The Geriatric Nutritional Risk Index Predicts Tolerability of Lenvatinib in Patients With Hepatocellular Carcinoma

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Abstract. *Background/Aim: We aimed to investigate the association between The Geriatric Nutritional Risk Index (GNRI) and the tolerability of lenvatinib in patients with hepatocellular carcinoma (HCC). Patients and Methods: We retrospectively evaluated 61 HCC patients treated with lenvatinib and compared those with low GNRI (≤98, n=26) to those with high GNRI (>98, n=35). Results: The discontinuation of lenvatinib due to adverse events was more frequent in the low GNRI group (46.2%) than in the high GNRI group (17.1%) (p=0.014). Multivariate analysis revealed that low GNRI (p=0.014), hypothyroidism (model 1 p=0.021, model 2 p=0.013), and advanced age (p=0.026) were independently associated with the discontinuation of lenvatinib. The progression-free survival in the low GNRI group was significantly shorter than that in the high GNRI group (p=0.047). Conclusion: The GNRI might be independently associated with the tolerability of lenvatinib in patients with HCC.*

Hepatocellular carcinoma (HCC), the most common primary liver cancer, is a major health concern worldwide, and its incidence is rising in Western countries (1). In 2017, there were 953,000 incident cases of liver cancer and 819,000 deaths globally (2), indicating the poor outcomes of this disease despite recent advances in treatment modalities.

Since the REFLECT study showed the non-inferiority of lenvatinib to sorafenib regarding the overall survival of patients with untreated advanced HCC (3), many investigators have reported the efficacy and feasibility of lenvatinib in patients with advanced HCC (4, 5).

However, several investigators showed that an advanced age, poor liver functional reserve, and some adverse events, such as fatigue and appetite loss, were associated with dose reduction or discontinuation of lenvatinib (6-8), leading to a lower dose intensity and reduced objective response of lenvatinib, followed ultimately by a poor survival outcome. Thus, predicting the tolerability of lenvatinib before the initiation of treatment is crucial for achieving favorable survival outcomes in patients with HCC.

The Geriatric Nutritional Risk Index (GNRI) (9), based on the serum albumin level, present body weight, and ideal body weight, was first reported to predict prognosis among elderly patients with acute ill, hemodialysis, and heart failure. Recently, this index was also found to be useful to predict postoperative complications or survival outcomes in cancer patients, including those with HCC (10, 11).

We herein focus on predictive markers for HCC, and report our investigation of the association between the GNRI and the tolerability of lenvatinib in patients with HCC.

Patients and Methods

Patients. Sixty-one consecutive HCC patients who were treated with lenvatinib from May 2018 to December 2020 at Jikei University Hospital, Jikei University Kashiwa Hospital, and Jikei University Daisan Hospital were enrolled. All medical records were reviewed retrospectively for patients' demographic and clinical data, administration period, dose intensity, objective response, adverse effects (AEs) of lenvatinib, and survival outcomes.

This study was conducted according to the Declaration of Helsinki and the current ethical guidelines and was approved by each institutional ethics board [approval number: 31-023(9522)].

