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Effect of Nutritional Index on Lenvatinib Treatment Retention Rates in Unresectable Hepatocellular Carcinoma

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Abstract

Background/Aim: Several studies have reported the association between lenvatinib (LEN) treatment and nutritional indices. However, no study has used multiple nutritional indices or reported their changes during treatment. This study aimed to clarify the association between LEN treatment and nutritional status.
Patients and Methods: Patients with hepatocellular carcinoma (n=103) treated with LEN were divided into two groups, namely normal and poor nutritional groups, using the Controlling Nutritional Status (CONUT) score, Onodera-Prognostic Nutritional Index (O-PNI), modified Glasgow Prognostic Score (mGPS), and Geriatric Nutritional Risk Index (GNRI). Treatment retention rates were then compared between the two groups. Additionally, changes in nutritional indices from the start of treatment to the end of the observation period or treatment were analyzed to determine their relationship with treatment continuation.
Results: Patients with normal nutrition according to the CONUT score, O-PNI, mGPS, and GNRI had a significantly higher rate of treatment retention than those with poor nutrition. Furthermore, both a normal CONUT score and mGPS indicated a lower likelihood of discontinuation due to adverse events. Patients in whom treatment was continued were significantly more likely to maintain or improve their CONUT score.
Conclusion: Maintaining or restoring a normal nutritional status is important to ensure continued treatment with LEN. Both the combination of the CONUT score and mGPS at the start of LEN treatment, and the CONUT score during treatment, are useful indicators of nutritional status.

Keywords: Lenvatinib, CONUT score, O-PNI, mGPS, GNRI.

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Introduction

Liver cancer exhibits a poor prognosis and ranks as the third leading cause of cancer-related death worldwide (1), while in Japan it ranks as the fifth leading cause (2). In Japan, approximately 90% of liver cancers are hepatocellular carcinomas (HCC) (2). Recent advances in the treatment of unresectable hepatocellular carcinoma include molecularly targeted drugs and immune checkpoint inhibitors (3-5); however, these therapies require distinct management strategies for adverse events (AEs) that differ from those used with conventional cytotoxic anticancer drugs (6, 7). Lenvatinib (LEN), a tyrosine kinase inhibitor, is used as second-line treatment for unresectable hepatocellular carcinoma. In the REFLECT study (4), AEs including hypertension, diarrhea, fatigue, hand-foot syndrome, and proteinuria were observed, posing challenges to continued treatment. We have encountered numerous dose reductions and withdrawals of LEN, particularly owing to fatigue.

In our medical facility, pharmacists meet patients with cancer prior to their consultation to assess medication adherence and monitor AEs. Considering the high case volume, LEN is one of the drugs we are actively intervening with. We have previously reported that meetings with pharmacists can detect AEs associated with LEN at an early stage, and significantly prolong the duration of treatment (8). However, one limitation of this study is the lack of evaluation of the patient's nutritional status. Several studies have reported the association between LEN treatment and nutritional indices (9-12); however, no studies have used multiple nutritional indices or reported alterations in nutritional indices following the start of treatment. This study investigated the association between multiple nutritional indices and treatment continuation rates as well as changes in nutritional indices during LEN treatment to identify strategies for extending the duration of LEN treatment.

Patients and Methods

Target patients. Patients with hepatocellular carcinoma at JA Hokkaido Sapporo Koseiren Hospital who initiated treatment with LEN between June 2019 and September 2022 were included. Patients who did not have laboratory measurements required for the calculation of nutritional index pre-treatment were excluded. The diagnosis of HCC was confirmed pathologically or using imaging techniques (computed tomography or magnetic resonance imaging) (13). The initial dose of LEN was determined based on the body weight at the start of treatment: patients with a body weight ≥60 kg received 12 mg/day, while those weighing <60 kg received 8 mg/day. At the discretion of the attending physician, the initial dose of LEN was reduced based on the performance status or liver functional reserve. In case of any Grade ≥3 severe AEs or unacceptable treatment-related AEs, the dose of LEN was reduced, or the treatment was discontinued. Grades were classified based on the Common Terminology Criteria for Adverse Events (CTCAE) ver 5.0.

Patient background. We assessed the patient backgrounds, including age, sex, height, weight, body mass index (BMI), LEN dosage, non-drug therapy history, drug therapy history, and ALBI (albumin-bilirubin) grade. Pre-treatment ALBI grades were classified as grade 1 (ALBI grade ≤-2.60), grade 2a (−2.60<ALBI grade<−2.27), grade 2b (−2.27≤ ALBI grade ≤−1.39) and grade 3 (ALBI grade <−1.39) (14).

Nutritional indices and continued treatment rate. Nutritional indices, including Controlling Nutritional Status (CONUT) score (15), Onodera Prognostic Nutritional Index (O-PNI) (16), modified Glasgow Prognostic Score (mGPS) (17, 18), and Geriatric Nutritional Risk Index (GNRI) (19) were investigated (Table I). The patients were classified by nutritional index into two categories: nutritional normal (CONUT score <5, O-PNI ≥40, mGPS=0 or 1, GNRI ≥98) and nutritional poor (CONUT score ≥5, O-PNI <40, mGPS=2, GNRI <98). This cutoff was set according to a previous report (9-12). The treatment continuation rate was evaluated using the Kaplan-Meier method with the discontinuation of treatment due to AEs during the first six months of treatment as the endpoint. Treatment discontinuation owing to AEs was defined as discontinuation within the

