Original Article

DOI: 10.5582/bst.2024.01108

The role of cholesterol-modified prognostic nutritional index in nutritional status assessment and predicting survival after liver resection for hepatocellular carcinoma

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SUMMARY Malnutrition, which is often underestimated in patients with hepatocellular carcinoma (HCC), has a proven adverse effect on survival rates. The purpose of this study was to verify the effectiveness of the cholesterol-modified prognostic nutritional index (CPNI) in determining the nutritional status and predicting overall survival (OS) and recurrence-free survival (RFS) in patients with HCC by comparing it with several other nutritional indicators. This retrospective single-center study enrolled 1450 consecutive HCC patients who underwent curative liver resection from January 2015 to November 2019. We evaluated the prognostic significance of several nutritional indicators, including CPNI, the controlling nutritional status (CONUT), the nutritional risk index (NRI), and the prognostic nutritional index (PNI), by applying time-dependent receiver operating characteristic (ROC) curves, Kaplan–Meier survival analysis, and Cox proportional hazards regression analysis. Among several objective nutrition evaluations (including CPNI, CONUT, NRI, and PNI), CPNI demonstrated the greatest prognostic predictive power for predicting OS. Meanwhile, CPNI demonstrated marginally higher accuracy in predicting RFS compared to PNI, and significantly outperformed CONUT and NRI. Univariate and multivariate analyses suggested that CPNI was an independent risk factor for the OS and RFS of patients with HCC undergoing curative liver resection. In most subgroups, malnutrition as identified by CPNI demonstrates strong stratification ability in predicting both OS and RFS. CPNI serves as an accurate and stable instrument for evaluating nutritional status and forecasting survival outcomes in HCC patients following liver resection, which has the potential to markedly influence clinical decision-making processes and the management of patient care.

Keywords malnutrition, cholesterol-modified prognostic nutritional index, hepatocellular carcinoma

1. Introduction

Malnutrition is a common problem among patients with cancer, although it is frequently undiagnosed (*1*). It is estimated that 32% of the individuals diagnosed with cancer experience malnutrition (*2*). Malnutrition can weaken immunity and treatment tolerance, potentially affecting cancer therapy outcomes and patient prognosis (*3,4*). Hepatocellular carcinoma (HCC) is the primary type of liver cancer, representing 90% of such cases, and is the fourth leading cause of cancer-related deaths worldwide (*5*). Hepatectomy is widely recognized as a curative therapeutic approach for HCC (*6*). Most HCC cases are associated with liver cirrhosis (*7*). Malnutrition often affects 20-50% of patients with liver cirrhosis, representing a significant health burden (*4*). Therefore, assessing the nutritional status before liver resection is essential to ensure positive patient outcomes.

Despite the development of several screening instruments to detect malnutrition in cancer patients, a universally accepted gold standard has yet to be established. The Controlling Nutritional Status (CONUT) score, proposed by Ulibarri *et al*. in 2005, is designed to screen the nutritional condition of patients in a hospital setting, utilizing parameters such as serum albumin concentration, total cholesterol, and lymphocyte count (*8*). The CONUT score has been demonstrated to serve as a prognostic indicator and predictor of complications across a variety of cancer types, including HCC (*9-12*). The Nutritional Risk Index (NRI) has become a simple tool for predicting

nutritional risk and has shown strong prognostic value in medical and surgical patients (*13,14*). The Prognostic Nutritional Index (PNI) is an indicator formulated using serum albumin levels and lymphocyte counts. It offers a convenient metric to describe the association between a patient's nutritional health and immunological status and correlates with the prognosis following liver resection (*15-18*). Recently, the Cholesterol-modified Prognostic Nutritional Index (CPNI), which was proposed as a new nutritional assessment based on PNI, has shown greater predictive accuracy for overall survival (OS) in breast cancer patients than other indices, including PNI, CONUT, NRI, global leadership initiative on malnutrition (GLIM), and patient-generated subjective nutrition assessment (PGSGA) (*19*).

However, the performance of CPNI in determining the nutritional status and forecasting survival outcome among patients with HCC following liver resection remains unclear. This study explored the relationship between CPNI and OS and recurrence-free survival (RFS) in HCC patients and assessed its predictive accuracy relative to other objective nutritional indicators such as CONUT, NRI, and PNI.

2. Materials and Methods

2.1. Patient election

This retrospective cohort study was approved by the Ethics Committee of West China Hospital, Sichuan University and was conducted in accordance with the Declaration of Helsinki (NO.2024(189)). Between January 2015 and November 2019, 1,450 consecutive HCC patients who underwent curative liver resection were retrospectively enrolled in this study at the West China Hospital of Sichuan University. Due to the nature of this retrospective analysis, consent forms were not required.

The inclusion criteria were patients with HCC who underwent R0 liver resection and had HCC confirmed by histopathological examination.

The exclusion criteria were: (1) the presence of other types of primary liver cancer (such as cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma) and a history of cancer in another organ at the same time or in the past; (2) bile duct invasion; (3) vascular invasion; (4) lymph node metastases; and (5) invasion of the adjacent organs. (6) Patients with incomplete clinicopathological information or follow-up data. The process for selecting patients is shown in Supplemental Figure S1 (*https://www.biosciencetrends.com/supplementaldata/206*).

2.2. Patient characteristics, surgical procedures and endpoints

Clinicodemographic factors such as sex, age, body mass index (BMI), the albumin-bilirubin (ALBI) grade, hepatitis B infection, hepatitis C infection, tumor stage, comorbidities, preoperative blood test results, serum α-fetoprotein (AFP) level, type of resection and pathological findings were collected from electronic medical records.

Major hepatectomy is defined as the surgical removal of three or more segments from the liver, according to Couinaud's classification. In contrast, a minor hepatectomy involves the excision of less than three segments. Liver resection is classified either as anatomical, conforming to the Brisbane 2000 liver anatomy nomenclature, or as non-anatomical, which includes limited forms of resection such as wedge resections. The Edmondson-Steiner classification system was used to grade tumor differentiation.

Patients underwent necessary imaging modalities such as enhanced abdominal computed tomography (CT), chest CT, contrast-enhanced ultrasound, or magnetic resonance imaging (MRI) for a thorough assessment. Comprehensive laboratory tests including liver function, hepatitis B and C screenings, and tumor markers were also performed. The volume of the remaining liver was gauged using CT or MRI to ensure post-surgery viability. Liver function was assessed using the Child-Pugh scores and ALBI grades. Candidates for liver resection had adequate liver volumes and potential for complete tumor removal. The surgical approach was tailored to the tumor characteristics, with intraoperative ultrasound utilized as required to guide the procedure.

