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Original Article

Geriatric nutritional risk index predicts clinical outcomes in hepatocellular carcinoma after transarterial chemoembolization: a retrospective cohort study

Jiaxi Zheng[1*], Songsong Pan[1*], Qiuyan Li[1], Weiwei Yu[1], Changsheng Shi[2], Xixiang Yu[1]

[1]Department of Interventional Vascular Surgery, Wenzhou Medical University, Wenzhou No. 3 Clinical College, Wenzhou, Zhejiang, People's Republic of China; [2]Department of Interventional Radiology, The Third Affiliated Hospital of Wenzhou Medical University, Ruian, Zhejiang, People's Republic of China. [*]Equal contributors.

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Abstract: Objective: To explore the effects of geriatric nutritional risk index (GNRI) on clinical outcomes of elderly patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE) and its underlying mechanisms. Method: Data from 154 HCC patients over 65 years old undergoing TACE as the initial treatment was retrospectively collected. Patients were divided into the low-risk group (GNRI≥92) and the high-risk group (GNRI<92). Factors affecting tumor response after the first TACE were analyzed using univariate and multivariate logistic regression. A Spearman correlation was performed to assess the relationship between the GRNI and total lymphocyte count (TLC). Finally, the prognostic value of GNRI was examined using Cox regression models. Results: The GNRI score was a risk factor for the disease control rate (P=0.002). A weak but statistically significant correlation was observed between GNRI and TLC (r=0.220, P=0.006). The combination of GNRI≥92 and TLC≥1500 was able to exclude the occurring of progressive disease. During 5-year follow-up, the low-risk group showed statistically longer overall survival (OS) and progression-free survival (PFS) than the high-risk group (median OS=21.0 vs. 13.0 months, P=0.006; median PFS=12.0 vs. 6.0 months, P<0.001). Multivariate analyses revealed that GNRI was independently correlated with OS. Compared with the high-risk group, the low-risk group showed a lower risk of death (hazard ratio =0.622, 95% confidence interval (CI), 0.421-0.919, P=0.017). Conclusion: GNRI is an independent prognostic factor in HCC patients undergoing TACE. Aggressive nutritional intervention targeting GNRI may help improve clinical outcomes.

Keywords: Geriatric nutritional risk index, malnutrition, hepatocellular carcinoma, elderly, transarterial chemoembolization, clinical outcomes, treatment response, prognosis, total lymphocyte count

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with both incidence and mortality rates increasing [1, 2]. Malnutrition is a common disease in patients with advanced HCC, especially in the elderly [3-5]. Many studies have shown that malnutrition is associated with adverse clinical outcomes for multiple diseases, and treatment for malnutrition is becoming an increasing concern for clinicians. In elderly patients with HCC, malnutrition is a risk factor for adverse clinical outcomes, including adverse treatment response, impaired performance status, damaged immune function, and decreased survival [4, 6]. At present, no standard of nutritional assessment or models of nutrition-related risks has been developed in patients with advanced HCC. Transarterial chemoembolization (TACE) as a treatment method of transarterial intervention has been recommended as the first-line therapy for intermediate and advanced HCC [1]. It uses embolization to block the blood vessels supplying the tumors as well as the infusion of chemotherapy agents to kill the tumor cells, which causes ischemia, necrosis, and atrophy of tumors [3]. Although the relationship between HCC and malnutrition has been studied extensively, the effects of preoperative malnutrition on elderly patients with HCC undergoing TACE are still unclear. In recent years, the geriatric nutritional risk index (GNRI) has been proposed as a

new indicator of nutritional status to predict nutrition-related risks and clinical outcomes in elderly patients [7, 8]. GNRI is a simple and rapid tool, requiring only weight, height, and serum albumin levels. It is currently known that GNRI can predict clinical outcomes in patients with several cancers, including lung, kidney, esophageal, and gastric cancers [8-10]. However, little is known about its impacts on clinical outcomes in elderly patients with HCC undergoing TACE. Thus, the purpose of this study is to explore the effects of the GNRI on clinical outcomes of elderly patients with HCC undergoing TACE as the initial treatment and its underlying mechanisms.

Patients and methods

Study design and patients

We retrospectively analyzed 253 consecutive patients with HCC who underwent TACE from January 2010 to December 2014. The diagnosis of HCC was based on typical imaging according to the European Association for the Study of the Liver (EASL Guideline) [11]. A total of 154 patients were included in this study, the inclusion criteria were as follows: (1) diagnosed as HCC; (2) undergoing TACE as first-line therapy (2) age above 65 years; (3) Child-Pugh grade A or B; (4) Eastern Cooperative Oncology Group (ECOG) score not more than 2; (5) Barcelona Clinic Liver Cancer (BCLC) stage B or C. The exclusion criteria were as follows: (1) prior TACE; (2) additional treatment (surgical resection or radiofrequency ablation); (3) diagnosed as hepatocellular carcinoma rupture; (4) diagnosed as hepatic angioma; (5) other primary malignancies; (6) incomplete clinical data.

