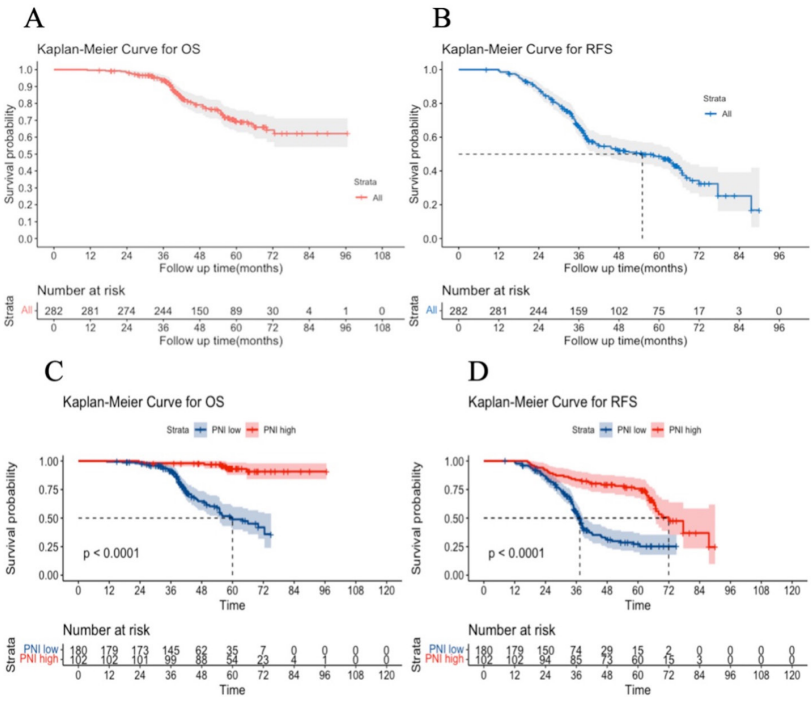

Figure 2. Kaplan-Meier curves of overall survival (OS) and recurrence-free survival (RFS) for different cohorts. (**A**) Kaplan-Meier curves of OS for the entire cohort; (**B**) Kaplan-Meier curves of RFS for the entire cohort; (**C**) Kaplan-Meier curves of OS for patients with high and low prognostic nutrition index (PNI) (log-rank test, $P < 0.001$); and (**D**) Kaplan-Meier curves of RFS for patients with high and low PNI (log-rank test, $P < 0.001$).

have a good calibration and discrimination value.

As life expectancy increases worldwide, the proportion of elderly patients with HCC in need of oncological treatment is likely to increase (*5,6,17-19*). However, even today there is no clinical guideline for this population. Thus, clinical management investigation for elderly HCC patients is important. In our study, we introduced an easily accessible clinical variable, the PNI, which is calculated using the formula: [10 × serum albumin level (gr/dL)] + [0.005 × total lymphocyte count (per mm^3)] by peripheral blood to devalue nutrition and inflammation status.

Nutrition and inflammation status are parts of tumor microcirculation and affect tumor prognosis (*20-22*). This relation in elderly HCC patients has not been explored yet. The PNI measured by laboratory tests is a valuable and convenient tool to evaluate the patient's inflammation and nutritional status. Interestingly, many studies did report that PNI has great clinical significance in evaluating the prognosis of many solid neoplasms (*9,23,24*). It is well known that HCC arises because of hepatocellular carcinoma exposure to proinflammatory

Table 2. Baseline Characteristics of Patients in The Developing and Validation Cohorts