Table I. *Nutritional indexes.*

CONUT score				
Alb (g/dl)	≥3.5	3.0-3.49	2.5-2.99	<2.5
Alb Score	0	2	4	6
TLC (/μl)	≥1,600	1,200-1,599	800-1,199	<800
TLC Score	0	1	2	3
T-cho (mg/dl)	≥180	140-179	100-139	<100
T-cho Score	0	1	2	3
CONUT score=Alb Score+TLC Score+T-cho Score				
CONUT score	0-1	2-4	5-8	9-12
Nutritional assessment	Normal	Light	Moderate	Severe
O-PNI				
O-PNI=(10×Alb [g/dl])+(0.005×TLC [/mm^3])				
O-PNI	≥45	40≤ O-PNI <45	<40	
Nutritional assessment	Safety	Caution	Hazards	
mGPS				
Score		Nutritional assessment		
CRP ≤0.5 mg/dl and Alb ≥3.5 g/dl	0	Normal		
CRP >0.5 mg/dl or Alb <3.5 g/dl	1	Low		
CRP >0.5 mg/dl and Alb <3.5 g/dl	2	Cachexia		
GNRI				
GNRI=14.89×Alb (g/dl)+41.7×Weight (kg)/IBW (kg) IBW: Height (cm)-100-(Height-150)/4* *Use 2.5 for women				
GNRI	≥98	92≤ GNRI <98	82≤ GNRI <92	<82
Nutritional assessment	No risk	Light risk	Moderate risk	Severe risk

CONUT: Controlling nutritional status; Alb: albumin; TLC: total lymphocyte count; T-cho: total cholesterol; O-PNI: Onodera Prognostic Nutritional Index; mGPS: modified Glasgow Prognostic Score; CRP: C-reactive protein; GNRI: Geriatric Nutritional Risk Index; IBW: ideal body weight.

observation period (excluding temporary drug withdrawal). Treatment discontinuation due to progressive disease [PD; tumor imaging evaluation was determined by the attending physician based on the Modified RECIST (20)], and cases not followed up within the observation period (transfer to another hospital) were censored.

LEN treatment continuation and AEs. Patients were classified into those who were able to continue treatment and those who discontinued because of AEs during the first six months of treatment. For patients who continued treatment, each nutritional index at six months was examined, while for those who discontinued treatment, each nutritional index at the time of discontinuation was examined. Patients in whom treatment was discontinued due to PD and those transferred to other hospitals were excluded.

Statistical analysis. Statistical analyses were performed using the JMP® Pro 17 software (SAS Institute Inc., Cary, NC, USA). Student's *t*-test or Mann-Whitney *U*-test was

Table II. *Patient background.*

Age, year	72.9±9.2
Sex, males/females	84/19
Height, cm	162.0±8.9
Weight, kg	63.7±10.7
BMI, kg/m^2	24.1±3.3
LEN dosage	
4 mg/day	14
8 mg/day	58
12 mg/day	30
Unequal	1
Non-drug therapy history*	
OPE	44
RFA	37
TACE	40
Drug therapy history*	
Sorafenib	11
Regorafenib	5
Cabozantinib	3
Atezo+BEV	17
ALBI grade, 1/2a/2b/3	26/25/45/7

Data are expressed as mean±SD. *There are duplicates. BMI: Body mass index; LEN: Lenvatinib; OPE: operation; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization; Atezo+BEV: Atezolizumab+Bevacizumab; ALBI: albumin-bilirubin grade.

Table III. *Nutrition index at the start of lenvatinib (LEN) treatment.*

	Nutritional status	
	Normal	Poor
CCONUT score, <5/≥5	69/34	
O-PNI, ≥40/<40	55/48	
mGPS, 0 or 1/2	73/30	
GNRI, ≥98/<98	46/57	

CONUT: Controlling nutritional status; O-PNI: Onodera Prognostic Nutritional Index; mGPS: modified Glasgow Prognostic Score; GNRI: Geriatric Nutritional Risk Index.

used to assess two related groups. Fisher's exact test was used to test proportions. Continued treatment rate was estimated using the Kaplan-Meier method, and the log-rank test was used to evaluate the continued treatment distributions among the different patient groups. *p*-Values <0.05 were considered statistically significant. Sensitivity and specificity were calculated using receiver operating characteristic (ROC) curves.

Ethics approval. This study was approved by the Ethics Committee of Sapporo Kosei Hospital (approval number: 619). This study used only existing data without acquiring written or oral consent from the patients. Therefore, we disclosed the data regarding the study and guaranteed an opportunity for all patients to decline their participation.

Results

Patient background and nutritional indices. A total of 103 patients with HCC were treated with LEN during the study period (Table II). The average age of the patients was 72.9 years, and 84 were male. The most prevalent ALBI grade, an index of liver reserve, was 2b (n=45). The nutritional statuses of the patients were classified as either normal or poor using four different nutritional indices (Table III). Normal nutrition was most frequently classified using mGPS (n=73), followed by CONUT score (n=69), O-PNI (n=55), and GNRI (n=46). The classification varied greatly depending on the nutritional indices used.

Treatment continuation rate by nutritional indices. The treatment continuation rate according to the nutritional indices is shown in Figure 1. The reasons for treatment discontinuation were PD (n=26), and AEs (n=28). Significant differences were observed in the treatment continuation rates between the normal and poor nutrition groups in CONUT score (p<0.01), O-PNI (p<0.01), mGPS (p<0.01), and GNRI (p<0.05).

