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ORIGINAL SCIENTIFIC REPORT

Preoperative Controlling Nutritional Status (CONUT) Score for Assessment of Prognosis Following Hepatectomy for Hepatocellular Carcinoma

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Abstract

Background Immune-nutritional status has been recently reported as a prognostic factor in hepatocellular carcinoma (HCC). The controlling nutritional status (CONUT) score has been established as a useful tool to evaluate immune-nutritional status. This study aimed to investigate the efficacy of the CONUT score as a prognostic factor in patients undergoing hepatectomy for HCC.
Methods A total of 295 patients who underwent curative hepatectomy for HCC between January 2007 and December 2014 were retrospectively analyzed. Patients were divided into two groups according to the CONUT score. The impact of the CONUT score on clinicopathological, surgical, and long-term outcomes was evaluated. Subsequently, the impact of prognostic factors, including the CONUT score, associated with outcomes was assessed using multivariate analyses.
Results Of 295 patients, 118 (40%) belonged to the high CONUT group (CONUT score $\geq$ 3). The high CONUT group had a significantly lower 5-year recurrence-free survival rate than the low CONUT group (27.9 vs. 41.4%, $p = 0.011$) and a significantly lower 5-year overall survival rate (61.9 vs. 74.9%, $p = 0.006$). In multivariate analyses of prognostic factors, the CONUT score was an independent predictor of recurrence-free survival (hazard ratio = 1.64, $p = 0.006$) and overall survival (hazard ratio = 2.50, $p = 0.001$).
Conclusions The CONUT score is a valuable preoperative predictor of survival in patients undergoing hepatectomy for HCC.

Introduction

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related deaths worldwide [1]. Although preoperative diagnosis, surgical technique, and radiofrequency ablation procedures for HCC have improved, the clinical outcomes of HCC remain poor, with a 5-year recurrence rate of 70% even in patients undergoing curative treatment [2]. Several studies have evaluated potential prognostic factors for HCC. In contrast to other solid malignancies, the prognosis and treatment options of HCC depend on tumor stage and hepatic functional reserve [3]. The two most commonly used scoring systems are the Cancer of the Liver Italian Program (CLIP) score [4] and Barcelona Clinic Liver Cancer (BCLC) staging classification [5]. However, these scoring systems focus on tumor status, basic liver function, and physical condition. Hypothetically, patients' immune-nutritional status would be an essential factor for survival in HCC.

Recently, the presence of a systemic inflammatory response and immune-nutritional status, as indicated by the prognostic

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nutritional index (PNI) [6], have been reported to correlate with poor survival in patients with HCC [7–9]. The PNI, which is calculated from serum albumin level and total lymphocyte count, has conventionally been used to evaluate immune-nutritional status and surgical risk in gastrointestinal surgery [6].

The controlling nutritional status (CONUT) score is another automatic tool to assess nutritional status, taking into account laboratory information, including serum albumin, total cholesterol level, and total lymphocyte count [10]. The prognostic significance of CONUT has been reported in patients undergoing curative surgery for colorectal cancer [11]; however, no previous reports have evaluated the relationship between CONUT and clinical outcomes after hepatectomy for HCC.

This retrospective study evaluated the prognostic significance of the preoperative CONUT score on clinical outcomes and verified whether CONUT could predict survival in patients undergoing hepatectomy for HCC.

Materials and methods

Patients

We retrospectively reviewed the medical records of 295 consecutive patients who underwent curative resection of HCC at Okayama University Hospital (Okayama, Japan) between January 2007 and December 2014. This study was approved by the Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital and conducted in accordance with the Declaration of Helsinki.

Clinical data

From our database, the following preoperative factors were evaluated: sex, age, height, weight, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, etiology of liver disease, laboratory values, tumor marker levels, liver function according to the Child–Pugh score and technetium-99 m-galactosyl human serum albumin (^{99}mTc-GSA), and comorbidities.

The CONUT score was calculated using albumin level, total lymphocyte count, and total cholesterol level in each patient, as described in Table 1 [10]. In this study, patients were divided into 2 groups: the low CONUT group (score $\leq$ 2) and the high CONUT group (score $\geq$ 3) [11]. Concerning PNI, on the basis of the original report, we used the following formula: 10 $\times$ albumin levels (g/dL) + 0.005 $\times$ total lymphocyte count (/mm^3). Patients were divided into 2 groups based on PNI: the low PNI group (score $<$ 40) and high PNI group (score $\geq$ 40) [11].

