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ORIGINAL RESEARCH

Naples Prognostic Score is an Independent Prognostic Factor in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma

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Background: Nutritional and inflammatory status has been reported to be associated with the prognosis of hepatocellular carcinoma (HCC), but many studies did not include all biomarkers simultaneously. The present study aimed to determine the impact of Naples prognostic score (NPS) on the long-term survival in patients undergoing hepatectomy for HCC.

Methods: Patients with HCC after curative resection were eligible. Then, all patients were stratified into three groups according to the NPS. Clinical features and survival outcomes were compared among the three groups. Independent prognostic factors were determined by COX analysis. The time dependent receiver operating characteristic (ROC) curves were used to compare prognostic performance with other immunonutrition scoring systems.

Results: A total of 476 patients were enrolled eventually. Baseline characteristics showed that patients with higher NPS had a higher proportion of poor liver function and advanced tumor features. Accordingly, Kaplan-Meier survival curves showed that patients with higher NPS had a lower rate of overall survival (OS) and recurrence-free survival (RFS). Multivariable COX analysis demonstrated that NPS was an independent risk factor of OS (NPS group 2 vs 1: HR=1.958, 95% CI: 1.038–3.369, p = 0.038; NPS group 3 vs 1: HR=2.608, 95% CI: 1.358–5.008, p=0.004, respectively) and RFS (NPS group 2 vs 1: HR=2.014, 95% CI: 1.299-2-3.124, p=0.002; NPS group 3 vs 1: HR=2.002, 95% CI: 1.262–3.175, p=0.003, respectively). The time-dependent ROC curve showed that NPS was superior to other models in prognostic performance and discriminatory power for long-term survival (median AUC 0.675, 95% CI: 0.586–0.712, P < 0.05).

Conclusion: The NPS is a simple tool strongly associated with long-term survival in patients undergoing curative hepatectomy for HCC.

Keywords: hepatocellular carcinoma, Naples prognostic score, nutritional indicator, inflammatory indicator, prognostic performance

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death globally, and its rate of incidence is still increasing.[1] Hepatectomy is the most commonly chosen radical treatment for patients with removable HCC. However, long-term survival remains far from satisfactory. Postoperative recurrence occurs in almost 70% of the patient,[2] with a 5-year survival rate of merely 19.6%.[3] Despite the identification of some clinicopathological associated risk factors that are significantly associated with HCC prognosis, their predictive value does not produce the expected results for a variety of reasons.

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Inflammatory and nutritional indicators have gained attention in recent years as prognostic correlates for predicting prognosis in a variety of cancers, especially in HCC.[4,5] Previous studies indicate that HCC is an inflammation-related malignant tumor, and inflammation is involved in the occurrence and development of HCC.[5,6] Meanwhile, the liver is an important organ involved in nutrient metabolism and protein production. For patients with HCC, nutritional metabolism is often affected by cirrhosis, as well as the huge requirements of the tumor itself, which often leads to nutritional deficiency in patients. Previous studies have shown that the nutritional status of patients can be reflected through the assessment of fat and muscle components, such as triceps skinfold thickness measurement,[7] and it is related to the prognosis of HCC.[8,9] However, this method has high requirements for clinicians, and the assessment is relatively subjective, so it cannot be unified in the clinic.

A series of nutrition-related or inflammation-related indicators based on serological tests, such as the controlled nutritional status score (CONUT),[10,11] prognostic nutritional index (PNI),[12] systemic inflammation score (SIS),[13] neutrophil-lymphocyte ratio (NLR),[14–16] platelet-lymphocyte ratio (PLR),[17] and lymphocyte-monocyte ratio (LMR)[14–16] were reported to be correlated with the prognosis of patients with HCC. These aforementioned indicators of inflammation and/or nutrition are, however, to some extent inadequate and the results remain controversial. Thus, there is an urgent need for a comprehensive prognostic model that integrates indicators related to inflammation and nutrition.

The Naples Prognostic Score (NPS), a new prognostic index combining inflammatory with nutritional biomarkers, has been proposed by Galizia et al, including serum albumin, total cholesterol levels, the NLR, and the LMR.[18] These scores have been widely used to study a variety of gastrointestinal and other malignancies.[19–21] However, the relevance of NPS to the prognosis of patients with HCC after hepatectomy remains uncertain. Therefore, the present study aimed to evaluate the prognostic significance of preoperative NPS on the long-term survival in patients with HCC.

Patients and Methods

Patients

Patients with HCC after curative hepatectomy (R0) were reviewed between January 2013 and October 2018 at Zhejiang Provincial People's Hospital. Patients with HCC were confirmed by the pathological diagnosis of postoperative specimens. R0 resection was defined as the sub-endoscopic margin being negative. Exclusion criteria were as follows: (1) other concurrent malignancies; (2) preoperative antitumor therapy, (3) inflammatory diseases or other infection (including glomerulonephritis, arthritis, nervous system infection, pneumonia, acute pancreatitis or cholecystitis, etc.) one month before surgery, (4) received preoperative anti-infection or nutrition. Institutional review board at Zhejiang Provincial People's Hospital approved this study and waived the requirement for patient informed consent because only deidentified data were used. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study complies with the Declaration of Helsinki.

