Original Article

Comprehensive nutritional index for predicting overall survival in hepatocellular carcinoma patients after multiple transarterial chemoembolization

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Background and Objectives: Little is known about nutritional status in patients with hepatocellular carcinoma (HCC) after multiple rounds of transarterial chemoembolization (TACE). We established a comprehensive nutritional index (CNI) and evaluated its prognostic value for overall survival (OS) and time to progression (TTP). **Methods and Study Design:** HCC patients (N=282) who underwent multiple TACE treatments were enrolled. CNI was established by principal component analysis based on body mass index, usual body weight percentage, hemoglobin, total lymphocyte count, and albumin; the cutoff value was determined by receiver operating characteristic curve and Youden index analysis. The correlation between CNI and treatment-related complications was analyzed with Spearman's method. The Kaplan–Meier method with log-rank test and Cox proportional hazards model were used to compare the prognostic values of CNI, prognostic nutritional index (PNI), and nutrition risk index (NRI) for OS and TTP. **Results:** Nutritional status declined after repeated TACE (p<0.001). CNI (cutoff=0.251) varied according to albumin-bilirubin grade, tumor size, and number of TACE treatments (p<0.001 or 0.025) and was negatively correlated with rate of serious complications (r=−0.185, p=0.002). Patients with low CNI had shorter OS (p=0.014) and TTP (p=0.007); high CNI predicted longer OS (hazard ratio [HR], 0.72; 95% confidence interval [CI]: 0.52–1.00, p=0.048) and TTP (HR, 0.69; 95% CI: 0.50–0.94, p=0.019). Post-treatment PNI and NRI were unrelated to prognosis (p>0.05). **Conclusions:** HCC patients have poor nutritional status after multiple TACE treatments, which predicts shorter OS and TTP. The prognostic performance of CNI is superior to those of PNI and NRI.

Key Words: hepatocellular carcinoma, post-transarterial chemoembolization, nutrition, prognosis, overall survival

INTRODUCTION

Liver cancer is the sixth most common cancer and was the fourth leading cause of cancer-related death worldwide in 2018 (ranking second in males), with about 841,000 new cases and 782,000 deaths per year.[1] Hepatocellular carcinoma (HCC) accounts for 90% of cases of primary liver cancer.[2] Hepatectomy and liver transplantation are the first-line curative treatments for HCC.[2,3] However, as there are no obvious clinical manifestations in the early stage of HCC, the optimal window for resection is often missed, with only 9%–29% of patients benefiting from hepatectomy.[4] Transarterial chemoembolization (TACE) is the first-choice treatment for HCC patients with unresectable disease.[5]

Malnutrition is common in cancer patients and has many negative effects including lower tolerance to treatment, reduced quality of life, longer length of hospital stay, higher infections rates and costs of care, and shorter overall survival (OS). Malnutrition reportedly affects anywhere from 20% to >70% of cancer patients,[6] and 86.6% of those with liver cancer.[7] There are several possible causes of malnutrition in cancer patients. 1) The tumor induces the production of proinflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-1, and IL-6, resulting in systemic inflammation; this leads to anorexia, muscle wasting, altered liver metabolism, and fat usage and depletion.[6,8,9] 2) Carbohydrate, fat, and protein metabolism mainly occurs in the liver; however, most HCC patients have impaired liver function because of the co-occurrence of chronic hepatitis, cirrhosis, and hepatic insufficiency.[10] 3) TACE treatments often lead to post-embolization syndrome (nausea and vomiting, pain, fever, etc), which affects appetite and nutrient intake. 4) Anxiety and depression in cancer patients may also contribute

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Manuscript received 27 December 2020. Initial review completed 08 January 2021. Revision accepted 25 January 2021.
doi: 10.6133/apjcn.202103_30(1).0002

to loss of appetite, thereby exacerbating malnutrition.[11,12] Hence, the management of nutrition in HCC patients is critical for improving clinical outcomes.

