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Prognostic significance of sarcopenia in patients with hepatocellular carcinoma treated with lenvatinib

A retrospective analysis

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Abstract

Our study investigated the correlation between sarcopenia and clinical outcomes in patients with hepatocellular carcinoma (HCC) treated with lenvatinib. We retrospectively evaluated 40 consecutive patients with unresectable HCC receiving lenvatinib between November 2018 and May 2020 at the First Hospital of Jilin University. Skeletal muscle mass was measured before treatment initiation. Prognostic significance was assessed with univariate and multivariate Cox proportional hazards models. Overall survival (OS) and progression-free survival (PFS) were evaluated for patients with and without sarcopenia. Sarcopenia was present in 23/40 patients (57.5%). After a median follow-up of 9.2 months, patients with sarcopenia had significantly worse OS and PFS compared with those without sarcopenia (OS: 8.4 months [m] vs 14.7 m, $P = .02$; PFS: 4.2 m vs 9.0 m, $P = .04$). Multivariate Cox proportional hazards models identified presence of sarcopenia as an independent risk factor for shorter OS (hazard ratio [HR], 0.257; 95% confidence interval [CI], 0.083–0.794; $P = .02$). In subgroup analysis, sarcopenia was associated with worse survival than non-sarcopenic patients, irrespective of age, Barcelona clinic liver cancer stage, or albumin–bilirubin grade. Our results show sarcopenia may be a predictor of poor prognosis in patients with HCC receiving lenvatinib. Management of sarcopenia is a vital factor for improving survival outcomes in patients with HCC.

Abbreviations: AE = adverse event, AFP = alpha-fetoprotein, Alb = albumin, ALBI = modified albumin–bilirubin, ALT = alanine aminotransferase, AST = aspartate transaminase, BCLC = Barcelona clinic liver cancer, BMI = body mass index, CI = confidence interval, CT = computed tomography, DCR = disease control rate, ECOG PS = eastern cooperative oncology group performance status, Hb = hemoglobin, HBsAG = hepatitis B virus surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, INR = international normalized ratio, L3 = third lumbar vertebral, ORR = objective response rate, OS = overall survival, PD = progressive disease, PD-1 = programmed cell death-1, PFS = progression free survival, PR = partial response, RECIST = response evaluation criteria in solid tumors, SD = stable disease, SMI = skeletal muscle index.

Keywords: hepatocellular carcinoma, lenvatinib, PD-1 inhibitor, sarcopenia, survival outcome

1. Introduction

Liver cancer is the sixth most common malignancy and the fourth leading cause of cancer-related mortality worldwide.[1] Hepatocellular carcinoma (HCC) is the most common primary liver cancer and accounts for 75% to 85% of cases, the majority of which are diagnosed at a late stage, precluding surgical intervention. Recent advances in treatment have significantly improved the prognosis of patients with unresectable HCC, including the introduction of lenvatinib.[2–4] Lenvatinib is an oral, multi-tyrosine kinase inhibitor that targets vascular endothelial growth factors 1 to 3, fibroblast growth factor receptors 1 to 4, and the RET and KIT proto-oncogenes.[5]

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DD and JYS contributed equally to this work.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the First Hospital of Jilin University, approval number 2020-560 on 27 May 2020.

Informed Consent Statement: Written, informed consent for the data to be used for clinical researches was obtained from enrolled patients or their families.

The authors have no conflicts of interest to disclose. The sponsors had no role in the design, execution, interpretation, or writing of the study.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Lenvatinib is the first drug to show non-inferiority to sorafenib in the treatment of advanced HCC and is recommended as a standard first-line treatment in this indication.[2] However, a relatively high cost and adverse event (AE) rate has limited access to lenvatinib.[6–9] Therefore, the search for prognostic tools to stratify risk, predict efficacy, and allow for tailored treatment for every patient is of great clinical significance. Previous studies of prognostic factors for HCC have mainly focused on baseline tumor size, liver function, serum biomarkers, and AEs.[10–13]

Sarcopenia is a muscle disease, characterized by progressive and generalized loss of skeletal muscle mass and strength.[14] Measurement of skeletal muscle at the third lumbar vertebral (L3) level using abdominal computed tomography (CT) is almost universally recommended to evaluate the presence of sarcopenia.[15] Recently, sarcopenia has been recognized as not only an aging-associated condition, but also linked to liver cirrhosis, HCC, melanoma, and pancreatic cancer.[16–19] Many studies have revealed sarcopenia as an independent predictor of poor prognosis in patients with HCC undergoing surgical resection, radiofrequency ablation, transarterial chemoembolization, or systemic treatment with sorafenib.[20–23] However, few studies have investigated the impact of sarcopenia on tumor response and prognosis in patients with HCC treated with lenvatinib.