LEN treatment continuation and AEs. A total of 47 and 28 cases of LEN treatment continuation and discontinuation owing to AEs were observed, respectively. Among the 75 patients, 47 were able to continue treatment for six months; the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy to nutritional normal at the start of treatment are shown in Table IV. In addition, a combination of nutritional indices was examined. The combination of CONUT score and mGPS had a sensitivity of 78.7%, specificity of 85.7%,

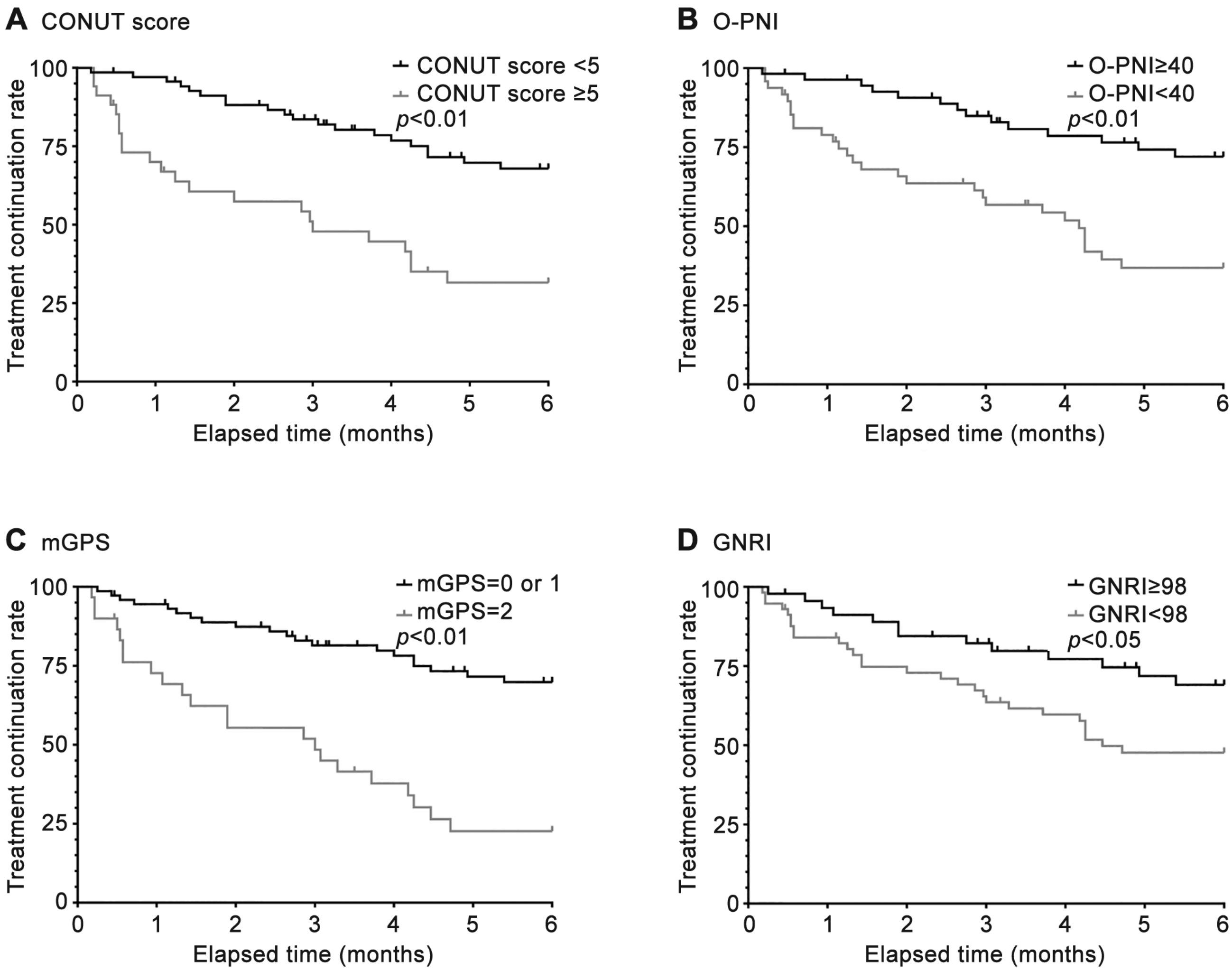

Figure 1. *Treatment continuation rate by nutritional status. A) Controlling nutritional status (CONUT) score, B) Onodera prognostic nutritional index (O-PNI), C) modified Glasgow Prognostic Score (mGPS), and D) Geriatric Nutritional Risk Index (GNRI) results. As with all nutritional indices, the black line of the Kaplan-Meier curve indicates normal nutritional status, while the gray line indicates poor nutritional status. Analysis was performed using log-rank test.*

PPV of 90.2%, NPV of 70.6%, and accuracy of 81.3%, which were higher than those of other nutritional indices or their combinations. This indicates that discontinuation owing to AEs is less likely to occur when both the CONUT score and mGPS are normal at the start of treatment.

Altered nutritional indices (cases with normal nutrition at the start of treatment). From the 75 patients (treatment continuation: n=47, discontinuation owing to AEs: n=28), those with normal nutritional status at the start of treatment were selected (CONUT score, n=46; O-PNI, n=41; mGPS, n=47; GNRI, n=31). Patients with a normal nutritional status were divided into treatment continuation and discontinuation groups, and their nutritional status was examined at the end of six months or at the time of treatment discontinuation. A significant difference was observed in the CONUT score (Figure 2, $p<0.01$) and mGPS ($p<0.05$), indicating that patients in the treatment

Table IV. *The sensitivity, specificity, positive and negative predictive values, and accuracy of lenvatinib (LEN) treatment continuation.*