In the study, the primary endpoint was overall survival (OS), defined as the time from the date of surgery until the patient's death or the last follow-up date. The secondary endpoint was recurrence-free survival (RFS), which was measured from the date of surgery to the date of confirmation of recurrence and/or metastasis. Recurrent HCC is diagnosed through CT and/or MRI imaging, along with elevated AFP tumor marker levels. Patients experiencing HCC recurrence would undergo suitable treatments, preferably radiofrequency ablation or another liver resection for curative intent. The vital status of patients discharged alive was monitored through outpatient visits, telephone calls every two months, or during hospital admissions. Starting from the third year after discharge, the follow-up frequency was adjusted to every three months. We continued to follow-up with the patients until they died of any cause or were lost to follow-up.

2.3. Malnutrition assessment

For every patient, BMI = weight (kg)/height^2 (m). Then, all patients were sorted in four categories based on their BMI: underweight (< 18.5 kg/m^2), normal weight (18.5 to 24.0 kg/m^2), overweight (24.0 to 28.0 kg/m^2), and obese (≥ 28.0 kg/m^2) (*19,20*).

The CONUT score is an assessment tool that

evaluates an individual's nutritional status by three biomarkers: serum albumin, total cholesterol, and lymphocyte count. Scores for albumin, lymphocytes, and cholesterol are as follows: albumin: >35 g/L = 0 points, 30-34 g/L = 2 points, 25-29 g/L = 4 points, <25 g/L = 6 points; lymphocytes: ≥ 1.6×10^9/L = 0 points, 1.2-1.59 × 10^9/L = 1 points, 0.8-1.19 × 10^9/L = 2 points, < 0.8×10^9/L = 3 points; cholesterol: ≥180 mg/dL = 0 points, 140-179 mg/dL = 1 points, 100-139 mg/dL = 2 points, <100 mg/dL = 3 points (*20*). This scoring system ranges from 0 to 12, with a score > 2 indicating malnutrition (19). To calculate the NRI: ideal body weight (IBW) = Height^2 (m) × 22; NRI = 1.519 × albumin (g/L) + 41.7 × (current weight/IBW) (*19*). An NRI of < 100 indicates malnutrition. The PNI = albumin (g/L) + 5 × lymphocyte count ($\times 10^9$) (*20*). The Cholesterol-modified Prognostic Nutritional Index (CPNI) = 4.8 × cholesterol (mmol/L) - 1.5 × albumin (g/L) - 7.7 × lymphocyte ($\times 10^9$) + 126 (*19*).

2.4. Statistics analysis

Continuous variables are expressed as a median with interquartile range (25th to 75th percentiles). The Student's *t*-test was used to evaluate distributed continuous variables, while the Mann–Whitney *U* test was used to assess non-normally distributed variables. Categorical data were reported as percentages and analyzed using $\chi 2$ or Fisher's exact tests. The prognostic effectiveness of several nutritional indices for OS and RFS was examined using the time-dependent ROC curves. The relationships between the malnutrition markers and OS were examined using restricted cubic spline (RCS) plots. Continuous nutritional indicators were split into two groups using optimal cut-offs, which were determined by maximally selected rank statistics. Kaplan-Meier curves and the log-rank tests were used for survival comparisons between the groups. To determine the independent predictive significance of nutritional markers for OS in HCC, univariate and multivariate Cox regression analyses were performed. Four nutritional indicators were evaluated using separate multivariate models designed to assess the impact of malnutrition on OS and RFS. Variables with *p*-values < 0.05 in the univariate Cox regression were included in the multivariate Cox regression analysis. Statistical analysis was considered significant when the two-tailed *P*-value was less than 0.05. All statistical procedures were conducted using R software, version 4.3.2.

3. Results

3.1. Patents' characteristic

Finally, 1,450 patients with hepatocellular carcinoma were included in this retrospective study. The cohort comprised 219 (15.1%) females and 1231 (84.9%) males, with a median age of 53 years. 1194 (82.3%) patients had HBV infection, whereas 24 patients had HCV infection. The median BMI of the patients was 23 kg/m^2, 804 (55.6%) were classified as normal weight, 446 (30.8%) were classified as overweight, 114 (16.4%) as obese, and 84 (5.79%) as underweight. Patients were classified according to the BCLC staging system: 146 (10.1%) were in BCLC stage 0, 1132 (78.1%) were in BCLC stage A, and 172 (11.9%) were in BCLC stage B. Additionally, we compared the baseline data of male and female patients; the detailed baseline characteristics of the patients are shown in Table 1.

3.2. Assessment of malnutrition

There was a nonlinear relationship between nutritional indices (PNI and CPNI) and OS of HCC patients, according to RCS analysis using the Cox proportional hazards model, as depicted in Figure 1. According to maximally selected log rank statistics, the optimal cutoffs for PNI and CPNI were 50.25 and 70.48 points, respectively (Supplemental Figure S2, *https://www.biosciencetrends.com/supplementaldata/206*). PNI ≤ 50.25 points indicates malnutrition, while CPNI > 70.48 points indicates malnutrition. The incidence of malnutrition in patients with HCC was notably inconsistent, ranging from 21.2% under the NRI criteria to 62.8% when assessed with CONUT. Evaluations using different indicators, CONUT score, NRI, PNI, and CPNI, diagnosed malnutrition in 911 (62.8%), 308 (21.2%), 721 (49.7%), and 695 (47.9%) patients, respectively (Table 1). A total of 198 cases were identified as malnutrition using four nutritional indicators (CONUT, NRI, PNI, and CPNI), as shown in Figure 2. The frequency of malnutrition within both sex and BMI groups was established using each of the nutritional indices and is shown in Supplemental Figure S3 (*https://www.biosciencetrends.com/supplementaldata/206*). Under the CONUT diagnostic criteria, females showed a higher incidence of malnutrition than males. However, according to the NRI, PNI, and CPNI criteria, no notable difference was found in the malnutrition rates between the two groups. When evaluated using the CONUT, NRI, PNI, and CPNI criteria, the incidence of malnutrition decreased as the BMI increased.

