ORIGINAL ARTICLE

Comparison of the prognostic effect of sarcopenia on atezolizumab plus bevacizumab and lenvatinib therapy in hepatocellular carcinoma patients

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Abstract

Background and Aim: Sarcopenia has received much attention as a poor prognostic factor in various fields, and has also been reported to worsen prognosis in patients with hepatocellular carcinoma (HCC) treated with sorafenib or lenvatinib (LEN). Atezolizumab/bevacizumab (ATZ/BEV) is recommended as first-line drug therapy for unresectable-HCC, but the effect of sarcopenia on patients treated with ATZ/BEV is unknown.

Methods: We enrolled 98 patients treated with ATZ/BEV or LEN. Computed tomography performed before the initiation of drug therapy was used to diagnose sarcopenia in accordance with the criteria proposed by the Japanese Society of Hepatology. Patients were divided into two groups based on the presence or absence of sarcopenia in each regimen, and patient characteristics, adverse events, and prognosis were compared.

Results: In ATZ/BEV therapy, 57.1% of patients had sarcopenia. The sarcopenia group had significantly more women ($P = 0.0125$) and more macroscopic vascular invasion ($P = 0.0270$). Sarcopenia had no significant effect on progression-free survival (PFS) and overall survival (OS). In LEN therapy, 63.4% of patients had sarcopenia. The sarcopenia group was significantly older ($P = 0.0064$) and had a higher number of women ($P = 0.0003$), a higher neutrophil–lymphocyte ratio ($P = 0.0222$), worse albumin–bilirubin grade ($P = 0.0087$), and worse best response ($P = 0.0255$). PFS ($P = 0.0091$) and OS ($P = 0.0006$) were worse in the sarcopenia group. In multivariate analysis, age ($P = 0.0362$), lymphocyte–monocyte ratio ($P = 0.0365$), and sarcopenia ($P = 0.0268$) were independent prognostic factors for OS.

Conclusion: In ATZ/BEV therapy, sarcopenia does not determine prognosis, and therapeutic efficacy can be expected even in cases of sarcopenia.

Introduction

Hepatocellular carcinoma (HCC) is a common cancer in patients with chronic liver disease and is the leading cause of cancer mortality.[1] While surgery is selected as a curative treatment for HCC, many patients are not eligible because of rapid disease progression.[2,3] In this situation, systemic therapy has made remarkable progress in recent decades, especially since immune checkpoint inhibitors (ICIs) have become available. Atezolizumab plus

bevacizumab (ATZ/BEV) therapy became the first regimen to show superiority to sorafenib for unresectable-HCC (u-HCC).[4]

Sarcopenia is defined as the progressive and generalized loss of skeletal muscle mass and strength,[5] and a correlation between sarcopenia and unfavorable prognosis has been reported in various malignancies.[6] In HCC, the presence of sarcopenia is correlated with poor prognosis not only in surgical resection[7,8] but also in systemic therapy with sorafenib (SOR) and lenvatinib (LEN).[9–12] In the context of the recent use of ICIs for various types of malignancies, many studies regarding the impact of sarcopenia on patients treated with ICIs have been performed.[13,14] However, there is no report about the association between sarcopenia and ATZ/BEV therapy. In this study, we compared the effect of sarcopenia on the prognosis of u-HCC patients treated with ATZ/BEV and LEN, which has a high response rate.