NPS and Other Scoring Systems

The definition of NPS is the same as previously reported by Galizia et al[18] NPS score is the sum of the four metrics' scores. NPS = serum albumin (≥4 g/dL = 0, <4 g/dL = 1) + total cholesterol concentrations (≥180 mg/dL = 0, <180 mg/dL = 1) + NLR (<2.96 = 0, ≥2.96 = 1) and LMR (≥4.44 = 0, <4.44 = 1). All patients were subsequently stratified into 3 groups: Group 1 (NPS = 0); Group 2 (NPS = 1 or 2), and Group 3 (NPS = 3 or 4), respectively (Figure 1). SIS score = (serum albumin ≥ 4 g/dL and LMR ≥ 4.44 = 0, either serum albumin < 4 g/dL or LMR < 4.44 = 1, both serum albumin < 4 g/dL and LMR < 4.44 = 2).[22] CONUT score was calculated by serum albumin and total cholesterol level and the lymphocyte count, and the cut-off value was set at 2 scores as the previous study reported.[10] PNI score = 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count. And the cut-off value was set at 44 according to the time-dependent receiver operating characteristic (ROC) curves.

Followed-Up and Data Collection

After hepatectomy, patients were follow-up visited 2 months per time in the first 2 years, thereafter 3 to 6 months per time. Serum tumor markers (AFP) and abdominal ultrasound were evaluated at each of the follow-up visits. Contrast-enhanced

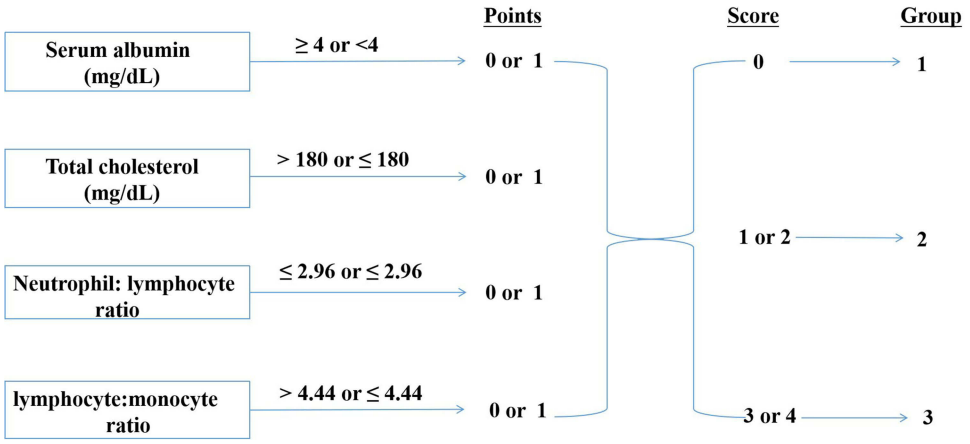

Figure 1 Calculation of the Naples Prognostic Score.

Computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 3 months, or HCC metastasis or recurrence was suspected. Tumor recurrence or metastasis was mainly confirmed on Contrast-enhanced CT or MRI. The most recent follow-up visit took place in December 2022. The following clinical and oncological characteristics of the patients were collected retrospectively from the medical record system at Zhejiang Provincial People's Hospital. Baseline characteristics: age (>60 vs ≤60 years), sex (male vs female), American Society of Anesthesiologists (ASA) classification, performance status, hepatitis B virus (HBV), cirrhosis, portal hypertension, platelet count (PLT), Child-Pugh A/B, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total cholesterol, neutrophil count, monocyte count lymphocyte count, alpha-fetoprotein (AFP). Pathological manifestations: tumor size (≥5 vs <5 cm), tumor number (solitary vs multiple), surgical margins (≥1 vs <1 cm), microscopic vascular, satellite nodes, tumor differentiation. Intraoperative variables: blood loss and transfusion, and operative time. Portal hypertension was confirmed as the presence of either esophageal varices or splenomegaly along with a decline in platelet count (≤ 100×109/L). All diagnoses of cirrhosis were based on pathological examinations, with the criteria being the presence of diffuse liver fibrosis and pseudolobule formation observed in liver tissue histopathology.

Statistical Methods

Frequencies and percentages were used to express the distribution of each categorical variable, and Pearson's chi-square or Fisher's exact tests were adopted to estimate the differences among the variables, as appropriate. Kaplan-Meier survival curves were used to estimate the OS and RFS in each group and compared by Log rank tests. Variables with $P < 0.1$ in the univariate analysis were enrolled into the forward stepwise multivariate Cox proportional hazard regression analysis. ROC curves and the areas under the curve (AUC) were estimated to evaluate the discriminatory and predictive ability of each scoring system, respectively. P values <0.05 were set as statistically significant. The statistical analysis in this study was performed by using the software of R 4.2.3 (http://www.r-project.org/).