Variable Name	Validation Cohort (*n* = 85)	Development Cohort (*n* = 197)	*P* Value
AGE, Median (IQR)	70.00 (67.00 To 73.00)	69.00 (67.00 To 73.00)	0.414
SEX			
Female	15 (17.6%)	24 (12.2%)	0.302
Male	70 (82.4%)	173 (87.8%)	
PNI, Median (IQR)	48.50 (45.15 To 52.85)	47.85 (45.10 To 51.30)	0.360
PNI GROUP			
> 49.05 (High)	49 (57.6%)	131 (66.5%)	0.199
≤ 49.05 (Low)	36 (42.4%)	66 (33.5%)	
BMI, kg/m^2, Median (IQR)	22.67 (20.20 To 25.95)	22.67 (20.94 To 24.74)	0.500
BMI Group, Median (IQR)			
< 18.5 (Underweight)	3 (3.5%)	6 (3%)	0.069
≥ 18.5 ≤ 23.9(Healthy Weight)	43 (50.6%)	119 (60.4%)	
≥ 24 ≤ 27.9(Overweight)	25 (29.4%)	59 (29.9%)	
≥ 28(Obesity)	14 (16.5%)	13 (6.6%)	
DB Presence, Y	36 (42.4%)	81 (41.1%)	0.951
HBP Presence, Y	40 (47.1%)	95 (48.2%)	0.960
COPD Presence, Y	21 (24.7%)	51 (25.9%)	0.952
Cardiovascular disease	29 (34.1%)	76 (38.6%)	0.564
Abdornimal Surgery History,Y	9 (10.6%)	15 (7.6%)	0.556
HBV Infection History, Y	80 (94.1%)	193 (98%)	0.187
HCV Infection History, Y	0 (0%)	3 (1.5%)	0.609
Smoking History ≥ 20 Years, Y	42 (49.4%)	105 (53.3%)	0.638
Drinking History ≥ 20 Years, Y	32 (37.6%)	79 (40.1%)	0.799
ISHAK			
F0	29 (34.1%)	76 (38.6%)	0.564
F1	56 (65.9%)	121 (61.4%)	
Tumor Number			
1	73 (85.9%)	170 (86.3%)	0.969
2	8 (9.4%)	19 (9.6%)	
3	4 (4.7%)	8 (4.1%)	
Tumor Size, Median (IQR)	5.50 (4.00 To 8.00)	5.00 (3.20 To 7.50)	0.198
CNLC			
IA	32 (37.6%)	85 (43.1%)	0.684
IB	45 (52.9%)	96 (48.7%)	
IIA	8 (9.4%)	16 (8.1%)	
Differentiation Degree			
High	14 (16.5%)	37 (18.8%)	0.281
Moderate	42 (49.4%)	111 (56.3%)	
Poor	29 (34.1%)	49 (24.9%)	
Tumor Invasion onto The Capsule			
N	41 (48.2%)	100 (50.8%)	0.795
Y	44 (51.8%)	97 (49.2%)	
Satellite Nodules			
N	69 (81.2%)	159 (80.7%)	1.000
Y	16 (18.8%)	38 (19.3%)	
MVI			
N	50 (58.8%)	121 (61.4%)	0.782
Y	35 (41.2%)	76 (38.6%)	
Surgery Methods			
Non-AR	36 (42.3%)	96 (48.7%)	0.399
Right hemi-hepatectomy	7 (8.2%)	20 (10.2%)	
Left hemi-hepatectomy	9 (10.6%)	18 (9.1%)	
AR	33 (38.8%)	63(40.0%)	
Blood Loss,ml, Median (IQR)	200.00 (200.00 To 400.00)	200.00 (200.00 To 400.00)	0.394
Operation Time,min, Median (IQR)	200.00 (145.00 To 255.00)	195.00 (140.00 To 250.00)	0.814
CV			
I	17 (20%)	37 (18.8%)	0.941
II	68 (80%)	160 (81.2%)	
Hospital Stay,days, Median (IQR)	12.00 (11.00 To 15.00)	12.00 (11.00 To 15.00)	0.747
PLT,10*^{9}/L, Median (IQR)	109.00 (80.00 To 155.00)	119.00 (85.00 To 164.00)	0.428
WBC, 10*^{9}/L, Median (IQR)	5.41 (4.66 To 6.40)	4.91 (4.10 To 5.98)	0.002
TB, umol/L, Median (IQR)	14.60 (10.90 To 18.00)	13.30 (10.20 To 17.10)	0.141

HBP: Hypertension, DB: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, PNI: Prognostic Nutritional Index, MVI: Microvascular Invasion, BMI: Body Mass Index, CNLC: China Liver Cancer Staging System, TB: Total Bilirubin, Cancer Antigen 19-9, AFP: Alpha-Fetoprotein, HBV And HCV: Hepatitis B And C Virus, CV: Clavien-Dindo Classification, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, AR: Anatomical Resection, PLT: Blood Platelet Count, WBC: White Blood Cell, N: No, Y: Yes, MVI: Microvascular Invasion.