Prognostic nutritional index (PNI)[13] and nutrition risk index (NRI)[14] are used to evaluate preoperative nutritional status and predict postoperative risk of complications and probability of survival. Body mass index (BMI), albumin (ALB), and total lymphocyte count (TLC) also serve as indicators of nutritional status. However, a single parameter or either PNI or NRI alone does not adequately reflect overall nutritional status; moreover, the latter two have been used almost exclusively for preoperative assessment and have provided no information on nutritional status after multiple rounds of TACE. The comprehensive nutrition index (CNI), which is based on five nutrition parameters—namely, BMI, usual body weight percentage (UBW%), hemoglobin (Hb), TLC, and ALB—has been applied to the assessment of nasopharyngeal carcinoma patients following treatment.[15,16] However, few studies have used CNI to assess the overall nutritional status of HCC patients.

To this end, in the present study we established a CNI to evaluate nutritional status in HCC patients who have undergone multiple TACE treatments, and investigated the relationship between CNI and OS, time to progression (TTP), and rate of treatment-related complications. We also compared the prognostic performance of CNI, PNI, and NRI in order to identify the index with the greatest clinical utility.

METHODS

Study population

This retrospective study included 282 HCC patients who underwent TACE as a first-line treatment at Sun Yat-sen University Cancer Center (Guangzhou, China) between October 2014 and December 2015. The inclusion criteria were as follows: 1) newly diagnosed primary HCC according to the Standards for the Diagnosis and Treatment of Primary Liver Cancer (2011 version);[17] 2) unresectable HCC or refusal of liver resection; 3) accepted TACE as first-line treatment and underwent at least two TACE treatments; 4) ≥18 years old; and 5) follow-up time >2 months. Patients for whom complete medical records were unavailable or whose first visit and follow-up were at other centers were excluded. The study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center, and the protocol was in accordance with the ethical standards outlined in the Helsinki Declaration. The patient selection process is outlined in Figure 1.

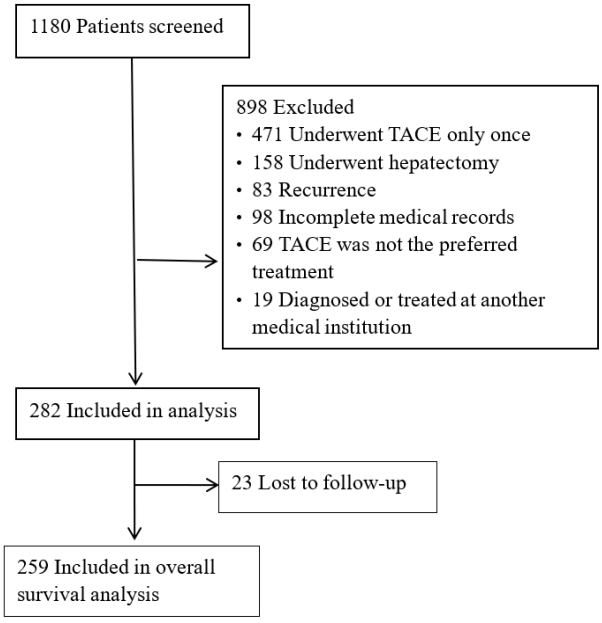

Figure 1. Flow diagram of patient enrollment and follow-up

Treatment

The TACE procedure was performed by a physician who had received training in interventional radiology. Using the Seldinger technique, percutaneous puncture of the femoral artery was performed and a microcatheter (Renegade Hi-Flo; Boston Scientific, Boston, MA, USA) was inserted into the celiac artery or common hepatic artery, and angiography was used to assess blood supply to the tumor. A mixture of lobaplatin (30–50 mg) and pirarubicin (30–50 mg) with lipiodol (5–15 mL) was injected under fluoroscopic monitoring; the amount of mixture injected depended on tumor size, number, and arterial blood flow. Technical success was defined as no tumor staining observed by angiography at the end of the procedure. After removing the microcatheter, patients returned to the ward for postoperative observation until they were discharged. According to the patient's physical condition, treatment tolerance, efficacy, and needs, TACE was repeated every 4–6 weeks.

A subset of patients was treated by TACE combined with other therapies: 95 patients (33.7%) underwent microwave ablation and 41 (14.5%) received ^{125}I particle implantation, radiotherapy, or targeted therapy.