Results

Clinicopathological Characteristics

The baseline characteristics of the 476 patients were shown in Table 1. According to preoperative NPS, all patients were stratified into 3 groups (group 1: NPS = 0, n = 53; group 2: NPS = 1 or 2, n = 297; group 3: NPS = 3 or 4, n = 126). As shown in Table 1, patients with a higher score of NPS often have a higher proportion of ASA > 2, performance status ≥ 1, cirrhosis and portal hypertension, Child-Pugh B, multiple tumors, intraoperative blood loss > 600 mL (all $P < 0.05$). Meanwhile, Table 1 showed that NPS was positively correlated with CONUT, SIS, and NLR values, and had a negative correlation with PNI and LMR values.

Table 1 Comparisons of Clinical Characteristics Among the Three Groups According to Preoperative Naples Prognostic Score

Variables, %	Overall (N=476)	Group 1 (n=53)	Group 2 (n=297)	Group 3 (n=126)	P
Sex, male	409 (85.9)	45 (84.9)	256 (86.2)	108 (85.7)	0.520
Age, >60 years	182 (38.2)	23 (43.3)	108 (36.4)	51 (40.5)	0.967
ASA, > 2	58 (12.2)	1 (1.9)	42 (14.1)	15 (11.9)	0.042
Performance status, ≥ 1	113 (23.7)	10 (18.9)	62 (20.9)	41 (32.5)	0.024
HBV (+)	399 (83.8)	44 (83.0)	252 (84.8)	103 (81.7)	0.824
Cirrhosis	353 (74.2)	38 (71.7)	223 (75.1)	92 (73.0)	0.005
Portal hypertension	160 (33.6)	11 (20.8)	93 (31.3)	56 (44.4)	0.004
Child-Pugh, A/B	438 (92.0)/38 (8.0)	50 (94.3)/3 (5.7)	283 (95.3)/ 14 (4.7)	105 (83.3)/ 21 (16.7)	<0.001
PLT, ≥ $100*10^9$/L	358 (75.2)	43 (81.1)	220 (74.1)	95 (75.4)	0.547
ALT, >40 U/L	143 (30.0)	15 (28.3)	98 (33.0)	30 (23.8)	0.162
AST, >40 U/L	176 (37.0)	19 (35.8)	104 (35.0)	53 (42.1)	0.383
COUNT, >2/ ≤2	220 (46.2)/256 (53.8)	6 (11.3)/47 (88.7)	119 (40.1)/178 (59.8)	95 (75.4)/31 (24.6)	<0.001
PNI, ≤44/ >44	130 (27.3)/346 (72.7)	2 (3.8)/51 (96.2)	50 (16.8)/247 (83.2)	78 (61.9)/48 (38.1)	<0.001
SIS, 0/1/2	168 (35.3)/196 (41.2)/112 (23.5)	50 (94.3)/2 (3.8)/1 (1.9)	116 (31.9)/159 (53.5)/ 22 (7.4)	2 (1.6)/35 (27.8)/89 (70.6)	<0.001
NLR,>2.96/≤2.96	124 (26.1)/352 (73.9)	3 (5.7)/50 (94.3)	47 (15.8)/250 (84.2)	74 (58.7)/52 (41.3)	<0.001
LMR,≤4.4/>4.4	197 (41.4)/279 (58.6)	2 (3.8)/51 (96.2)	83 (27.9)/214 (72.1)	112 (88.9)/14 (11.1)	<0.001
AFP, > 400 ug/L	115 (24.2)	9 (17.0)	72 (24.2)	34 (27.0)	0.361
Maximum tumor size > 5cm	170 (35.7)	17 (32.1)	101 (34.0)	52 (41.3)	0.305
Multiple tumors, 1/≥ 2	373 (78.4)/103 (21.6)	43 (81.1)/10 (18.9)	242 (81.5)/55 (18.5)	88 (69.8)/38 (30.2)	0.025
Resection margin, <1cm	122 (25.6)	8 (15.1)	85 (28.6)	29 (23.0)	0.085
Microscopic vascular	198 (41.6)	19 (35.8)	120 (40.4)	59 (46.8)	0.315
Satellite nodes	42 (8.8)	4 (7.5)	22 (7.4)	16 (12.7)	0.202
Poor differentiation	112 (23.5)	15 (28.3)	62 (20.9)	35 (27.8)	0.213
Operation time, >180 min	267 (56.1)	28 (52.8)	161 (54.2)	78 (69.1)	0.303
Intraoperative blood loss, > 600 mL	94 (19.7)	5 (9.4)	60 (20.2)	29 (23.0)	0.047
Blood transfusion	109 (22.9)	9 (17.0)	65 (21.9)	35 (27.8)	0.232

Abbreviations: ASA, physical Status classification system; HBV, hepatitis B virus; AFP, alpha fetoprotein; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SIS, systemic inflammation score; PNI, prognostic nutritional index; COUNT, controlling nutritional status; NPS, Naples prognostic score.