	Sensitivity	Specificity	PPV	NPV	Accuracy
CONUT score	80.9	71.4	82.6	69.0	77.3
O-PNI	51.1	39.3	58.5	32.4	46.7
mGPS	78.7	64.3	78.7	64.3	73.3
GNRI	51.1	75.0	77.4	47.7	60.0
CONUT score+O-PNI	42.6	75.0	74.1	43.8	54.7
CONUT score+mGPS	78.7	85.7	90.2	70.6	81.3
CONUT score+GNRI	34.3	32.1	54.8	17.0	33.7
O-PNI+mGPS	48.9	82.1	82.1	48.9	61.3
OPNI+GNRI	25.5	42.9	42.9	25.5	32.0
mGPS+GNRI	46.8	42.9	57.9	32.4	45.3

Cases (n=75, 6-month treatment continuation=47). CONUT score: Controlling nutritional status score; O-PNI: Onodera Prognostic Nutritional Index; mGPS: modified Glasgow Prognostic Score; GNRI: Geriatric Nutritional Risk Index; PPV: positive predictive value; NPV: negative predictive value.

discontinuation group had worsening nutritional status (CONUT score ≥5, mGPS=2), whereas those in the treatment continuation group maintained a normal nutritional status (CONUT score <5, mGPS=0 or 1).

Altered nutritional indices (cases with poor nutrition at the start of treatment). From the 75 patients (treatment continuation: n=47, discontinuation owing to AEs: n=28), those with poor nutritional status at the start of treatment were selected (CONUT score, n=29; O-PNI, n=34; mGPS, n=28; GNRI, n=44). Patients with a poor nutritional status were divided into treatment continuation and discontinuation groups, and their nutritional status was examined at the end of six months or at the time of treatment discontinuation. The nutritional status of seven of the nine patients in the treatment continuation group had improved (CONUT score < 5), with a significantly different CONUT score (Figure 3, p<0.01). The transitions in the nutritional statuses of these seven patients are shown in Figure 4. The CONUT score showed improvement in nutritional status in five patients after one month, one patient after two months, and one patient after three months.

Discussion

This study revealed the importance of maintaining a normal nutritional status to continue treatment with LEN. These results suggest that the combination of the CNOUT score and mGPS is useful as an index to determine the nutritional status at the start of treatment. Furthermore, even if the nutritional status is poor at the start of treatment, improving it can help prevent treatment discontinuation due to AEs, with the CNOUT score suggested as a useful indicator of nutritional status.

Regarding LEN treatment, the CNOUT score (9), O-PNI (10), GPS (11), and GNRI (12) have been reported as prognostic factors. As HCC progresses, the ability to synthesize albumin decreases. The four nutritional indices investigated in this study included albumin as a criterion for assessing nutritional status. In HCC, monitoring albumin in terms of both nutritional status and cancer progression is important. The novelty of this study lies in demonstrating the usefulness of combined CNOUT score and mGPS in assessing cases wherein treatment continuation is possible. A distinguishing feature of mGPS compared with other nutritional indices is that it includes C-reactive protein (CRP) in its assessment. Cancer and inflammation are closely related (21), and CRP levels are elevated in patients with cancer. An association between CRP level and tumor size, vascular invasion, lymph node metastasis, distant metastasis, and cancer stage has been reported in HCC (22, 23). We believe that combining the CNOUT score with the mGPS, which includes CRP, enhances the evaluation of aspects related to cancer