Nutritional evaluation

HCC patients' nutritional status was evaluated with three indices (CNI, PNI, and NRI) that were calculated from hematologic, biochemical, and anthropometric data obtained from medical records within 48 h before or after the first admission and immediately after the last TACE treatment. CNI was calculated based on five nutrition parameters - ie, BMI, UBW%, Hb, TLC, and ALB. BMI was calculated as weight (kg)/height^2 (m). UBW was defined as body weight at first admission, and UBW% was calculated as present body weight (kg)/UBW (kg) × 100%. PNI was calculated as ALB (g/L) + 0.005 × TLC (count/μL), and NRI as (1.519 × ALB, g/L) + (41.7 × present/usual body weight [kg]). The detailed measurement methods of all nutrition parameters are described elsewhere.[16]

Data collection and follow-up

Demographic (age, sex, height, and weight) and medical (underlying disease, viral hepatitis, cirrhosis, Barcelona Clinic Liver Cancer [BCLC] stage, ALB-bilirubin [ALBI] grade, tumor size, tumor number, tumor capsule, vascular invasion, neoplasm metastasis, and portal vein tumor thrombus) data were obtained from medical records and using a self-report questionnaire. Treatment approaches, post-embolism syndrome, and complications were also recorded. OS was the primary outcome measure and was calculated from the date of first diagnosis to last follow-

up or death from any cause. Survival status was determined from medical records and through the follow-up system at our center. Patients whose survival status was uncertain as of April 2020 were followed up with another telephone interview. TTP was defined as the time from first diagnosis to the occurrence of new lesions or metastasis by computed tomography, magnetic resonance imaging, B-mode ultrasound, or chest X-ray.

Statistical analysis

All data were entered into a spreadsheet in Excel 2016 (Microsoft, Redmond, WA, USA). SPSS v21.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses, and a two-tailed p value <0.05 was taken as statistical significance. Demographic and disease-related information and single nutrition parameters are presented as mean±standard deviation or frequency (percentage) depending on the data type. Nutrition parameters before and after multiple TACE treatments were compared with the paired-samples t test. Principal component analysis was used to extract several principal components that reflected >70% of the original data information, and CNI was calculated according to their respective contributions. A receiver operating characteristic (ROC) curve and the Youden index were used to establish cutoff values for CNI, PNI, and NRI. The correlation between complications associated with TACE and CNI was evaluated with Spearman's rank correlation coefficient. The Kaplan–Meier method and log-rank test were used to assess survival and disease progression. Univariate and multivariable Cox regression analyses were performed to determine whether CNI, PNI, and NRI affect OS and TTP.

RESULTS

Clinicopathologic features and follow-up of the study population

A total of 282 patients who underwent multiple rounds of TACE for primary HCC were included in the analysis (mean age, 5 2.5±11.3 years; 261 men [92.6%]). Hypertension, diabetes, heart disease, and other underlying diseases were present in 24.1% of patients; 84.8% had hepatitis B virus (HBV) and 41.8% had cirrhosis. Most patients had intermediate-to-advanced–stage cancer (BCLC stage B, 101/281 [35.8%]; BCLC stage C, 171/252 [60.6%]). According to ALBI grade, 140 patients (49.6%) had varying degrees of liver damage before TACE. Tumor characteristics and treatment information are shown in Table 1.

A total of 23 patients (8.2%) were lost to follow-up and their survival status was therefore unknown. The median duration of follow-up was 14 months (range, 2–69 months); 185 patients (71.4%) died from various causes. The median TTP was 5 months (range, 1–66 months) and 188 patients (66.7%) experienced disease progression.

Single nutrition parameters

All nutrition parameters decreased significantly (p<0.001) after multiple TACE treatments compared to the baseline measurements (taken at first admission) (Table 2). Weight loss occurred in 64.2% of patients (n=181) after multiple rounds of TACE, with 34.0% (n=96) losing >5% and 7.8% (n=22) losing >10% of their initial body weight.