This retrospective study was therefore designed to assess the correlation between sarcopenia and clinical outcomes in patients with HCC treated with lenvatinib. We also aimed to determine whether sarcopenia is a significant prognostic factor for patients with HCC receiving lenvatinib.

2. Materials and methods

Ethical approval for this study was provided by the Institutional Review Board of the Jilin University First Hospital (2020-560 – May 27, 2020).

2.1. Patients

We retrospectively analyzed patients with advanced HCC treated with lenvatinib between November 2018 and May 2020 at the First Hospital of Jilin University. In the present study, advanced HCC was defined as Barcelona Clinic Liver Cancer (BCLC) stage C patients, and those patients with BCLC stage B but unfit to any or failed to respond to locoregional therapies. All patients were initially diagnosed based on the guidelines for the Diagnosis and Treatment of Primary Liver Cancer of China (Version 2019). In the present study, imaging examination of HCC includes dynamic enhanced magnetic resonance imaging (MRI), dynamic enhanced computed tomography (CT), contrast-enhanced ultrasonography (US) or liver cell-specific contrast agent GD-Eob-DTPA enhanced MRI (EOB-MRI). The clinical diagnosis of HCC requires HBV and/or HCV infection and/or cirrhosis, and one of the following criterias must be meet:

1. the lesion was >2 cm or AFP ≥400 μg/L, and there were at least one kind of imaging examination has the typical imaging feactures of HCC,
2. the lesion was ≤2 cm, and there were at least two kinds of imaging examination has the typical imaging feactures of HCC.

Patients were included if they underwent abdominal CT or magnetic resonance imaging in our hospital within 1 month before the initiation of lenvatinib. This study was approved by the Institutional Review Board of the First Hospital of Jilin University. Written, informed consent for the data to be used for clinical researches was obtained from enrolled patients or their families.

2.2. Definition, treatment procedure, and effects

Skeletal muscle mass was determined by analyzing cross-sectional CT images at L3 with Neusoft Picture Archiving and Communication System, prior to the initiation of lenvatinib. Muscle areas included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles.[24] The muscle area (cm^2) was normalized by the square of patient height (m) to obtain the skeletal muscle index (SMI, cm^2/m^2) at L3. Sarcopenia was defined as SMI <42 cm^2/m^2 for men and <38 cm^2/m^2 for women according to the Japan Society of Hepatology.[25] The standard dose of lenvatinib (Lenvima; Eisai Co, Ltd, Tokyo, Japan) was determined by body weight: patients weighing <60 kg were given 8 mg/day and those weighing ≥60 kg were given 12 mg/day orally in 28-day cycles. Patients were permitted to initiate lenvatinib at a reduced dose based on their condition and the preference of the attending physicians. During the administration of treatment, the daily dose of lenvatinib could be adjusted according to the frequency and severity of AEs. Lenvatinib was continued until disease progression, unmanageable AEs, or discontinuation at the patient's discretion. Treatment response was assessed once every 8 to 12 weeks following the initiation of therapy based on the Response Evaluation Criteria in Solid Tumors (RECIST).[26]

2.3. Endpoints

The primary endpoints include overall survival (OS) and progression free survival (PFS), the secondary endpoints include objective response rate (ORR) and disease control rate (DCR). OS was defined as the period between treatment start and patient death. And the PFS was defined as the time from initiation of treatment to tumor progression or death. An objective response rate was defined as the proportion of patients achieving a complete response or partial response. The disease control rate (DCR) was defined as the proportion of patients achieving an objective response or stable disease.

2.4. Statistical analysis

Continuous variables were summarized using median and range, and intergroup values were compared using Mann–Whitney *U* tests. Categorical variables were summarized as number and percentage, and were compared using Fisher's exact tests or Chi-squared tests. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method and intergroup differences compared with a log-rank test. Potential prognostic factors for PFS and OS were assessed with univariate and multivariate Cox proportional hazards models. All factors exhibiting significant association with PFS or OS in the univariate analyses were included in the multivariate models. Throughout the study, $P < .05$ was considered statistically significant and all reported *P* values are two-sided. All statistical analyses were performed using R software (version 3.6.3, The R Foundation).

3. Results

3.1. Patient characteristics

From November 2018 to May 2020, 40 patients with unresectable HCC who received lenvatinib treatment were

Table 1

Patient characteristics.