Table I. *Baseline characteristics of patients.*

Median (range)	Low GNRI group (n=26)	High GNRI group (n=35)	*p*-Value
Age (years)	75 (47-89)	72 (44-89)	0.061
Gender (men/women)	23/3	30/5	0.53
ECOG-PS (0/1/2)[†a]	20/1/2	29/4/0	0.83
Body weight (kg)	59.0 (43.7-71.3)	65.6 (47.8-96.1)	0.003
Body mass index	22.0 (17.3-27.9)	24.1 (20.4-32.9)	<0.0001
Body surface area (m^2)	1.6 (1.4-1.8)	1.7 (1.4-2.1)	0.023
AST (IU/l)	41 (16-140)	34 (17-132)	0.34
ALT (IU/l)	27 (9-140)	28 (9-149)	0.97
Albumin (g/dl)	3.5 (2.8-4.0)	4.0 (3.1-4.8)	<0.0001
Total bilirubin (mg/dl)	0.6 (0.2-1.8)	0.7 (0.3-6.2)	0.23
Creatinine (mg/dl)	0.9 (0.6-4.3)	0.8 (0.5-1.8)	0.51
eGFR (ml/min./1.73 m^2)	68 (11-107)	67 (29-121)	0.48
Platelet count (10^4/mm^3)	15.5 (9.7-34.6)	14.9 (5.5-30.8)	0.41
Prothrombin time (%)	92 (67-100)	100 (26-100)	0.45
Maximum tumor diameter (mm)	45 (12-145)	34 (12-148)	0.22
Child-Pugh score (5/6/7/8)	11/10/4/1	28/3/4/0	0.0059
mALBI grade (1/2a/2b/3)	2/12/12/0	20/11/3/1	<0.0001
BCLC stage (B/C)	14/12	20/15	0.8
Portal vein invasion (yes/no)	7/18	7/28	0.47
Extrahepatic spread (yes/no)	4/22	10/25	0.36
AFP (ng/ml)	4.9 (1.6-48,500)	12 (1.3-71,100)	0.97
DCP (mAU/ml)	154 (10-91,832)	187 (17-19,673)	0.77
Initial dose of lenvatinib (4 mg/8 mg/12 mg)	3/19/4	4/20/11	0.34
Initial dose reduction of lenvatinib (yes/no)	7/19	13/22	0.4
History of tyrosine kinase inhibitor treatment (yes/no)	0/26	2/33	0.33
Comorbidities (absent/present)	4/22	6/29	0.57

[†a]n=55. ECOG-PS: Eastern Cooperative Oncology Group Performance status; AST: aspartate aminotransferase; ALT,:alanine aminotransferase; AFP: α-fetoprotein; DCP: des-γ-carboxy prothrombin; eGFR: estimated glomerular filtration rate; mALBI grade: modified albumin-bilirubin grade; BCLC stage: Barcelona Clinical Liver Cancer stage.

Written informed consent for participation in this study was waived because this study was retrospective and analyzed anonymously.

The diagnosis of HCC and evaluation of the liver functional reserve. The diagnosis of HCC was confirmed either pathologically or using imaging techniques obtained by four-phase multidetector-row computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI). The diagnosis was made according to the typical hallmarks of HCC (combination of hypervascularity in the late arterial phase and wash out in the portal venous and/or delayed phase) (12).

Tumor-related variables, including the maximum tumor diameter, presence of vascular invasion, presence of extrahepatic metastases, and Barcelona Clinic Liver Cancer (BCLC) classification (12), were evaluated based on these imaging techniques and other variables.

The liver functional reserve was assessed by the Child-Pugh score and modified albumin-bilirubin (mALBI) grade (13, 14).

Definition and cut-off value of the GNRI. The GNRI was defined as follows: 1.489×serum albumin concentrations (g/l)+41.7×pretreatment body weight/ideal body weight (kg) (9). The GNRI is divided into four risk groups: no risk (>98), low risk (92 to 98), moderate risk (82 to <92), and major risk (<82) (9). According to a previous study (11), we set the cut-off value at 98: to create a low GNRI group (≤98) and a high GNRI group (>98).

Treatment protocol. The initial dose of lenvatinib was determined based on the body weight at inclusion, with a dose of 12 mg/day administered to patients with a body weight ≥60 kg and 8 mg/day to patients with a body weight <60 kg. At the discretion of the attending physician, the initial dose of lenvatinib 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 lenvatinib was reduced, or the treatment was discontinued. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Based on the guideline provided by the manufacturer, dose reduction or temporary interruption of lenvatinib was maintained until the AEs resolved to Grade 1 or 2.

The evaluation of the treatment response and follow-up. Patients were followed carefully after the treatment. The treatment response [complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)] was evaluated by four-phase multidetector-row CT or dynamic contrast-enhanced MRI four to eight weeks after the initiation of treatment, based on the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines (15). The relative dose intensity (RDI) was calculated by dividing the actual delivered dose by the standard dose.