Table 1. Clinicopathologic features of study participants (N=282)

Characteristic	n (%)/ Mean±SD
Age (years)	
18–44	71 (25.2)
45–59	126 (44.7)
≥60	85 (30.1)
Sex	
Male	261 (92.6)
Female	21 (7.4)
Underlying disease	
Yes	68 (24.1)
No	214 (75.9)
HBV virus hepatitis	
Yes	239 (84.8)
No	43 (15.2)
Cirrhosis	
Yes	118 (41.8)
No	164 (58.2)
BCLC stage	
A	10 (3.5)
B	101 (35.8)
C	171 (60.6)
ALBI grade	
1	142 (50.4)
2/3	140 (49.6)
AFP (ng/ml)	
≤400	139 (49.3)
>400	143 (50.7)
Tumor size (cm)	
≤5	50 (17.7)
>5	232 (82.3)
Tumor number	
Solitary	63 (22.3)
Multiple	219 (77.7)
Tumor capsule	
Wrapped	162 (57.4)
Invasive	120 (42.6)
Vascular invasion	
Yes	121 (42.9)
No	161 (57.1)
Neoplasm metastasis	
Yes	119 (42.2)
No	163 (57.8)
Portal vein tumor thrombus	
Yes	91 (32.3)
No	191 (67.7)
Number of TACE treatments	2.6±1.1
Ablation	
Yes	95 (33.7)
No	187 (66.3)
Combination therapy	
Yes	38 (13.5)
No	244 (86.5)

AFP: alpha fetoprotein; ALBI: albumin-bilirubin score; BCLC: Barcelona Clinic Liver Cancer; HBV: hepatitis B virus; TACE: transarterial chemoembolization.

The nutritional parameter showing the greatest decrease was ALB; 62.8% of patients (n=177) had abnormal ALB level (<35 g/L) after TACE, with 18.8% (n=53) showing a significant reduction (<30 g/L).

Calculation of CNI, PNI, and NRI and their cutoff values

CNI was established by principal components analysis based on five nutrition parameters (Hb, TLC, ALB, BMI, and UBW%) measured after multiple TACE treatments.

Table 2. Pre- and post-treatment single nutrition indices (N=282)

Variable	Pre-treatment (T1) mean±SD	Post-treatment (T2) mean±SD	T1−T2 mean±SD	t	*p* value
Weight (kg)	63.1±9.92	60.8±9.22	2.32±3.12	12.5	<0.001*
BMI (kg/m^2)	22.6±3.11	21.7±2.84	0.83±1.11	12.6	<0.001*
UBW%	100	96.5±4.48	3.47±4.48	13.0	<0.001*
Albumin (g/L)	39.7±4.60	33.6±4.42	6.03±4.56	22.3	<0.001*
TP (g/L)	72.4±6.28	64.5±7.59	7.86±8.18	16.1	<0.001*
CHO (mmol/L)	5.09±1.75	4.26±1.64	0.83±1.33	10.5	<0.001*
RBC (10^{12}/L)	4.74±0.78	4.11±0.81	0.63±0.53	19.7	<0.001*
Hb (g/L)	140±19.5	122±21.0	17.7±14.6	20.3	<0.001*
TLC (10^9/L)	1.60±0.64	0.92±0.56	0.68±0.68	16.7	<0.001*

BMI: body mass index; CHO: total cholesterol; Hb: hemoglobin; RBC: red blood cell count; SD: standard deviation; T1−T2: difference between pre- and post-treatment values; TLC: total lymphocyte count; TP: total protein; UBW%: usual body weight percentage.
*p value <0.05.

To ensure that the extracted principal components contained the maximum information on nutritional status, the first three principal components were retained; their contributions to the original data were determined to be 32.2%, 20.5%, and 18.7%, respectively, and their cumulative contribution was 71.4%. The three principal components were calculated using the following equations:

C1 = 0.828 × ZX1 + 0.266 × ZX2 + 0.771 × ZX3 + 0.388 × ZX4 + 0.327 × ZX5

C2= -0.033 × ZX1 + 0.651 × ZX2 − 0.203 × ZX3 + 0.497 × ZX4 − 0.557 × ZX5

C3= -0.106 × ZX1 + 0.709 × ZX2 − 0.015 × ZX3 - 0.537 × ZX4 − 0.363 × ZX5

where ZX1, ZX2, ZX3, ZX4, and ZX5 represent normalized Hb, TLC, ALB, BMI, and UBW%, respectively.