Data regarding surgical procedure, operative time, and blood loss were recorded as operative factors. Details of the surgical techniques have been reported previously [12]. Tumor specimens and the degree of hepatic fibrosis were evaluated by pathologists in accordance with the rules of the Liver Cancer Study Group of Japan [13].

Short-term and long-term outcomes

Postoperative complications were assessed using the Clavien–Dindo classification [14], with major complications defined as Clavien grade ≥3. All patients underwent follow-up examination every 3 or 6 months at our institution or another affiliated hospital to examine their physical condition, liver function, and recurrence. The last data of this cohort were updated in February 2016.

The relationship between the CONUT score and other clinical parameters

To identify the clinical meaning of the CONUT score, patients were also divided into 4 conventional categories of

Table 1 Assessment of undernutrition status by the CONUT score

	Undernutrition status			
	Normal	Light	Moderate	Severe
Albumin (g/dL)	≥3.5	3.0–3.49	2.5–2.9	<2.5
Score	0	2	4	6
Total lymphocytes (/mm3)	>1600	1200–1599	800–1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	>180	140–180	100–139	<100
Score	0	1	2	3
Total score	0–1	2–4	5–8	9–12
Classification (total score)	≤2 low CONUT group			
	≥3 high CONUT group			

CONUT controlling nutritional status [10] undernutrition status (normal, light, moderate, and severe) (Table 1) [11]. Then, the relationship between the CONUT score and other clinical parameters was examined.

Statistical analysis

Data are presented as mean, median, and standard deviation for continuous variables. Categorical data are presented as proportions. Differences between groups were assessed using the Mann–Whitney *U* test for continuous variables and Fisher's exact test or Chi-square test for categorical variables. Overall and recurrence-free survival rates were calculated using the Kaplan–Meier method, and differences between curves were analyzed using the log rank test. To investigate the impact of prognostic factors associated with overall and recurrence-free survival, the Cox proportional hazard model was used for univariate and multivariate analyses, and hazard ratios (HRs) and 95% confidence intervals were calculated. A p value < 0.05 was considered statistically significant. JMP version 10 software (SAS Institute, Cary, NC) was used for statistical analysis.

Results

Demographics

Table 2 shows the clinicopathological characteristics of the 295 patients. The median CONUT score was 2 (interquartile range, 1–3) (Fig. 1). The low CONUT group included 177 patients, and the high CONUT group included 118 patients. Sex ratio, age, BMI, ASA physical status, etiology of liver disease, tumor marker levels, comorbidities, operative factors, pathological factors, and incidence of major complications were not significantly different between the two groups. Patients with Child–Pugh score B were significantly more frequent in the high CONUT group ($p = 0.01$).

Median PNI was 47.3 (interquartile range, 42.7–51.7). Most patients ($n = 263$) were in the high PNI group, and 32 patients (10.8%) were in the low PNI group. Table 3 shows the relationship between CONUT score and PNI. Overall, 177 patients (60%) had normal CONUT scores (low CONUT group) and PNI (high PNI group). Eighty-six patients (29.2%) belonged to the normal PNI group and the abnormal CONUT group.

Recurrence after hepatectomy for HCC

The recurrence-free survival curve in patients with high and low CONUT scores is shown in Fig. 2a. One hundred fifty patients (50.8%) had recurrence at intrahepatic sites ($n = 120$), extrahepatic sites ($n = 13$), and both intrahepatic and extrahepatic sites ($n = 17$). The 2- and 5-year recurrence-free survival rates were 45.8 and 27.9% in the high CONUT group and 57.6 and 41.4% in the low CONUT group, respectively ($p = 0.011$). Table 4 shows the results of univariate and multivariate analyses to identify prognostic factors for HCC recurrence after hepatectomy. Multivariate analysis revealed that high CONUT score, ASA physical status of 3 or 4, Child–Pugh score B, presence of multiple tumors, and microvascular invasion were significant independent factors for HCC recurrence.

Survival after hepatectomy for HCC

After a mean follow-up of 42.3 months, 74 patients (25.1%) died from the following causes: cancer progression ($n = 48$); liver failure ($n = 15$); infection ($n = 3$); and other reasons ($n = 8$). Patients with high CONUT scores had a significantly worse prognosis than those with low CONUT scores ($p = 0.006$) (Fig. 2b). The 2- and 5-year overall survival rates following hepatectomy were 77.7 and 61.9% in the high CONUT group and 89.3 and 74.9% in the low CONUT group, respectively. Table 5 shows the results of univariate and multivariate analyses to identify prognostic factors closely related to overall survival after hepatectomy. In univariate analysis, 9 variables were independent factors associated with poor prognosis; of these, 5 variables were significant poor prognostic factors in multivariate analysis: high CONUT score, ASA physical status of 3 or 4, Child–Pugh score B, presence of multiple tumors, and microvascular invasion.