Table 2. Baseline Characteristics of Patients in The Developing and Validation Cohorts (continued)

Variable Name	Validation Cohort (*n* = 85)	Development Cohort (*n* = 197)	*P* Value
ALT, U/L, Median (IQR)	36.00 (26.00 To 55.00)	36.00 (24.00 To 56.00)	0.866
AST, U/L, Median (IQR)	39.00 (31.00 To 53.00)	38.00 (29.00 To 53.00)	0.875
ALP, U/L, Median (IQR)	101.00 (75.00 To 128.00)	99.00 (75.00 To 128.00)	0.926
PT, Seconds, Median (IQR)	11.80 (11.20 To 12.60)	11.80 (11.10 To 12.50)	0.431
AFP, ng/ml, Median (IQR)	42.63 (5.02 To 294.50)	12.50 (3.38 To 301.85)	0.183
AFP ≥ 400 ng/mL	27 (31.8%)	54 (27.4%)	0.550
CA19-9, U/mL, Median (IQR)	26.49 (16.02 To 38.06)	21.88 (11.24 To 48.31)	0.390
CA19-9 ≥ 37.0 U/mL	21 (24.7%)	57 (28.9%)	0.560

HBP: Hypertension, DB: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, PNI: Prognostic Nutritional Index, MVI: Microvascular Invasion, BMI: Body Mass Index, CNLC: China Liver Cancer Staging System, TB: Total Bilirubin, Cancer Antigen 19-9, AFP: Alpha-Fetoprotein, HBV And HCV: Hepatitis B And C Virus, CV: Clavien-Dindo Classification, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, AR: Anatomical Resection, PLT: Blood Platelet Count, WBC: White Blood Cell, N: No, Y: Yes, MVI: Microvascular Invasion.

stimuli, such as hepatotropic virus infection, or ethanol consumption (*2*). Patients with hepatitis have impaired liver function, which then leads to a deterioration in their nutritional status. Thus, the PNI may also be associated with HCC patients' survival. Pinato (*13*) *et al*. and Wang (*14*) *et al*. reported that PNI-low is an independent predictor of poor prognosis for HCC patients. However, in their study, elderly HCC patients were not separately considered. Previous studies have identified age might not be a precise risk factor for mortality or morbidity (*8*), but it is a surrogate marker for comorbidities, in other words, older patients are more likely to have comorbid conditions than younger patients. Since elderly HCC patients more commonly had comorbidities, many researchers such as Rocio I.R. Macias (*15*) *et al*. noticed that elderly HCC patients were more likely to present with chronic inflammatory conditions and nutrition impairment status. Thus, the value of PNI for elderly HCC patients may not be comparable to the younger populations.

Based on the published literature for other tumors, the predictive value of the PNI in older patients may be more representative than in other age groups. In the study by Yan (*25*) *et al.*, the authors found that compared with other variables such as liver invasion and central nervous system invasion, PNI was a stronger predictor of prognosis in elderly patients with diffuse large B-cell lymphoma. Zhang *et al*. (*26*) studied 454 patients with a diagnosis of gastric cancer who were over 60 years of age. A more sensitive prognostic value of PNI was observed in the subgroup aged ≥ 75 years compared to those aged 60 -74 years. Zhu *et al*. (*27*) evaluated the stratified effect of age on gastric cancer and demonstrated the association of low PNI with short disease-free survival and OS in older patients (≥ 65 years). Unfortunately, the predictive value of PNI in older HCC patients has not been reported in the literature. In fact, to our knowledge, a limited number of studies have focused on the effect of age on the prognostic role of PNI. Our study is the first to report the predicted value of PNI for elderly HCC patients. Based on our results, the relationship between nutritional status and prognosis of elderly HCC patients could be accurately interpreted, and precise stratification of patients in the low-risk and high-risk groups could be achieved.