Variables	Total (N = 40)	Sarcopenia (N = 23)	Non-sarcopenia (N = 17)	*P*
Age, years	59 (47–63)	62.0 (50.5–64.5)	56.0 (46.0–61.0)	.20
Gender, male/female	37/3 (92.5%/7.5%)	20/3 (87.0%/13.0%)	17/0 (100%/0)	.25
BMI, kg/m^2	22.7 (20.8–24.2)	21.8 (20.2–24.2)	23.4 (22.5–25.1)	**.03**
L3 SMI, cm^2/m^2	41.2 (37.3–45.2)	38.3 (33.9–40.3)	45.8 (42.7–47.5)	**<.001**
HBV/HCV/non-B non-C	35/3/2 (87.5%/7.5%/5%)	19/2/2 (82.6%/8.7%/8.7%)	16/1/0 (94.1%/5.9%/0)	.62
Child-Pugh class, A/B	27/13 (67.5%/32.5%)	13/10 (56.5%/43.5%)	14/3 (82.4%/17.6%)	.09
mALBI grade, 1/2a/2b	14/11/15 (35.0%/27.5%/37.5%)	8/8/7 (34.8%/34.8%/30.4%)	6/3/8 (35.3%/17.6%/47.1%)	.48
BCLC stage, B/C	12/28 (30%/70%)	8/15 (34.8%/65.2%)	4/13 (23.5%/76.5%)	.44
TNM, II/III/IV	5/15/20 (12.5%/37.5%/50%)	4/11/8 (17.4%/47.8%/34.8%)	1/4/12 (5.9%/23.5%/70.6%)	.10
AST, U/L	43.1 (28.5–65.3)	42.7 (29.0–64.9)	44.4 (29.1–60.5)	.82
ALT, U/L	39.4 (25.9–74.2)	43.7 (30.7–69.3)	34.9 (20.7–70.6)	.54
Platelet, $\times 10^9$/L	125.0 (95.5–193.5)	122.0 (84.0–167.5)	138.0 (109.0–194.0)	.28
INR	1.07 (1.00–1.16)	1.08 (1.00–1.17)	1.05 (1.01–1.12)	1.000
Hb, g/L	145.5 (132.3–155.0)	142.0 (129.0–153.5)	148.0 (134.0–155.0)	.54
Alb, g/dL	3.8 (3.3–4.2)	3.7 (3.3–3.9)	4.1 (3.6–4.2)	.16
Total bilirubin, μmol/L	20.3 (14.8–32.2)	23.6 (16.6–33.3)	18.1 (13.1–22.8)	.12
AFP, ng/mL	394.4 (58.4–5307.3)	354.0 (31.4–4978.0)	681.8 (108.4–19410.0)	.39
Extrahepatic metastasis, yes/no	19/21 (47.5%/52.5%)	11/12 (47.8%/52.2%)	8/9 (47.1%/52.9%)	.96
Portal vein thrombosis, yes/no	21/19 (52.5%/47.5%)	13/10 (56.5%/43.5%)	8/9 (47.1%/52.9%)	.55
Maximum tumor diameter, cm	5.4 (3.1–8.8)	5.4 (2.9–9.2)	5.4 (3.8–7.7)	.85
Number of tumors, solitary/multiple	24/16 (60%/40%)	14/9 (60.9%/39.1%)	10/7 (58.8/41.2%)	.90
ECOG PS, 0/1	21/19 (52.5%/47.5%)	10/13 (43.5%/56.5%)	11/6 (64.7%/35.3%)	.18
Ascites, yes/no	21/19 (52.5%/47.5%)	14/9 (60.9%/39.1%)	7/10 (41.2%/58.8%)	.22
Lenvatinib as first-line treatment, yes/no	32/8 (80%/20%)	18/5 (78.3%/21.7%)	14/3 (82.4%/17.6%)	1.000
Relative dose intensity	1 (0.976–1)	1 (0.976–1)	1 (0.977–1)	.58
Treatment duration (months)	7.45 (5.38–10.60)	7.0 (3.5–7.9)	9.0 (6.25–13.15)	.03
Therapeutic efficacy, PR/SD/PD	5/11/24 (12.5%/27.5%/60%)	2/6/15 (8.7%/26.1%/65.2%)	3/5/9 (17.6%/29.4%/52.9%)	.73
ORR	12.5% (5/40)	8.7% (2/23)	17.6% (3/17)	.63
DCR	40% (16/40)	34.8% (8/23)	47.1% (8/17)	.43

AFP = alpha-fetoprotein, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate transaminase, BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index, DCR = disease control rate, ECOG PS = Eastern Cooperative Oncology Group performance status, Hb = hemoglobin, HBV = hepatitis B virus, HCV = hepatitis C virus, INR = international normalized ratio, L3 SMI = third lumbar vertebra skeletal muscle index, mALBI = modified albumin-bilirubin, ORR = overall response rate, PD = progressive disease, PR = partial response, SD = stable disease.