3.3. Evaluating the prognostic effectiveness of nutritional indices

The time-dependent ROC analysis assessing the prognostic predictive power of CONUT, NRI, PNI, and CPNI in HCC patients showed that CPNI was the most accurate in predicting OS compared to the other nutritional indices (Figure 3A). Additionally, CPNI demonstrated marginally higher accuracy in predicting RFS compared to PNI, and was clearly superior to both CONUT and NRI (Figure 3B). Detailed information,

Table 1. Baseline table of patients' characteristics

Characteristic	Overall (*n* = 1,450)	Female (*n* = 219)	Male (*n* = 1,231)	*P* value
Age, years, median (IQR)	53.0 [46.0;62.0]	54.0 [45.0;63.0]	53.0 [46.0;62.0]	0.713
Height, cm, median (IQR)	165 [160;170]	156 [152;160]	167 [163;170]	< 0.001
Weight, kg, median (IQR)	63.0 [56.0;70.0]	56.0 [50.0;61.2]	65.0 [58.0;71.0]	< 0.001
BMI, kg/m^2, median (IQR)	23.0 [20.9;25.3]	22.6 [20.7;25.2]	23.1 [21.0;25.3]	0.159
BMI group, *n* (%)				0.216
Normal weight	806 (55.6)	121 (55.3)	685 (55.6)	
Obesity	114 (7.86)	18 (8.22)	96 (7.80)	
Overweight	446 (30.8)	61 (27.9)	385 (31.3)	
Underweight	84 (5.79)	19 (8.68)	65 (5.28)	
HBV, yes, *n* (%)	1194 (82.3)	183 (83.6)	1011 (82.1)	0.677
HCV, yes, *n* (%)	24 (1.66)	6 (2.74)	18 (1.46)	0.243
AFP, ng/mL, *n* (%)				0.496
< 400	1,224 (84.4)	181 (82.6)	1,043 (84.7)	
≥ 400	226 (15.6)	38 (17.4)	188 (15.3)	
Hemoglobin, g/L, median (IQR)	144 [132;155]	128 [118;136]	147 [136;157]	< 0.001
Platelets, 10^9/L, median (IQR)	130 [93.0;179]	121 [86.0;181]	131 [94.0;179]	0.224
WBC, 10^9/L, median (IQR)	5.24 [4.23;6.55]	4.31 [3.54;5.68]	5.38 [4.41;6.65]	< 0.001
NE, 10^9/L, median (IQR)	3.08 [2.33;4.05]	2.53 [1.99;3.62]	3.14 [2.42;4.13]	< 0.001
LY, 10^9/L, median (IQR)	1.45 [1.15;1.85]	1.31 [1.06;1.61]	1.49 [1.17;1.88]	< 0.001
ALT, U/L, median (IQR)	35.0 [24.0;52.0]	26.0 [19.0;37.0]	37.0 [25.0;53.0]	< 0.001
AST, U/L, median (IQR)	35.0 [27.0;50.0]	35.0 [26.0;49.0]	36.0 [27.0;50.0]	0.313
Cholesterol, mmol/L, median (IQR)	4.02 [3.50;4.61]	4.04 [3.54;4.56]	4.00 [3.49;4.61]	0.581
Prothrombin time, s, median (IQR)	12.0 [11.4;12.7]	12.0 [11.4;12.8]	12.0 [11.4;12.7]	0.733
Tbil, μmol/L, median (IQR)	13.7 [10.5;17.9]	13.5 [10.1;17.1]	13.7 [10.6;18.2]	0.187
Total protein, g/L, median (IQR)	70.4 [66.6;74.1]	71.6 [68.5;75.8]	70.2 [66.4;73.8]	< 0.001
Albumin, g/L, median (IQR)	42.5 [39.9;45.1]	42.6 [39.8;45.5]	42.5 [39.9;45.0]	0.663
Triglyceride, mmol/L, median (IQR)	0.94 [0.72;1.28]	0.92 [0.69;1.29]	0.94 [0.72;1.27]	0.433
HDL, mmol/L, median (IQR)	1.20 [0.98;1.47]	1.40 [1.15;1.69]	1.17 [0.96;1.42]	< 0.001
LDL, mmol/L, median (IQR)	2.30 [1.88;2.80]	2.21 [1.83;2.60]	2.33 [1.89;2.83]	0.006
ALBI grade, *n* (%)				0.855
1	1,142 (78.8)	174 (79.5)	968 (78.6)	
2	308 (21.2)	45 (20.5)	263 (21.4)	
Tumor diameter, cm, *n* (%)				1.000
< 5	731 (50.4)	110 (50.2)	621 (50.4)	
≥ 5	719 (49.6)	109 (49.8)	610 (49.6)	
Number of tumors, *n* (%)				0.411
multiple	229 (15.8)	30 (13.7)	199 (16.2)	
single	1,221 (84.2)	189 (86.3)	1,032 (83.8)	
BCLC stage, *n* (%)				0.067
0	146 (10.1)	17 (7.76)	129 (10.5)	
A	1,132 (78.1)	184 (84.0)	948 (77.0)	
B	172 (11.9)	18 (8.22)	154 (12.5)	
Hypertension, yes, *n* (%)	231 (15.9)	36 (16.4)	195 (15.8)	0.903
Diabetes, yes, *n* (%)	122 (8.41)	17 (7.76)	105 (8.53)	0.807
Cardiovascular disease, yes, *n* (%)	26 (1.79)	5 (2.28)	21 (1.71)	0.578
Anatomical resection, yes, *n* (%)	494 (34.1)	68 (31.1)	426 (34.6)	0.344
Major hepatectomy, yes, *n* (%)	190 (13.1)	23 (10.5)	167 (13.6)	0.259
Transfusion, yes, *n* (%)	71 (4.90)	12 (5.48)	59 (4.79)	0.792
Differentiation, *n* (%)				0.455
I-II	818 (56.4)	118 (53.9)	700 (56.9)	
III-IV	632 (43.6)	101 (46.1)	531 (43.1)	
Microsatellites, yes, *n* (%)	106 (7.31)	8 (3.65)	98 (7.96)	0.034
Microvascular invasion, yes, *n* (%)	389 (26.8)	51 (23.3)	338 (27.5)	0.230
Cirrhosis, yes, *n* (%)	750 (51.7)	120 (54.8)	630 (51.2)	0.361
CONUT, *n* (%)				0.004
Malnutrition	911 (62.8)	157 (71.7)	754 (61.3)	
No malnutrition	539 (37.2)	62 (28.3)	477 (38.7)	
NRI, *n* (%)				0.281
Malnutrition	308 (21.2)	40 (18.3)	268 (21.8)	
No malnutrition	1,142 (78.8)	179 (81.7)	963 (78.2)	
PNI, *n* (%)				0.333
Malnutrition	721 (49.7)	116 (53.0)	605 (49.1)	
No malnutrition	729 (50.3)	103 (47.0)	626 (50.9)	
CPNI, *n* (%)				0.066
Malnutrition	695 (47.9)	118 (53.9)	577 (46.9)	
No malnutrition	755 (52.1)	101 (46.1)	654 (53.1)	

BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, a-fetoprotein; WBC, white blood cells; NE, neutrophil; LY, lymphocyte; ALT, glutamate aminotransferase; AST, aspartate aminotransferase; Tbil, total bilirubin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BCLC, Barcelona Clinic Liver Cancer; CONUT, Controlling Nutritional Status score; NRI, Nutritional Risk Index; PNI, Prognostic Nutritional Index; CPNI, Cholesterol-modified Prognostic Nutritional Index.