Although elderly HCC patients constitute over one-third of all HCC patients, they were not adequately represented in prognostic and treatment studies. Currently, there is no consensus in the literature as to which system is the most reliable to predict the prognosis for HCC especially in elderly HCC patients. Thus, there is also not enough clinical evidence to guide the treatment for these patients. Unlike other malignancies, the survival of HCC patients is significantly influenced by both primary tumor stages and underlying liver function. These factors may be more important for elderly HCC patients (*28-31*). Considering the specificity of elderly HCC patients when compared with the younger population, such as the higher rates of comorbidities and more severe liver cirrhosis. It was impossible to accurately evaluate the prognosis of elderly patients with HCC by constructing a full age spectrum prognosis model of patients with HCC. However, most studies have failed to distinguish this specific group, making it even more rare to have prognostic models for older people with HCC. Published medical literature supported that advanced tumor stages, tumor presence of vascular invasion, and poorer differentiation were risk factors for a poorer prognosis of HCC (*17,19,29*). We hypothesize the prognostic model for elderly HCC patients should also include the above variables. However, considering the specificity of the elderly population, other indicators should also be considered together. Thus, a prognostic model combining PNI, and other indicators was therefore developed. Based on univariate and multivariate Cox analyses, we identified other independent risk factors besides PNI that affect the prognosis of elderly HCC patients. These included patient age, diagnosis of COPD, tumor microvascular invasion, capsule invasion, low differentiation, and satellite nodules. Most of our independent factors were in line with previous studies. The parameters of the nomogram model constructed in this study include PNI, patient age, diagnosis of COPD, whether the tumor infiltrated blood vessels or invaded the capsule, whether it had satellite nodules, and whether it was a poorly differentiated type of

Table 3. Univariate and Multivariate Cox Proportional Hazards Regression Analyses of Prognostic Factors for OS and RFS in the Training Cohorts.