Overall Survival and Recurrence-Free Survival

The median follow-up time was 68.0 months. During the follow-up, 301 (63.2%) and 182 (38.2%) patients developed HCC recurrence and death, respectively. The 1-, 3-, and 5- years OS among each NPS group were 96.2%, 84.8%, and 79.5% in group 1; 91.9%, 82.2%, and 80.4% in group 2; and 87.3%, 66.9%, and 66.0% in group 3, respectively (Figure 2A). Accordingly, the 1-, 3-, and 5- years RFS among each NPS group were 86.8%, 67%, and 51.8% in group 1; 73.7%, 47.5%, and 34.2% in group 2; and 65.1%, 40.5%, and 23.9% in group 3, respectively (Figure 2B). The K-M curves showed that NPS had a negative effect on OS and RFS for HCC after hepatectomy (all $P < 0.001$).

Univariable and Multivariable Analyses

Variables with $P < 0.1$ in the univariate Cox regression analysis were enrolled into the forward stepwise multivariate Cox proportional hazard regression analysis. And the results were shown in Table 2 and Table 3. The results demonstrated that NPS was an independent risk factor of OS (NPS group 2 vs 1: HR=1.958, 95% CI: 1.038–3.369, p = 0.038; NPS group 3 vs 1: HR=2.608, 95% CI: 1.358–5.008, p=0.004, respectively). Meanwhile, the result also showed that NPS was an independent risk factor of RFS (NPS group 2 vs 1: HR=2.014, 95% CI: 1.299-2-3.124, p=0.002; NPS group 3 vs 1: HR=2.002, 95% CI: 1.262–3.175, p=0.003, respectively).

To avoid collinearity with NPS, SIS, PNI, COUNT, NLR, and LMR were analyzed separately with other variables. And the results showed that SIS (group 2 vs 0: HR: 1.467, 95% CI: 1.013–2.123, P = 0.042), PNI (HR: 1.436, 95%:1.043–1.976, P = 0.026), NLR (HR:1.376, 95% CI: 1.004–1.886, P = 0.047) and LMR (HR:1.416, 95% CI:

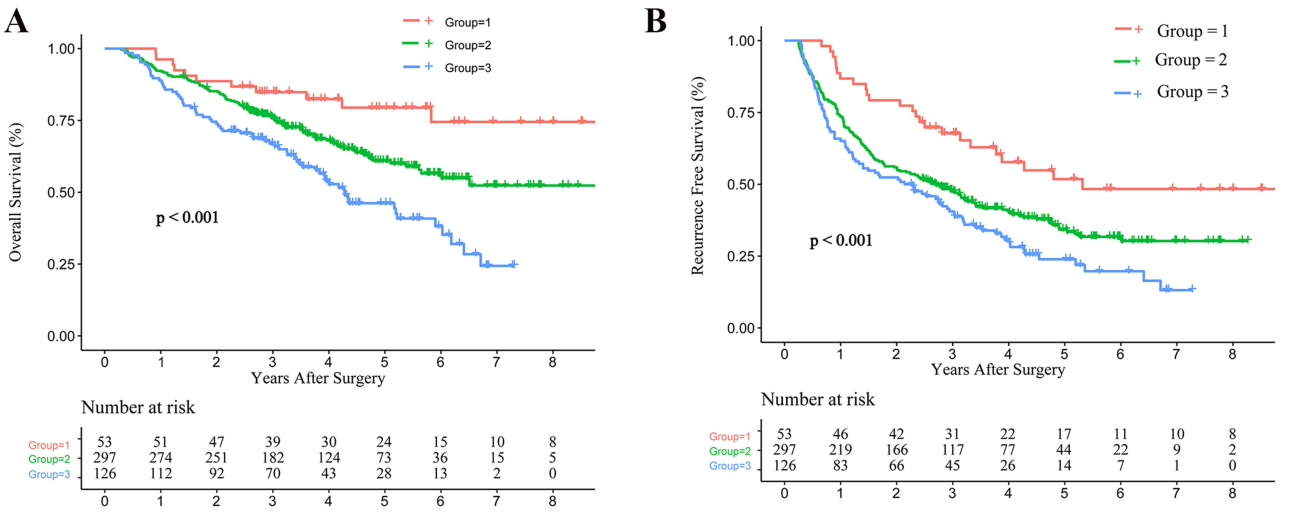

Figure 2 Curves comparisons of overall survival and recurrence free survival among each group (calculated by Log rank test). Group 1 (NPS = 0); Group 2 (NPS = 1 or 2), and Group 3 (NPS = 3 or 4), respectively. (**A**) Overall survival, (**B**) Recurrence-free survival.