Methods

Patients. This retrospective study was approved by the ethics committee of Kyushu University Hospital. All patients provided informed consent. It was conducted by reviewing the medical records of 98 patients who were diagnosed with u-HCC and treated with ATZ/BEV and LEN between April 2018 and March 2022 at Kyushu University Hospital. The HCC diagnoses were based on contrast-enhanced computed tomography (CT) or magnetic resonance imaging of tumors that displayed vascular enhancement in the early phase and washout in the later phase, in accordance with the guidelines of the Japan Society of Hepatology.[15]

Diagnosis and cutoff value of sarcopenia. The skeletal muscle mass index (SMI) was calculated by dividing the skeletal muscle mass at lumbar vertebral body 3 (cm^2) by the square of the height (cm^2/m^2) using abdominal CT, which was performed within 1 month of the initiation of therapy.[16] The cutoff values of the sarcopenia-related factors were based on the Japan Society of Hepatology guidelines for sarcopenia in liver disease, defined as SMI <42 cm^2/m^2 and <38 cm^2/m^2 in men and women, respectively.[17] In each regimen, patients were divided into two groups based on the presence or absence of sarcopenia.

Table 1 Univariate analysis for clinical characteristics of patients treated with atezolizumab plus bevacizumab and lenvatinib

Factors	Non-Sarcopenia ($n = 38$)	Sarcopenia ($n = 60$)	*P* value
Age (years)	70 (36–84)	74 (55–88)	0.0011
Sex, male/female	37/1	34/26	<0.0001
BMI (kg/m²)	23.7 (18.6–32.0)	22.5 (15.9–35.3)	0.1685
HBs-Ag positive	7 (18.4%)	7 (11.6%)	0.3518
HCV-Ab positive	11 (28.9%)	19 (31.6%)	0.8252
Total bilirubin (mg/dL)	0.9 (0.3–2.0)	0.9 (0.3–4.0)	0.8220
Albumin (g/dL)	3.9 (2.6–4.9)	3.6 (2.4–4.6)	0.0003
Prothrombin time (%)	90 (37–122)	89 (33–117)	0.4563
Platelet count (10⁴ μL)	16.5 (7.1–30.3)	15.1 (5.6–40.6)	0.3233
AST (U/L)	29 (16–139)	38 (16–186)	0.0823
ALT (U/L)	21 (7–108)	22 (7–127)	0.8350
NLR	2.31 (0.90–4.65)	2.61 (0.41–9.49)	0.0223
LMR	3.84 (2.14–8.60)	3.06 (1.34–12.07)	0.1610
Child–Pugh, A/B	38/0	56/4	0.1554
ALBI grade, 1/2/3	16/20/2	10/46/4	0.0208
AFP (ng/mL)	6.5 (0.9–28 100)	93.1 (0.6–273 870)	0.1744
DCP (mAU/mL)	125 (0.5–10 338)	548 (10–229 500)	0.0725
Maximum tumor size (cm)	2.5 (0.6–13.4)	2.4 (1.0–15.0)	0.3628
Number of intrahepatic tumors, none/solitary/multiple	4/4/30	8/15/37	0.1588
Macroscopic vascular invasion	2 (5.2%)	17 (28.3%)	0.0074
Extrahepatic metastasis	14 (36.8%)	19 (31.6%)	0.5973
BCLC, A/B/C	8/14/16	8/23/29	0.5888
History of systemic therapy	12 (31.5%)	15 (25.0%)	0.4952
Number of systemic therapy lines, 1/2/3/4	26/7/1/4	43/10/6/1	0.1433
History of TACE	15 (40.5%)	15 (25.0%)	0.1077
Recurrent cases	36 (94.7%)	51 (85.0%)	0.1368
Temporary drug suspension or drug reduction	17 (45.9%)	32 (56.1%)	0.4000
AEs (any grade)	32 (84.2%)	46 (85.1%)	0.8980
AEs (≥Grade 3)	10 (26.3%)	15 (27.7%)	0.8767
Best response (RECIST): PR or CR	16 (42.1%)	14 (23.3%)	0.0495
Best response (modified-RECIST): PR or CR	18 (47.3%)	19 (31.6%)	0.1182

Data are presented as *n* (%) or the median (range).
AEs, adverse events; AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; CR, complete response; DCP, des-gamma-carboxyprothrombin; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transcatheter arterial chemoembolization.