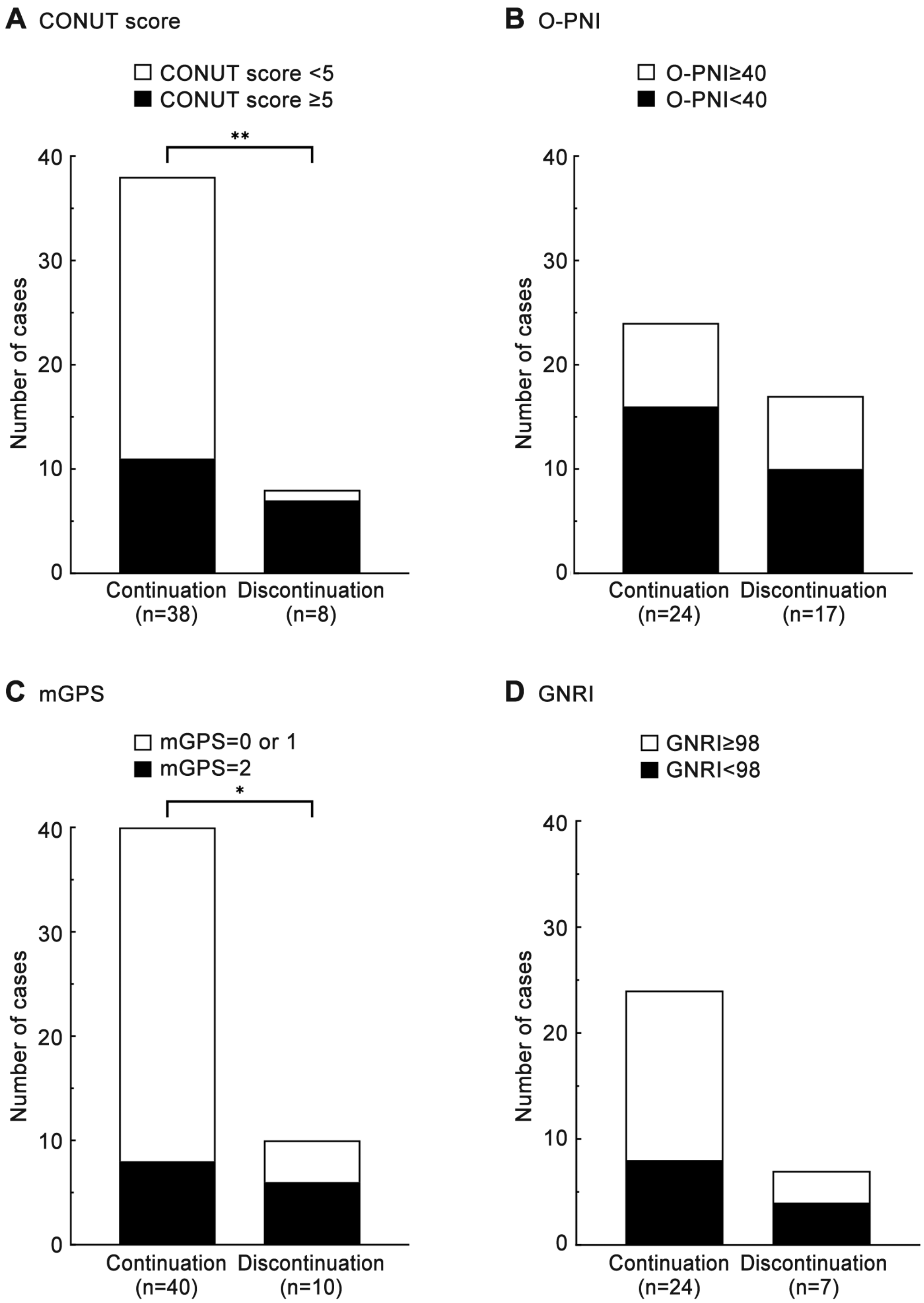

Figure 2. *Alterations in nutritional indices in cases with normal nutritional status. A) Controlling Nutritional Status (CONUT) score, B) Onodera-Prognostic Nutritional Index (O-PNI), C) modified Glasgow Prognostic Score (mGPS), and D) Geriatric Nutritional Risk Index (GNRI) results. As with all nutritional indices, the ■ indicates normal nutritional status, while the □ indicates poor nutritional status. Statistical analysis was performed using the Fisher's exact test, *p<0.05, **p<0.01.*

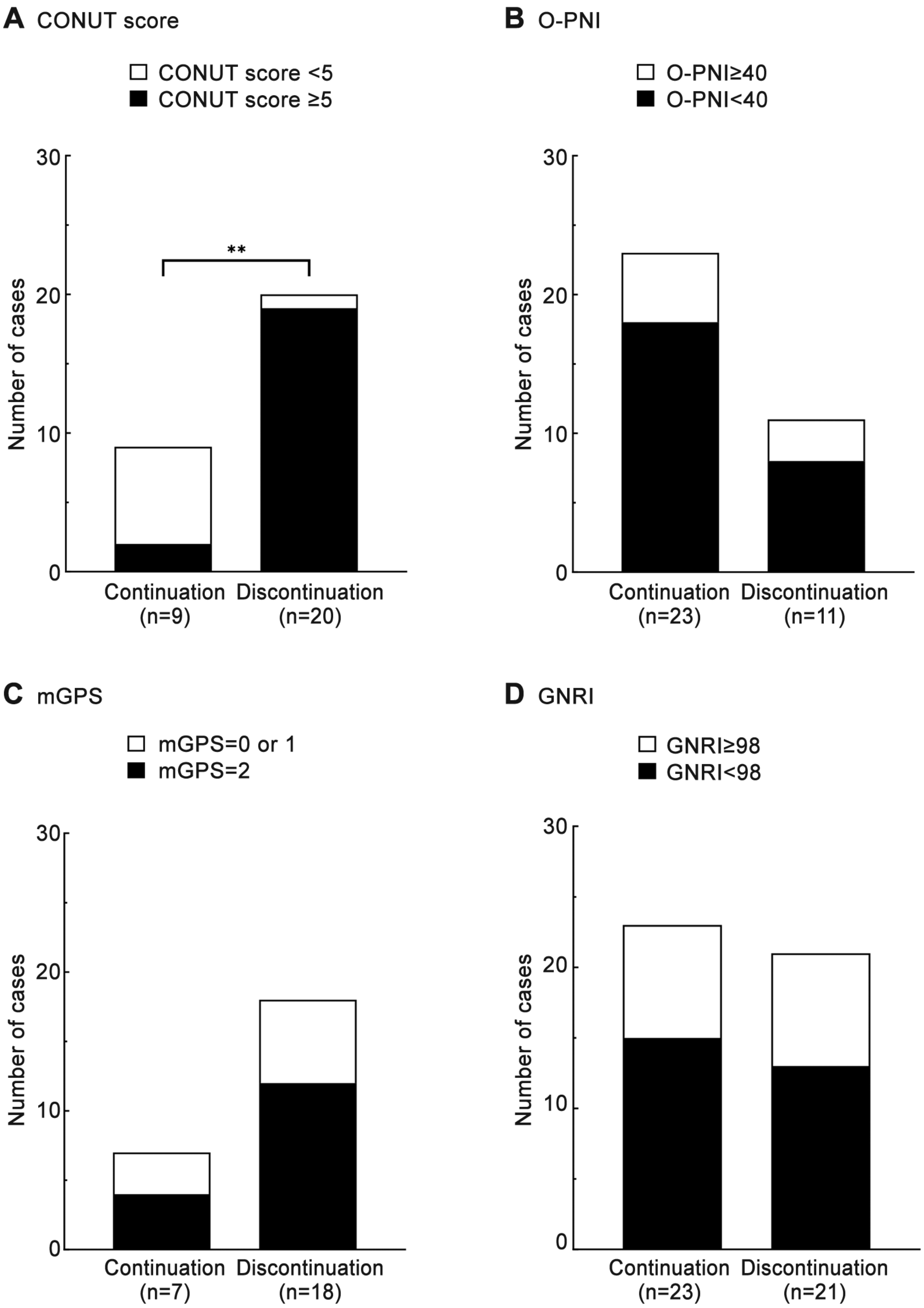

Figure 3. *Alterations in nutritional indices in cases with poor nutritional status. A) Controlling Nutritional Status (CONUT) score, B) Onodera-Prognostic Nutritional Index (O-PNI), C) modified Glasgow Prognostic Score (mGPS), and D) Geriatric Nutritional Risk Index (GNRI) results. As with all nutritional indices, the ■ indicates normal nutritional status, while the □ indicates poor nutritional status. Statistical analysis was performed using the Fisher's exact test, **p<0.01.*