This study was approved by the Wenzhou People's Hospital medical ethics committee. Informed consent was not required because of the retrospective nature of the study.

Methods

The GNRI score of patients at admission was calculated as follows: GNRI=1.487 × albumin (g/l)+41.7 × preoperative measured weight/ideal weight. Serum albumin levels were measured on a fasting basis and blood was taken 3-5 days before operation. Ideal weight =22 × the square of height (m). The ratio of preoperatively measured weight to ideal weight was adjusted not to exceed 1 [7]. Based on the distribution of the GNRI score and previous reports [12, 13], patients were divided into the high-risk group (GNRI<92) and the low-risk group (GNRI≥92). Clinical characteristics, tumor response, PFS, and OS were compared between groups, and factors influencing clinical outcomes were analyzed.

Treatment procedure

TACE was conducted under a standardized protocol. Before conventional embolization, an angiogram was performed under CT guidance to check for arterial shunts and to identify arterial feeders for the tumors. For patients with conventional TACE (cTACE), they were treated with super-selective catheterization using a microcatheter and were given an injection of the emulsion of iodized oil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., Shanghai, China) and epirubicin solution into the targeted artery followed by gelatin sponge particles. The dose administered was determined according to liver function, size, and number of tumors. The maximum doses of epirubicin and iodized oil were 60 mg and 10 mL for a single treatment. Among 154 patients, 5 patients underwent doxorubicin-loaded drug-eluting beads (DEB-TACE) using CalliSpheres (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) beads loaded epirubicin. Each time tumor recurrence was identified, TACE was repeated. If the remnant liver function and performance status were tolerant, other treatment methods (radiotherapy or targeted therapy such as sorafenib) may be used in the treatment regimen.

Follow-up and assessment of treatment response

Routine laboratory examinations and imaging were performed 4-6 weeks after the TACE procedure. Treatment response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [14]. The disease control rate (DCR) was defined as treated tumors that achieved complete response (CR), partial response (PR), and stable disease (SD). PR means at least a 30% reduction in the sum of the diameter of the visible target lesions compared with baseline. Progressive disease (PD) means more than 20% increases in the sum of the diameters of tumors compared with the smallest of the

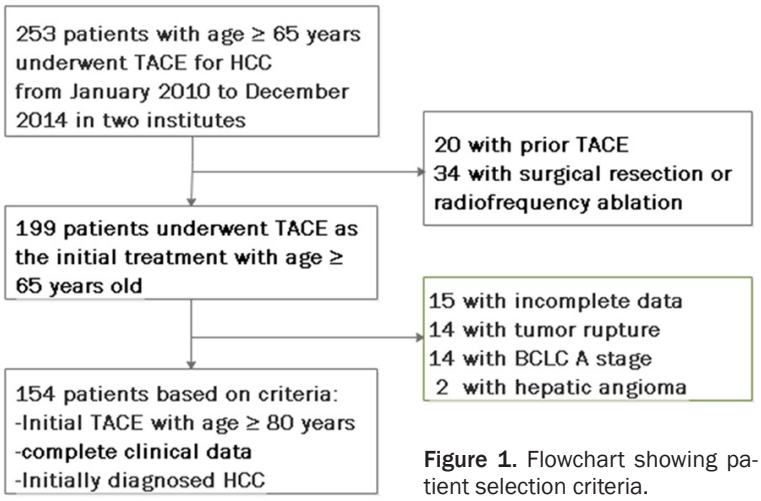

Figure 1. Flowchart showing patient selection criteria.

previously observed measurements. SD was defined as insufficient changes to qualify as PR or PD. In addition, TACE was repeated when tumors were still active; when there was a remission of the tumor, follow-up observations were usually done at 3-month intervals. After each follow-up visit, the progression and recurrence of tumors were evaluated to determine whether patients needed another TACE treatment. The safety of treatment was evaluated throughout the study.

Observation indexes

The primary endpoint was the OS and PFS. DCR was the secondary endpoint. OS was defined as the time from the first operation to death or the last follow-up visit. PFS was defined as the time from the first operation to death or progression of cancer by mRECIST. Death was defined as all-cause mortality. Median OS was defined as the corresponding survival time at a cumulative survival rate of 0.5.