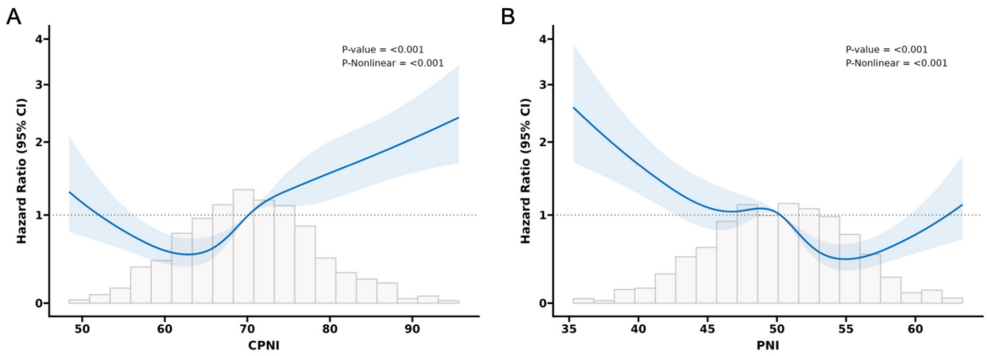

Figure 1. RCS analysis using the Cox proportional hazards model to explore the nonlinear relationship between nutritional indices (CPNI and PNI) and OS. RCS, restricted cubic spline; CPNI, Cholesterol-modified Prognostic Nutritional Index, PNI, Prognostic Nutritional Index; OS, overall survival.

including the 1-year, 3-year, and 5-year area under the curve (AUC) values for each nutritional indicator for both OS and RFS, was presented in Table 2.

The Kaplan-Meier method was employed to explore the relationship between malnutrition, as determined by various nutritional indices, and OS and RFS. Meanwhile, all subgroup analyses predicting OS and RFS based on different nutritional indicators were respectively presented in Supplementary Figures S10 and S11 (*https://www.biosciencetrends.com/supplementaldata/206*). According to the CPNI diagnostic criteria, survival curves for OS demonstrated that malnourished patients had lower survival rates across the overall cohort and within specific subgroups such as males and females, and patients classified as underweight, normal weight, and overweight, as well as those categorized as BCLC stage A and B (Figure 4). Similarly, survival curves for RFS revealed that malnourished patients had higher recurrence rates among the overall patient cohort, males, and patients of normal weight, overweight, underweight, and those classified as BCLC stage A and B (Figure 5).

Under the CONUT diagnostic criteria, survival curve comparisons predicting OS revealed no significant differences across several groups, including overall HCC patients, as well as subgroups such as males and females, patients categorized as underweight, of normal weight, overweight, or obese, and those classified in the BCLC stages 0, A, and B (Supplemental Figure S4, *https://www.biosciencetrends.com/supplementaldata/206*). However, survival curves predicting RFS indicated that malnourished patients had higher recurrence rates among female patients (Supplemental Figure S7C, *https://www.biosciencetrends.com/supplementaldata/206*).

Under the NRI diagnostic criteria, survival curves predicting OS showed that malnourished patients had lower survival rates across several groups, including the overall patient cohort and specific subgroups such as males, females, those of normal weight, and patients classified in BCLC stages A and B (Supplemental

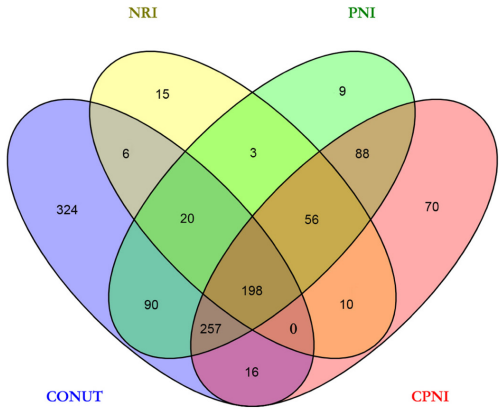

Figure 2. Venn diagram for malnutrition diagnosis criteria: overlapping patient counts. CONUT, Controlling Nutritional Status score; CPNI, Cholesterol-modified Prognostic Nutritional Index. NRI, Nutritional Risk Index; PNI, Prognostic Nutritional Index.

Figure S5, *https://www.biosciencetrends.com/supplementaldata/206*). Additionally, survival curves predicting recurrence-free survival (RFS) revealed that malnourished patients had higher recurrence rates in the overall patient cohort, among males, patients of normal weight, and those classified as BCLC stage A (Supplemental Figure S8, *https://www.biosciencetrends.com/supplementaldata/206*).

Under the PNI diagnostic criteria, survival curves predicting OS showed that malnourished patients exhibited lower survival rates in the overall cohort, as well as within specific subgroups including male and female patients, those classified as underweight, normal weight, overweight, and categorized as BCLC stage A (Supplemental Figure S6, *https://www.biosciencetrends.com/supplementaldata/206*). Furthermore, survival curves predicting RFS revealed that malnourished patients had higher recurrence rates in the overall patient cohort, among males, females, patients of normal weight, overweight, and those classified as BCLC stages 0 and A (Supplemental Figure S9, *https://www.biosciencetrends.com/supplementaldata/206*).

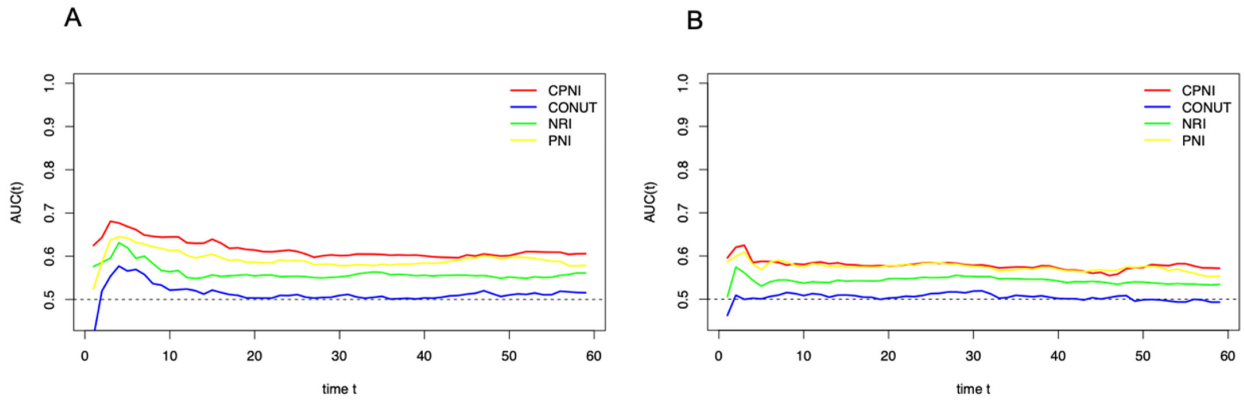

Figure 3. The time-dependent ROC of different nutritional indices predicting (A) OS and (B) RFS in patients with HCC. OS, overall survival; RFS, Recurrence-free survival; CONUT, Controlling Nutritional Status score; CPNI, Cholesterol-modified Prognostic Nutritional Index. NRI, Nutritional Risk Index; PNI, Prognostic Nutritional Index.