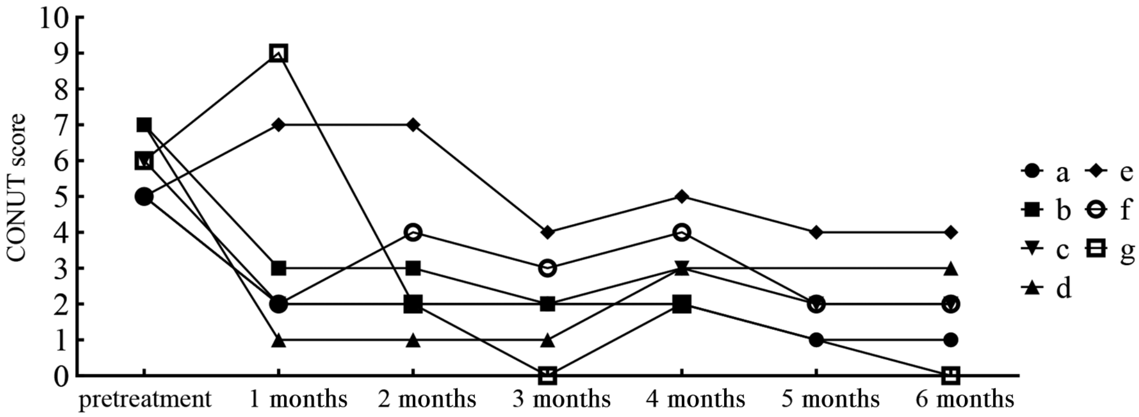

Figure 4. *Altered nutritional indices in poor patients who were able to continue treatment. Alterations are shown in seven patients who had a Controlling Nutritional Status (CONUT) score of ≥5 before the treatment began. Nutritionally normal (CONUT score <5) and poor nutritional status (CONUT score <5).*

progression and provides high accuracy. This study focused on the occurrence of AEs (n=28) leading to treatment discontinuation from the start of treatment for up to six months. The AEs are presented in Supplementary Material. Reasons for discontinuation of LEN involved AEs, such as fatigue and anorexia, which could potentially impact the nutritional status. For the 47 patients who were able to continue treatment six months after initiation, follow-up was conducted for up to one year, with the following outcomes: continued treatment, n=22; discontinued treatment owing to PD, n=21; discontinued treatment owing to AEs, n=3; and transferred to another hospital, n=1. During the first year of treatment, approximately 90% (28/31) of treatment discontinuations due to AEs occurred within the first six months. Based on this, our study used the six-month treatment continuation as an indicator.

A significant difference in nutritional alterations after the start of treatment was observed only in the CONUT score for both normal and poor nutritional statuses. Among patients with normal nutritional status at the start of treatment, those who discontinued treatment within six months had a deteriorated nutritional status. Furthermore, among patients with poor nutritional status at the start of treatment who continued treatment for six months, a significantly higher number of patients showed improvement from poor to normal nutritional status. These results suggest that maintaining normal nutritional status and improving poor nutritional status may facilitate continued treatment. Few studies reported on nutritional indices after the initiation of treatment, and the CONUT score is novel in demonstrating its usefulness as a nutritional index. However, this study was unable to provide a sufficient explanation for why this trend was observed only with the CONUT score.

Cases in which nutritional improvement was observed and treatment could be continued (n=7) included interventions by the medical staff (physicians, pharmacists, nurses, and dietitians) to improve nutrition. Pharmacist interventions included recommending the prescription of nutraceuticals, BCAA formulations, and supportive medications for AEs to physicians and providing oral care instructions for patients with stomatitis. The early period after the start of treatment (1-2 months) may be effective in improving nutritional status. Further studies are warranted to determine the optimal timing and approach for intervention; however, the importance of maintaining normal nutritional status through continuous patient monitoring is unequivocal.

The delivered dose intensity to body surface area ratio at 60 days (2M-DBR) has been reported as a predictive marker for the response to LEN in HCC (24). Evidence indicates that patients with high 2M-DBR achieve longer progression-free survival (PFS) compared to those with low 2M-DBR (24). Furthermore, Shibano *et al.* suggested that PNI is an important factor contributing to high 2M-DBR and a PNI cutoff value of <39.15 may indicate poor response to LEN therapy (25). This study examined the treatment duration of LEN, and does not address its association with treatment outcomes, such as objective response rate, disease control rate, or PFS. Future studies are warranted to explore the relationship between the combination of COUNT and mGPS and 2M-DBR.

Study limitations. First, we did not evaluate sarcopenia. Studies have reported the relationship between sarcopenia and treatment outcomes in various treatment settings for HCC, including surgical liver resection (26, 27), postoperative complications (28), living donor liver transplantation (29), and radiofrequency ablation (30, 31); all of which have shown that non-sarcopenic cases are associated with better treatment results. Regarding LEN treatment, non-sarcopenic patients experience fewer AEs and have a longer duration of treatment (32, 33). However, this study was conducted retrospectively, making it difficult to collect grip strength, physical function (6 m walk speed or 5 times chair rise test or short physical Performance Battery), and skeletal muscle mass (Dual Energy X-Ray Absorptiometer or Bioelectrical impedance analysis), which are essential for the diagnosis of sarcopenia from routine clinical data. Second, we were unable to examine the dietary intake, exercise status, and control status of metabolic comorbidities, such as diabetes mellitus and dyslipidemia. These limitations stem from the fact that the study was conducted retrospectively, and a larger prospective study is required to confirm these findings.