Statistical analysis

Continuous variables are expressed as median (interquartile range), and categorical variables were expressed as values and percentages. Continuous and ranked variables between groups were compared using the Mann-Whitney U test. Categorical variables between groups were compared using the chi-square test. Spearman correlation was performed to assess the relationship between the geriatric nutritional risk index and total lymphocyte count. Logistic regressions were performed to evaluate the predicting factors for DCR. OS and PFS were evaluated by Kaplan-Meier analysis (using the log-rank test). A forward stepwise multivariate Cox hazard regression was performed to determine independent factors for OS. Statistical analyses were performed using SPSS 19 (IBM, USA). $P<0.05$ was considered statistically significant.

Results

Patients and distribution of the GNRI

A total of 154 patients were included in this study (**Figure 1**). The total GNRI ranged from 66.3 to 112.9 with a median score of 91.6 (quartile range, 86.1-98.4), which was a generally normal distribution (P=0.581, **Figure 2A**). The cut-off point of GNRI was determined as 92 based on the current distribution and previous studies (**Figure 2B**). All patients were divided into two groups. 79 patients were assigned to the high-risk group (GNRI<92) and 75 patients to the low-risk group (GNRI≥92). The median value of GNRI score in the high-risk group was 86.2 (quartile range is 82.9-89.8), and 98.4 (quartile range is 94.9-100.5) in the low-risk group (**Figures 1** and **2**).

Relationship between the GNRI and clinical characteristics

The median age of patients was 71 (quartile range, 67-74) years old and of all patients, 117 (75.9%) were men (**Table 1**). Clinical characteristics before the TACE procedure were equivalent between high-risk and low-risk groups except for body mass index (BMI), albumin (ALB), and total lymphocyte count (TLC). The median TLC of patients in the high-risk group was lower than those in the low-risk group (1100 vs. 1300, P=0.028). The median maximum diameter of tumors was 4.4 cm (3.0-6.2, cm) and several patients (47.4%) had ≤3 tumors. In addition, there was no significant difference in preoperative adverse events (AE), alpha-fetoprotein (AFP), treatment history of radiotherapy and sorafenib between the two groups after the first TACE procedure (**Table 2**). For common adverse events after operation, including pain, fever, nausea, and vomiting,

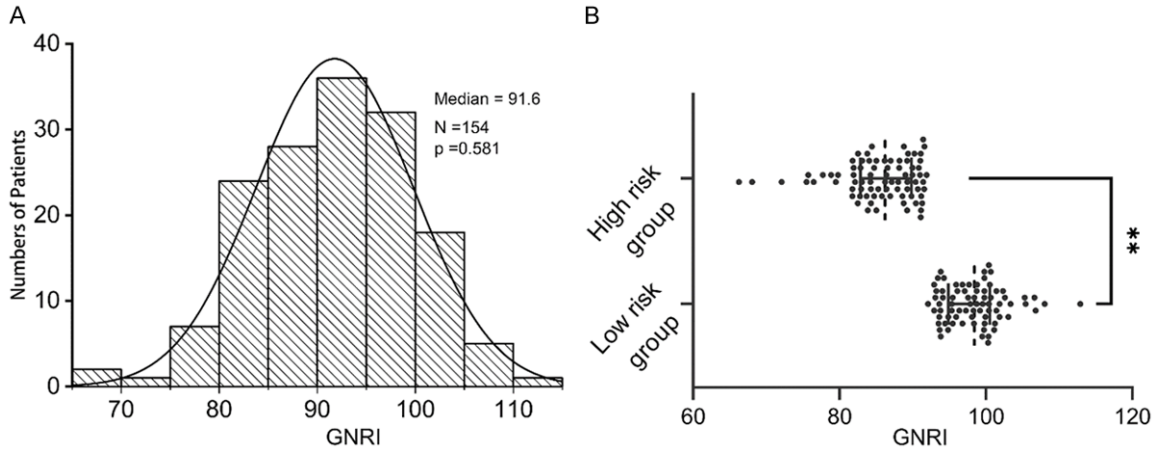

Figure 2. General distribution of geriatric nutritional risk index according to Kolmogorov-Smirnov test (A, P=0.581) and comparison of the distribution of geriatric nutritional risk index (score) in two groups according to Mann-Whitney U-test (B, **: P<0.01).

although the safety of TACE treatment was considered favorable, there were still some serious adverse events (SAE) (6 vs. 3, including liver dysfunction, renal dysfunction, bone marrow suppression) in the high-risk group. The median number of TACE procedures was 2 (1-4). During 5-year follow-up, 116 patients (75.3%) died (**Tables 1** and **2**).

