

GASTROENTEROLOGY

Clinical importance of muscle volume in lenvatinib treatment for hepatocellular carcinoma: Analysis adjusted with inverse probability weighting

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Key words

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Abstract

Background and Aim: This study aimed to elucidate the clinical importance of muscle volume loss (pre-sarcopenia) in patients receiving lenvatinib as treatment for unresectable hepatocellular carcinoma (u-HCC).

Methods: Of 437 u-HCC patients treated with lenvatinib at specific institutions in Japan between March 2018 and May 2020, 151 with available computed tomography imaging data from the time of lenvatinib introduction were enrolled. Pre-sarcopenia was diagnosed based on a previously reported cut-off value calculation formula [psoas muscle area at level of middle of third lumbar vertebra (cm²)/height (m)²]. Clinical features and prognostic factors for overall survival (OS) with inverse probability weighting were investigated retrospectively for their relationship with pre-sarcopenia.

Results: Cox hazard multivariate analysis showed alpha-fetoprotein (≥400 ng/mL) (hazard ratio [HR] 2.271, *P* < 0.001), Barcelona Clinic Liver Cancer stage (C and D) (HR 1.625, *P* = 0.018), and positive for pre-sarcopenia (HR 1.652, *P* = 0.042) to be significant prognostic factors. OS rates for the pre-sarcopenia group (*n* = 41) were worse than those for the non-pre-sarcopenia group (*n* = 110) (0.5-, 1-, and 1.5-year OS: 72.5%, 27.9%, and 7.0% vs 80.7%, 56.7%, and 46.1%, respectively; *P* < 0.001), as was progression-free survival (*P* = 0.025). Time to stopping lenvatinib or disease progression was better in the non-pre-sarcopenia group (0.5-, 1-, and 1.5-year OS: 48.0%, 24.5%, and 8.4% vs 20.0%, 10.3%, and 4.2%, respectively; *P* < 0.001). Also, the frequency of the adverse event appetite loss (any grade) was greater in the pre-sarcopenia group (43.9% vs 18.2%, *P* = 0.003).

Conclusion: Pre-sarcopenia was shown to be a significant prognostic factor in patients treated with lenvatinib for u-HCC.

Author contribution: AH and TK conceived the study and participated in its design and coordination. AH, TK, Kka, TT, JT, SF, MA, MH, KTs, TI, KTak, EI, KTaj, NS, HS, HOc, KK, SY, HT, HOh, KN, AT, TN, NI, KH, TA, MI, YK, SN, KM, KJ, MK, and YH performed data curation. AH performed statistical analyses and interpretation. AH and TK drafted the text. All authors have read and approved the final version of the manuscript.

Ethical approval: The present study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (IRB No. 30-66). The research was conducted in an ethical manner in accordance with the World Medical Association Declaration of Helsinki.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the fifth most common malignancy worldwide.¹ Progression of surveillance and therapeutic modalities has improved the prognosis of affected patients,^{2,3} with four different molecular targeting agents (MTAs), including sorafenib,⁴ regorafenib,⁵ lenvatinib,⁶ and ramucirumab,⁷ developed for unresectable HCC (u-HCC) now available in Japan. Generally, tumor burden and hepatic reserve function have great influence on the prognosis of HCC patients.^{8,9} To improve that of u-HCC patients, sequential MTA treatment has an important role, and it has been shown that introduction of that in patients with good hepatic function is important for continued effective sequential MTA therapy.^{10–13}

Recent clinical studies have found that in addition to tumor burden, malignant potential, hepatic reserve function, and muscle volume depletion are important prognostic factors not only in patients undergoing curative treatment but also in those receiving palliative therapy.¹⁴ Muscle volume depletion is not rare in chronic liver disease (CLD) cases,^{15–17} and it has also been reported that worse prognosis was observed in u-HCC patients with as compared with those without muscle volume loss who were receiving sorafenib treatment.^{18–21} On the other hand, although lenvatinib has been used as a powerful MTA drug against u-HCC in Japan,²² few reports have investigated the association between prognosis and muscle volume depletion in lenvatinib-treated u-HCC patients.²³ The present study aimed to evaluate the clinical role of muscle volume depletion in u-HCC patients undergoing treatment with lenvatinib.