Conclusion

At the start of LEN treatment, a combination of CONUT score and mGPS was used, and following the start of treatment, the use of the CONUT score alone was suggested as necessary to consistently maintain or improve the nutritional status for the continuation of treatment. Therefore, early nutritional intervention is important at the beginning of LEN treatment. Pharmacists can contribute to the continuation of LEN treatment by making prescription recommendations to physicians that focus on maintaining and improving nutritional status.

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Supplementary Material

Available at: https://doi.org/10.6084/m9.figshare.28051064.v1

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

RW, AS, and KH designed the research. MN, AW, and YY acquired and analyzed data. RW, HS, MK, and KH participated in interpretation of the results. RW drafted the manuscript, and KH revised the manuscript and provided an editorial review. All Authors read and approved the final manuscript.

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References

1 Globocan 2020. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf [Last accessed on June 12, 2024]
2 2018 vital statistics in japan, trends up to2016, director-general for statistics, information policy, ministry of health, labour and welfare. Available at: https://www.mhlw.go.jp/toukei/list/dl/81-1a2.pdf [Last accessed on June 12, 2024]

3 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382(20): 1894-1905, 2020. DOI: 10.1056/NEJMoa1915745

4 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL: Lenvatinib *versus* sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 391(10126): 1163-1173, 2018. DOI: 10.1016/s0140-6736(18)30207-1

5 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359(4): 378-390, 2008. DOI: 10.1056/NEJMoa0708857

6 Kim BH, Yu SJ, Kang W, Cho SB, Park SY, Kim SU, Kim DY: Expert consensus on the management of adverse events in patients receiving lenvatinib for hepatocellular carcinoma. J Gastroenterol Hepatol 37(3): 428-439, 2022. DOI: 10.1111/jgh.15727

7 Ventura I, Sanchiz L, Legidos-García ME, Murillo-Llorente MT, Pérez-Bermejo M: Atezolizumab and bevacizumab combination therapy in the treatment of advanced hepatocellular cancer. Cancers (Basel) 16(1): 197, 2023. DOI: 10.3390/cancers16010197

8 Katsuragawa M, Oshita K, Yamashita Y, Ishizuka N, Matsuki Y, Okubo R, Shibanami A, Hiura K: Usefulness of outpatient pharmacist interventions for lenvatinib-treated patients. Jpn J Pharm Health Care Sci 47(11): 623-630, 2021.

9 Shimose S, Kawaguchi T, Iwamoto H, Tanaka M, Miyazaki K, Ono M, Niizeki T, Shirono T, Okamura S, Nakano M, Suga H, Yamaguchi T, Yokokura Y, Noguchi K, Koga H, Torimura T: Controlling Nutritional Status (CONUT) score is associated with overall survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib: a multicenter cohort study. Nutrients 12(4): 1076, 2020. DOI: 10.3390/nu12041076

10 Hiraoka A, Kumada T, Tada T, Fukunishi S, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, Takaguchi K, Kariyama K, Itobayashi E, Tajiri K, Shimada N, Shibata H, Ochi H, Kawata K, Toyoda H, Ohama H, Tsutsui A, Itokawa N, Hayama K, Arai T, Imai M, Nakamura S, Michitaka K, Hiasa Y, Kudo M, Real-Life Practice Experts for HCC (RELPEC) Study Group and HCC 48 Group: Nutritional Index as prognostic indicator in patients receiving lenvatinib treatment for unresectable hepatocellular carcinoma. Oncology 98(5): 295-302, 2020. DOI: 10.1159/000506293

11 Tada T, Kumada T, Hiraoka A, Hirooka M, Kariyama K, Tani J, Atsukawa M, Takaguchi K, Itobayashi E, Fukunishi S, Tsuji K, Ishikawa T, Tajiri K, Ochi H, Yasuda S, Toyoda H, Hatanaka T, Kakizaki S, Shimada N, Kawata K, Tanaka T, Ohama H, Nouso K, Morishita A, Tsutsui A, Nagano T, Itokawa N, Okubo T, Arai T, Imai M, Naganuma A, Aoki T, Koizumi Y, Nakamura S, Joko K, Hiasa Y, Kudo M, Real-life Practice Experts for HCC (RELPEC) Study Group and the Hepatocellular Carcinoma Experts from 48 Clinics in Japan (HCC 48) Group: Glasgow prognostic score predicts survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib: A multicenter analysis. Eur J Gastroenterol Hepatol 34(8): 857-864, 2022. DOI: 10.1097/meg.0000000000002398

12 Kinoshita A, Hagiwara N, Osawa A, Akasu T, Matsumoto Y, Ueda K, Saeki C, Oikawa T, Koike K, Saruta M: The Geriatric Nutritional Risk Index predicts tolerability of lenvatinib in patients with hepatocellular carcinoma. In Vivo 36(2): 865-873, 2022. DOI: 10.21873/invivo.12775

13 European Association for the Study of the Liver: EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 69(1): 182-236, 2018. DOI: 10.1016/j.jhep.2018.03.019

14 Hiraoka A, Kumada T, Tsuji K, Takaguchi K, Itobayashi E, Kariyama K, Ochi H, Tajiri K, Hirooka M, Shimada N, Ishikawa T, Tachi Y, Tada T, Toyoda H, Nouso K, Joko K, Hiasa Y, Michitaka K, Kudo M: Validation of modified ALBI grade for more detailed assessment of hepatic function in hepatocellular carcinoma patients: a multicenter analysis. Liver Cancer 8(2): 121-129, 2019. DOI: 10.1159/000488778

15 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 20(1): 38-45, 2005.