Associations of GNRI groups with tumor response and association of GNRI score with TLC

After the first TACE treatment, no significant difference in treatment response was observed between the two groups (P=0.141). A total DCR of tumors was 90.3% (139/154) with 12 (6.5%) reaching CR (**Figure 3A**). The DCR in the high-risk group was 86.1% (68/79), with 5 (6.3%) reaching CR. In the low-risk group, DCR was 94.7% (71/75), with 5 (6.7%) reaching CR (**Figure 3A**). The association of the GNRI score with TLC was estimated by a Spearman correlation. A weak but statistically significant correlation was observed between GNRI and TLC (r=0.220, P=0.006, **Figure 3B**). The combination of GNRI≥92 and TLC≥1500 was able to exclude the occurrence of PD (**Figure 3**).

Logistic regression analysis for factors affecting the disease control rate

The GNRI score was a risk factor for DCR according to univariate logistic regression analysis (P=0.002). Besides, univariate logistic regression analysis also revealed that the high AFP level, high ECOG (Eastern Cooperative Oncology Group) score, high BCLC stage, and metastasis were risk factors for DCR (P<0.05). Multivariate logistic regression analysis was done using the factors that had shown significance in the univariate logistic regression analysis. It was observed that metastasis and preoperative AFP were independently associated with DCR (**Table 3**).

Long-term survival outcomes in the two groups after treatment

The median OS and median PFS for the overall population were 17.0 months (95% confidence interval (CI), 12.5-21.5 months) and 9.0 months (95% CI, 7.1-10.9 months), respectively (**Figure 4**). The overall 1-year, 3-year, and 5-year survival rates of all patients were 57.1%, 19.5%, and 5.8%, respectively (**Figure 4**). When compared between the two groups, a significant difference in survival time was observed by the log-rank test. The median OS was 13.0 months (95% CI, 8.8-17.1) in the high-risk group and 21.0 months (95% CI, 11.6-30.4) in the low-risk group (P=0.006). The median PFS was 6.0 months (95% CI, 4.6-7.3) in the high-risk group and 12.0 months (95% CI, 10.6-13.4) in the low-risk group (P=0.011). The 1-year (74.7%), 3-year (25.3%), and 5-year (8.0%) survival rates in the low-risk group were all higher than those in the high-risk group (40.5%, 13.9%, and 3.8%, respectively, P< 0.05). When univariate Cox regression analysis was performed, it was observed that BMI, ALB, GNRI, AFP, ECOG score, BCLC stage,

Table 1. Relationship between GNRI and clinical characteristics

Variables	Total (154)	High-risk GNRI<92 (79)	Low-risk GNRI≥92 (75)	*P*-value
Gender				
Male	117	59	58	
Female	37	20	17	0.701
Age, years	71 (67-74)	71 (67-74)	70 (67-74)	0.709
BMI, kg/m^2	21.7 (20.1-24.0)	20.4 (18.7-22.9)	23.0 (21.6-24.6)	<0.001
Hypertension, n (%)	70 (45.5)	36 (45.6)	34 (45.3)	0.977
Diabetes, n (%)	25 (16.2)	13 (16.5)	12 (16.0)	0.939
Smoking, n (%)	61 (39.6)	28 (35.4)	33 (44.0)	0.278
Drinking, n (%)	55 (35.7)	31 (39.2)	24 (32.0)	0.349
HBV, n (%)	84 (54.5)	44 (55.7)	40 (53.3)	0.769
ECOG score				
0	100	47	53	
1	39	21	18	
2	15	11	4	0.249
Child-Pugh grade				
A	125	63	62	
B	29	16	13	0.643
BCLC stage				
B	86	34	41	
C	67	45	34	0.149
Preoperative AFP, ng/ml				
<400	116	56	60	
≥400	38	23	15	0.190
WBC, 10^9/L	5.0 (4.1-6.0)	4.6 (4.1-6.0)	5.2 (4.3-6.2)	0.189
Hb, g/L	124.0 (113.0-134.0)	123.0 (113.0-133.0)	125.0 (113.0-136.0)	0.374
PLT, 10^9/L	140.5 (100.5-185.3)	133.0 (85.0-189.0)	151.0 (114.0-183.0)	0.273
TLC, /mm^3	1200 (900-1500)	1100 (800-1400)	1300 (1100-1600)	0.028
ALT, u/L	30.0 (19.0-50.5)	30.5 (20.0-49.3)	26.0 (18.0-51.0)	0.665
AST, u/L	41.0 (28.0-77.3)	44.0 (28.0-78.0)	36.0 (25.0-77.0)	0.375
ALB, g/L	35.2 (33.3-38.6)	32.4 (29.9-34.0)	38.7 (36.4-40.3)	<0.001
TBIL, μmol/L	14.4 (8.9-24.1)	14.2 (8.2-24.2)	14.5 (9.2-24.1)	0.901
INR	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.081
BUN, mmol/L	5.6 (4.3-7.5)	5.6 (4.1-7.4)	5.6 (4.5-7.7)	0.521
Cr, μmol/L	79.0 (61.5-104.8)	79. 0 (62.0-104.0)	80.0 (58.0-107.0)	0.968
Number of tumours				
1	74	31	43	
2	11	6	5	
≥3	69	42	27	0.074
Maximum tumor diameter, cm	4.4 (3.0-6.2)	3.5 (3.2-6.4)	4.4 (2.6-6.1)	0.675
PVTT, n (%)	21 (13.6)	13 (16.5)	8 (10.7)	0.295
Metastasis, n (%)	26 (16.9)	16 (20.3)	10 (13.3)	0.864