enrolled in the study. Patients had a median age of 59 years (interquartile range 47–63) and 92.5% were male (Table 1). The median body mass index (BMI) and L3 SMI were 22.7 kg/m^2 and 41.2 cm^2/m^2, respectively. The baseline Child-Pugh class was A in 27 (67.5%) and B in 13 patients (32.5%), and the Barcelona Clinic Liver Cancer (BCLC) stages were B in 12 (30%) and C in 28 patients (70%). Modified albumin–bilirubin (ALBI) grade 1, 2a, and 2b were observed in 14 (35.0%), 11 (27.5%), and 15 (37.5%) patients, respectively. The median maximum tumor diameter was 5.4 cm, and 16 patients (40%) had more than one tumor. Portal vein thrombosis was observed in 21 patients (52.5%) and extrahepatic metastasis occurred in 19 patients (47.5%). In total, 32 patients (80%) received lenvatinib as first-line treatment and 12 patients (30%) received lenvatinib plus programmed cell death-1 (PD-1) inhibitor. The median duration of lenvatinib treatment was 7.45 months. The median observation period after initiation of lenvatinib was 9.2 months (range, 1–16 months). Grade 3 to 4 AEs were reported in 43.5% (sarcopenia group) and 29.4% (non-sarcopenia group). In the non-sarcopenia group, there were 4 patients (23.5%) had the dose reduction and 1 (5.9%) received interruption due to AEs. However in the sarcopenia group, there were 9 patients (39.1%) had the dose reduction and 3 (13.0%) received interruption due to AEs.

Sarcopenia was found in 23 patients (57.5%) and the remaining 17 patients (43.5%) were classified into the non-sarcopenia group. Patients with sarcopenia had lower BMI (21.8 kg/m^2 vs 23.4 kg/m^2, $P = .03$) and L3 SMI (38.3 cm^2/m^2 vs 45.8 cm^2/m^2, $P < .001$) compared with patients without sarcopenia. Other baseline characteristics were comparable between the sarcopenia and non-sarcopenia group (Table 1).

3.2. Association between sarcopenia and tumor response

Of the study population, no patients achieved complete response. The objective response rate (ORR) and DCR were 12.5% and 40%, respectively. Among patients with sarcopenia, partial response, stable disease, and progressive disease were observed in 2 (8.7%), 6 (26.1%), and 15 (65.2%) cases, respectively. The corresponding cases were 3 (17.6%), 5 (29.4%), and 9 (52.9%) in non-sarcopenia patients. The sarcopenia group tended to experience lower ORR and DCR than the non-sarcopenia group (8.7% vs 17.6%, $P = .63$; 34.8% vs 47.1%, $P = .43$) (Table 1).

3.3. Association between sarcopenia and survival

After a median follow-up of 9.2 months (range, 1–16 months), 19 patients had died. Patients with sarcopenia had a significantly shorter survival than those without sarcopenia (Fig. 1). The median OS was 8.4 months in the sarcopenia group and 14.7 months in the non-sarcopenia group ($P = .02$). The median PFS was 4.2 months vs 9.0 months in the sarcopenia group and non-sarcopenia group, respectively ($P = .04$).