The influence of the CONUT score on tumor recurrence

In the high CONUT group, HCC recurred at intrahepatic sites ($n = 53$), extrahepatic sites ($n = 3$), and both intrahepatic and extrahepatic sites ($n = 9$). The low CONUT group had HCC recurrence at intrahepatic sites ($n = 67$), extrahepatic sites ($n = 10$), and both intrahepatic and extrahepatic sites ($n = 8$). There was no difference in the HCC recurrence patterns between groups ($p = 0.22$).

CONUT score and other clinical parameters

The relationship between the CONUT score and other clinical parameters is shown in Table 6. Categories of undernutrition status were: normal ($n = 118$); light ($n = 148$); moderate ($n = 29$); and severe ($n = 0$). CONUT score was significantly associated with platelet count, prothrombin time, Child–Pugh score, the value of ^{99}mTc-GSA, and the degree of hepatic fibrosis.

Table 2 Demographic and clinicopathological factors in patients with low and high CONUT scores

	All patients ($n = 295$)	Low CONUT ($n = 177$)	High CONUT ($n = 118$)	p value
Demographic variables				
Sex (men)	241 (82)	144 (81)	97 (82)	0.85
Age (years)	65.8 (10.4)	65.4 (10.5)	66.3 (10.1)	0.46
BMI (kg/m^2)	23.7 (3.6)	24.0 (3.6)	23.3 (3.5)	0.15
ASA physical status				
Grades 1–2/3–4	257/38	158/19	99/19	0.18
Etiology of liver disease				
HBV and/or HCV	198 (67)	112 (63)	86 (73)	0.08
Others	97 (33)	65 (37)	32 (27)	
Laboratory values				
Alb (g/dL)	4.0 (0.5)	4.2 (0.4)	3.8 (0.5)	<0.001
Total lymphocytes (/mm^3)	1466 (554)	1703 (497)	1111 (434)	<0.001
Total cholesterol (mg/dL)	172 (36.6)	186 (32.7)	152 (33.0)	<0.001
CONUT score (median, range)	2 (1–3)	1 (0–2)	3 (3–4.25)	<0.001
PNI (median, range)	47.3 (42.7–51.7)	50.3 (46.8–53.3)	43.6 (39.7–46.7)	<0.001
Tumor markers				
AFP (ng/mL)	5119 (27,003)	5628 (28,987)	4355 (23,819)	0.97
PIVKA–2 (mAU/mL)	23,987 (181,686)	20,575 (192,400)	28,832 (164,997)	0.21
Child–Pugh score				
A/B	288/7	176/1	112/6	0.01
Operative factors				
Type of hepatectomy				
≥lobectomy	116 (39)	72 (41)	44 (37)	0.56
≤segmentectomy	179 (61)	105 (59)	74 (63)	
Operative time (min)	284 (113)	284 (110)	285 (117)	0.99
Blood loss (mL)	1028 (1741)	992 (1695)	1083 (1819)	0.67
Tumor characteristics				
Tumor size (cm)	4.8 (3.7)	4.6 (3.4)	5.1 (4.0)	0.56
Tumor number				
Solitary/multiple	202/93	128/49	74/44	0.08
Poor differentiation	43 (15)	23 (13)	20 (17)	0.35
Microvascular invasion	89 (30)	51 (29)	38 (32)	0.53
Tumor stage				
I/II/III/IV	36/126/92/41	22/81/52/22	14/45/40/19	0.55
Major complications	43 (15)	25 (14)	18 (15)	0.79

Data are presented as numbers (percentages) or means (±SD), unless otherwise indicated

AFP alpha-fetoprotein, *Alb* albumin, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *CONUT* controlling nutritional status, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *PIVKA-2* prothrombin induced by vitamin K absence-II, *PNI* prognostic nutritional index

Discussion

This retrospective study demonstrates that the preoperative CONUT score was an independent prognostic factor after hepatectomy for HCC in our series. The prognostic significance of the CONUT score in patients with colorectal cancer has been reported [11]; however, this is the first report to identify the prognostic significance of the CONUT score in patients with HCC.