the number of tumors, portal vein tumor thrombosis (PVTT), metastasis, and disease control rate were significantly correlated with OS (P<0.05, **Table 4**). According to the univariate Cox regression analysis, we selected several prognostic factors with P≤0.1 in the univariate analysis to be included in multivariate Cox regression analysis. Finally, it was found

Table 2. Postoperative adverse events and treatment

Variables	Total (154)	High-risk GNRI<92 (79)	Low-risk GNRI≥92 (75)	*P*-value
Adverse events				
Pain, n (%)	89 (57.8)	44 (54.5)	45 (60.0)	0.588
Fever, n (%)	71 (46.1)	37 (46.8)	34 (45.3)	0.851
Nausea, n (%)	42 (27.3)	17 (21.5)	25 (33.3)	0.099
Vomiting, n (%)	36 (23.4)	14 (17.7)	22 (29.3)	0.088
Serious adverse events, n (%)	9 (5.8)	6 (7.6)	3 (4.0)	0.496
Postoperative AFP, ng/ml				0.288
<400	124	61	63	
≥400	30	18	12	
Radiotherapy, n (%)	17 (11.0)	6 (7.6)	11(14.7)	0.162
Sorafenib, n (%)	11 (0.07)	4 (5.0)	7 (9.0)	0.304
Microsphere	5 (3.2)	3 (3.8)	2 (2.7)	0.952

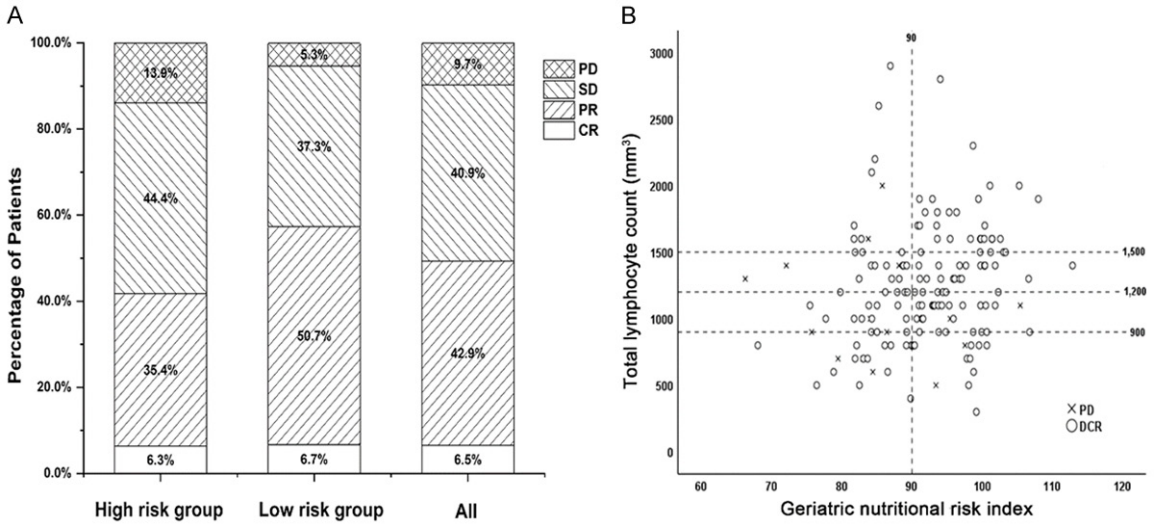

Figure 3. Comparison of treatment response between groups according to chi-square test (A, P=0.141) and association of geriatric nutritional risk index with total lymphocyte count according to Spearman correlation (r=0.22, P=0.006) and their relationship with treatment response (B).

that high postoperative AFP level, metastasis, and high BCLC stage were independent risk factors for overall survival in elderly patients with HCC following TACE. However, high GNRI and DCR were protective factors. Compared with the high-risk group, the low-risk group (GNRI≥92) had a lower risk of death (hazard ratio, HR=0.622, 95% CI, 0.421-0.919, P= 0.017) (**Figure 4** and **Table 4**).