Materials and methods

Patients. Of 437 patients with u-HCC and being treated with lenvatinib at specific institutions in Japan between March 2018 and May 2020 (Ehime Prefectural Central Hospital, Ogaki Municipal Hospital, Okayama City Hospital, Himeji Red Cross Hospital, Kagawa University Hospital, Osaka Medical School, Nippon Medical School, Ehime University Graduate Hospital, Teine Keijinkai Hospital, Saiseikai Niigata Hospital, Kagawa Prefectural Central Hospital, Asahi General Hospital, Toyama University Hospital, Otakanomori Hospital, Tokushima Prefectural Central Hospital, Matsuyama Red Cross Hospital, Kagawa University Hospital, and Hamamatsu University School of Medicine Hospital), clinical features of 151, whose computed tomography (CT) imaging data at introducing lenvatinib were sent to Ehime Prefectural Central Hospital from each hospital, were evaluated in a retrospective manner. Those positive for hepatitis B virus surface antigen were judged to have HCC due to the presence of the

hepatitis B virus, while those positive for the anti-hepatitis C virus were judged to have HCC due to hepatitis C virus.

Hepatocellular carcinoma diagnosis. Based on an increasing course of alpha-fetoprotein (AFP), as well as findings obtained in dynamic CT,²⁴ magnetic resonance imaging,^{25,26} contrast enhanced ultrasonography with perflubutane (Sonazoid®, Daiichi Sankyo Co., Ltd., Tokyo, Japan) examinations,^{27,28} and/or pathological findings, HCC was diagnosed. To evaluate tumor progression, we used Barcelona Clinic Liver Cancer (BCLC) stage²⁹ and tumor node metastasis (TNM) stage, determined as previously reported in a study for TNM staging of HCC conducted by the Liver Cancer Study Group of Japan (LCSGJ) 6th edition³⁰ (TNM-LCSGJ).

Assessment methods for hepatic reserve function and therapeutic response. Child-Pugh classification³¹ and albumin–bilirubin (ALBI) grade were used for assessment of hepatic reserve function. ALBI grade was calculated based on serum albumin and total bilirubin values using the following formula: ALBI score = $[(\log_{10} \text{bilirubin } (\mu\text{mol/L}) \times 0.66) + (\text{albumin } (\text{g/L}) \times -0.085)]$, with the results defined by the following scores: ≤ -2.60 , grade 1; > -2.60 to ≤ -1.39 , grade 2; and > -1.39 , grade 3.^{9,32,33} To perform more detailed evaluations of patients with the middle ALBI grade of 2, we used a revised grading system consisting of four levels that included sub-grading for the middle grade of 2 (2a and 2b) based on an ALBI score of -2.27 as the cut-off (modified ALBI grade [mALBI grade]), which was previously developed based on the value for indocyanine green retention after 15 min (ICG-R15) of 30%.^{34,35}

Evaluation of muscle volume depletion. Muscle volume depletion was defined as “pre-sarcopenia” following the definition provided by the European Working Group on Sarcopenia in Older People³⁶ and evaluated based on psoas muscle area index (PSI) [psoas muscle area at level of middle of third lumbar vertebra (cm^2)/height (m^2)], which was a simple method to calculate from CT findings using the DICOM viewer personal computer software package (OsiriX 11.0®, <https://www.osirix-viewer.com>) by manually hand-tracing. Previously reported cut-off values for muscle wasting in men and women (4.24 and $2.50 \text{ cm}^2/\text{m}^2$, respectively) were used.¹⁵ All patients underwent a CT examination within 1 month before starting lenvatinib; then the first follow-up CT examination was performed at 4 weeks after starting treatment, whenever possible. For calculation of PSI, a hepatologist (AH) performed manual calculations using the

DICOM software package, while other hepatologist (KM) confirmed the traced area of the bilateral psoas muscle in order to avoid human error or a mistake with tracing.

Lenvatinib treatment and assessment of adverse events. After obtaining written informed consent from each patient, lenvatinib treatment was started. Lenvatinib was orally administered at 8 mg/day in patients weighing <60 kg or 12 mg/day in those \geq 60 kg and discontinued when any unacceptable or serious adverse event (AE) or clinical tumor progression was observed. According to the guidelines for administration of lenvatinib, the drug dose was reduced or treatment interrupted when a patient developed any grade 3 or more severe AE or if any unacceptable grade 2 drug-related AE occurred. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.³⁷ AEs of grade 3 or more were defined as severe, and the worst grade for each AE during the present observation period was recorded. If a drug-related AE was noted, dose reduction or temporary interruption was maintained until the symptom was resolved to grade 1 or 2, according to the guidelines provided by the manufacturer.