Table 2. The AUCs of nutrition indicators for OS and RFS in patients with HCC

Indicators	OS			RFS		
	1-year AUC	3-year AUC	5-year AUC	1-year AUC	3-year AUC	5-year AUC
CONUT	0.524	0.501	0.512	0.511	0.507	0.494
NRI	0.551	0.557	0.563	0.539	0.547	0.537
PNI	0.602	0.579	0.583	0.580	0.571	0.556
CPNI	0.631	0.602	0.612	0.586	0.575	0.573

AUC, area under the curve; OS, overall survival; HCC, hepatocellular carcinoma; RFS, Recurrence-free survival; CONUT, Controlling Nutritional Status score; NRI, Nutritional Risk Index; PNI, Prognostic Nutritional Index; CPNI, Cholesterol-modified Prognostic Nutritional Index.

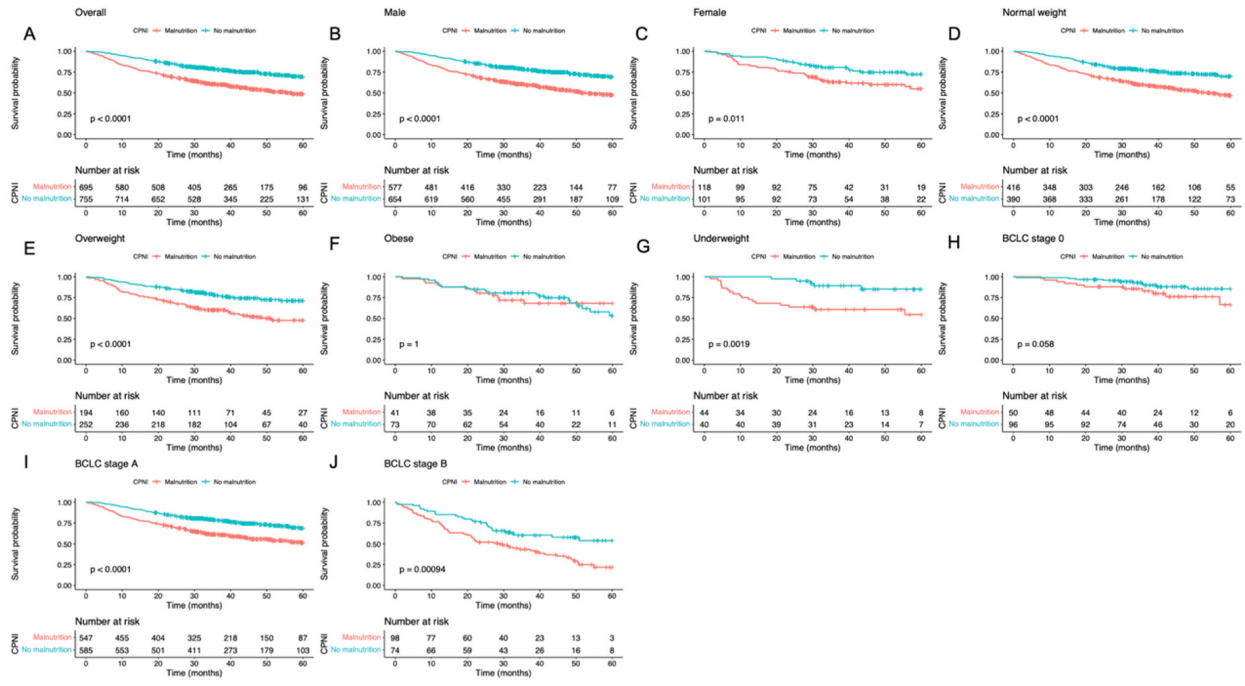

Figure 4. Kaplan-Meier analysis of OS in HCC patients classified by CPNI criteria into malnourished and non-malnourished groups across all populations and subgroups.

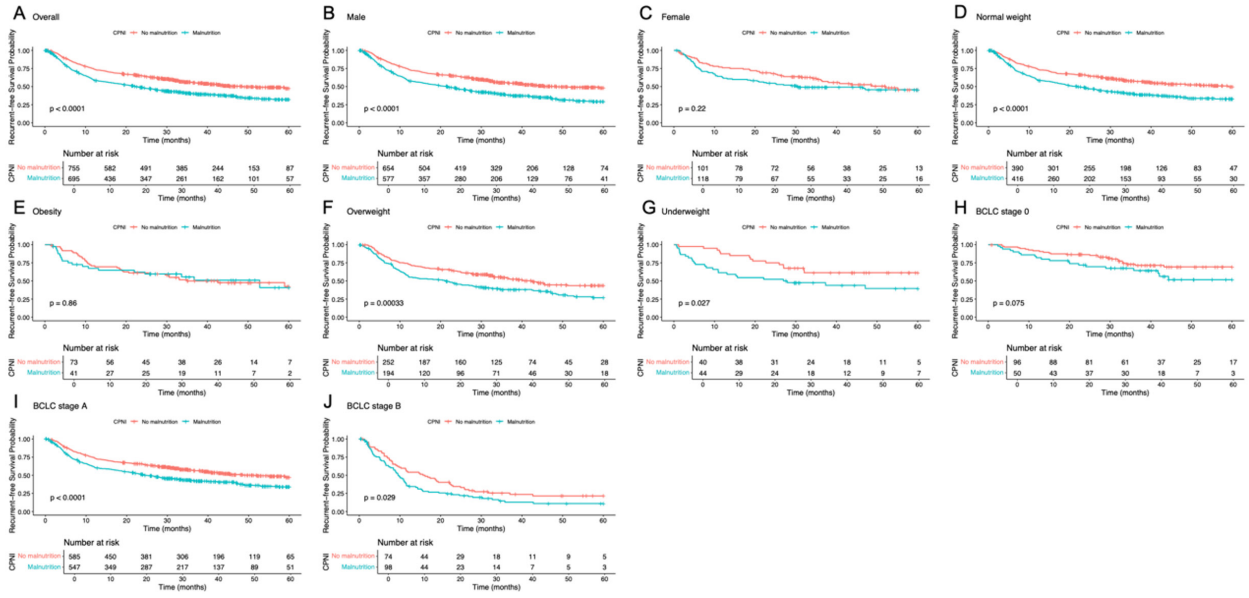

Figure 5. Kaplan-Meier analysis of RFS in HCC patients classified by CPNI criteria into malnourished and non-malnourished groups across all populations and subgroups.