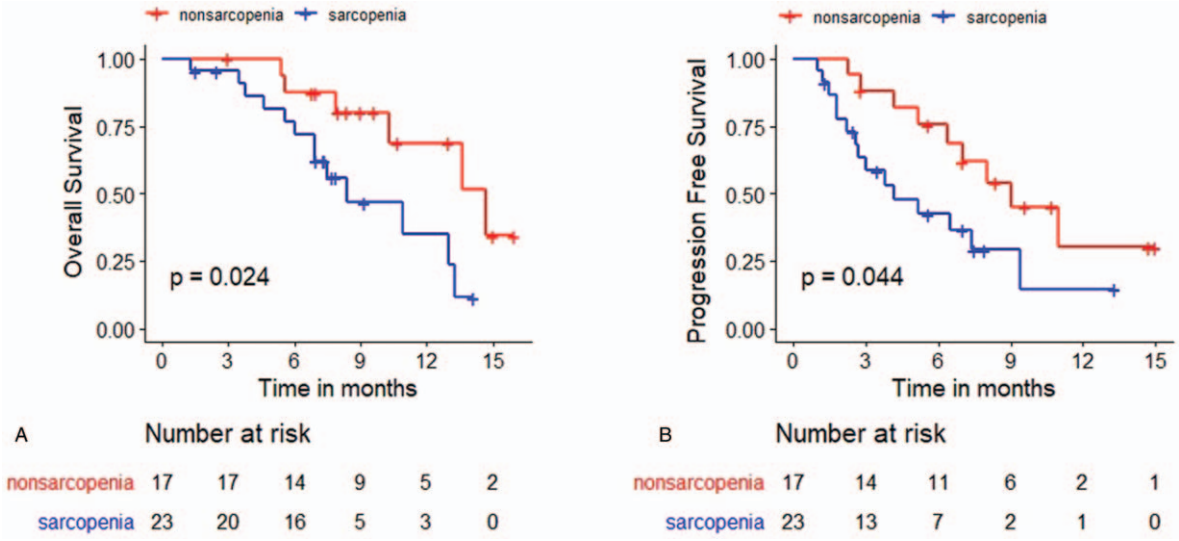

Figure 1. Kaplan–Meier curves for (A) OS and (B) PFS in sarcopenia patients and non-sarcopenia patients. The median OS was 8.4 months in the sarcopenia group and 14.7 months in non-sarcopenia patients ($P = .02$). The median PFS was 4.2 months vs 9.0 months in sarcopenia patients and non-sarcopenia patients, respectively ($P = .04$). OS = overall survival, PFS = progression free survival.

3.4. Prognostic factors for OS

Univariate analysis revealed that presence of sarcopenia (hazard ratio [HR], 0.316; 95% confidence interval [CI], 0.110–0.905; $P = .03$), albumin (HR, 0.906, 95% CI, 0.829–0.989; $P = .03$), maximum tumor diameter (HR, 1.168, 95% CI, 1.041–1.310; $P = .01$), and portal vein thrombosis (HR, 2.753, 95% CI, 1.043–7.271; $P = .04$) were significantly associated with OS. In the multivariate analysis, presence of sarcopenia (HR, 0.257, 95% CI, 0.083–0.794; $P = .02$) and maximum tumor diameter (HR, 1.179, 95% CI, 1.044–1.332; $P = .01$) were identified as independent risk factors for shorter OS (Table 2).

3.5. Prognostic factors for PFS

Univariate analysis revealed that extrahepatic metastasis (HR, 2.438, 95% CI, 1.054–5.637; $P = .04$) and Eastern Cooperative Oncology Group performance status (ECOG PS) (HR, 0.267, 95% CI, 0.111–0.640; $P = .003$) were significantly associated with PFS. Furthermore, multivariate analysis confirmed that ECOG PS (HR, 0.324, 95% CI, 0.124–0.853; $P = .02$) was a significant independent factor for lower PFS (Table 3).

3.6. Subgroup analysis

The benefits with respect to PFS associated with the non-sarcopenia group were consistent regardless of age, BCLC stage, ALBI grade,

Table 2

Univariate and multivariate analysis of factors related to overall survival.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age ≥60 vs <60, years	1.542 (0.603–3.944)	.37		
BMI, kg/m^2	0.866 (0.729–1.030)	.10		
Sarcopenia, absence vs presence	0.316 (0.110–0.905)	.03	0.257 (0.083–0.794)	.02
HBsAg, (+) vs (−)	1.004 (0.285–3.538)	>.99		
AST, U/L	1.003 (0.998–1.008)	.28		
ALT, U/L	1.000 (0.996–1.005)	.86		
Alb, g/dL	0.906 (0.829–0.989)	.03	0.943 (0.853–1.043)	.26
Total bilirubin, μmol/L	1.011 (0.974–1.050)	.57		
AFP ≥400 vs <400, ng/mL	0.599 (0.240–1.498)	.27		
Maximum tumor diameter, cm	1.168 (1.041–1.310)	.01	1.179 (1.044–1.332)	.01
Tumor number, solitary/multiple	0.645 (0.256–1.626)	.35		
Ascites, yes vs no	1.550 (0.606–3.964)	.36		
Extrahepatic metastasis, yes vs no	1.904 (0.732–4.949)	.19		
Portal vein thrombosis, yes vs no	2.753 (1.043–7.271)	.04	1.815 (0.560–5.884)	.32
ECOG PS, 0 vs1	0.509 (0.198–1.313)	.16		
BCLC, B vs C	0.714 (0.246–2.072)	.54		
Child-Pugh, A vs B	0.484 (0.193–1.210)	.12		

AFP = alpha-fetoprotein, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate transaminase, BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index, CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, HBsAG = hepatitis B virus surface antigen, HR = hazard ratio.