1.052–1.906, P = 0.022) were independent risk factors of OS. Meanwhile, PNI (HR:1.351, 95% CI: 1.214–2.068, P = 0.019) and NLR (HR:1.371, 95% CI: 1.052–1.787, P = 0.020) were also independent risk factors of RFS. SIS (group 2 vs 0: HR: 1.335, 95% CI: 0.979–1.821, P = 0.068) and LMR (HR:1.045, 95% CI: 0.902–1.428, P = 0.126) were not prognosis factors of RFS. Moreover, COUNT is neither an independent risk factor for OS (HR:1.237, 95% CI: 0.906–1.689, P = 0.181) nor RFS (HR:0.976, 95% CI: 0.754–1.239, P = 0.789).

Table 2 Univariable and Multivariable Cox Regression Analyses of Risk Factors Associated with Overall Survival for HCC After Hepatectomy

Variables	OR Comparison	UV OR (95% CI)	UV P	MV OR (95% CI)	MV P[a]
Sex	Male vs Female	0.675 (0.461–0.990)	0.044	NS	
Age	> 60 vs.≤ 60 years	1.022 (0.758–1.378)	0.886		
ASA	> 2 vs ≤ 2	1.163 (0.757–1.788)	0.491		
Performance status	≥1 vs 0	1.506 (1.087–2.088)	0.014	NS	
HBV	Yes vs No	0.958 (0.651–1.411)	0.829		
Cirrhosis	Yes vs No	1.172 (0.832–1.650)	0.364		
Portal hypertension	Yes vs No	1.678 (1.252–2.249)	0.001	1.709 (1.257–2.325)	0.001
Child-Pugh	B vs A	1.340 (0.839–2.141)	0.220		
PLT	< 100 vs ≥ 100*10^9/L	0.975 (0.740–1.351)	0.897		
AST	> 40 vs ≤ 40 U/L	1.253 (0.923–1.700)	0.148		
ALT	>40 vs ≤ 40 U/L	1.649 (1.233–2.207)	0.001	NS	
AFP	> 400 vs ≤ 400 ug/L	2.255 (1.661–3.061)	<0.001	1.530 (1.102–2.125)	0.011
Maximum tumor size	> 5 vs ≤ 5 cm	1.464 (1.088–1.969)	0.012	1.387 (1.003–1.918)	0.048
Tumor number	Multiple vs Solitary	1.872 (1.348–2.598)	<0.001	1.638 (1.161–2.311)	0.005
Resection margin	< 1 vs ≥ 1 cm	1.582 (1.152–2.172)	0.005	1.217 (1.013–1.317)	0.036
Macroscopic vascular	Yes vs No	2.338 (1.740–3.139)	<0.001	1.706 (1.241–2.345)	0.001
Satellite nodes	Yes vs No	2.673 (1.773–4.030)	<0.001	2.229 (1.417–3.508)	0.001
Differentiation	Poor vs Moderate/Well	1.294 (0.926–1.809)	0.131		
Anatomical resection	Yes vs No	1.183 (0.883–1.585)	0.259		
Operation time	≥180 vs < 180 min	1.280 (0.952–1.721)	0.102		
Intraoperative blood loss	> 600 vs ≤600 mL	2.115 (1.535–2.913)	<0.001	1.647 (1.120–2.422)	0.011
Blood transfusion	Yes vs No	1.892 (1.383–2.589)	<0.001		

(*Continued*)

Table 2 (Continued).

Variables	OR Comparison	UV OR (95% CI)	UV P	MV OR (95% CI)	MV P[a]
NPS	1	Reference		Reference	
	2	2.085 (1.119–3.888)	0.021	1.958 (1.038–3.369)	0.038
	3	3.515 (1.855–6.662)	<0.001	2.608 (1.358–5.008)	0.004
SIS[b]	0	Reference		Reference	
	1	1.061 (0.740–1.522)	0.747	1.009 (0.623–1.301)	0.576
	2	2.123 (1.483–3.041)	<0.001	1.467 (1.013–2.123)	0.042
PNI	≤ 44 vs > 44	2.248 (1.670–3.025)	<0.001	1.436 (1.043–1.976)	0.026
COUNT	> 2 vs ≤2	1.507 (1.125–2.018)	0.006	1.237 (0.906–1.689)	0.181
NLR	>2.96 vs.≤2.96	1.638 (1.208–2.221)	0.001	1.376 (1.004–1.886)	0.047
LMR	≤4.4 vs >4.4	1.575 (1.177–2.109)	0.002	1.416 (1.052–1.906)	0.022

Notes: [a]Those variables found significant at P < 0.1 in univariable analyses were entered into multivariable logistic analyses. [b]To avoid collinearity with NPS, SIS, PNI, COUNT, NLR and LMR were analyzed separately with other variables.
Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; AFP, alpha-fetoprotein; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SIS, systemic inflammation score; PNI, prognostic nutritional index; COUNT, controlling nutritional status; NPS, Naples prognostic score. MV, multivariable; NA, not available; OR, odds ratio; UV, univariable.