3.4. Association of CPNI with clinicopathological factors in HCC patients

Among 1,450 HCC patients, 695 (47.9%) were classified as malnourished and 755 (52.1%) were not malnourished. The baseline clinicopathological characteristics of both groups are presented in Table 3. Malnutrition, as identified by the CPNI criteria, was significantly related to several clinical and pathological features: increased age, lower BMI, a higher prevalence of underweight, and reduced hemoglobin levels. Additional associations include decreased white blood cell count, neutrophil count, total bilirubin and triglyceride, as well as increased aspartate aminotransferase, prolonged prothrombin time, high-density lipoprotein and low-density lipoprotein. Malnourished patients also frequently exhibited worse liver function, larger tumor diameters, higher BCLC stages, and higher rates of major hepatectomy, and transfusion requirements. Poor tumor differentiation, microsatellites, microvascular invasion, and cirrhosis were also more common in this group.

3.5. Univariate and multivariate cox regression analyses of nutritional Indices for OS and RFS

Univariate and multivariate analyses with Cox proportional hazards model showed that CONUT scores were not significantly correlated with OS or RFS in HCC patients, as depicted in Table 4. Under the NRI criteria, univariate analysis showed a significant association between malnutrition and both OS and RFS; however, this association was not maintained in the multivariate analysis. In contrast, both PNI and CPNI were identified as independent prognostic factors in both univariate and multivariate analyses. Detailed results from these analyses for each nutritional indicator are presented separately in Supplemental Tables S1-S4 (*https://www.biosciencetrends.com/supplementaldata/206*).

Multivariable analysis for OS was adjusted by age, HBsAg, AFP, PLT, WBC, NE, ALT, AST, PT, HDL, LDL, ALBI Grade, BCLC stage, hypertension, major hepatectomy, transfusion, Differentiation, Microsatellites, MVI; Multivariable analysis for RFS was adjusted by age, HBsAg, AFP, HB, PLT, WBC, NE, ALT, AST, PT, TP, ALBI Grade, BCLC stage, hypertension, major hepatectomy, transfusion, Differentiation, Microsatellites, MVI.

4. Discussion

To our knowledge, this is the first study to explore the association between CPNI and prognosis of HCC patients undergoing liver resection. In this study, we assessed the capability of the CPNI to evaluate nutritional status and predict survival in HCC patients undergoing liver resection. Univariate and multivariate Cox regression analyses revealed that the CPNI was an independent predictor of both OS and RFS in HCC patients after liver resection. Under CPNI criteria, malnutrition was significantly associated with a range of adverse conditions including underweight, deteriorated liver function, larger tumor diameters, advanced BCLC stages, increased occurrences of major hepatectomy, and higher transfusion requirements. Additionally, malnourished patients exhibited poor tumor differentiation, the presence of microsatellites, microvascular invasion, and cirrhosis. Time-dependent ROC curves used to assess predictive accuracy over time showed that CPNI had superior prognostic performance

Table 3. Comparison of clinicopathological factors between malnourished and non-malnourished patients stratified by CPNI

Characteristics	No malnutrition *n* =755	Malnutrition *n* = 695	*P* value
Sex, male, *n* (%)	654 (86.6)	577 (83.0)	0.066
Age, years, median (IQR)	52.0 [45.0;61.0]	55.0 [47.0;64.0]	< 0.001
BMI, kg/m^2, median (IQR)	23.4 [21.3;25.7]	22.6 [20.7;24.8]	< 0.001
BMI group, n (%)			0.002
Normal weight	390 (51.7)	416 (59.9)	
Obesity	73 (9.67)	41 (5.90)	
Overweight	252 (33.4)	194 (27.9)	
Underweight	40 (5.30)	44 (6.33)	
HBsAg, positive, *n* (%)	617 (81.7)	577 (83.0)	0.562
HCV, positive, *n* (%)	15 (1.99)	9 (1.29)	0.409
AFP, ≥ 400ng/mL, *n* (%)	109 (14.4)	117 (16.8)	0.236
Hemoglobin, g/L, median (IQR)	148 [137;158]	139 [128;151]	< 0.001
Platelets, 10^9/L, median (IQR)	132 [99.0;174]	129 [89.0;184]	0.442
WBC, 10^9/L, median (IQR)	5.57 [4.60;6.82]	4.89 [3.97;6.10]	< 0.001
NE, 10^9/L, median (IQR)	3.19 [2.43;4.10]	2.91 [2.22;3.95]	0.001
LY, 10^9/L, median (IQR)	1.67 [1.31;2.10]	1.29 [1.00;1.59]	< 0.001
Cholesterol, mmol/L, median (IQR)	3.85 [3.40;4.36]	4.22 [3.64;4.83]	< 0.001
Albumin, g/L, median (IQR)	44.7 [42.7;46.8]	40.0 [37.7;42.1]	< 0.001
ALT, U/L, median (IQR)	34.0 [24.0;50.0]	35.0 [24.0;53.0]	0.410
AST, U/L, median (IQR)	33.0 [26.0;43.0]	40.0 [28.0;56.0]	< 0.001
Prothrombin time, s, median (IQR)	11.9 [11.3;12.6]	12.2 [11.5;12.9]	< 0.001
Tbil, μmol/L, median (IQR)	14.0 [10.8;18.0]	13.3 [10.1;17.9]	0.035
Total protein, g/L, median (IQR)	72.1 [68.8;75.8]	68.2 [64.8;71.7]	< 0.001
Triglyceride, mmol/L, median (IQR)	0.97 [0.74;1.33]	0.91 [0.70;1.21]	0.007
HDL, mmol/L, median (IQR)	1.18 [0.96;1.42]	1.22 [1.00;1.52]	0.011
LDL, mmol/L, median (IQR)	2.21 [1.82;2.66]	2.40 [2.00;2.99]	< 0.001
ALBI grade, 2, *n* (%)	26 (3.44)	282 (40.6)	< 0.001
Tumor diameter, ≥ 5cm, *n* (%)	307 (40.7)	412 (59.3)	< 0.001
Number of tumors, multiple, *n* (%)	110 (14.6)	119 (17.1)	0.208
BCLC stage, *n* (%)			< 0.001
0	96 (12.7)	50 (7.19)	
A	585 (77.5)	547 (78.7)	
B	74 (9.80)	98 (14.1)	
Hypertension, yes, *n* (%)	140 (18.5)	91 (13.1)	0.006
Diabetes, yes, *n* (%)	66 (8.74)	56 (8.06)	0.708
Cardiovascular disease, yes, *n* (%)	16 (2.12)	10 (1.44)	0.437
Anatomical resection, yes, *n* (%)	247 (32.7)	247 (35.5)	0.281
Major hepatectomy, yes, *n* (%)	79 (10.5)	111 (16.0)	0.002
Transfusion, yes, *n* (%)	22 (2.91)	49 (7.05)	< 0.001
Differentiation, III-IV, *n* (%)	310 (41.1)	322 (46.3)	0.049
Microsatellites, yes, *n* (%)	45 (5.96)	61 (8.78)	0.050
Microvascular invasion, yes, *n* (%)	182 (24.1)	207 (29.8)	0.017
Cirrhosis, yes, *n* (%)	370 (49.0)	380 (54.7)	0.035

CPNI, Cholesterol-modified Prognostic Nutritional Index.