Evaluations of overall and progression-free survival, and ethical approval. Patients were divided into those with (pre-sarcopenia, $n = 41$) and without (non-pre-sarcopenia, $n = 110$) pre-sarcopenia. Overall survival (OS) rate and progression-free survival were analyzed according to the modified Response Evaluation Criteria In Solid Tumors criteria^{38,39} based on results of dynamic CT examinations performed at intervals of 8–12 weeks and rate of discontinuation of lenvatinib medication.

Written informed consent for lenvatinib treatment was obtained from each patient. This was a retrospective analysis of records stored in a database, and official approval was received based on the Guidelines for Clinical Research issued by Ministry of Health and Welfare in Japan. All procedures complied with the Declaration of Helsinki.

Statistical analysis. Continuous variables are expressed as median values (the first–third quartile). Statistical analyses were performed using Welch's *t*-test, Student's *t*-test, Fisher's exact test, or Mann–Whitney's *U* test, as appropriate. Prognosis was analyzed by Cox hazard analysis, the Kaplan–Meier method, and a log–rank test.

Table 1 Clinical features of unresectable hepatocellular carcinoma patients with and without pre-sarcopenia

	Non-pre-sarcopenia group ($n = 110$)	Pre-sarcopenia group ($n = 41$)	<i>P</i> value
Age, years	72 (65–79)	74 (68–82)	0.219
Gender, male : female	78:32	38:3	0.004
Viral : non-viral hepatitis (HCV : HBV : alcohol : others)	70:40 (50:20:12:28)	25:16 (21:4:12:4)	0.850
BMI, kg/m ²	23.2 (16.4–42.2)	20.6 (14.2–32.0)	< 0.001
ECOG PS, 0:1:2:3	82:20:7:1	33:7:1:0	0.815
Lenvatinib introduction at reduced dose	19 (17.3%)	9 (22.0%)	0.491
Platelets, $\geq 10^4/\mu\text{L}$	12.9 (10.6–17.0)	13.1 (10.3–18.1)	0.699
AST, U/L	44 (29–65)	32 (29–50)	0.147
ALT, U/L	30 (21–46)	23 (18–33)	0.075
Prothrombin time, %	87 (78–97)	85 (77–96)	0.627
Total bilirubin, mg/dL	0.8 (0.6–1.1)	0.7 (0.6–1.0)	0.137
Albumin, g/dL	3.7 (3.2–4.0)	3.4 (3.1–3.7)	0.012
NH ₃ , $\mu\text{g/dL}$	45 (28–59)	36 (24–53)	0.152
eGFR, mL/min/1.73 m ²	70.0 (56.6–83.4)	69.1 (54.1–86.0)	0.771
AFP, ng/mL	30.7 (5.6–1454.5)	134.5 (5.0–766.0)	0.953
Past history of sorafenib	49 (44.5%)	19 (46.3%)	0.856
Past history of regorafenib	15 (13.6%)	7 (17.1%)	0.609
Child-Pugh class, A : B	98:12	33:8	0.183
mALBI, 1:2a:2b:3	38:25:44:3	7:11:21:2	0.160
BCLC stage, A : B : C : D	2:38:69:1	0:14:27:0	1.0
TNM-LCSGJ, I : II : III : IVa : IVb	2:13:34:10:51	0:3:16:3:19	0.694
Observation period, years	1.0 (0.4–1.5)	0.8 (0.4–1.3)	0.186
Best therapeutic response, mRECIST, CR; PR : SD : PD : NA/NE (ORR/DCR)	11:44:31:15:9 (54.5%/85.1%)	3:15:17:5:1 (45.0%/87.5%)	0.751
IPW	1.37 (1.08–1.66)	3.61 (0.44–6.78)	< 0.001

Median values (interquartile range) are shown as numbers, unless otherwise indicated. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase; BCLC, Barcelona Clinic Liver Cancer stage; BMI, body mass index; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; IPW, inverse probability weighting; mALBI, modified albumin–bilirubin grade; mRECIST, modified Response Evaluation Criteria In Solid Tumors; NA/NE, not available or not examined; ORR, objective response rate; PD, progression of disease; PR, partial response; SD, stable disease; TNM LCSGJ 6th, tumor node metastasis stage by Liver Cancer Study Group of Japan 6th edition.