Table 3 Univariable and Multivariable Cox Regression Analyses of Risk Factors Associated with Recurrence-Free Survival for HCC After Hepatectomy

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P[a]
Sex	Male vs Female	0.917 (0.664–1.266)	0.597		
Age	> 60 vs.≤ 60 years	1.044 (0.829–1.315)	0.751		
ASA	> 2 vs ≤ 2	1.263 (0.909–1.757)	0.164		
Performance status	≥1 vs 0	1.207 (0.927–1.572)	0.163		
HBV	Yes vs No	1.034 (0.763–1.401)	0.829		
Cirrhosis	Yes vs No	1.395 (1.065–1.828)	0.016	NS	
Portal hypertension	Yes vs No	1.275 (1.008–1.612)	0.043	1.131 (1.006–1.439)	0.044
Child-Pugh	B vs A	1.048 (0.695–1.581)	0.822		
PLT	< 100 vs ≥ 100*10^9/L	1.021 (0.789–1.321)	0.024	NS	
AST	> 40 vs ≤ 40 U/L	1.417 (1.117–1.789)	0.004	NS	
ALT	>40 vs ≤ 40 U/L	1.671 (1.331–2.099)	<0.001	1.592 (1.187–2.137)	0.002
AFP	> 400 vs ≤ 400 ug/L	1.985 (1.546–2.548)	<0.001	1.492 (1.134–1.963)	0.004
Maximum tumor size	> 3 vs ≤ 3 cm	1.346 (1.066–1.699)	0.013	1.371 (1.074–1.750)	0.011
Tumor number	Multiple vs Solitary	1.614 (1.241–2.099)	<0.001	1.532 (1.164–2.016)	0.002
Resection margin	<1 vs ≥1 cm	1.611 (1.257–2.064)	<0.001	1.521 (1.178–1.964)	0.001
Macroscopic vascular	Yes vs No	2.082 (1.645–2.621)	<0.001	1.540 (1.193–1.986)	0.001
Satellite nodes	Yes vs No	2.604 (1.833–3.700)	<0.001	1.802 (1.222–2.657)	0.003
Differentiation	Poor vs Moderate/Well	1.361 (1.047–1.768)	0.021	NS	
Anatomical resection	Yes vs No	0.963 (0.768–1.207)	0.741		
Operation time	≥180 vs < 180 min	1.279 (1.017–1.610)	0.036	NS	
Intraoperative blood loss	> 600 vs ≤600 mL	1.626 (1.240–2.132)	<0.001	NS	
Blood transfusion	Yes vs No	1.863 (1.448–2.397)	<0.001	NS	
NPS	0	Reference		Reference	
	1	1.823 (1.196–2.806)	0.005	2.014 (1.299–3.124)	0.002
	2	2.414 (1.539–3.786)	<0.001	2.002 (1.262–3.175)	0.003
SIS[b]	0	Reference		Reference	
	1	1.247 (0.953–1.631)	0.108	1.086 (0.826–1.429)	0.555
	2	1.746 (1.301–2.343)	<0.001	1.335 (0.979–1.821)	0.068

(*Continued*)

Table 3 (Continued).

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P[a]
PNI	≤ 44 vs > 44	1.933 (1.523–2.454)	<0.001	1.351 (1.214–2.068)	0.019
COUNT	> 2 vs ≤2	1.185 (0.964–1.487)	0.139	0.976 (0.754–1.239)	0.789
NLR	>2.96 vs.≤2.96	1.419 (1.107–1.818)	0.006	1.371 (1.052–1.787)	0.020
LMR	≤4.4 vs >4.4	1.271 (1.012–1.596)	0.039	1.045 (0.902–1.428)	0.126

Notes: [a]Those variables found significant at P < 0.1 in univariable analyses were entered into multivariable logistic analyses. [b]To avoid collinearity with NPS, SIS (including PNI, COUNT, NLR and LMR) was analyzed separately with other variables.
Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; AFP, alpha-fetoprotein; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SIS, systemic inflammation score; PNI, prognostic nutritional index; COUNT, controlling nutritional status; NPS, Naples prognostic score. MV, multivariable; NA, not available; HR, hazard ratio; UV, univariable.

Prognostic Performance

The area under the time-dependent ROC was calculated to determine which indicator was good at predicting survival. Firstly, we calculated the model's ability to predict overall survival at 5 years (Figure 3A). The AUC value of the NPS was 0.692, which is higher than SIS (AUC: 0.621), PNI (AUC: 0.603), COUNT (AUC: 0.526), NLR (AUC: 0.589), and LMR (AUC: 0.574) (all P < 0.05). Meanwhile, we used time-dependent ROC curves to calculate the estimated AUC at different time points. Results showed that the AUC was stable (median AUC 0.687, range 0.648–0.716), and the diagnostic capacity of the model was higher than that of any other indicators, including SIS (median AUC: 0.651, Range: 0.605–0.676), PNI (median AUC: 0.638, range: 0.581–0.695), COUNT (median AUC: 0.565, range: 0.518–0.612), NLR (median AUC: 0.603, range: 0.568–0.659) and LMR (median AUC: 0.588, range: 0.536–0.651) (Figure 3B).