16 Onodera T, Goseki N, Kosaki G: [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi 85(9): 1001-1005, 1984.

17 Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ: Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 89(6): 1028-1030, 2003. DOI: 10.1038/sj.bjc.6601242

18 Toiyama Y, Miki C, Inoue Y, Tanaka K, Mohri Y, Kusunoki M: Evaluation of an inflammation-based prognostic score for the identification of patients requiring postoperative adjuvant chemotherapy for stage II colorectal cancer. Exp Ther Med 2(1): 95-101, 2011. DOI: 10.3892/etm.2010.175

19 Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L, Aussel C: Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 82(4): 777-783, 2005. DOI: 10.1093/ajcn/82.4.777

20 Lencioni R, Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30(01): 052-060, 2010. DOI: 10.1055/s-0030-1247132

21 Coussens LM, Werb Z: Inflammation and cancer. Nature 420(6917): 860-867, 2002. DOI: 10.1038/nature01322

22 Kinoshita A, Onoda H, Takano K, Imai N, Saeki C, Fushiya N, Miyakawa Y, Nishino H, Tajiri H: Pretreatment serum C-reactive protein level predicts poor prognosis in patients with hepatocellular carcinoma. Med Oncol 29(4): 2800-2808, 2012. DOI: 10.1007/s12032-012-0220-1

23 Sieghart W, Pinter M, Hucke F, Graziadei I, Schöniger-Hekele M, Müller C, Vogel W, Trauner M, Peck-Radosavljevic M: Single determination of C-reactive protein at the time of diagnosis predicts long-term outcome of patients with hepatocellular carcinoma. Hepatology 57(6): 2224-2234, 2013. DOI: 10.1002/hep.26057

24 Eso Y, Nakano S, Mishima M, Arasawa S, Iguchi E, Nakamura F, Takeda H, Takai A, Takahashi K, Taura K, Seno H: Dose intensity/body surface area ratio is a novel marker useful for predicting response to lenvatinib against hepatocellular carcinoma. Cancers (Basel) 12(1): 49, 2019. DOI: 10.3390/cancers12010049

25 Shibano M, Takahashi K, Takahashi M, Uchida-Kobayashi S, Kawada N, Nakamura Y, Otori T, Nagayama K: Prognostic Nutrition Index as an indicator of therapeutic response to lenvatinib therapy in hepatocellular carcinoma. Anticancer Res 42(12): 6019-6026, 2022. DOI: 10.21873/anticanres.16113

26 Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, Ikeda T, Maehara Y, Nishie A, Yamanaka T: Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 100(11): 1523-1530, 2013. DOI: 10.1002/bjs.9258

27 Omiya S, Komatsu S, Kido M, Kuramitsu K, Gon H, Fukushima K, Urade T, So S, Sofue K, Yano Y, Sakai Y, Yanagimoto H, Toyama H, Ajiki T, Fukumoto T: Impact of sarcopenia as a prognostic factor on reductive hepatectomy for advanced hepatocellular carcinoma. Anticancer Res 41(11): 5775-5783, 2021. DOI: 10.21873/anticanres.15394

28 Higashi T, Hayashi H, Taki K, Sakamoto K, Kuroki H, Nitta H, Hashimoto D, Chikamoto A, Beppu T, Baba H: Sarcopenia, but not visceral fat amount, is a risk factor of postoperative complications after major hepatectomy. Int J Clin Oncol 21(2): 310-319, 2016. DOI: 10.1007/s10147-015-0898-0

29 Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, Tomiyama K, Yagi S, Mori A, Uemoto S: Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant 13(6): 1549-1556, 2013. DOI: 10.1111/ajt.12221

30 Yuri Y, Nishikawa H, Enomoto H, Ishii A, Iwata Y, Miyamoto Y, Ishii N, Hasegawa K, Nakano C, Nishimura T, Yoh K, Aizawa N, Sakai Y, Ikeda N, Takashima T, Takata R, Iijima H, Nishiguchi S: Implication of Psoas muscle index on survival for hepatocellular carcinoma undergoing radiofrequency ablation therapy. J Cancer 8(9): 1507-1516, 2017. DOI: 10.7150/jca.19175

31 Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, Nakagomi R, Kondo M, Nakatsuka T, Minami T, Sato M, Uchino K, Enooku K, Kondo Y, Asaoka Y, Tanaka Y, Ohtomo K, Shiina S, Koike K: Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol 63(1): 131-140, 2015. DOI: 10.1016/j.jhep.2015.02.031

32 Endo K, Kuroda H, Kanazawa J, Sato T, Fujiwara Y, Abe T, Sato H, Kooka Y, Oikawa T, Sawara K, Takikawa Y: Impact of grip strength in patients with unresectable hepatocellular carcinoma treated with lenvatinib. Cancers (Basel) 12(8): 2146, 2020. DOI: 10.3390/cancers12082146

33 Uojima H, Chuma M, Tanaka Y, Hidaka H, Nakazawa T, Iwabuchi S, Kobayashi S, Hattori N, Ogushi K, Morimoto M, Kagawa T, Tanaka K, Kako M, Koizumi W: Skeletal muscle mass influences tolerability and prognosis in hepatocellular carcinoma patients treated with lenvatinib. Liver Cancer 9(2): 193-206, 2020. DOI: 10.1159/000504604