Discussion

In this retrospective cohort study, clinical outcomes of elderly patients with HCC (>65 years) who underwent TACE as the initial treatment were compared between two different nutritional risk groups of the geriatric nutritional risk index. Over the 5-year follow-up period, the overall survival time in the low-risk group (GNRI≥92) was longer than that in the high-risk group and the time to disease progression differed between groups. The prognosis of HCC is generally considered to be closely correlated to AFP, ECOG, stage of tumors, number and size of tumors, vascular invasion, or metastasis [3, 4, 6, 15]. This coincided with our results, but it was also found in this study that GNRI as a simple nutritional indicator was a significantly

Table 3. Logistic regression analysis for factors affecting DCR

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Gender, male vs. female	0.457 (0.098-2.126)	0.318		
Age, 71 vs. <71, years	2.212 (0.719-6.807)	0.166		
BMI, ≥22 vs. <22, kg/m^2	0.358 (0.109-1.180)	0.092		
HBV	1.181 (0.687-2.033)	0.547		
GNRI score	0.897 (0.837-0.962)	0.002		
GNRI grade, ≥92 vs. <92	0.348 (0.106-1.147)	0.083		
ECOG score, 0 vs. 1/2	0.232 (0.075-0.718)	0.011		
Child-Pugh grade, B vs.A	1.087 (0.286-4.129)	0.903		
BCLC stage, C vs. B	7.189 (1.564-33.052)	0.011		
TLC, ≥1500 vs. <1500, /mm^3	0.368 (0.079-1.703)	0.201		
Number of tumors, multiple vs. isolated	2.790 (0.847-9.186)	0.092		
Maximum tumor diameter, ≥3 vs. <3, cm	2.187 (0.470-10.175)	0.318		
PVTT	0.972 (0.203-4.649)	0.971		
Metastasis	7.683 (2.485-23.753)	<0.001	8.207 (2.435-27.653)	0.001
Preoperative AFP, ≥400 vs. <400, ng/ml	5.690 (1.873-17.283)	0.002	6.088 (1.830-20.255)	0.003

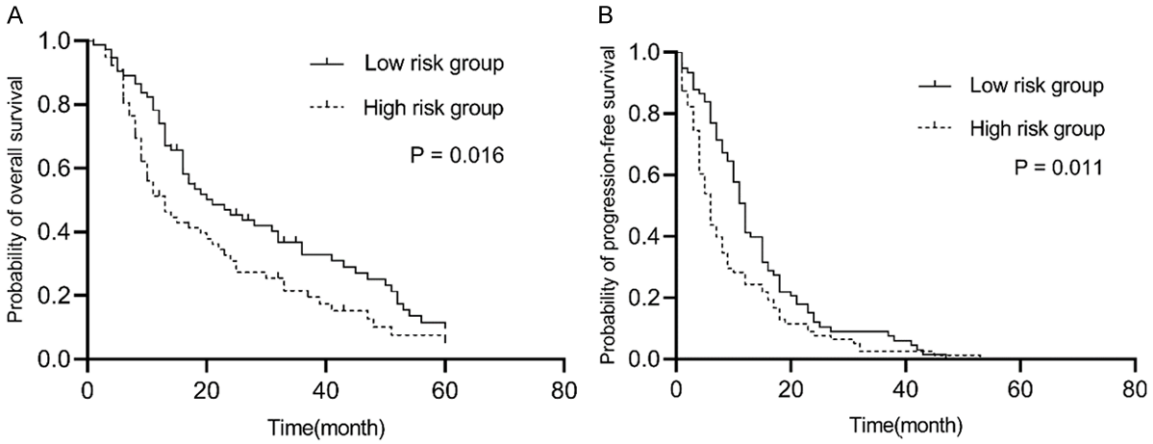

Figure 4. Kaplan-Meier curves of OS (A) and PFS (B) by treatments (using log-rank test). (A) The estimated median OS was derived as 21.0 months (95% CI, 11.6-30.4) for the low-risk group and 13.0 months (95% CI, 8.8-17.1) for the high-risk group (P=0.009). (B) The estimated median PFS time was derived as 12.0 months (95% CI, 10.6-13.4) for the low-risk group and 6.0 months (95% CI, 4.6-7.3) for the high-risk group (P=0.011).