The start date of the follow-up was the date of the first administration of lenvatinib. The end date of the follow-up was the

Table II. *Summary of adverse events*.

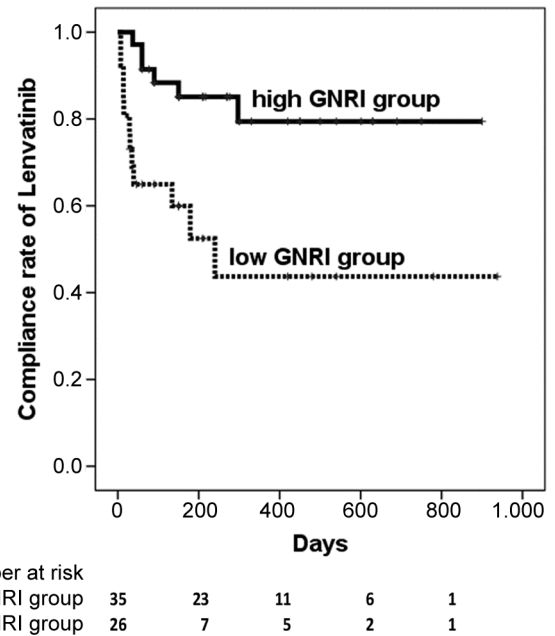| Event, n (%)	Low GNRI group (n=26)	High GNRI group (n=35)	*p*-Value
Hypertension			
Any grade	6 (23.1%)	15 (42.9%)	0.11
Grade ≥3	0 (0%)	3 (8.6%)	0.18
Hand-foot skin reaction			
Any grade	7 (26.9%)	8 (22.9%)	0.72
Grade ≥3	2 (7.7%)	1 (2.9%)	0.39
Fatigue			
Any grade	10 (38.5%)	12 (34.3%)	0.74
Grade ≥3	2 (7.7%)	0 (0%)	0.18
Appetite loss			
Any grade	7 (26.9%)	7 (20%)	0.52
Grade ≥3	4 (15.4%)	2 (5.7%)	0.21
Diarrhea			
Any grade	7 (26.9%)	11 (31.4%)	0.70
Grade ≥3	0 (0%)	1 (2.9%)	0.57
Proteinuria			
Any grade	6 (23.1%)	9 (25.7%)	0.81
Grade ≥3	4 (15.4%)	4 (11.4%)	0.47
Hypothyroidism			
Any grade	13 (50%)	19 (54.3%)	0.74
Grade ≥3	0 (0%)	4 (11.4%)	0.10
Others			
Any grade	12 (46.2%)	11 (31.4%)	0.24
Grade ≥3	5 (19.2%)	5 (14.3%)	0.43
Discontinuation of Lenvatinib due to adverse events	12 (46.2%)	6 (17.1%)	0.014
Cause of discontinuation (overlapped)	Fatigue 3 Appetite loss 3 Tumorlysis syndrome 2 Hepatic encephalopathy 2 Proteinuria 2 Liver damage 1 Hand-foot skin reaction 1 Anemia 1 Renal insufficiency 1	Proteinuria 1 Fatigue 1 Appetite loss 1 Liver damage 1 Hand-foot skin reaction 1 Renal insufficiency 1 Deterioration of PS 1	

PS: Performance status.

Figure 1. *The time to the discontinuation of lenvatinib due to adverse events was significantly shorter in the low Geriatric Nutritional Risk Index (GNRI) group (median 240 days) compared to that in the high GNRI group (not reached during the period) (p=0.003).*

time of the last follow-up covered by this study (December 2020) or the time of the patient's death. The progression-free survival (PFS) is defined as the time from the first administration of lenvatinib to disease progression or death from any cause.