Pre-sarcopenia and non-pre-sarcopenia group probabilities (propensity) were calculated using logistic regression analysis with a set of covariates deemed likely to have effects on OS, including age, gender, AFP (tumor malignant potential), BCLC stage (tumor burden), and mALBI (hepatic reserve function). Inverse probability weighting (IPW) was defined as $1/(\text{propensity score})$ for the pre-sarcopenia group and $1/(1 - \text{propensity score})$ for the non-pre-sarcopenia group. Prognostic factors for OS and difference in OS were tested using IPW-adjusted Cox hazard analysis and an IPW-adjusted log-rank test, respectively.^{40,41}

A *P* value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Easy R (EZR) version 1.42 (Saitama Medical Center, Jichi Medical University, Saitama, Japan),⁴² a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical features of patients. Of 437 u-HCC patients (mALBI 1:2a:2b:3 = 138:110:172:17) (median survival 1.4 years, 95% confidence interval [CI]: 1.2–1.5 years) (Fig. S1) with records in the databases of the participating institutions, 151 with CT imaging data available were evaluated for the present study. They were divided into the non-pre-sarcopenia (*n* = 110) and pre-sarcopenia (*n* = 41) groups. Frequency of male gender was greater (*P* = 0.004), and serum level of albumin and body mass index were lower in the pre-sarcopenia group (*P* = 0.012 and *P* < 0.001, respectively), while viral hepatitis, AFP level, Child-Pugh classification, mALBI grade, BCLC stage, TNM-LCSGJ, and past history of sorafenib and regorafenib treatments were not significantly different between the groups (Table 1). In addition, the calculated IPW scores of patients in the non-pre-sarcopenia and pre-sarcopenia groups were 1.37 (1.08–1.66) and 3.61 (0.44–6.78), respectively (*P* < 0.001). During the observation period, 81 patients died.

Assessment of prognosis. Prognostic factors for OS were evaluated using Cox hazard univariate analysis adjusted for IPW, and the results showed body mass index ($\geq 22 \text{ kg/m}^2$), AFP ($\geq 400 \text{ ng/mL}$), BCLC stage (C and D), and positive for pre-sarcopenia as significant factors related to prognosis. Using multivariate analysis adjusted for IPW, AFP ($\geq 400 \text{ ng/mL}$) (hazard ratio [HR] 2.271, 96% CI: 1.399–3.685, *P* < 0.001), BCLC stage (C and D) (HR 1.625, 95% CI: 1.089–2.427, *P* = 0.018), and positive for pre-sarcopenia (HR 1.652, 95% CI: 1.017–2.686, *P* = 0.042) were chosen as significant prognostic factors (Table 2).

When the Kaplan–Meier method was performed with adjustment for IPW, the 0.5-, 1-, and 1.5-year OS rates for the pre-sarcopenia group were worse than those for the non-pre-sarcopenia group (72.5%, 27.9%, and 7.0% vs 80.7%, 56.7%, and 46.1%, respectively, *P* < 0.001; log-rank test adjusted for IPW) (Fig. 1a), while progression-free survival rates were better in patients without pre-sarcopenia (55.3%, 25.5%, and 11.6% vs 45.5%, 8.5%, and 4.5%, respectively, *P* = 0.025; log-rank test adjusted for IPW) (Fig. 1b). When time to stopping lenvatinib or progression of disease was analyzed, that was better in patients without than in those with pre-sarcopenia at 0.5, 1, and 1.5 years (48.0%, 24.5%, and 8.4% vs 20.0%, 10.3%, and 4.2%, respectively, *P* < 0.001; log-rank test for IPW adjusted) (Fig. 2). Objective response rate and disease control rate were not significantly different between the groups (Table 1).