The CNI was calculated from the statistical weight coefficients of the three principal components as CNI=0.322×C1+0.205×C2+0.187×C3. The median CNI was −0.016 (range, −1.54–2.34); mean PNI and NRI were 38.20±5.38 (range, 23.10–58.00) and 91.32±7.17 (range, 70.92–107.98), respectively.

ROC curves and the Youden index were used to determine the cutoff values of the three nutritional indices for OS. The cutoff value for CNI was 0.251 (sensitivity, 0.419; specificity, 0.719; area under curve [AUC]=0.527). Patients were divided into two groups: those with high CNI (>0.2505; n=92) and those with low CNI (<0.2505; n=190). Cutoff values were 31.35 (sensitivity, 0.935; specificity, 0.149; AUC=0.506) for PNI and 93.38 (sensitivity=0.405; specificity=0.643; AUC=0.507) for NRI.

Relationship between CNI and clinicopathologic features

ALBI grade, tumor size, and number of TACE treatments differed significantly between patients with low and high CNI (p<0.05); however, no differences were observed for BCLC stage and other clinicopathologic features (Table 3). A higher ALBI grade was related to low CNI (p<0.001); 93.1% of patients with ALBI grade 3 had low CNI. Tumor size >5 cm (p=0.001) and more TACE treatments (p=0.025) were also associated with low CNI.

Correlations between CNI and complications of TACE

Complications following TACE treatment are summarized in Table 4. The most common complications were fever (n=225, 79.8%), upper abdominal pain (n=139, 49.3%), and nausea and vomiting (n=104, 36.9%). Serious complications included 13 cases of myelosuppression, two cases of upper gastrointestinal hemorrhage, and one case each of liver abscess and biloma. The correlation analysis indicated that CNI was negatively correlated with the incidence of serious complications (r=−0.185, p=0.002).

Predictive value of CNI for OS and TTP

The survival analysis revealed that patients with lower

Table 3. Comprehensive nutritional index scores for clinicopathologic parameters (N=282)

Parameter	Low CNI (n=190)	High CNI (n=92)	χ^2/Z	*p* value
BCLC stage				
A	5 (50.0)	5 (50.0)	2.402	0.301
B	65 (64.4)	36 (35.6)		
C	120 (70.2)	63 (29.8)		
Post-treatment ALBI				
1	8 (34.8)	15 (65.2)	19.849	<0.001*
2	155 (67.4)	75 (32.6)		
3	27 (93.1)	2 (6.9)		
Tumor size (cm)				
≤5	24 (48.0)	26 (52.0)	10.380	0.001*
>5	166 (71.6)	66 (28.4)		
Number of TACE treatments	2.7±1.1	2.5±2.5	2.235	0.025*

ALBI: albumin-bilirubin score; BCLC: Barcelona Clinic Liver Cancer; CNI: comprehensive nutritional index; TACE: transarterial chemoembolization.
*p value <0.05.

Table 4. Correlations between CNI and complications (N=282)

Variable	n (%)	r value	*p* value
Fever	225 (79.8)	−0.030	0.612
Upper abdominal pain	139 (49.3)	−0.074	0.217
Nausea and vomiting	104 (36.9)	0.063	0.289
Bloating and ascites	75 (26.6)	−0.011	0.857
Impaired hepatic function	88 (31.2)	−0.052	0.388
Impairment of renal function	9 (3.2)	−0.010	0.873
Jaundice	13 (4.6)	0.053	0.375
Serious complications	17 (6.0)	−0.185	0.002*

CNI: comprehensive nutritional index.
*p value <0.05.