Statistical analyses. Comparisons between the groups were carried out using the Mann-Whitney *U*-test for continuous and ordinal variables and the χ^2-test or Fisher's exact test for categorical variables. The time to discontinuation of lenvatinib due to AEs and the progression-free survival (PFS) were calculated using the Kaplan-Meier method, and differences between the groups were compared by the log-rank test. To evaluate the predictive factors for the discontinuation of lenvatinib, logistic regression analyses were used to calculate the odds ratio (OR) with 95% confidence intervals (CIs). Both univariate and multivariate analyses for the PFS were performed using the Cox proportional hazard model. The cut-off points of continuous variables for the univariate and multivariate analyses were determined based on the median values. Variables that proved to be significant in the univariate analyses were tested subsequently with a multivariate Cox proportional hazard model. *p*<0.05 was considered statistically significant.

To assess the predictive ability of GNRI and age for the discontinuation of lenvatinib due to AEs or RDI for the objective response (CR or PR), receiver-operating characteristic curves (ROCs) were constructed, and the areas under the curves (AUCs) were compared. All statistical analyses were performed using the IBM SPSS Statistics software program, version 19.0 (IBM SPSS, Chicago, IL, USA).

Results

Baseline characteristics (Table I). A total of 26 patients (GNRI ≤98) were classified into the low GNRI group, and the remaining 35 patients (GNRI >98) were classified into the high GNRI group.

Significant differences were found between the two groups in the body weight, body mass index, body

Table III. *Results of a multivariate analysis for predicting discontinuation of Lenvatinib.*

Factors	Univariate *p*-Value	Multivariate Model 1 Odds ratio (95%CI)	*p*-Value	Multivariate Model 2 Odds ratio (95%CI)	*p*-Value
Age group (≥73 years old)	**0.035**	-		4.77 (1.21-18.82)	0.026
Gender (female)	0.60	-		-	
Creatinine (≥0.84 mg/dl)	0.48	-		-	
mALBI grade (2a/2b/3)	0.39	-		-	
Portal vein invasion (yes)	0.89	-		-	
Extrahepatic spread (yes)	0.93	-		-	
Adverse event: hypertension (yes)	0.48	-		-	
Adverse event: hand-foot skin reaction (yes)	0.71	-		-	
Adverse event: fatigue (yes)	0.77	-		-	
Adverse event: appetite loss (yes)	0.22	-		-	
Adverse event: diarrhea (yes)	0.42	-		-	
Adverse event: proteinuria (yes)	0.31	-		-	
Adverse event: hypothyroidism (yes)	**0.016**	0.22 (0.06-0.79)	**0.021**	0.18 (0.046-0.69)	**0.013**
GNRI (≤98)	**0.017**	4.82 (1.37-16.95)	**0.014**	-	
Initial dose of lenvatinib (12 mg)	0.78	-		-	

CI: Confidence interval; mALBI grade: modified albumin-bilirubin grade; GNRI: Geriatric Nutritional Risk Index. Significant *p*-Values are shown in bold.

surface area, serum albumin, Child-Pugh score, and mALBI grade.

AEs and the tolerability of lenvatinib. A total of 95.1% (58/61) developed treatment-related AEs. There were no fatal treatment-related AEs. The most common AEs were hypothyroidism (52.5%), followed by fatigue (36.1%), hypertension (34.4%), diarrhea (29.5%), hand-foot skin reaction (24.6%), proteinuria (24.6%), and appetite loss (22.3%).

The frequency of AEs (both any grade and Grade ≥3) was not significantly different between the two groups. However, the discontinuation of lenvatinib due to AEs was more frequent in the low GNRI group (12/26, 46.2%) than in the high GNRI group (6/35, 17.1%) (*p*=0.014) (Table II).

The time to discontinuation of lenvatinib due to AEs was also significantly shorter in the low GNRI group (240 days) compared to the high GNRI group (not reached during the period) (*p*=0.003) (Figure 1).