Assessments of adverse events and relative changes in psoas muscle area index. There were no significant differences in regard to AEs between the pre-sarcopenia and non-pre-sarcopenia groups, except for appetite loss (any grade) (*P* = 0.003) (Table 3). Although there was no difference for appetite loss (severe grade) between the groups (14.6% vs 4.5%, *P* = 0.070), patients with pre-sarcopenia showed a greater frequency of severe grade in a sub-analysis conducted after

Table 2 Cox hazard analysis adjusted with inverse probability weighting for prognostic factors of overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age (≥ 75 years)	1.474	0.965–2.252	0.073	—	—	—
Male gender	1.256	0.819–1.924	0.296	—	—	—
ECOG PS (≥ 2)	0.933	0.314–2.729	0.900	—	—	—
BMI ($\geq 22 \text{ kg/m}^2$)	0.604	0.385–0.945	0.027	0.660	0.382–1.140	0.136
Viral hepatitis	0.953	0.613–1.481	0.830	—	—	—
Lenvatinib introduction at reduced dose	1.318	0.691–2.513	0.402	—	—	—
ALT ($\geq 40 \text{ U/L}$)	1.259	0.804–1.971	0.314	—	—	—
Platelet ($\geq 10^4/\mu\text{L}$)	0.850	0.480–1.506	0.578	—	—	—
AFP ($\geq 400 \text{ ng/mL}$)	2.254	1.427–3.562	< 0.001	2.271	1.399–3.685	< 0.001
mALBI 2b or 3	1.355	0.774–2.370	0.288	—	—	—
Past history of sorafenib	1.222	0.8122–1.840	0.336	—	—	—
Past history of regorafenib	1.345	0.908–1.993	0.139	—	—	—
BCLC stage C/D	1.749	1.149–2.660	0.009	1.625	1.089–2.427	0.018
Pre-sarcopenia	1.955	1.297–2.946	0.0014	1.652	1.017–2.686	0.042

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer stage; BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mALBI, modified albumin–bilirubin grade.

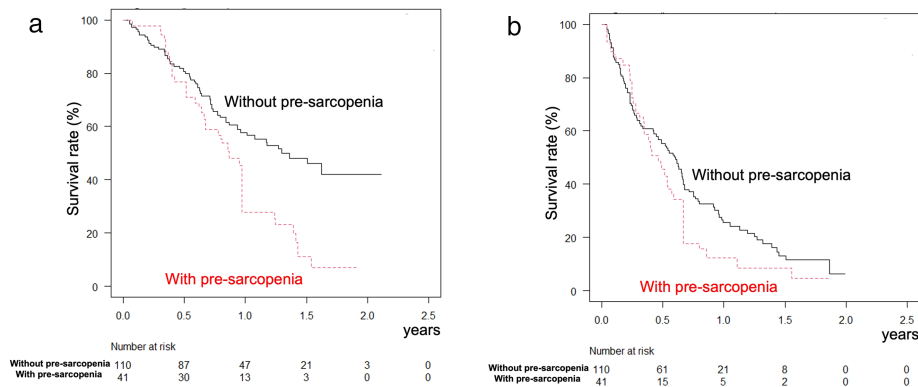


Figure 1 Overall and progression-free survival adjusted for inverse probability weighting. (a) Overall survival was better in patients without (solid line) than those with (broken line) pre-sarcopenia at 0.5, 1, and 1.5 years (80.7%, 56.7%, and 46.1% vs 72.5%, 27.9%, and 7.0%, respectively; $P < 0.001$). (b) Progression-free survival was better in patients without (solid line) than those with (broken line) pre-sarcopenia at 0.5, 1, and 1.5 years (55.3%, 25.5%, and 11.6% vs 45.5%, 8.5%, and 4.5%, respectively; $P = 0.025$). [Color figure can be viewed at wileyonlinelibrary.com]