Regimen of ATZ/BEV and LEN. Intravenous ATZ/BEV treatment composed of 1200 mg atezolizumab plus 15 mg/kg of body weight of bevacizumab was administered every 3 weeks. The dosage and administration of LEN were previously described.[18] A reduced starting dose was permitted depending on the patient's condition. Follow-up visits for all patients included blood chemistry and tumor marker measurements. All patients were checked for the presence and grade of adverse events (AEs) by attending clinicians and pharmacists at each of their regular visits. AEs were graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Data collection. Data of the patients' characteristics (age, sex, body mass index [BMI], hepatitis B surface-antigen [HBV-Ag]-positive, hepatitis C virus-antibody [HCV-Ab] positive, total bilirubin, albumin, prothrombin time, platelet count, aspartate aminotransferase [AST], alanine aminotransferase [ALT], neutrophil–lymphocyte ratio [NLR], lymphocyte–monocyte ratio [LMR], Child–Pugh score, albumin–bilirubin [ALBI] score, ALBI grade, alpha-fetoprotein

[AFP], des-gamma-carboxyprothrombin [DCP], maximum tumor size, number of intrahepatic tumors, macroscopic vascular invasion, extrahepatic metastasis, Barcelona Clinic Liver Cancer stage [BCLC], history of systemic therapy, number of systemic therapy lines, history of transcatheter arterial chemoembolization [TACE], recurrent cases, temporary drug suspension or drug reduction, AEs (any grade), AEs [≥Grade 3], and best response [Response Evaluation Criteria in Solid Tumors, RECIST and modified-RECIST]) were recorded. RECIST includes progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR).

Statistical analysis. All statistical analyses were performed using SAS software (JMP Pro 15; SAS Institute Inc., Cary, NC, USA). The Shapiro–Wilk test was used to assess whether continuous variables were normally distributed. Continuous variables were presented as the median and were compared using the Mann–Whitney U test. Categorical variables were reported as percentages and compared using the χ^2 test or Fisher's exact test. Cumulative progression-free survival (PFS) and overall survival

Table 2 Univariate analysis for clinical characteristics of patients treated with atezolizumab plus bevacizumab

Factors	Non-Sarcopenia ($n = 15$)	Sarcopenia ($n = 20$)	P value
Age (years)	71 (37–82)	72 (60–84)	0.0915
Sex, male/female	15/0	13/7	0.0125
BMI (kg/m^2)	23.9 (18.6–32.0)	22.7 (20.1–34.8)	0.8000
HBs-Ag positive	2 (13.3%)	3 (15.0%)	0.8891
HCV-Ab positive	4 (26.7%)	5 (25.0%)	0.9111
Total bilirubin (mg/dL)	1.0 (0.3–1.6)	1.1 (0.5–1.7)	0.6683
Albumin (g/dL)	3.5 (2.6–4.9)	3.6 (2.5–4.1)	0.5873
Prothrombin time (%)	90 (44–105)	89 (33–117)	0.8764
Platelet count (10^4 μL)	16.2 (7.1–25.0)	14.4 (7.8–33.8)	0.7133
AST (U/L)	28 (16–139)	39 (19–186)	0.5015
ALT (U/L)	18 (7–104)	20 (7–86)	0.8881
NLR	2.47 (0.90–3.92)	2.32 (0.53–8.83)	0.4307
LMR	2.71 (0.76–14.75)	2.27 (0.80–7.15)	0.7541
Child–Pugh, A/B	15/0	18/2	0.4958
ALBI grade, 1/2/3	2/11/2	1/16/3	0.6837
AFP (ng/mL)	11.4 (2.2–28 100)	38 (1.5–63 949)	0.7433
DCP (mAU/mL)	155 (13–10 338)	1135 (10–25 711)	0.1874
Maximum tumor size (cm)	2.5 (0.6–11.0)	2.0 (1.0–14.0)	0.9452
Number of intrahepatic tumors, none/solitary/multiple	2/1/12	2/5/13	0.3617
Macroscopic vascular invasion	0 (0%)	6 (30.0%)	0.0270
Extrahepatic metastasis	7 (46.7%)	6 (30.0%)	0.4810
BCLC, A/B/C	4/4/7	2/10/8	0.2665
History of systemic therapy	10 (66.7%)	10 (50.0%)	0.4916
Number of systemic therapy lines, 1/2/3/4	5/5/1/4	10/4/5/1	0.1302
History of TACE	5 (35.7%)	6 (30.0%)	0.7259
Recurrent cases	15 (100%)	16 (80.0%)	0.0657
Temporary drug suspension or drug reduction	1 (6.7%)	6 (30.0%)	0.1987
AEs (any grade)	11 (73.3%)	15 (75.0%)	0.9111
AEs (≥Grade 3)	5 (33.3%)	4 (20.0%)	0.4505
Best response (RECIST): PR or CR	4 (26.6%)	5 (25.0%)	0.9111
Best response (modified-RECIST): PR or CR	5 (33.3%)	7 (35.0%)	0.9181