The CONUT score is a screening tool designed to easily and objectively assess patients' nutritional status [10]. Various methods to evaluate immune-nutritional status have been developed, and recently PNI was reported to correlate with survival in patients with HCC [7–9]. The CONUT score and PNI have common factors (serum albumin and total lymphocyte count); the relationship between the CONUT score and PNI is shown in Table 3. We found that all patients with a low PNI belonged to the

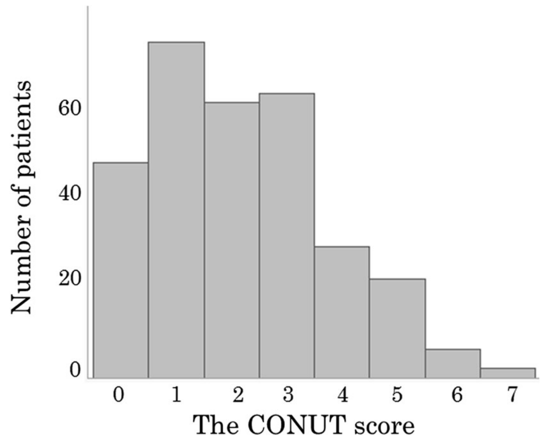

Fig. 1 Distribution of the CONUT scores

Table 3 Relationship between CONUT score and PNI

		PNI	
		Low	High
CONUT score	Low	0	177
	High	32	86

CONUT controlling nutritional status, *PNI* prognostic nutritional index

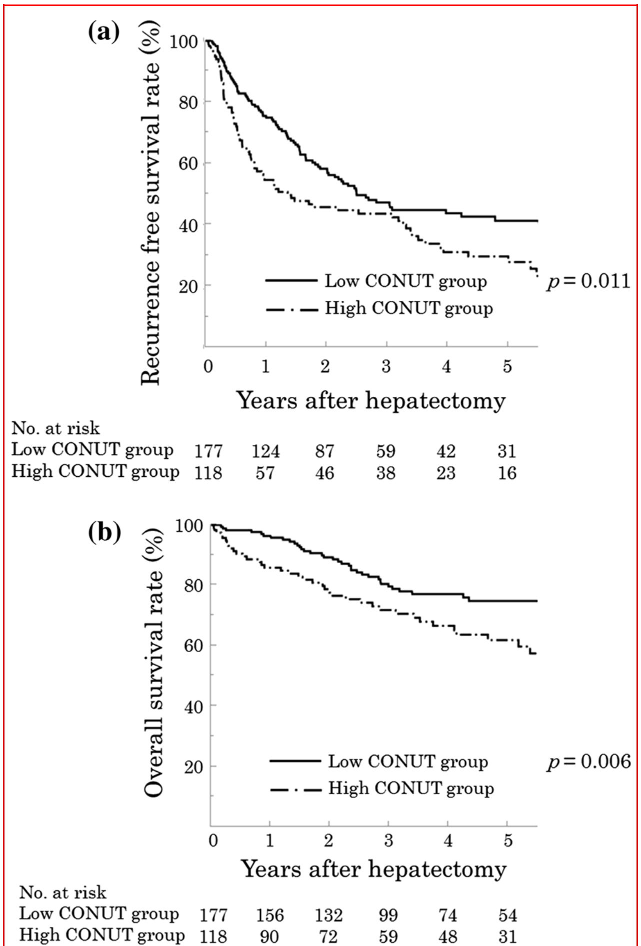

Fig. 2 **a** Recurrence-free and **b** overall survival curves after hepatectomy in patients with low or high CONUT scores **a** $p = 0.011$, **b** $p = 0.006$ (log rank test)

high CONUT group. CONUT score additionally identified patients expected to have poor survival who were not detected by PNI.

With regard to CONUT score parameters, serum albumin concentration is a reliable nutritional screening tool, influenced by not only nutritional status but also non-nutritional factors such as hepatic functional reserve, inflammation, and hydration status [15]. A lower albumin level is associated with increased levels of inflammatory cytokines, such as interleukin-6, which are associated with progression of liver fibrosis and HCC [7]. Most patients with HCC have chronic viral hepatitis as well as persistent chronic inflammation. The systemic and chronic inflammatory response to virus or tumor is also associated with decreased serum albumin concentration and poor prognosis in patients with HCC [9].