Variable Names	Univariate Analyses of OS		Multivariate Analyses of OS		Univariate Analyses of RFS		Multivariate Analyses of RFS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, years	1.08 (1.03-1.15)	0.005			1.02 (0.98-1.06)	0.438		
Age (≥ 75 years *vs.* 75 Years)	2.61 (1.42-4.81)	0.002	2.46 (1.16-5.24)	0.02	1.37 (0.86-2.18)	0.185		
SEX (Male *vs.* Female)	1.3 (0.55-3.03)	0.550			2.92 (1.34-6.38)	0.007	2.14 (0.92-4.99)	0.078
PNI (High *vs.* Low)	0.1 (0.04-0.24)	< 0.001	0.16 (0.06-0.44)	< 0.01	0.24 (0.14-0.39)	< 0.001	0.22 (0.12-0.41)	< 0.001
BMI (Healthy Weight *vs*. Underweight)	0.43 (0.1-1.8)	0.246	0.49 (0.1-2.37)	0.372	0.77 (0.24-2.47)	0.662		
BMI (Overweight *vs.* Underweight)	0.21 (0.05-0.96)	0.045	0.31 (0.05-1.82)	0.196	0.79 (0.24-2.6)	0.704		
BMI (Obesity *vs*. Underweight)	0.17 (0.02-1.22)	0.077	0.19 (0.02-1.63)	0.129	0.88 (0.23-3.4)	0.848		
DB (N *vs.* Y)	0.7 (0.4-1.23)	0.213			0.61 (0.4-0.93)	0.02	0.22 (0.12-0.41)	0.169
HBP (N *vs.* Y)	0.89 (0.52-1.53)	0.678			0.81 (0.55-1.19)	0.285		
COPD (N *vs.* Y)	2.53 (1.44-4.45)	0.001	2.83 (1.39-5.75)	0.004	1.74 (1.14-2.66)	0.011	0.22 (0.12-0.41)	0.639
CNLC (IIA vs IA *vs.* IB)	1.12 (0.5-2.54)	0.777			1.04 (0.59-1.83)	0.902		
Differentiation Degree (M/H *vs.* L)	0.19 (0.11-0.33)	< 0.001	0.38 (0.17-0.86)	0.02	0.23 (0.15-0.35)	< 0.001	0.22 (0.12-0.41)	0.025
Tumor Number (Single *vs.* Multiple)	1.49 (0.64-3.48)	0.359			1.81 (0.97-3.39)	0.064		
Tumor Invasion onto The Capsule (Y *vs.* N)	3.41 (1.79-6.48)	< 0.001	2.68 (1.17-6.12)	0.02	1.8 (1.21-2.68)	0.003	1.26 (0.77-2.08)	0.361
Satellite Nodules (Y *vs.* N)	8.53 (4.85-15)	< 0.001	4.52 (1.95-10.45)	< 0.01	2.83 (1.82-4.39)	< 0.001	1.28 (0.78-2.1)	0.33
MVI (Y *vs.* N)	2.67 (1.56-4.58)	< 0.001	1.12 (0.49-2.53)	0.789	6.25 (4.07-9.61)	< 0.001	0.22 (0.12-0.41)	< 0.001
Surgery (Non-AR *vs.* AR vs hemi-hepatectomy)	1.51 (0.82-2.77)	0.188			1.92 (1.24-2.97)	0.004	0.22 (0.12-0.41)	0.433
Surgery (hemi-hepatectomy *vs.* non-hemi-hepatectomy)	1.02 (0.91-1.14)	0.707			1 (0.92-1.08)	0.96		
HBV Infection History (Y *vs.* N)	0.32 (0.08-1.34)	0.120			0.54 (0.17-1.7)	0.289		
AFP (≥ 400 ng/mL *vs.* < 400 ng/mL)	1.33 (0.75-2.34)	0.330			1.36 (0.89-2.06)	0.155		
CA19-9 (≥ 37.0 U/mL *vs.* < 37.0 U/mL)	0.85 (0.47-1.55)	0.606			0.74 (0.47-1.15)	0.184		