Table 4. Univariate and multivariate analyses with Cox proportional hazards in the entire population

	OS				RFS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
CONUT	1.06 (0.88-1.27)	0.522	1.15 (0.93-1.43)	0.202	1.02 (0.88-1.17)	0.756	1.00 (0.86-1.19)	0.913
NRI	1.74 (1.44-2.11)	< 0.001	1.12 (0.88-1.43)	0.345	1.50 (1.27-1.76)	< 0.001	1.08 (0.88-1.32)	0.481
PNI	1.81 (1.51-2.16)	< 0.001	1.48 (1.19-1.83)	< 0.001	1.54 (1.34-1.78)	< 0.001	1.43 (1.19-1.71)	< 0.001
CPNI	2.08 (1.73-2.49)	< 0.001	1.77 (1.43-2.18)	< 0.001	1.60 (1.38-1.84)	< 0.001	1.50 (1.26-1.77)	< 0.001

OS, overall survival; RFS, Recurrence-free survival; CONUT, Controlling Nutritional Status score; NRI, Nutritional Risk Index; PNI, Prognostic Nutritional Index; CPNI, Cholesterol-modified Prognostic Nutritional Index.

for OS compared to other nutritional indices such as CONUT, NRI, and PNI. Additionally, CPNI showed marginally higher accuracy in predicting RFS than PNI and significantly outperformed both CONUT and NRI. Subgroup analyses indicated that malnutrition, as identified by CPNI criteria, was associated with a lower

OS rate across various groups. This included males and females, and those categorized as underweight, normal weight, and overweight, as well as patients classified in BCLC stages A and B. Similarly, the analyses showed a higher recurrence rate associated with malnutrition in similar groups, including males, those classified as underweight, normal weight, or overweight, and patients categorized in BCLC stages A and B.

Malnutrition was prevalent in HCC patients who underwent liver resection, with rates ranging from 21.2% to 62.8% according to four different nutritional assessment tools. Consistent with previous studies, malnutrition represents a significant burden that is frequently underdiagnosed in patients with HCC undergoing liver resection (*4*). BMI is a widely used, clinically available objective variable for assessing malnutrition (*21,22*). However, BMI has become less universally applicable as newer nutritional assessment indices, which identify malnutrition more effectively, provide a more comprehensive evaluation of health (*23-25*). As BMI increases, the incidence of malnutrition decreases. Consistent with previous studies, this study also found a high proportion of malnutrition among overweight and obese patients(*26-28*). Malnourished patients who are overweight, normal weight and underweight faced poorer OS and RFS. Nevertheless, no significant differences in survival rates and recurrence rates were observed among the obese subgroups.

CPNI, as a newly proposed tool for malnutrition assessment, has shown more accurate and stable capabilities in assessing the nutritional status of patients than several objective malnutrition assessment indices. Owing to its objectivity calculated from regular blood test indicators and non-invasiveness, CPNI has shown greater potential to assess the nutritional status of preoperative HCC patients and predict their prognosis. The predictive value of CPNI for patient prognosis may be explained by the incorporation of key factors such as serum cholesterol, lymphocyte counts, and serum albumin. High cholesterol levels may increase cancer risk, intensify tumor aggressiveness, and worsen patient outcomes (*29-32*). Albumin is the most thoroughly investigated protein in the context of malnutrition diagnosis (*33*). Furthermore, albumin serves as an important predictor for HCC outcomes and is shown to inhibit HCC cell proliferation (*34,35*). Lower lymphocyte levels are associated with poor prognosis in solid tumors, highlighting the vital role of the immune response in HCC outcomes (*36*).

However, this study has some limitations. First, it was a retrospective single-center study, and the findings need to be confirmed through randomized controlled trials or large-cohort studies. Second, the predominance of hepatitis B in the patient sample may not represent regions such as Europe or the United States. Third, additional studies are essential to clarify the influence of CPNI in particularly smaller patient subgroups, such as those with BCLC stage 0 and those who are obese.

In conclusion, this study suggests that CPNI is a precise and stable instrument for evaluating nutritional status and forecasting survival in HCC patients who underwent liver resection, potentially offering advantages over other indicators such as CONUT, NRI, and PNI, and thus could improve clinical decision-making.

Funding: This work was supported by grants from the National Natural Science Foundation of China (Nos. 81770566, 82000599), NHC Key Laboratory of Echinococcosis Prevention and Control (No. 2021WZK1004) and Health Commission of the Tibet Autonomous Region (No.311220432).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Elia M, Zellipour L, Stratton RJ. To screen or not to screen for adult malnutrition? Clin Nutr. 2005; 24:867-884.
2. Schütte K, Tippelt B, Schulz C, Röhl FW, Feneberg A, Seidensticker R, Arend J, Malfertheiner P.. Malnutrition is a prognostic factor in patients with hepatocellular carcinoma (HCC). Clin Nutr. 2015; 34:1122-1127.
3. Arends J. Struggling with nutrition in patients with advanced cancer: nutrition and nourishment-focusing on metabolism and supportive care. Ann Oncol. 2018; 29(suppl_2):ii27-ii34.
4. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol. 2019; 70:172-193.
5. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021; 7:7.
6. Lee KF, Chong CCN, Fong AKW, Fung AKY, Lok HT, Cheung YS, Wong J, Lai PBS. Pattern of disease recurrence and its implications for postoperative surveillance after curative hepatectomy for hepatocellular carcinoma: experience from a single center. Hepatobiliary Surg Nutr. 2018; 7:320-330.
7. Schütte K, Kipper M, Kahl S, Bornschein J, Götze T, Adolf D, Arend J, Seidensticker R, Lippert H, Ricke J, Malfertheiner P. Clinical characteristics and time trends in etiology of hepatocellular cancer in Germany. Digestion. 2013; 87:147-159.
8. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, Rodríguez F, Fernández G. CONUT: A tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp. 2005; 20:38-45.
9. Harimoto N, Yoshizumi T, Inokuchi S, *et al.* Prognostic Significance of Preoperative Controlling Nutritional Status (CONUT) Score in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma: A Multi-institutional Study. Ann Surg Oncol. 2018; 25:3316-3323.
10. Tokunaga R, Sakamoto Y, Nakagawa S, Ohuchi M, Izumi D, Kosumi K, Taki K, Higashi T, Miyamoto Y, Yoshida N, Oki E, Watanabe M, Baba H. CONUT: A novel independent predictive score for colorectal cancer patients undergoing potentially curative resection. Int J Colorectal Dis. 2017; 32:99-106.
11. Zhang Y, Zhang X. Controlling nutritional status score, a promising prognostic marker in patients with