The total lymphocyte count is a surrogate marker of nutritional and immune status in patients with HCC [16–18]. Total lymphocytes are reportedly associated with the development of HCC [19]. Lymphocytes, such as $CD4^+$ cells and natural killer cells, play a key role in antiviral and cellular immunity [20]. Lower lymphocyte count is associated with poor prognostic factors in patients with HCC because of inadequate immune response to cancer [18, 21].

Serum cholesterol level was reported to be a prognostic factor for outcomes of for HCC [22]. A decrease in cholesterol level implies not only a calorie deficiency but also that cells are being deprived of an essential nutrient required to maintain metabolic and hormonal equilibrium and membrane integrity [23]. Therefore, inadequate immunocompetent cells would be unable to exert their immunological function against cancer cells because of membrane structure changes [24]. This might explain why cholesterol level is associated with prognosis in patients with HCC.

In the present study, we found a strong correlation between the CONUT score and survival. Patients with HCC with a high CONUT score had significantly lower recurrence-free and overall survival rates (Fig. 2), similar to results among colorectal cancer patients [11]. Our multivariate analysis revealed that the CONUT score was an independent preoperative predictor related to

Table 4 Univariate and multivariate analyses of prognostic factors associated with recurrence-free survival in patients who underwent hepatectomy

Variable	No. patients ($n = 295$)	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p* value	HR	95% CI	*p* value
CONUT score (≥3)	118	1.47	1.09–1.99	0.013	1.64	1.15–2.30	0.006
PNI (<40)	32	1.34	0.84–2.06	0.21	0.74	0.42–1.25	0.27
Sex (male)	241	1.18	0.81–1.78	0.39			
Age (≥70 years)	120	1.38	1.02–1.87	0.04	1.34	0.98–1.83	0.07
BMI (≥25 kg/m^2)	95	0.99	0.71–1.37	0.97			
ASA (≥grade 3)	38	1.89	1.22–2.81	0.005	2.03	1.29–3.11	0.003
HBV and/or HCV	198	1.01	0.73–1.40	0.97			
AFP (≥400 ng/ml)	48	1.49	1.00–2.14	0.048	0.97	0.61–1.51	0.90
Child–Pugh score (grade B)	7	2.65	1.12–5.23	0.029	3.12	1.23–6.81	0.019
Tumor size (≥50 mm)	93	2.04	1.49–2.78	<0.001	1.06	0.71–1.57	0.79
Tumor number (≥2 tumors)	93	2.07	1.52–2.81	<0.001	1.92	1.40–2.63	<0.0001
Poor differentiation	43	1.59	1.04–2.35	0.033	1.13	0.70–1.77	0.62
Microvascular invasion	89	2.95	2.16–4.01	<0.001	3.04	2.05–4.48	<0.0001
Major complications	43	1.44	0.93–2.13	0.10	0.96	0.60–1.48	0.86

HR hazard ratio, *CI* confidence interval, *CONUT* controlling nutritional status, *PNI* prognostic nutritional index, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein

Table 5 Univariate and multivariate analyses of prognostic factors associated with overall survival in patients who underwent hepatectomy

Variable	No. patients ($n = 295$)	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p* value	HR	95% CI	*p* value
CONUT score (≥3)	118	1.87	1.19–2.97	0.007	2.50	1.47–4.23	0.001
PNI (<40)	32	1.78	0.91–3.18	0.09	0.71	0.33–1.46	0.37
Sex (male)	241	1.81	0.95–3.90	0.07	1.45	0.73–3.21	0.30
Age (≥70 years)	120	1.23	0.77–1.94	0.38			
BMI (≥25 kg/m^2)	95	0.84	0.49–1.38	0.49			
ASA (≥grade 3)	38	3.04	1.71–5.13	0.0003	3.45	1.82–6.26	0.0003
HBV and/or HCV	198	0.73	0.46–1.18	0.20			
AFP (≥400 ng/ml)	48	2.30	1.36–3.75	0.003	1.17	0.64–2.08	0.61
Child–Pugh score (grade B)	7	5.23	2.02–11.1	0.002	8.62	2.89–22.4	0.0004
Tumor size (≥50 mm)	93	3.84	2.43–6.13	<0.001	1.21	0.70–2.11	0.49
Tumor number (≥2 tumors)	93	2.04	1.29–3.23	0.003	1.78	1.08–2.93	0.025
Poor differentiation	43	2.88	1.64–4.82	0.0004	1.32	0.69–2.43	0.39
Microvascular invasion	89	6.11	3.83–9.95	<0.001	6.24	3.46–11.4	<0.0001
Major complications	43	2.22	1.21–3.81	0.011	0.97	0.50–1.78	0.92

HR hazard ratio, *CI* confidence interval, *CONUT* controlling nutritional status, *PNI* prognostic nutritional index, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein

recurrence-free and overall survival after hepatectomy (Tables 4, 5).