HBP: hypertension, DB: diabetes mellitus, PNI: prognostic nutritional index, MVI: microvascular invasion, BMI: body mass index, CNLC: China Liver Cancer Staging System, AR: anatomical resection, HBV and HCV: hepatitis B virus infection history: no, Y: yes;COPD:Chronic Obstructive Pulmonary Disease, AFP: Alpha-Fetoprotein.

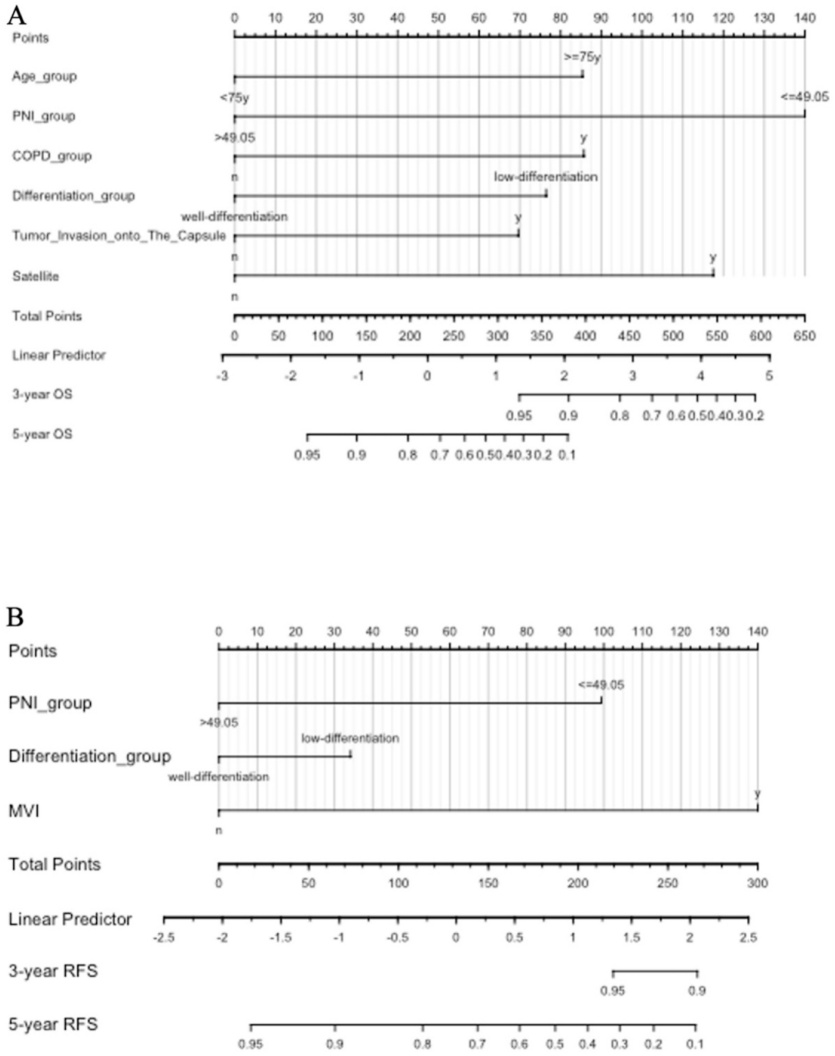

Figure 3. Nomograms to calculate the expected patients' (A) overall survival (OS) and (B) recurrence-free survival (RFS).

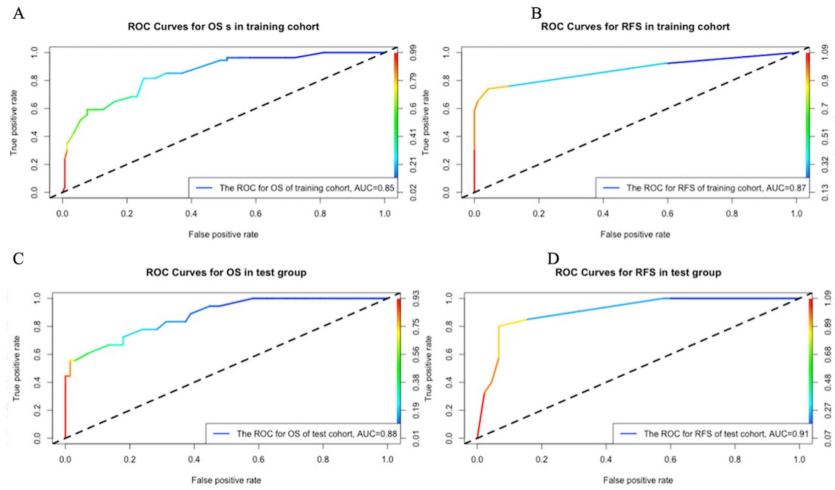

Figure 4. Receiver-operating characteristic (ROC) curve and the corresponding area (AUC) of the predictive models of overall survival (OS) and recurrence-free survival (RFS) for different cohorts. (A) ROC curve of OS and **(B)** RFS in the training cohort. **(C)** ROC curve of OS and **(D)** RFS in the test cohort.

tumor. These can be easily collected in clinical practice. We validated the accuracy and predictive ability of the nomograms for older HCC patients using the calibration curve. In summary, the nomogram was found to be able to accurately predict the OS and RFS of elderly HCC patients at 3 and 5 years. It has good potential for clinical application.

Our study had some limitations. First, this was a retrospective analysis performed in a single medical center. The sample size was not large. External validation could not be performed. There was also a selection bias in the patient population. Second, we could not evaluate the supportive nutritional care methods or the dynamic nutritional status of patients after surgical resection during the postoperative treatment period. This was due to missing data in most of the patient files. Third,