Given the correlations between the GNRI and mALBI grade (both include albumin), we constructed two multivariate models: model 1 included the variables of age, sex, creatinine, portal vein invasion, extrahepatic spread, each adverse event, GNRI, and initial dose of lenvatinib. Model 2 included the variables of age, sex, creatinine, mALBI grade, portal vein invasion, extrahepatic spread, each adverse event, and initial dose of lenvatinib. A multivariate logistic regression analysis revealed that a low GNRI (OR=4.82; 95%CI=1.37-16.95, *p*=0.014), hypothyroidism (model 1 OR=0.22; 95%CI=0.06-0.79, *p*=0.021, model 2 OR=0.18; 95%CI=0.046-0.69, *p*=0.013), and advanced age

(OR=4.77; 95%CI=1.21-18.82, *p*=0.026) were independently associated with the discontinuation of lenvatinib (Table III).

The GNRI (0.671, *p*=0.037) and hypothyroidism (0.675, *p*=0.032) had higher AUC values for the discontinuation of lenvatinib due to AEs compared to the advanced age (0.652, *p*=0.063).

Therapeutic response to lenvatinib and the association with RDI. The objective response rate (ORR) and disease control rate (DCR) were 34.6% (9/26) and 57.7% (15/26), respectively, in the low GNRI group and 51.4% (18/35) and 94.3% (33/35), respectively, in the high GNRI group (*p*=0.19; 0.0021).

The ROC curves of the 4-, 8-, and 12-week RDI were constructed for the objective response (CR or PR), and the AUCs were then compared. The 8-week RDI (0.679) had a higher AUC value than the 4-week RDI (0.565) or 12-week RDI (0.586).

Patients with CR or PR had a significantly higher 8-week RDI (78.6%) than those with SD or PD (50.9%) (*p*=0.02). Patients with mALBI 1 had a significantly higher 8-week RDI (92.9%) than those with mALBI 2a or 2b (62.5%) (*p*=0.003). Patients in the low GNRI group had a significantly lower 8-week RDI (56.7%) than those in the high GNRI group (75%) (*p*=0.019).

The PFS and prognostic factors. The cumulative PFS at 50, 100, 150, and 200 days was 82.8%, 65.3%, 43.6%, and 38.7% in the low GNRI group, respectively, and 97.1%, 91.3%, 84.7%, and 81.3% in the high GNRI group, respectively. The PFS in the low GNRI group was
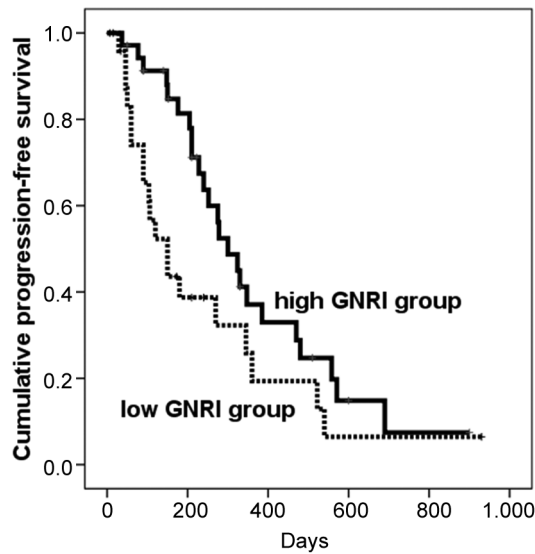
Figure 2. *Progression-free survival in the low Geriatric Nutritional Risk Index (GNRI) group was shorter than that in the high GNRI group (hazard ratio=1.83, 95%CI=0.996-3.351, p=0.047).*

significantly shorter than that in the high GNRI group [hazard ratio (HR)=1.83, 95%CI=0.99-3.35, *p*=0.047) (Figure 2).

Given the correlations between the GNRI and mALBI grade (both include albumin), we constructed two multivariate models: model 1 included the variables of age, sex, creatinine, BCLC stage, portal vein invasion, extrahepatic spread, AFP, objective response, GNRI, initial dose of lenvatinib, and 8-week RDI. Model 2 included the variables of age, sex, creatinine, mALBI grade, BCLC stage, portal vein invasion, extrahepatic spread, AFP, objective response, initial dose of lenvatinib, and 8-week RDI. The results of the univariate and multivariate analyses are shown in Table IV. The multivariate analysis revealed that objective response (HR=0.39; 95%CI=0.17-0.88, *p*=0.023) was independently associated with PFS.