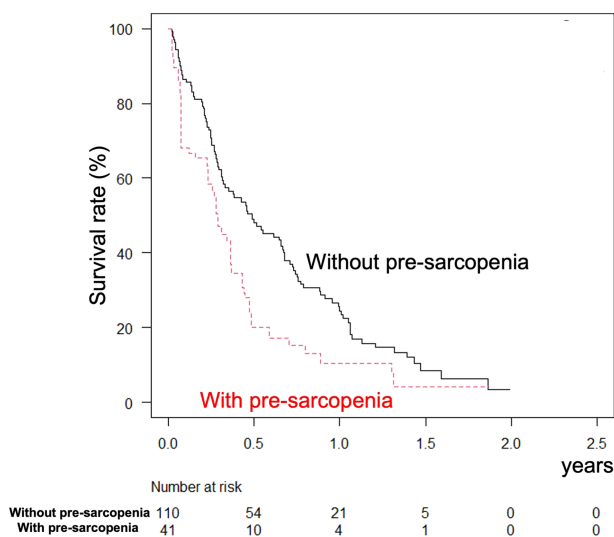


Figure 2 Lenvatinib medication period, after adjustment for inverse probability weighting. The lenvatinib medication period was better in patients without (solid line) than with (broken line) pre-sarcopenia at 0.5, 1, and 1.5 years (48.0%, 24.5%, and 8.4% vs 20.0%, 10.3%, and 4.2%; $P < 0.001$). [Color figure can be viewed at wileyonlinelibrary.com]

exclusion of patients whose initial dose was reduced (15.6% vs 3.3%, $P = 0.028$). In patients whose serial CT imaging examinations after introduction of lenvatinib could be evaluated ($n = 106$), the delta PSI per month values after beginning that therapy were not significantly different between the pre-sarcopenia and non-pre-sarcopenia groups ($-0.11 [-0.27 \text{ to } 0.09]$ vs $-0.13 [-0.38 \text{ to } 0.08]$, $P = 0.414$).

Discussion

In this study, we applied IPW to the Kaplan–Meier method for hepatocarcinogenesis to adjust for potential imbalances, and the present results showed that muscle volume depletion is a

prognostic factor for survival in u-HCC patients undergoing treatment with lenvatinib. A previously reported meta-analysis found that low skeletal muscle mass at the time of cancer diagnosis was associated with poor prognosis in patients with solid tumors and also noted that 19–74% of patients with advanced tumors were sarcopenic.⁴³ Recently, muscle volume loss and muscle function decline have been reported to be not only primary but also secondary prognostic factors in patients with various chronic diseases.³⁶ HCC often occurs due to CLD (e.g. chronic viral hepatitis, alcohol abuse, and non-alcoholic steatohepatitis); thus, muscle volume depletion is not a rare finding in HCC patients. Several studies have shown a relationship of muscle volume loss with worse prognosis in u-HCC patients treated with sorafenib,^{18–21} with similar results seen in the present study. In addition, our present result of skeletal muscle loss during lenvatinib treatment after introduction is similar to past reports.^{18,44} We should keep in mind that muscle mass will be maintained during the course of treatment, regardless of the amount of muscle mass at the time of introduction of the MTA therapeutic agent.

The frequency of appetite loss (any grade) was significantly greater in the pre-sarcopenia group (43.9% vs 18.2%, $P = 0.003$). Although the difference in frequency of appetite loss (severe grade) was not significant ($P = 0.070$), the pre-sarcopenia group showed a greater frequency of that in sub-analysis findings after exclusion of patients whose initial dose was reduced (15.6% vs 3.3%, $P = 0.028$). On the other hand, there were no significant differences in the appetite loss between patients with and without previous MTA treatment history (any grade and severe grade: $P = 0.145$ and $P = 0.980$, respectively) (data not shown). The present findings indicate that muscle volume depletion might have an association with appetite loss, which has been revealed to be a significant prognostic factor in patients receiving lenvatinib treatment.¹² Uojima *et al.* also reported that low skeletal muscle mass was associated with occurrence of severe AEs in patients undergoing lenvatinib therapy and considered that skeletal muscle mass is more important than bodyweight in those patients.²³ For u-HCC patients with pre-sarcopenia, even a regular dosage based on bodyweight might actually be an overdose; thus, a dose reduction strategy for such cases should be considered.

Table 3 Adverse events in unresectable hepatocellular carcinoma patients with and without pre-sarcopenia

	Grade 3 or more			Any grade		
	Non-pre-sarcopenia group	Pre-sarcopenia group	<i>P</i> value	Non-pre-sarcopenia group	Pre-sarcopenia group	<i>P</i> value
Appetite loss	5 (4.5%)	6 (14.6%)	0.070	20 (18.2%)	18 (43.9%)	0.003
Fatigue	7 (6.4%)	0 (0%)	0.190	27 (24.5%)	11 (26.8%)	0.834
Hypertension	5 (4.5%)	1 (2.4%)	1.0	17 (15.5%)	5 (12.2%)	0.797
HFSR	5 (4.5%)	2 (4.9%)	1.0	29 (26.4%)	11 (26.8%)	1.0
Urine protein	7 (6.4%)	4 (9.8%)	0.491	19 (17.3%)	6 (14.6%)	0.809
Thyroid function abnormality	3 (2.7%)	1 (2.4%)	1.0	22 (20.0%)	13 (31.7%)	0.136
Diarrhea	5 (4.5%)	0 (0%)	0.324	24 (21.8%)	6 (14.6%)	0.369
Hepatic coma	6 (5.5%)	1 (2.4%)	0.675	7 (6.4%)	1 (2.4%)	0.684
Others	29 (26.4%)	13 (31.7%)	0.544	47 (42.7%)	18 (43.9%)	1.0