Data are presented as *n* (%) or the median (range).
AEs, adverse events; AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; CR, complete response; DCP, des-gamma-carboxyprothrombin; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transcatheter arterial chemoembolization.

(OS) rates were calculated using the Kaplan–Meier method, and differences between the curves were evaluated using the log-rank test. Survival data were used to establish a univariate Cox proportional hazards model. Covariates that were significant at $P < 0.05$ were included in the multivariate Cox proportional hazards model.

This retrospective study was approved by the ethics committee of Kyushu University (approval code: 2020-671).

Results

Patient characteristics. Thirty-five patients treated with ATZ/BEV and 63 patients treated with LEN were enrolled in this study. The characteristics of all patients enrolled in this study are shown in Table 1. Sixty of 98 patients (61.2%) were included in the sarcopenia group. The sarcopenia group was significantly older ($P = 0.0011$), contained more women ($P < 0.0001$), had lower serum albumin (0.0003), higher NLR ($P = 0.0223$), worse ALBI grade ($P = 0.0208$), more macroscopic vascular invasion

($P = 0.0074$), and worse best response (RECIST) ($P = 0.0495$). The characteristics of patients who received ATZ/BEV therapy are shown in Table 2. Twenty of the 35 patients (57.1%) were diagnosed in the sarcopenia group. The sarcopenia group had significantly more women ($P = 0.0125$) and more macroscopic vascular invasion ($P = 0.0270$).

Patient characteristics of the LEN therapy group are shown in Table 3. Forty of 63 patients (63.4%) were diagnosed in the sarcopenia group. The sarcopenia group was significantly older ($P = 0.0064$), contained a higher number of women ($P = 0.0003$), had higher NLR ($P = 0.0222$), worse ALBI grade ($P = 0.0087$), and worse best response (RECIST and modified-RECIST) ($P = 0.0162$ and $P = 0.0255$, respectively).

Effect of sarcopenia on PFS and OS. The Kaplan–Meier curves of all patients are shown in Figure 1a. Kaplan–Meier analysis revealed the trend toward significantly impaired PFS ($P = 0.0180$) and OS ($P = 0.0035$) in the sarcopenia group. The Kaplan–Meier curves of the ATZ/BEV therapy group are

Table 3 Univariate analysis for clinical characteristics of patients treated with lenvatinib