Discussion

This study mainly aimed to evaluate the impact of NPS on survival in patients undergoing hepatectomy for HCC. Eventually, 476 patients were included and stratified into 3 groups based on the NPS. Baseline characteristics showed that patients with high NPS scores are more likely to be associated with poor performance status, poor liver function, advanced tumor stage, and more prone to intraoperative bleeding. Of note, the multivariable cox-regression analysis

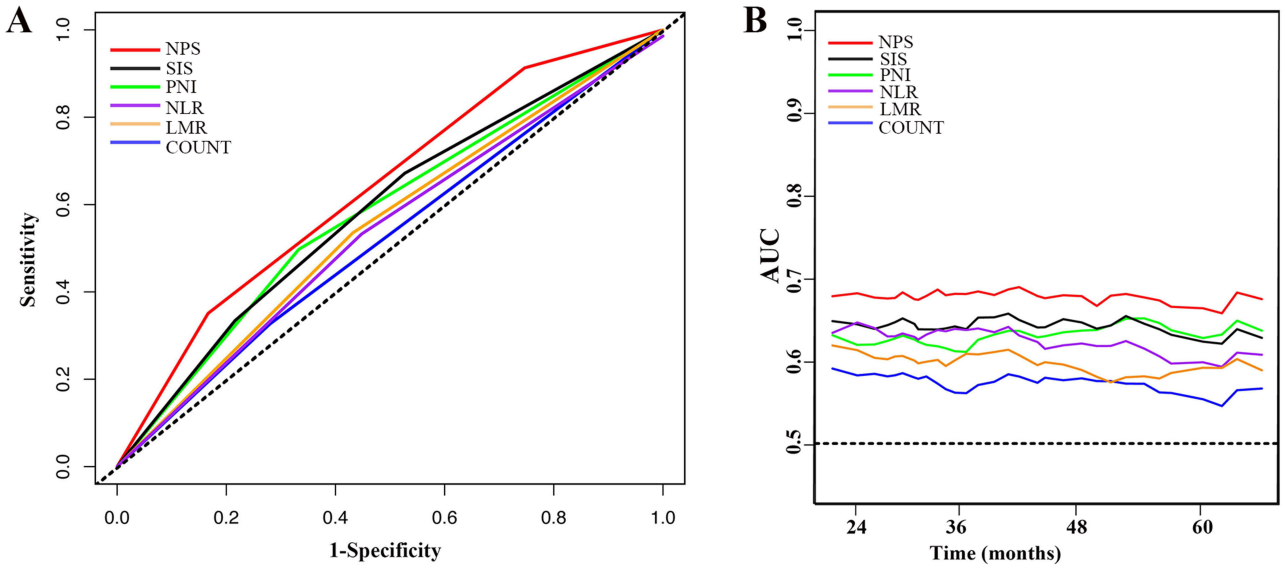

Figure 3 (**A**) Compared the predictive ability of postoperative overall survival at 5-year by time-dependent ROCs between the NPS scores and the other indicators. (**B**) Compared time-dependent AUCs between the NPS scores and the other indicators.
Abbreviations: ROCs, receiver operating characteristic curves; AUCs, areas under the curves; NPS, Naples prognostic score; SIS, systemic inflammation score; PNI, prognostic nutritional index; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; COUNT, controlling nutritional status.

indicated that NPS was an independent prognosis factor of OS and RFS. In other words, compared to group 1 (NPS = 0), patients in group 2 (NPS = 1/2) had a nearly 1.5-fold increased risk of HCC recurrence and death, and patients in group 3 (NPS = 3/4) had a nearly 2-fold increased risk of HCC recurrence and death. Furthermore, compared with previously reported prognostic models, the NPS showed the best performance of discriminatory and predictive ability (median AUC 0.687, range 0.648–0.716). To our knowledge, the present study is the first report to determine the prognostic significance of NPS on long-term outcomes in patients with HCC.