CNI had shorter OS; median OS for patients with low CNI was 16.0 months (95% CI: 12.3–19.7 months) compared to 22.0 months (95% CI: 11.5–32.5 months) for those with high CNI (p=0.014). High CNI predicted longer OS in the univariate (hazard ratio [HR], 0.674; 95% confidence interval [CI]: 0.488–0.930; p=0.016) and multivariate (HR, 0.718; 95% CI: 0.517–0.997; p=0.048) analyses. BCLC stage (HR, 1.490; 95% CI: 1.147–1.936; p=0.003), number of TACE treatments (HR, 0.847; 95% CI: 0.741–0.969; p=0.015), ablation (HR, 0.598; 95% CI: 0.432–0.827; p=0.002), and combination therapy (HR, 0.486; 95% CI: 0.517–0.997; p=0.002) were also independent predictors of OS using the multivariate Cox proportional hazards model. However, post-treatment PNI and NRI did not predict OS (p>0.05) (Figure 2 and Table 5).

Median TTP was significantly shorter for patients with low CNI (6.0 months, 95% CI: 4.8–7.2 months) than for those with high CNI (10.0 months, 95% CI: 7.0–13.1 months) (p=0.007; Figure 3). Univariate and multivariate analyses demonstrated that age (HR, 0.984; 95% CI: 0.971–0.996; p=0.010), ablation (HR, 0.657; 95% CI: 0.484–0.892; p=0.007), and CNI (HR, 0.685; 95% CI: 0.499–0.941; p=0.019) predicted longer TTP in HCC patients after repeated TACE (Table 6). PNI and NRI were not predictive of TTP (p>0.05).

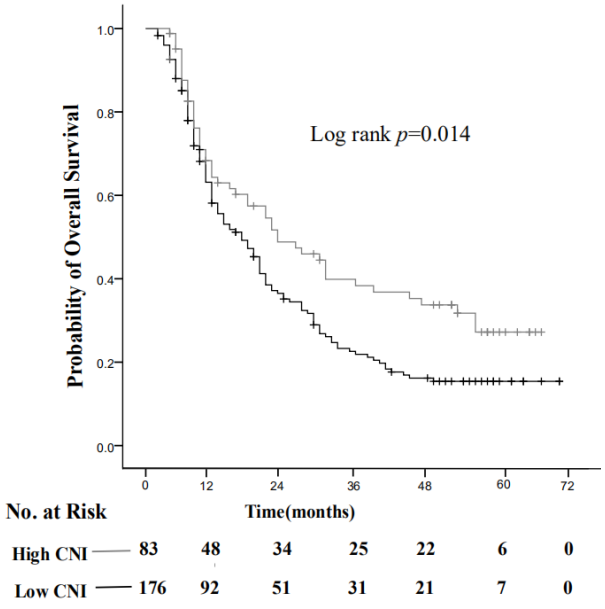

Figure 2. Kaplan–Meier analysis of OS in patients with low vs high CNI (N=259).

DISCUSSION

Malnourishment or being at risk of malnutrition is common in cancer patients, and has negative effects on recovery and survival. As such, nutrition is an important aspect of multimodal cancer care. This study investigated changes in nutritional status in HCC patients before and after multiple TACE treatments. A CNI was established that reflects overall nutritional status and its predictive value was evaluated. We found that CNI was a superior predictor of OS and TTP in HCC patients who have undergone repeated TACE than the previously used indices of PNI or NRI.

TACE is the first-line treatment for patients with intermediate-stage HCC according to the BCLC staging system,[5] but is the most common treatment for advanced-stage disease under Chinese guidelines.[17] The incidence or risk of malnutrition was shown to be positively correlated with cancer stage.[7, 18] Multiple rounds of TACE can lead to pain, fever, vomiting, and other features of embolism syndrome, which can affect nutrient intake. Energy consumption by the tumor and liver dysfunction can lead to a further decline in nutritional status. Therefore, improving nutritional status is critical for disease management in cancer patients.