Table 3

Univariate and multivariate analysis of factors related to progression free survival.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age ≥60 vs <60, years	0.771 (0.345–1.727)	.53		
BMI, kg/m^2	0.944 (0.796–1.118)	.50		
Sarcopenia, absence vs. presence	0.431 (0.185–1.003)	.05		
HBsAg (+) vs (−)	0.408 (0.094–1.776)	.23		
AST, U/L	1.000 (0.994–1.006)	.98		
ALT, U/L	1.002 (0.998–1.006)	.35		
Alb, g/dL	0.980 (0.912–1.054)	.59		
Total bilirubin, μmol/L	1.010 (0.976–1.045)	.57		
AFP ≥400 vs <400, ng/mL	1.029 (0.460–2.304)	.94		
Maximum tumor diameter, cm	0.939 (0.826–1.067)	.33		
Tumor number, solitary/multiple	1.467 (0.621–3.467)	.38		
Ascites, yes vs no	1.069 (0.476–2.398)	.87		
Extrahepatic metastasis, yes vs no	2.438 (1.054–5.637)	.04	1.520 (0.600–3.854)	.38
Portal vein thrombosis, yes vs no	1.460 (0.650–3.276)	.36		
ECOG PS, 0 vs 1	0.267 (0.111–0.640)	.003	0.324 (0.124–0.853)	.02
BCLC, B vs C	0.509 (0.199–1.301)	.16		
Child-Pugh, A vs B	0.581 (0.252–1.343)	.20		

AFP = alpha-fetoprotein, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate transaminase, BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index, CI = confidence interval, ECOG PS = the Eastern Cooperative Oncology Group performance status, HBsAG = hepatitis B virus surface antigen, HR = hazard ratio.

or extrahepatic metastasis. However, sarcopenia tended to lead to PFS benefit in patients receiving lenvatinib as second- or later-line therapy (HR, 1.094, 95% CI, 0.214–5.587) (Fig. 2). The benefits with respect to OS associated with the non-sarcopenia group were obtained regardless of age, BCLC stage, ALBI grade, or treatment setting of lenvatinib. However, sarcopenia tented to led to OS benefit in patients with extrahepatic metastasis (HR, 1.438, 95% CI, 0.358–5.774) (Fig. 3).

4. Discussion

Sarcopenia is known to be associated with poor outcomes in patients with HCC undergoing treatment with chemotherapy, sorafenib, resection, or radiofrequency ablation.[20,21,24,27] However, there is limited evidence for the impact of sarcopenia in patients with advanced HCC receiving lenvatinib. In the present study, 57.5% of patients had sarcopenia. This result is consistent with a meta-analysis showing that 11% to 74% of patients with advanced solid tumors were sarcopenic.[28]

In our study, the ORR and DCR were obviously lower (12.5% and 40%, respectively) than those reported in previous studies that showed the ORR of advanced HCC receiving lenvatinib was ~29.4% to 45.0% and the DCR was 60.0% to 93.0% in a real-world setting.[10,13,29–36] The phenomenon could be explained by differences in patient characteristics. Of our study patients, 87.5% were positive for serum hepatitis B virus surface antigen,