Prior studies have reported that immunonutritional status is associated with the postoperative prognosis of malignancy.[23–25] Immunonutritional status, on the other hand, is usually reflected in blood parameters such as cholesterol concentrations, albumin, and leukocyte count. Among them, serum albumin is present in each of these scoring systems. Because the albumin concentrations can be decreased by proinflammatory substances, hypoalbuminemia not only indicates a nutrient deficiency but also indicate systemic inflammation. However, due to changes in liver function and the volume of body fluids, albumin concentrations can also be affected.[26] It has also been reported that serum cholesterol levels correlate with cancer progression.[27] Since hypocholesterolemia affects the mobility of cell membranes, which affects cell surface receptor mobility and transmembrane signal transduction.[28] Resulting in an inability of immunoreactive cells to destroy cancer cells through alterations in their cellular membranes,[29] leading to its correlation with a worse prognosis HCC.[30]

In cancer, the immune system is critical because it either kills tumor cells or forms a tumor microenvironment that supports tumor progression[31] In turn, the cytomediated immune response relies heavily on lymphocytes, which inhibit cancer cell multiplication, invasion, and metastasis by stimulating immune response through cytotoxicity.[31,32] It has been reported that extensive lymphocyte invasion is associated with a favorable prognosis. In inclusion, substances produced by neutrophils, such as reactive oxygen species and arginase can decrease the activation and proliferation of T lymphocytes,[33,34] while lymphopenia is associated with reduced survival in cancer.[35,36] Neutrophilia has been consistently associated with disease severity, whereas a low absolute neutrophil count has been associated with an improved prognosis following tumor treatment.[37] Furthermore, related molecules such as intercellular adhesion molecules and chemokines contribute to neutrophil and monocyte recruitment to primary tumors, neutrophils as important inflammatory cells, in turn, release quantities of chemokines and cytokines, which are implicated in cancer-associated vasculogenesis.[38,39] In addition, monocytes can differentiate into tumor-associated macrophages (TAMs) within tumor tissues,[40] and these macrophages promote vasculogenesis, tumor progression, and metastasis.[41] Monocytes therefore also play a crucial role in the tumor microenvironment and may predict tumor prognosis. On the other hand, single indicators can be influenced by host conditions and other factors, ie they can even be misleading when using threshold values. LMR and NLR thus combine the importance of monocytes, lymphocytes, and neutrophils in tumor development and are better prognostic indicators of prognosis than the single endpoints noted above.[37,42]

While, as noted above, total cholesterol and albumin levels, as well as immune inflammatory cells, both predict the prognosis of patients with cancer, the use of only one nutritional biomarker or one or two types of inflammatory cells to assess the long-term prognosis of HCC patients after hepatectomy may be insufficient. Thus, the true predictive ability of these markers in the postoperative prognosis of HCC warrants further study. In contrast, NPS incorporates multiple factors and has been found to better predict tumor prognosis than other single markers.[18] NPS values have previously been shown to correlate with poor prognosis of multiple tumors after surgical clipping and to have different prognostic values.[20,43,44] Studies of the postoperative HCC, however, remain lacking. In this study, NPS was validated by multivariate Cox analysis to be an independent risk factor for OS and RFS in patients undergoing hepatectomy. In addition, K-M curves of OS and RFS showed that higher NPS scores corresponded with a worse prognosis. Analysis by time-dependent ROC also showed the NPS showed superiority at each time point when compared to the other immunonutrition scoring systems.

Based on the aforementioned studies, it appears that preoperative nutritional status and immune status are both associated with postoperative tumor prognosis. It has been previously reported in the literature that as nutritional status and immune status improve, the prognosis after hepatectomy may also improve as a result.[10,45] Despite this, there is a lack of prospective randomized studies to demonstrate whether an improvement in inflammatory and nutritional status is of prognostic benefit after HCC, it has been suggested that nutritional support can improve prognosis and tolerance in patients with HCC[4] and that anti-inflammatories, such as aspirin or other NSAIDs, can reduce inflammation and exert antitumor effects.[46] Thus, the use of NPS to evaluate the inflammatory and nutritional status of patients with HCC after

hepatectomy may aid in determining individualized treatment plans and provide a foundation for the determination of nonsurgical treatment choices.

There are still some limitations in this study. Although the AUC value (0.687) is not enough high, this is the impact of only one variable on prognosis. To better predict prognosis, it is important to consider other independent risk factors in combination. However, the purpose of this study is to explore the prognostic value of NPS. Therefore, in future studies, we will incorporate NPS as an independent factor into other models to improve the predictive ability of prognosis. In addition, we discussed the potential mechanisms by which NPS may affect prognosis in the discussion section, particularly the pathological features of inflammation. This includes the direct or indirect influence of inflammatory cells and factors through the tumor microenvironment on tumor occurrence and development. Regarding the correlation between NPS and microenvironmental factors in the specimen, we will further explore this in targeted investigations in future studies. As a retrospective study, there is some inherent bias, including variables that could not be standardized or identified, patients lost to follow-up, etc. in addition, some inflammatory indicators, such as CRP and heparin, were not included. Because we think it's collinearity with inflammatory cells. Further validation, especially multicenter RCT, still needed to be conducted.

Conclusion

The presence of preoperative NPS in patients with HCC after hepatectomy is an independent risk factor for both OS and RFS, and NPS has superior prognostic performance compared with other immunonutrition scoring systems.

Abbreviations

HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate transaminase; AFP, alpha-fetoprotein.

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Yaming Xie, Wenfeng Lu and Jian Cheng contributed equally to this work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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