Discussion

In the present study, the discontinuation of lenvatinib due to AEs was more frequent in the low GNRI group than in the high GNRI group. The time to discontinuation of lenvatinib due to AEs was also significantly shorter in the low GNRI group than in the high GNRI group. Multivariate analyses showed that a low GNRI was an independent predictor for the discontinuation of lenvatinib, which led to a lower dose intensity and poor survival outcomes in patients with low GNRI.

The GNRI was proposed for predicting the risk of morbidity and mortality in hospitalized elderly patients by Bouillanne *et al.* in 2005 (9). Recently, a lower GNRI was reported to be associated with postoperative complications and poor survival outcomes in patients with lung cancer (16), colorectal cancer (17), gastric cancer (18), esophageal cancer (18), prostate cancer (19), diffuse large B-cell lymphoma (20), and HCC (10, 11).

Body weight, one of the components of GNRI, is reported to be associated with tolerability of lenvatinib. The phase II study of lenvatinib in patients with advanced HCC showed that the median body weight (54.1 kg) was lower in patients with an early dose withdrawal or reduction than in those without it (67.6 kg) (21). A previous dose-finding study for lenvatinib in patients with HCC indicated that a greater lenvatinib area under the plasma concentration curve and lower body weight resulted in earlier drug withdrawal or dose reduction (22).

In addition to their lower body mass index and body weight, the factors of sarcopenia and frailty, which are likely to be common among low GNRI patients, may have affected the discontinuation of lenvatinib, although we were unable to evaluate sarcopenia or frailty in this study. Endo *et al.* showed that the time to discontinuation of lenvatinib due to AEs for HCC patients with a decreased grip strength was significantly shorter than that for patients with a normal grip strength (23). Uojima *et al.* also reported that HCC patients with a low skeletal muscle mass on CT had a significantly higher withdrawal rate of lenvatinib due to AEs than those with a high skeletal muscle mass (24). Cullinan *et al.* also reported that patients with frailty were twice as likely to experience at least one adverse drug reaction as those without frailty (25). As mentioned above, several researchers have shown the usefulness of sarcopenia or frailty for predicting the tolerability of cancer treatment. However, the measurement of sarcopenia or frailty in daily clinical practice is complex. Regarding sarcopenia, measuring the grip strength, gait speed, and area of the iliopsoas muscle at the third lumbar vertebra level on CT can be challenging in institutes that lack suitable equipment (11). Regarding frailty, there are many assessment tools for frailty or comprehensive geriatric assessments, such as Frailty phenotype, Frailty Index, Geriatric 8 frailty questionnaire for oncology (26), which are also challenging to implement in daily clinical practice. In contrast, Shoji showed that preoperative sarcopenia measured by CT was significantly related to the GNRI in patients with non-small cell lung cancer (27). Furthermore, Cereda showed that the GNRI was significantly associated with mid-upper arm muscle circumference and grip strength in institutionalized elderly patients (28).

Serum albumin, one of the components of the GNRI, reflects the nutritional status related to aging or comorbidities, inflammatory cytokines induced by cancer progression, and

Table IV. *Results of a multivariate analysis for factors associated with PFS.*

Factors	Univariate p-Value	Multivariate Model 1 Hazard ratio (95%CI)	p-Value	Multivariate Model 2 Hazard ratio (95%CI)	p-Value
Age group (≥73 years old)	0.14	-		-	
Gender (female)	0.14	-		-	
Creatinine (≥0.84 mg/dl)	0.40	-		-	
mALBI grade (2a/2b/3)	**0.042**	-		-	
BCLC stage (C)	0.39	-		-	
Portal vein invasion (yes)	0.22	-		-	
Extrahepatic spread (yes)	0.90	-		-	
AFP (≥9.2 ng/ml)	0.11	-		-	
Objective response (PR/CR)	0.063	-		0.39 (0.17-0.88)	**0.023**
GNRI (≤98)	0.052	-		-	
Initial dose of lenvatinib (12 mg)	0.40	-		-	
8w-RDI (≥67%)	0.074	-		-	