gastrointestinal cancers after surgery: A systematic review and meta-analysis. Int J Surg. 2018; 55:39-45.
12. Toyokawa G, Kozuma Y, Matsubara T, Haratake N, Takamori S, Akamine T, Takada K, Katsura M, Shimokawa M, Shoji F, Okamoto T, Maehara Y. Prognostic impact of controlling nutritional status score in resected lung squamous cell carcinoma. J Thorac Dis. 2017; 9:2942-2951.
13. Qian W, Xiao-Jian J, Jun H, Liang L, Xiao-Yong C. Comparison of the Value of Multiple Preoperative Objective Nutritional Indices for the Evaluation of Prognosis after Hepatectomy for Hepatocellular Carcinoma. Nutr Cancer. 2022; 74:3217-3227.
14. Bo Y, Yao M, Zhang L, Bekalo W, Lu W, Lu Q. Preoperative Nutritional Risk Index to predict postoperative survival time in primary liver cancer patients. Asia Pac J Clin Nutr. 2015; 24:591-597.
15. Imai D, Maeda T, Shimokawa M, Wang H, Yoshiya S, Takeishi K, Itoh S, Harada N, Ikegami T, Yoshizumi T, Mori M. Prognostic nutritional index is superior as a predictor of prognosis among various inflammation-based prognostic scores in patients with hepatocellular carcinoma after curative resection. Hepatol Res. 2020; 50:101-109.
16. Saito Y, Imura S, Morine Y, Ikemoto T, Yamada S, Shimada M. Preoperative prognostic nutritional index predicts short- and long-term outcomes after liver resection in patients with hepatocellular carcinoma. Oncol Lett. 2021; 21:153.
17. Sim JH, Kim SH, Jun IG, Kang SJ, Kim B, Kim S, Song JG. The Association between Prognostic Nutritional Index (PNI) and Intraoperative Transfusion in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma: A Retrospective Cohort Study. Cancers (Basel). 2021; 13:2508.
18. Wang D, Hu X, Xiao L, Long G, Yao L, Wang Z, Zhou L. Prognostic Nutritional Index and Systemic Immune-Inflammation Index Predict the Prognosis of Patients with HCC. J Gastrointest Surg. 2021; 25:421-427.
19. Shi J, Liu T, Ge Y, *et al*. Cholesterol-modified prognostic nutritional index (CPNI) as an effective tool for assessing the nutrition status and predicting survival in patients with breast cancer. BMC Med. 2023; 21:512.
20. Raposeiras Roubín S, Abu Assi E, Cespón Fernandez M, *et al*. Prevalence and Prognostic Significance of Malnutrition in Patients With Acute Coronary Syndrome. J Am Coll Cardiol. 2020; 76:828-840.
21. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, Muscaritoli M, Nyulasi I, Ockenga J, Schneider SM, de van der Schueren MA, Singer P. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015; 34:335-340.
22. Burman M, Säätelä S, Carlsson M, Olofsson B, Gustafson Y, Hörnsten C. Body mass index, Mini Nutritional Assessment, and their association with five-year mortality in very old people. J Nutr Health Aging. 2015; 19:461-467.
23. Mokaddem F. BMI and FFMI do not seem universally applicable in nutritional assessment and the usefulness of SGA and functional evaluation should not be overlooked. Clin Nutr. 2016; 35:236.
24. Tan S, Jiang J, Qiu L, Liang Y, Meng J, Tan N, Xiang B. Prevalence of Malnutrition in Patients with Hepatocellular Carcinoma: A Comparative Study of GLIM Criteria, NRS2002, and PG-SGA, and Identification of Independent Risk Factors. Nutr Cancer. 2024; 76:335-344.
25. Bell JJ, Pulle RC, Lee HB, Ferrier R, Crouch A, Whitehouse SL. Diagnosis of overweight or obese malnutrition spells DOOM for hip fracture patients: A prospective audit. Clin Nutr. 2021; 40:1905-1910.
26. Leibovitz E, Giryes S, Makhline R, Zikri Ditch M, Berlovitz Y, Boaz M. Malnutrition risk in newly hospitalized overweight and obese individuals: Mr NOI. Eur J Clin Nutr. 2013; 67:620-624.
27. Sharma K, Mogensen KM, Robinson MK. Under-Recognizing Malnutrition in Hospitalized Obese Populations: The Real Paradox. Curr Nutr Rep. 2019; 8:317-322.
28. Freeman AM, Aggarwal M. Malnutrition in the Obese: Commonly Overlooked But With Serious Consequences. J Am Coll Cardiol. 2020; 76:841-843.
29. Brindisi M, Fiorillo M, Frattaruolo L, Sotgia F, Lisanti MP, Cappello AR. Cholesterol and Mevalonate: Two Metabolites Involved in Breast Cancer Progression and Drug Resistance through the ERRα Pathway. Cells. 2020; 9:1819.
30. Ruan GT, Xie HL, Hu CL, *et al*. Comprehensive prognostic effects of systemic inflammation and Insulin resistance in women with breast cancer with different BMI: a prospective multicenter cohort. Sci Rep. 2023; 13:4303.
31. Che L, Chi W, Qiao Y, *et al*. Cholesterol biosynthesis supports the growth of hepatocarcinoma lesions depleted of fatty acid synthase in mice and humans. Gut. 2020; 69:177-186.
32. He M, Zhang W, Dong Y, Wang L, Fang T, Tang W, Lv B, Chen G, Yang B, Huang P, Xia J. Pro-inflammation NF-κB signaling triggers a positive feedback *via* enhancing cholesterol accumulation in liver cancer cells. J Exp Clin Cancer Res. 2017; 36:15.
33. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of Blood Biomarkers Associated with Risk of Malnutrition in Older Adults: A Systematic Review and Meta-Analysis. Nutrients. 2017; 9:829.
34. Fu X, Yang Y, Zhang D. Molecular mechanism of albumin in suppressing invasion and metastasis of hepatocellular carcinoma. Liver Int. 2022; 42:696-709.
35. Nojiri S, Joh T. Albumin suppresses human hepatocellular carcinoma proliferation and the cell cycle. Int J Mol Sci. 2014; 15:5163-5174.
36. Tan CS, Read JA, Phan VH, Beale PJ, Peat JK, Clarke SJ. The relationship between nutritional status, inflammatory markers and survival in patients with advanced cancer: a prospective cohort study. Support Care Cancer. 2015; 23:385-391.

Received April 30, 2024; Revised June 27, 2024; Accepted July 23, 2024.

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Released online in J-STAGE as advance publication Julr 27, 2024.