important factor influencing the prognosis of HCC. To explore the impact of nutrition on the prognosis of cancer, researchers developed complex models based on BMI, skin-fold thickness, lymphocyte count, albumin concentration, and inflammation indicators, such as the prognostic nutritional index (PNI), and hospital prognostic index (HPI) [16-18], improving limitations of simple and subjective models for nutritional assessment and enhancing predictions of the prognosis for cancers. Although these models for assessing nutrition-related risks have led to good predictive outcomes, some of these indicators are often difficult to measure accurately, and complex models after adjustments require experienced clinicians and are often time-consuming and laborious. Some patients with HCC underwent nutritional treatment may improve or correct nutritional indicators, such as albumin and hemoglobin, but they are still in a state of nutritional depletion during the hospitalization and postoperative period, which may affect treatment and prognosis [19, 20]. However, as a simple and rapid tool, GNRI combining albumin and height-weight legitimizes the ratio of albumin and weight and addresses the problem of masking muscle loss due to excessive

Table 4. Cox regression analysis for factors affecting overall survival Cox regression analysis for factors affecting overall survival

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender, male vs. female	1.524 (0.950-2.445)	0.081		
Age, ≥71 vs. <71, years	1.400 (0.971-2.019)	0.071		
HBV	1.056 (0.879-1.268)	0.564		
BMI, ≥22 vs. <22, kg/m^2	0.616 (0.425-0.892)	0.010		
GNRI grade, ≥92 vs. <92	0.644 (0.445-0.931)	0.019	0.622 (0.421-0.919)	0.017
ECOG score, 0 vs. 1/2	0.265 (0.174-0.402)	<0.001		
Child-Pugh grade, B vs. A	1.494 (0.933-2.390)	0.094		
BCLC stage, C vs. B	4.358 (2.916-6.512)	<0.001	4.063 (2.372-6.959)	<0.001
ALB, ≥35 vs. <35, g/L	0.622 (0.429-0.903)	0.013		
TLC, <1500 vs. ≥1500, /mm^3	0.758 (0.505-1.138)	0.182		
Number of tumors, multiple vs. isolated	1.532 (1.056-2.223)	0.025		
Maximum tumor diameter, ≥3 vs. <3, cm	1.090 (0.704-1.687)	0.699		
PVTT	2.290 (1.357-3.862)	0.002		
Metastasis	4.247 (2.550-7.074)	<0.001	1.941 (1.123-3.353)	0.017
Preoperative AFP, ≥400 vs. <400, ng/ml	2.000 (1.304-3.069)	0.002		
Postoperative AFP, ≥400 vs. <400, ng/ml	2.285 (1.421-3.675)	0.001	1.730 (1.038-2.885)	0.036
mRECIST, DCR vs. PD	0.078 (0.037-0.161)	<0.001	0.182 (0.084-0.393)	<0.001

fat, the vulnerability of laboratory indicators to infection and inflammation, and subjective determination of nutritional trends [21-23]. At present, it is known that GNRI can be used to predict complications related to malnutrition and clinical outcomes in patients with a variety of cancers [9, 10, 13, 24]. However, studies of the relationship between GNRI and the prognosis of elderly patients with HCC treated with TACE are still lacking. Therefore, it is necessary to assess the nutritional status of patients using GNRI and to make use of GNRI to predict the long-term clinical outcomes of HCC.

Similar to our findings, several clinical studies found that clinical outcomes of patients with HCC can benefit from a high GNRI score. An earlier study reported that low GNRI was an independent and important risk factor for postoperative complications and poor prognosis after hepatocellular carcinoma resection [13], but mechanisms of how GNRI had affected clinical outcome was unclear and rarely reported in HCC. In fact, the majority of patients with HCC treated by TACE are those with unresectable tumors in the intermediate and advanced-stage or people who are physically unable to tolerate surgery [25]. This group of people may be severely impaired in terms of their physical function and immune status [26]. We believe that the reason for low GNRI leading to adverse clinical outcomes in patients with HCC following TACE may be due to the absence of antitumor immunity. Moreover, in patients following TACE, the immune response of the body has an important influence on tumor responses and survival time [27]. Research showed that low GNRI often means poor liver function, lack of immune reserve, and attenuated antitumor immune responses because of hepatic insufficiency and malnutrition resulting in decreased albumin synthesis [27-29]. Moreover, GNRI may also be closely related to lymphocytes, which are an important component of the adaptive immune system, providing the cellular basis for tumor immune monitoring and immune response [30]. Gartner et al. investigated the relationship between GNRI and inflammation indicators during hospitalization and it was found that a higher risk score of the GNRI was associated with low lymphocyte counts [31]. In another study, it was proved that GNRI was significantly associated with total lymphocyte count (TLC) when it was found that the specificity (87.8%) was higher than the sensitivity (30.6%) in patients with low GNRI (<92) diagnosed using TLC<900 [12]. In