PFS: Progression-free survival; CI: confidence interval; mALBI grade: modified albumin-bilirubin grade; BCLC stage: Barcelona Clinical Liver Cancer stage; AFP: α-fetoprotein; CR: complete response; PR: partial response; GNRI: Geriatric Nutritional Risk Index; RDI: relative dose intensity. Significant *p*-Values are shown in bold.

liver functional reserve, which affects the tolerability of cancer treatment. Indeed, patients with hypoalbuminemia developed chemotherapy-induced toxicity (29) and showed early termination of chemotherapy more frequently than others (30).

Previous studies have found several factors associated with tolerability of lenvatinib. Shimose *et al*. demonstrated that age ≥71 years old and ALBI grade 2 were independently associated with the discontinuation of lenvatinib due to AEs in patients with HCC treated with lenvatinib (7). Sasaki *et al*. showed that the time to reduction or discontinuation of lenvatinib was significantly shorter in the elderly group (≥72 years old) than in the younger group (<72 years old) (8). Taken together, these findings suggest that age and liver functional reserve represented by the ALBI grade might affect the tolerability of lenvatinib in patients with HCC. The ROC analysis showed that the AUC values of the GNRI were higher than those of the age in the current study, implying that the GNRI is more strongly predictive of the tolerability of lenvatinib than the age.

The RDI at 8 weeks was significantly lower in the low GNRI group (56.7%) than in the high GNRI group (75%) in our study. Several studies have reported that the dose intensity of lenvatinib influenced the response to lenvatinib or the survival outcome. Takahashi *et al*. showed that patients with an RDI ≥75% at 8 weeks experienced a higher response rate and longer PFS than those with an RDI <75% (31). Kirino *et al*. also showed that patients with an RDI ≥70% at 4 weeks had a higher disease control rate, longer duration of lenvatinib therapy, and longer overall survival than those with an RDI <70% (32). In our study, the lower RDI at 8 weeks in the low GNRI group may have led to the lower DCR and shorter PFS compared to those in the high GNRI group.

The results of the current study suggest that the GNRI may be a useful and readily available tool for predicting the tolerability of lenvatinib in patients with HCC. Kanehira *et al*. reported that a low pretreatment GNRI (<92) independently predicted the early discontinuation of azacitidine and poor survival outcomes in patients with myelodysplastic syndrome (33). These results are consistent with our results. Predicting the tolerability of cancer treatment before treatment is crucial for better treatment outcomes and should be simple and easy to use in daily clinical practice. In this respect, the GNRI can be useful and serve even as a simple method without additional imaging techniques or measuring equipment.

The current study has several limitations. First, this was a retrospective study with a small sample size. Second, we were unable to match both groups using propensity score matching due to the small sample size. Third, we were unable to obtain sufficient data, including the prevalence of sarcopenia, frailty, and nutritional assessment because of the multicenter, retrospective observational nature of the study. These methodological drawbacks might have affected the results of our study. A large-scale prospective study is warranted to confirm the findings of the current study.

Conclusion

We demonstrated that the GNRI is independently associated with the tolerability of lenvatinib in patients with HCC and can serve as a simple method without additional imaging techniques or measuring equipment in clinical practice.

Conflicts of Interest

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

Authors' Contributions

Akiyoshi Kinoshita contributed to the data acquisition, study design, concept, statistical analysis and drafted the manuscript. Noriko Hagiwara, Akiyuki Osawa, Takafumi Akasu, Yoshihiro Matsumoto, Kaoru Ueda, Chisato Saeki, Tsunekazu Oikawa, Kazuhiko Koike contributed to data acquisition and edited the manuscript. Masayuki Saruta edited the manuscript.

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