Single nutrition parameters as well as PNI and NRI—which are both calculated based on two nutrition indicators—do not provide a complete view of nutritional status.[15,16,19] The CNI is composed of five parameters (BMI, UBW%, Hb, TLC, and ALB) that reflect various aspects of nutritional status. BMI is a widely used measure of healthy body weight and can indicate protein–energy malnutrition; a low BMI was shown to be correlated with nutrient depletion, muscle weakness, and metabolic changes.[20] UBW% reflects changes in body weight after multiple TACE treatments.[21] Hb is an indicator of iron storage in the body and is a measure of chronic protein deficiency.[21] Lymphocytes play an important role in the host immune response; thus, a decrease in TLC reflects low cellular immune function or malnutrition.[22,23] ALB is an indicator of protein reserves and liver function.[10] While all nutrition parameters examined in this study decreased after repeated TACE, the reduction was especially pronounced for ALB, which should be taken into consideration in nutritional interventions for HCC patients who undergo TACE.

The results of the present study showed that patients with worse liver function were more likely to have malnutrition. HCC patients usually have chronic hepatitis and cirrhosis as comorbidities; conversely, the tumor affects

Table 5. Univariate and multivariate Cox regression analyses of overall survival (N=259)

Independent variable	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*p* value	RR (95% CI)	*p* value
Age (years)	0.99 (0.98–1.01)	0.259		
Sex	1.84 (0.97–3.49)	0.061		
Underlying disease	0.98 (0.70–1.37)	0.917		
HBV	1.07 (0.71–1.61)	0.741		
Cirrhosis	1.03 (0.77–1.37)	0.864		
BCLC stage	1.50 (1.16–1.94)	0.002*	1.49 (1.15–1.94)	0.003*
ALBI grade (1 vs 2/3)	1.35 (1.01–1.80)	0.044*	–	–
AFP (>400 vs ≤400 ng/mL)	1.14 (0.86–1.52)	0.369		
Number of TACE treatments	0.87 (0.76–0.99)	0.038*	0.85 (0.74–0.97)	0.015*
Ablation	0.56 (0.41–0.77)	<0.001*	0.60 (0.43–0.83)	0.002*
Combination therapy	0.55 (0.35–0.86)	0.009*	0.49 (0.31–0.77)	0.002*
CNI	0.67 (0.49–0.93)	0.016*	0.72 (0.52–1.00)	0.048*
PNI	1.52 (0.84–2.72)	0.164		
NRI	0.75 (0.56–1.02)	0.064		

AFP: alpha fetoprotein; ALBI: albumin-bilirubin score; BCLC: Barcelona Clinic Liver Cancer Staging System; CI: confidence interval; CNI: comprehensive nutrition index; HBV: hepatitis B virus; NRI: nutrition risk index; PNI: prognostic nutritional index; RR: relative risk; TACE: transarterial chemoembolization.
*p value <0.05.

Table 6. Univariate and multivariate Cox regression analysis of time to progression (N=282)

Independent variable	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*p* value	RR (95% CI)	*p* value
Age (years)	0.99 (0.97-1.00)	0.014*	0.98 (0.97–1.00)	0.010*
Sex	1.16 (0.69–1.98)	0.575		
Underlying disease	0.85 (0.59–1.21)	0.366		
HBV	1.28 (0.84–1.95)	0.260		
Cirrhosis	0.86 (0.64–1.14)	0.295		
BCLC stage	1.29 (1.01–1.64)	0.040*	–	–
ALBI grade (1 vs 2/3)	1.28 (0.96–1.70)	0.097		
AFP (>400 vs ≤400 ng/mL)	1.12 (0.84–1.49)	0.443		
Number of TACE treatments	0.90 (0.80–1.02)	0.100		
Ablation	0.64 (0.47–0.87)	0.004*	0.66 (0.48–0.89)	0.007*
Combination therapy	0.82 (0.55–1.23)	0.330		
CNI	0.66 (0.48–0.91)	0.010*	0.69 (0.50–0.94)	0.019*
PNI	1.01 (0.63–1.63)	0.968		
NRI	0.79 (0.59–1.07)	0.123		

AFP: alpha fetoprotein; ALBI: albumin-bilirubin score; BCLC: Barcelona Clinic Liver Cancer Staging System; CI: confidence interval; CNI: comprehensive nutrition index; HBV: hepatitis B virus; NRI: nutrition risk index; PNI: prognostic nutritional index; RR: relative risk; TACE: transarterial chemoembolization.
*p value <0.05.