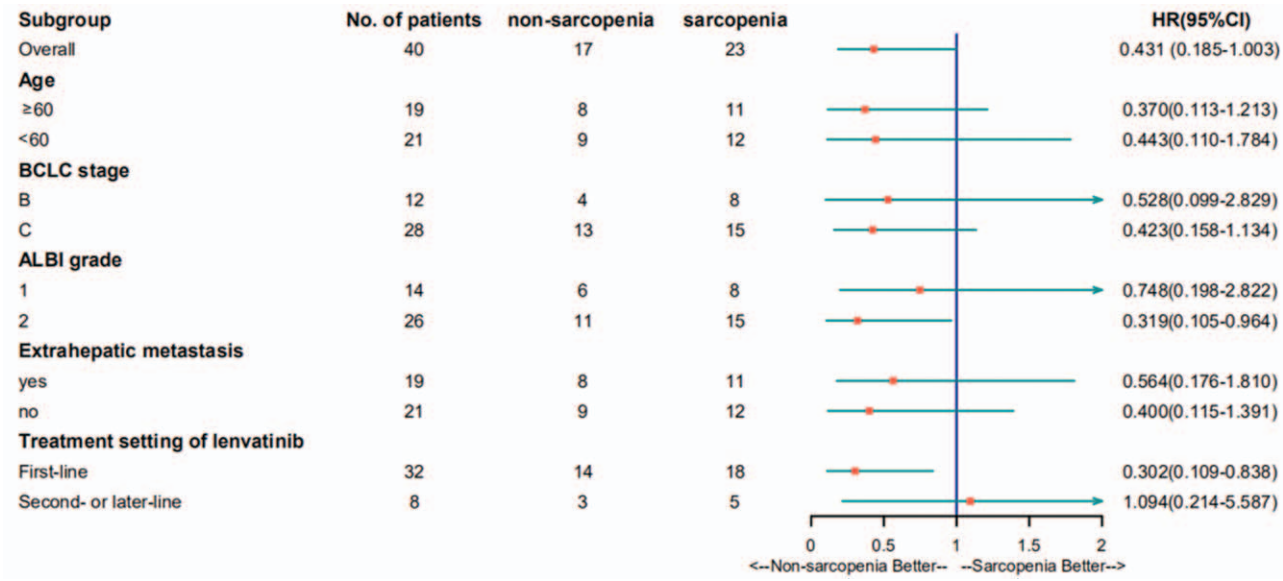

Figure 2. Forest plot of PFS in patient subgroups. ALBI = albumin-bilirubin, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, HR = hazard ratio, PFS = progression-free survival.

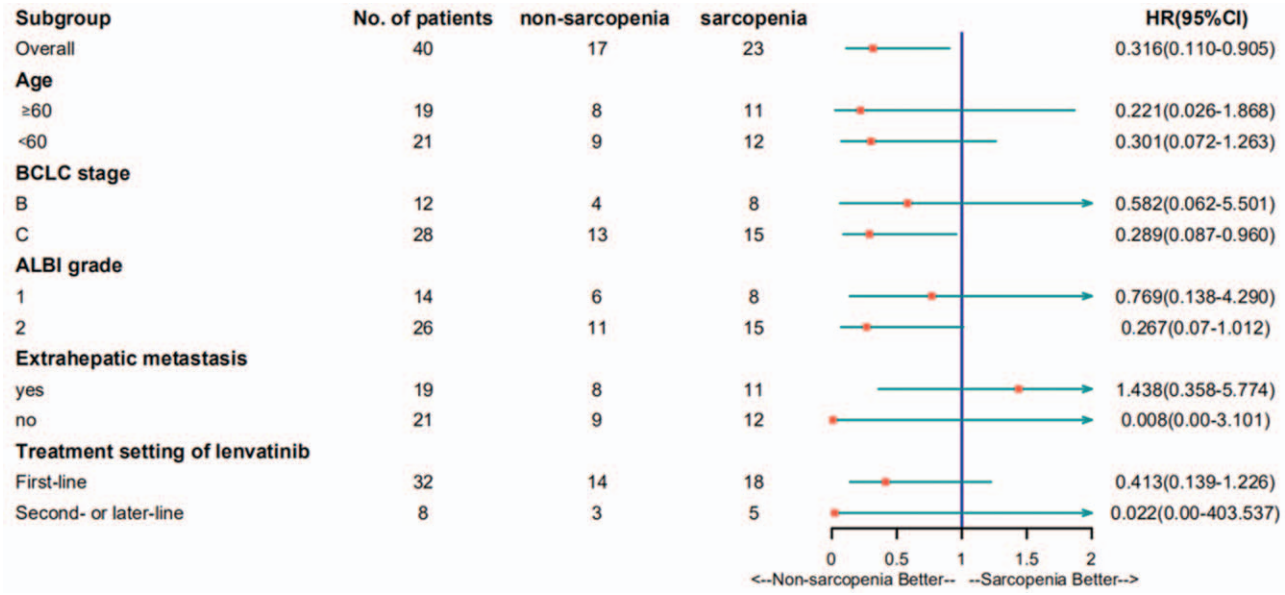

Figure 3. Forest plot of OS in patient subgroups. ALBI = albumin-bilirubin, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, OS = overall survival; HR, hazard ratio.

which was higher than that in the REFLECT study (50%),[2] and 43.5% had sarcopenia. These factors may portend a worse efficacy in HCC patients. Though our study included patients with Child-Pugh grade B (32.5%) that did not meet the REFLECT inclusion criteria, previous study revealed that the safety, efficacy, and PFS were similar between HCC patients with Child-Pugh grade A and B treated with lenvatinib.[37] Thus, liver function may not be a factor related to the poor tumor response in our study.