Factors	Non-Sarcopenia ($n = 23$)	Sarcopenia ($n = 40$)	*P* value
Age (years)	69 (36–84)	75 (55–88)	0.0064
Sex, male/female	22/1	21/19	0.0003
BMI (kg/m^2)	23.5 (18.6–30.8)	15.91 (15.9–35.3)	0.1383
HBs-Ag positive	5 (21.7%)	4 (10.0%)	0.2673
HCV-Ab positive	7 (30.4%)	14 (35.0%)	0.7113
Total bilirubin (mg/dL)	0.8 (0.4–2.0)	0.9 (0.3–2.6)	0.8966
Albumin (g/dL)	4.0 (3.7–4.8)	3.5 (2.4–4.6)	<0.0001
Prothrombin time (%)	88 (37–122)	89 (36–111)	0.2926
Platelet count (10^4 μL)	16.4 (8.4–30.3)	15.7 (5.6–40.6)	0.3785
AST (U/L)	31 (16–126)	38 (16–183)	0.1066
ALT (U/L)	23 (12–108)	23 (9–127)	0.6786
NLR	2.2 (0.99–4.65)	2.9 (0.41–9.49)	0.0222
LMR	3.85 (2.14–8.60)	2.94 (1.37–12.07)	0.1607
Child–Pugh, A/B	23/0	38/2	0.5289
ALBI grade, 1/2/3	14/9/0	9/30/1	0.0087
AFP (ng/mL)	3.7 (0.9–7836)	107 (0.6–273 870)	0.1955
DCP (mAU/mL)	125 (0.54–91 180)	328 (15–219 500)	0.1054
Maximum tumor size (cm)	2.2 (0.8–13.4)	3.0 (1.0–15.0)	0.2450
Number of intrahepatic tumors, none/solitary/multiple	2/3/18	6/10/24	0.3190
Macroscopic vascular invasion	2 (8.7%)	11 (27.5%)	0.1084
Extrahepatic metastasis	7 (30.4%)	13 (32.5%)	0.8654
BCLC, A/B/C	4/10/9	6/13/21	0.5819
History of systemic therapy	2 (8.7%)	5 (12.5%)	0.6437
Number of systemic therapy lines, 1/2	21/2	35/5	0.6437
History of TACE	10 (43.4%)	9 (22.5%)	0.0807
Recurrent cases	21 (91.3%)	35 (87.5%)	0.6457
Temporary drug suspension or drug reduction	16 (72.3%)	26 (70.2%)	0.8403
AEs (any Grade)	21 (91.3%)	31 (91.1%)	0.9866
AEs (≥Grade 3)	5 (21.7%)	11 (32.3%)	0.5493
Best response (RECIST): PR or CR	12 (52.1%)	9 (22.5%)	0.0162
Best response (modified-RECIST): PR or CR	13 (59.0%)	12 (30.0%)	0.0255

Data are presented as *n* (%) or the median (range).