liver function. As the liver is the site of carbohydrate, fat, and protein metabolism, impaired liver function can lead to metabolic dysfunction and malnutrition.[10] A tumor size >5 cm indicates a higher tumor burden; this is associated with greater nutrient consumption, which can also contribute to malnutrition. Patients who underwent more TACE treatments typically had low CNI, as TACE can lead to embolism syndrome, which includes nausea and vomiting. Previous studies have reported that nutritional status in cancer patients deteriorates with advanced tumor stage.[7,18] We observed this trend in our study, but the decline was nonsignificant, as only 10 patients with BCLC stage A HCC were enrolled. Clinicians should pay attention to the nutritional status of patients with poor liver function and tumor size >5 cm and who have undergone multiple rounds of TACE so that nutritional interventions can be initiated as early as possible. Depression[11,24] and psychological distress[12] also affect nutritional status, although these factors were not investigated in the present work.

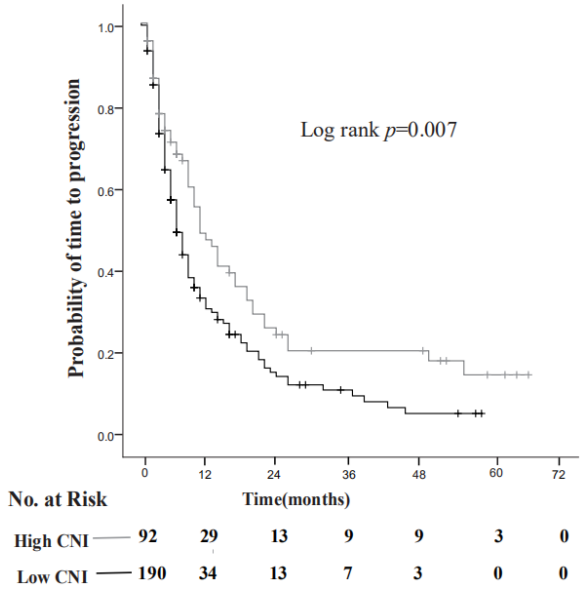

Figure 3. Kaplan–Meier analysis of TTP in patients with low vs high CNI (N=282).

An estimated 10%–20% of deaths in cancer patients can be attributed to malnutrition rather than to the malignancy itself.[6] Malnutrition in cancer patients is associated with higher rates of treatment-related complications,[25,26] which was confirmed by our analyses. Bone marrow suppression was the main serious complication observed in this study; this may have resulted from nutrient deficiency and weakened defense systems such as cellular immunity.[27] Malnutrition has been linked to decreases in OS, recurrence-free survival, and disease-free survival in cancer patients,[26,28,29] which was observed in HCC patients who underwent multiple rounds of TACE. Although preoperative PNI and NRI have shown prognostic value in HCC patients who undergo hepatectomy,[13,14] they were inferior to CNI in predicting OS and TTP in HCC patients who underwent repeated TACE and could not distinguish those with malnutrition.

Unlike hepatectomy, TACE is minimally invasive; as patients are hospitalized temporarily, clinicians may underestimate the value of nutritional management. Our findings argue for combining oncologic and nutritional management throughout the disease course with full nutritional assessment at diagnosis. The nutritional indicators of CNI are readily ascertained and nutritional intervention is implementable by disease stage, which can improve outcomes. The treatment options and their underlying mechanisms are shown in Figure 4.

This study had some limitations. Given that it was a single-center, retrospective study, the level of evidence was not extremely high and some information such as symptom severity was lacking. Additionally, the influence of psychosocial factors on nutrient intake was not addressed. Multicenter prospective studies are needed to validate the relationship between nutritional status and prognosis of HCC patients undergoing multiple rounds of TACE.

Conclusion

The nutritional status of HCC patients decreased with repeated TACE. Low CNI was associated with more serious treatment-related complications and predicted shorter OS and TTP. The prognostic performance of CNI was superior to that of PNI and NRI. Thus, CNI is a valuable method for evaluating nutritional status in HCC patients after multiple TACE treatments, and can be useful for informing clinical management strategies that address patients' specific nutritional needs.

AUTHOR DISCLOSURES

The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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