Our study demonstrated that HCC patients with sarcopenia achieved significantly worse OS and PFS compared with patients without sarcopenia. Multivariate analysis confirmed that sarcopenia was an independent negative prognostic factor for OS (HR, 0.257, 95% CI, 0.083–0.794; $P = .02$) in HCC patients treated with lenvatinib, and was associated with worse PFS although the association did not reach statistical significance (HR, 0.431, 95% CI, 0.185–1.003; $P = .05$). This finding is consistent with a study conducted by Nishikawa et al that established the presence of sarcopenia as a risk factor for OS in patients with HCC treated with sorafenib (HR, 0.365, 95% CI, 0.255–0.516; $P < .001$).[38] Moreover, Uojima et al recently reported that sarcopenia was a predictor of poor OS in patients with HCC receiving lenvatinib (HR, 2.246, 95% CI, 1.091–4.623; $P = .03$).[39] Previous studies in sarcopenia has examined that mitochondrial dysfunction is important contributor to sarcopenia, and mitochondrial dysfunction is associated with poor prognosis of patients with cancer. Thus, sarcopenia might impair the prognosis of patients with HCC possibly through impairment of mitochondrial function.[40,41] Moreover, sarcopenia has been shown to predict early dose-limiting toxicities and the pharmacokinetics of sorafenib in patients with HCC.[42] Sarcopenia might also be a predictor for drug toxicity and poor tolerability of lenvatinib. Toxicity can lead to dose reductions or the discontinuation of lenvatinib, resulting in a shorter duration of treatment, suggesting that the more favorable prognosis of HCC patients without sarcopenia may be due to these patients receiving a longer duration of lenvatinib treatment.

It is important to note that skeletal muscle mass can be evaluated before lenvatinib treatment. The identification of patients with sarcopenia before initiation of lenvatinib might permit selection of patients for lenvatinib treatment and ensure early preventive strategies are taken to maintain muscle mass. Of course, it is important to manage AEs associated with lenvatinib for the duration of treatment to improve prognosis.

In our study, multivariate analysis revealed that larger tumor size was an independent predictor for poor OS (HR, 1.179, 95% CI, 1.044–1.332; $P = .01$). Tumor burden is a known prognostic factor for HCC, especially in patients with sarcopenia.[43] Larger tumor size contributes to a lower probability of success following initial treatment for HCC. However, reducing tumor burden can prevent skeletal muscle loss, which in turn improves the prognosis. Therefore, early detection and curative therapy for HCC are effective measures to improve clinical outcomes.

According to previous studies, HCC patients with sarcopenia have a significantly lower OS than those without sarcopenia, which supports the findings of our study.[44,45] In the present study, both PFS and OS were lower among patients with sarcopenia compared with those without sarcopenia (PFS: 4.2 months [m] vs 9.0 m, $P = .04$; OS: 8.4 m vs 14.7 m, $P = .02$). Moreover, in subgroup analysis, sarcopenia was associated with worse survival outcomes than non-sarcopenic patients, irrespective of age, BCLC stage, or ALBI grade. This result clearly indicates that sarcopenia predicts a poor outcome in most patients with HCC receiving lenvatinib. The sarcopenia group tended to achieve longer OS in patients with extrahepatic metastasis (HR, 1.438, 95% CI, 0.358–5.774). Our study is the first to investigate the prognostic role of sarcopenia in patients with HCC treated with lenvatinib, and our findings suggest that management of sarcopenia is vital in improving survival outcomes for HCC patients.

Therefore, preventing skeletal muscle loss or increasing skeletal muscle mass might be an effective method to improve survival of HCC patients with sarcopenia receiving lenvatinib. It has been reported that nutritional support and exercise are two main treatment strategies for sarcopenia. Branched-chain amino acids

supplement is related to minimizing muscle mass atrophy in HCC patients.[46–49] Vitamin D is associated with muscle strength, and sarcopenia may be reduced by vitamin D supplement in patients with chronic liver disease.[50,51] A late-evening snack also has the potential to improve skeletal muscle loss by reducing the overnight fasting period.[15,52] Exercise may be effective in preserving muscle volume through eliminating factors that cause sarcopenia, including improve mitochondrial energetics, inflammation, oxidative stress, and insulin resistance.[40,53] Thus, lifestyle changes coupled with proper exercise are likely to be effective to prevent skeletal muscle loss and improve the survival of HCC patients with sarcopenia.

The present study has several limitations. First, the sample size was relatively small. Secondly, the study was retrospective, and this may have caused selection bias. Finally, although the quantity of skeletal muscle was evaluated, the study was not able to evaluate the quality of muscle, which is recommended in a sarcopenia diagnosis. Therefore, further prospective studies with a larger cohort are needed to verify these results and assess skeletal muscle comprehensively to draw definitive conclusions.

5. Conclusions

In summary, the findings of our study suggest that sarcopenia is common in patients with HCC and is an independent prognostic factor for HCC patients treated with lenvatinib, which has important implications for treatment decision-making. In order to improve the prognosis of HCC patients, it is necessary to properly evaluate skeletal muscle mass before initiation of lenvatinib.

Author contributions

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