this study, a weak association of the GNRI with total lymphocyte count was observed (P=0.006). Our results showed statistically significant differences in BMI, ALB, and TLC between high and low-risk groups. GNRI may be correlated with some nutritional assessment indicators like TLC, which was consistent with previous reports. In addition, inflammation of the tumor microenvironment after TACE treatment stimulates the immune response and affects the progression, invasion, and metastasis of the tumor, in which infiltrating lymphocytes play an important role. The lack of infiltrating lymphocytes and circulating lymphocytes may suggest an insufficient immune antitumor response resulting in a reduced patient's defense against cancer and therefore lead to tumor progression and poor clinical outcomes [29, 32]. New studies suggested that circulating lymphocytes and effector T cells were also associated with tumor sensitivity to target drugs and contributed to tumor resistance to sorafenib and anti-PD-1 drugs in HCC [27, 33, 34]. In addition to the above, the mechanism underlying the effect of GNRI on the survival of patients with HCC may also be related to cancer treatment. First, the poorer prognosis of elderly HCC with low GNRI may be associated with fewer TACE procedures, although no difference was observed. Those patients often have poor clinical outcomes because the presence of malnutrition may affect tolerance and compliance with TACE therapy, thereby reducing the number of TACE procedures in patients with active tumors. Also, our results showed that the DCR 1 month after operation between groups was associated with the GNRI score (P=0.002). With malnutrition affecting the efficacy of TACE treatment, the high-risk group had a lower disease control rate, thus leading to a reduced willingness of patients to return to TACE or alternative therapies.

The low GNRI score had indicated that patients with advanced HCC had been in a state of nutritional depletion and a less than expected treatment response after TACE [13]. Our results found that the combination of GNRI≥ 92 and TLC≥1500 was able to exclude the occurrence of PD, which may help clinical diagnosis and treatment. Furthermore, GNRI was an independent predictor of survival time in elderly HCC and the 5-year survival rate in low-risk group was higher than that in the high-risk group. Therefore, we believe that aggressive intervention of nutritional status can be of obvious importance to improve clinical outcomes. Some researchers found that early nutritional support had been shown to promote recovery and improve the quality of life for cancer patients when patients with HCC undergoing improvement of nutritional status had a shorter time to return to normal biochemical markers than patients without nutritional intervention [17, 26, 35]. Another study demonstrated that TACE resistance was related to OS and the number of TACE procedures in patients with progressive skeletal muscle volume loss following TACE, and they believed that prevention of skeletal muscle volume loss following TACE in HCC was the key to a good prognosis [36]. Besides, it is proposed in a recent study that timely aggressive nutritional intervention may, therefore, improve clinical outcomes for patients with HCC. Among the total 77 patients with BCLC stage B HCC recruited in the study, TACE was performed with the branched-chain amino acids (BCAA) in 54 (70.1%) patients, and eventually, the median OS was significantly prolonged in those who received TACE treatment [37]. Overall, these studies have shown that nutritional intervention can benefit survival in patients who underwent TACE treatment. Consequently, we strongly recommend aggressive nutritional intervention in HCC patients with low GNRI before the TACE procedure.

The present study has several limitations. Although strict exclusion criteria were used to minimize the risk of potential bias, bias cannot be ignored. No comparison between GNRI and other commonly used tools for assessing nutritional status was performed. Besides, no examination of the effects of sorafenib and microsphere for prognosis was performed due to a lack of significant clinical use.

In conclusion, GNRI is an independent prognostic factor in patients with TACE. Aggressive nutritional intervention targeting GNRI may help improve clinical outcomes.

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Disclosure of conflict of interest

None.

Address correspondence to: Xixiang Yu, Department of Interventional Vascular Surgery, Wenzhou People's Hospital, Wenzhou Medical University, Wenzhou No. 3 Clinical College, No. 299, Guan Road, Ouhai District, Wenzhou 325000, Zhejiang, People's Republic of China. Tel: +86-1380680-0330; E-mail: yudsa@126.com; Changsheng Shi, Department of Interventional Radiology, The Third Affiliated Hospital of Wenzhou Medical University, No. 108 Wansong Road, Ruian 325200, Wenzhou, Zhejiang, People's Republic of China. Tel: +86-13777795904; E-mail: 178842968@qq.com

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