HFSR, hand foot skin reaction.

In a previous study, Antoun *et al.* found that sorafenib treatment directly inhibits protein synthesis, because inhibition of VEGFR in a variety of cells by the drug was shown to result in downstream inhibition of PI3K, AKT, and mTOR, which are central for activation of muscle protein synthesis by amino acids.⁴⁵ Because lenvatinib has greater potential for inhibition of VEGFR, it has been suggested that its antiangiogenic characteristic may have a relationship with muscle wasting, with the same speculated for sorafenib.⁴⁵ In the present cohort as well, decreased muscle volume in association with lenvatinib treatment was common in both the pre-sarcopenia and non-pre-sarcopenia groups.

In lenvatinib treatment, mALBI 2b or 3 at the time of starting the treatment has been reported as a prognostic factor for poor prognosis (HR 4.632, 95% CI: 1.649–13.02, *P* = 0.004) in our previous report.¹² Although Kaplan–Meier curve of the 437 patients according to mALBI grade was thought to prove it (Fig. S1B), mALBI 2b or 3 was not significant factor in the analyzed cohort (*n* = 151). However, detailed assessment for hepatic function is very important in MTA treatments, because Kaplan–Meier curve of the present analyzed 151 from the 437 patients according to mALBI grade showed a similar result (median survival time of mALBI 1:2a:2b:3 = not reached:1.4:0.8:0.5 years) (*P* = 0.061) (Fig. S2). From the above, not only muscle volume loss but also decline of hepatic function, especially mALBI 2b or 3, should be kept in mind as prognostic factors for poor prognosis at the time of starting lenvatinib treatment. Introducing MTA should be considered in condition with better hepatic function to improve prognosis of u-HCC patients.

Recently, Finn *et al.* reported that atezolizumab plus bevacizumab treatment had a positive therapeutic efficacy in u-HCC patients, which was superior to that of sorafenib, used as a control arm, as first-line therapy.⁴⁶ Therefore, the combination of immunotherapy and MTA treatment is expected to be a highly effective first-line treatment for u-HCC available in the near future. In light of such dramatic changes in systemic chemotherapy for u-HCC, maintaining muscle volume during the clinical course of CLD patients has become an important clinical matter. Assessment of muscle volume in CLD patients and intervention in those with a decline should be kept in mind before development of HCC⁴⁷ as well as after starting treatment for HCC.⁴⁸

The present study has some limitations, including its retrospective protocol. Furthermore, the number of patients analyzed was insufficient to obtain concrete conclusions. Finally, no data in

regard to muscle strength (e.g. hand grip strength and walking speed) were available to evaluate its prognostic role. A prospective study with a greater number of patients should be planned to evaluate this clinical issue.

In conclusion, pre-sarcopenia was a significant prognostic factor in patients receiving lenvatinib treatment for u-HCC. Assessment of muscle volume is recommended, and attention should be given to severe appetite loss as an AE in order to improve the prognosis of pre-sarcopenia u-HCC patients.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. A. Overall survival of all 437 patients treated with lenvatinib at participating institutions (median survival 1.4 years). B. Survival curve of all 437 patients according to modified ALBI grade. The median survival of patients with modified albumin-bilirubin grade 1 was not reached, while that of those

with 2a, 2b, and 3 was 1.6, 0.9, and 0.4 years, respectively ($P < 0.001$).

Figure S2. Survival curve of patients, whose muscle volume data were available, according to modified ALBI grade ($n = 151$). The median survival of patients with modified albumin-bilirubin grade 1 was not reached, while that of those with 2a, 2b, and 3 was 1.4, 0.8, and 0.5, respectively ($P = 0.061$).