AEs, adverse events; AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; CR, complete response; DCP, des-gamma-carboxyprothrombin; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transcatheter arterial chemoembolization.
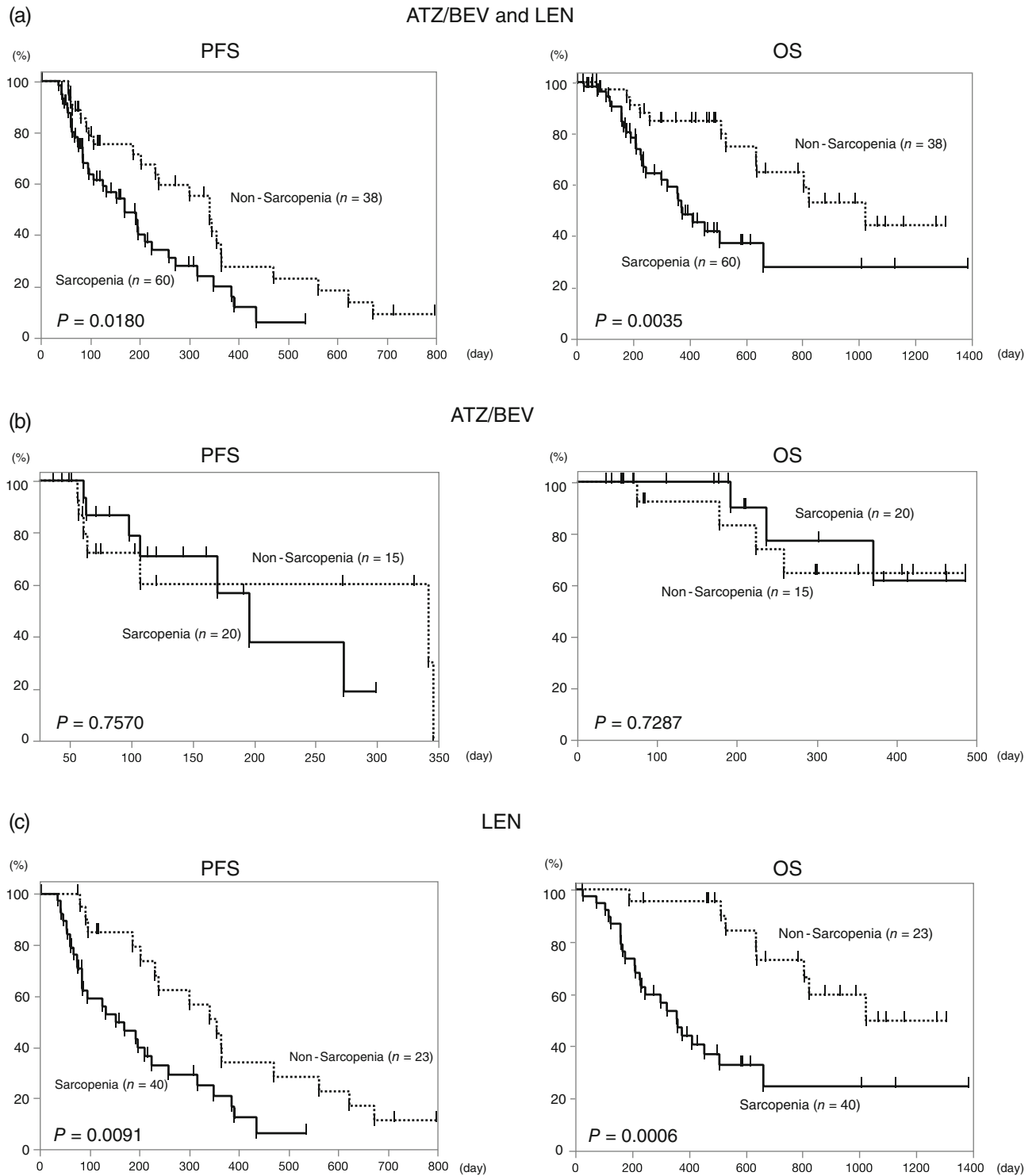
Figure 1 (a) Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in the sarcopenia and non-sarcopenia groups in patients with atezolizumab plus bevacizumab (ATZ/BEV) and lenvatinib (LEN) therapy. (b) Kaplan–Meier curves for PFS and OS in the sarcopenia and non-sarcopenia groups in patients with ATZ/BEV therapy. (c) Kaplan–Meier curves for PFS and OS in the sarcopenia and non-sarcopenia groups in patients with LEN therapy.

shown in Figure 1b. Kaplan–Meier analysis revealed no significant differences in PFS and OS between the two groups. The Kaplan–Meier curves of the LEN therapy group are shown in Figure 1c. Kaplan–Meier analysis revealed a trend toward significantly impaired PFS ($P = 0.0091$) and OS ($P = 0.0006$) in the sarcopenia group.

Risk factors associated with PFS. In all patients, univariate analysis of the association between PFS and patient characteristics showed that the significant prognostic factors were ALBI grade 2 or 3 (*vs* 1) ($P = 0.0167$) and sarcopenia ($P = 0.0202$), but multivariate analysis showed no significant prognostic factors (Table S1, Supporting information). In ATZ/BEV therapy, univariate analysis showed no significant prognostic factors (Table S2). In LEN therapy, univariate analysis showed that the significant prognostic factors were ALBI grade 2 or 3 (*vs* 1) ($P = 0.0253$) and sarcopenia ($P = 0.0112$), but multivariate analysis showed no significant prognostic factors (Table S3).