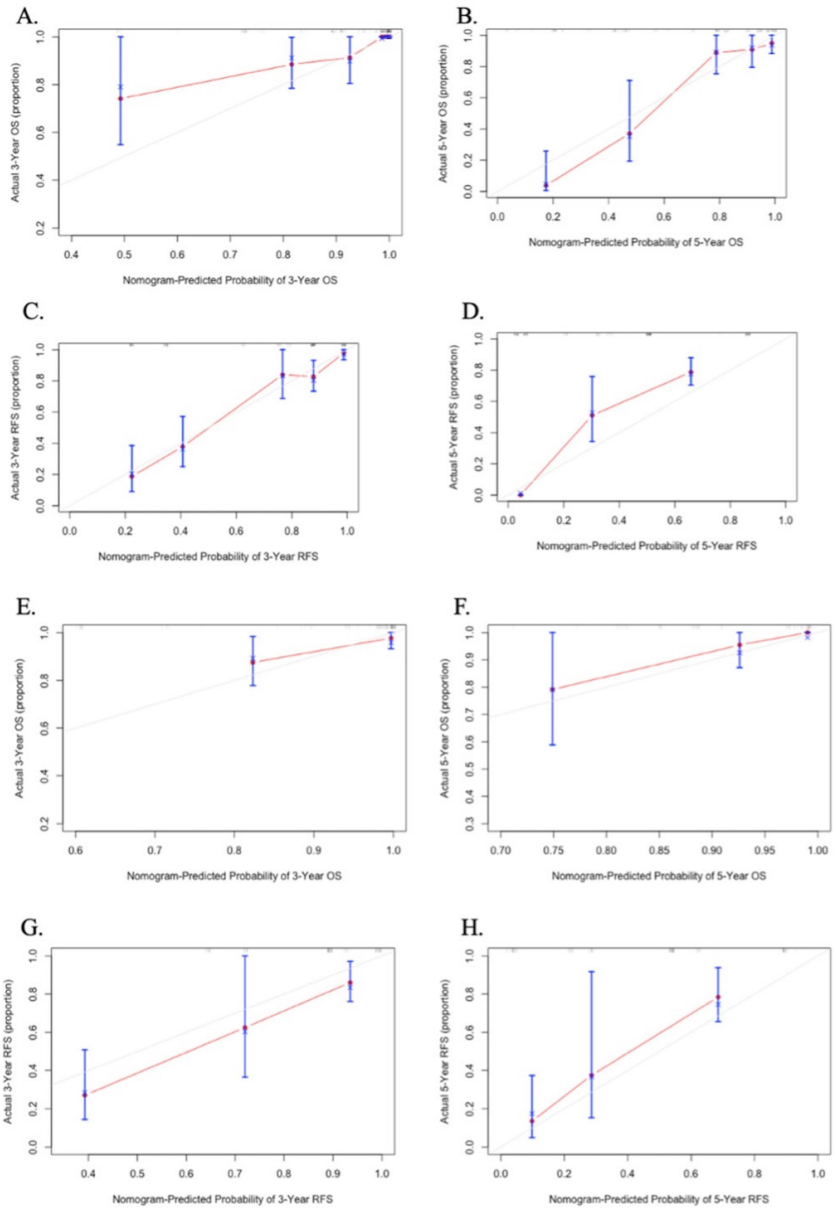

Figure 5. Calibration plots of the models for predicting **(A)** 3-year overall survival (OS) **(B)** 5-year OS. **(C)** 3-year recurrence-free survival (RFS) and **(D)** 5-year RFS for patients in the developing cohort **(E)** 3-year OS **(F)** 5-year OS **(G)** 3-year RFS and **(H)** 5-year RFS in the validation cohort, respectively.

the optimal PNI cut-off values are different in different studies due to different sample sizes and patient inclusion criteria, resulting in a bias in the values. Therefore, to validate the prognostic impact of PNI and its dynamics in elderly HCC patients after surgery, a further large-scale multicenter prospective study is needed.

In conclusion, the results of the present study suggest that the presence of systemic inflammatory response and nutritional status, as measured by PNI, is a useful tool for assessing prognosis in elderly HCC patients following surgery. Two nomogram models with high predictive value were developed after performing univariate and multivariate Cox screening, which could provide a reference for future evaluation of elderly patients with primary HCC. In view of the limited sample size, multicenter, large-sample clinical studies are necessary to investigate the accurate value of our preoperative PNI in the prediction of prognosis for elderly HCC patients after resection.

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