Among preoperative factors, ASA physical status and Child–Pugh score were also significant factors associated with survival. The ASA physical status is evaluated by anesthesiologists to assess surgical risk; it is also useful to assess patients' general condition, but it can be subjective. The Child–Pugh score is reportedly associated with hepatic functional reserve and prognosis in HCC. Similar to previous reports, tumor-specific factors, such as multiple

Table 6 Relationship between the CONUT score and other clinical parameters

	Undernutrition status			
	Normal ($n = 118$)	Light ($n = 148$)	Moderate ($n = 29$)	p value
Demographic variables				
Sex (men)	97 (82)	120 (81)	24 (83)	0.96
Age (years)	64.6 (10.6)	66.6 (10.2)	66.0 (9.8)	0.23
BMI (kg/m^2)	24.0 (3.8)	23.6 (3.5)	23.4 (2.9)	0.84
Laboratory values				
ICGR15 (%, $n = 213$)	13.2 (7.4)	15.0 (8.7)	17.3 (9.7)	0.13
Platelet count ($\times 10^4$/μL)	19.7 (7.2)	16.9 (7.9)	18.0 (12.9)	0.003
Total bilirubin (mg/dL)	0.75 (0.37)	0.88 (0.82)	0.68 (0.22)	0.09
Prothrombin time (%)	104 (18)	96 (19)	90 (14)	<0.001
Child–Pugh score				
A/B	288/7	176/1	112/6	0.01
^{99}mTc-GSA ($n = 273$)				
HH15	0.55 (0.08)	0.58 (0.08)	0.61 (0.10)	0.003
LHL15	0.88 (0.06)	0.87 (0.06)	0.84 (0.09)	0.003
Comorbidity				
Hypertension	54 (46)	58 (39)	9 (31)	0.28
Diabetes	40 (34)	43 (29)	8 (28)	0.64
Stage of fibrosis				
Fibrosis 0–2/3–4	72/46	72/76	10/19	0.017

Data are presented as numbers (percentages) or means (±SD), unless otherwise indicated

CONUT controlling nutritional status, *BMI* body mass index, *^{99}mTc-GSA* technetium-^{99}m-galactosyl human serum albumin

tumors and microvascular invasion, were strong independent factors associated with survival [25, 26], but tumor size and differentiation were not significantly associated with survival. Although PNI has been reported to correlate with survival in patients with HCC [7–9], PNI was not an independent predictor in this study. Therefore, the CONUT score might be a more accurate prognostic factor than the PNI.

Interestingly, a significant relationship was seen between the CONUT score and some clinical parameters (Table 6). These results might indicate that the CONUT score reflected hepatic functional reserve. Furthermore, the CONUT score had a significant relationship with hepatic fibrosis. Indeed, 19 patients (65.5%) with moderate undernutrition status had stage 3 or 4 fibrosis. The CONUT score could predict not only hepatic functional reserve but also the stage of fibrosis.

Despite our important findings, there are a few limitations to the current study. First, this was a retrospective, single-center study; therefore, there may be potential selection bias in the enrollment of patients for hepatectomy. Second, the number of patients is small. Third, although the CONUT score conventionally described four classes of undernutrition (Table 1), we used other cutoff values according to a previous report [11]. In the present study, the cutoff value for the CONUT score associated with survival using the receiver operating characteristic was also 3 (area under the curve = 0.59). Further studies are needed to determine more adequate cutoff values of the CONUT score to predict worse outcomes. Finally, we did not compare the efficiency of the CONUT score with that of other screening systems, such as nutrition risk index (NRI), malnutrition universal screening tool (MUST), and nutritional risk screening (NRS-2002) [27], because this study was conducted retrospectively and such screening systems were not assessed. However, a comparison of the four systems indicated that CONUT was clearly superior at predicting the statistical outcome [23, 28]. Future studies are required to assess the efficiency of screening systems to evaluate patients' status.

Conclusion

Our study indicates that the CONUT score is a reliable and independent preoperative predictor of survival after hepatectomy for HCC. Assessment of the CONUT score is an easy and feasible method and could help clinicians develop comprehensive approaches for decision-making regarding surgical indication.

Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest to disclose.

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