Risk factors associated with OS. In all patients, univariate analysis of the association between OS and patient characteristics showed that the significant prognostic factors were age ≥75 (years) ($P = 0.0148$), LMR ≤4.0 ($P = 0.0142$), ALBI grade 2 or 3 (*vs* 1) ($P = 0.0143$), sarcopenia ($P = 0.0048$), and best response (modified-RECIST) PD or SD (*vs* PR or CR)

($P = 0.0112$), and multivariate analysis showed that the independent prognostic factors for OS were age ≥75 (years) ($P = 0.0363$) and best response (modified-RECIST) PD or SD (*vs* PR or CR) ($P = 0.0371$) (Table 4, Fig. 2a).

In ATZ/BEV therapy, univariate analysis showed no significant prognostic factors (Table S4).

In LEN therapy, univariate analysis showed that the significant prognostic factors were age ≥75 years ($P = 0.0082$), female sex ($P = 0.0308$), LMR ≤4.0 ($P = 0.0142$), ALBI grade 2 or 3 (*vs* 1) ($P = 0.0153$), sarcopenia ($P = 0.0012$), and best response (modified-RECIST) PD or SD (*vs* PR or CR) ($P = 0.0389$), and in multivariate analysis, the independent prognostic factors for OS were age ≥75 years ($P = 0.0362$), LMR ≤4.0 ($P = 0.0365$), and sarcopenia ($P = 0.0288$) (Table 5, Fig. 2b).

Effect of sarcopenia on PFS and OS in the subgroup of background liver (viral/non-viral). The viral group was defined as patients whose HBV-Ag or HCV-Ab was positive. The Kaplan–Meier curves of all patients are shown in Figure S1. In the viral subgroup, Kaplan–Meier analysis revealed the trend toward significantly impaired OS ($P = 0.0347$) in the sarcopenia group. In the non-viral subgroup, Kaplan–Meier curves revealed a trend toward significantly impaired PFS ($P = 0.0319$) and OS ($P = 0.0411$) in the sarcopenia group. The Kaplan–Meier curves

Table 4 Risk factors associated with overall survival in atezolizumab plus bevacizumab and lenvatinib therapy

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥ 75 (years)	2.26 (1.17–4.33)	0.0148	2.06 (1.04–4.06)	0.0363
Sex, female	1.92 (0.96–3.84)	0.0633		
HBs-Ag positive	2.18 (0.77–6.18)	0.1397		
HCV-Ab positive	1.09 (0.56–2.14)	0.7807		
Total bilirubin (mg/dL)	1.42 (0.67–2.78)	0.3306		
Prothrombin time (%)	1.00 (0.98–1.02)	0.7075		
AST (U/L)	1.01 (0.99–1.01)	0.0980		
ALT (U/L)	1.01 (0.99–1.02)	0.1057		
Platelet count (10^4 μL)	0.98 (0.92–1.03)	0.5171		
NLR ≥ 3.0	1.16 (0.60–2.24)	0.6495		
LMR ≤ 4.0	2.73 (1.22–6.11)	0.0142	1.72 (0.86–3.42)	0.1192
ALBI grade, 2 or 3 (*vs* 1)	2.60 (1.21–5.58)	0.0143	1.83 (0.84–3.98)	0.1253
AFP ≥ 400 (ng/mL)	1.53 (0.73–3.16)	0.2516		
DCP ≥ 1000 (mAU/mL)	1.25 (0.62–2.53)	0.5283		
Maximum tumor size (cm)	1.03 (0.93–1.13)	0.4507		
Number of tumors, multiple (*vs* none/single)	1.00 (0.49–2.01)	0.9938		
Macroscopic vascular invasion	2.03 (0.88–4.65)	0.0935		
Extrahepatic metastasis	1.33 (0.70–2.53)	0.3752		
BCLC, C (*vs* A or B)	1.70 (0.90–3.21)	0.0995		
History of systemic therapy	2.31 (0.90–5.95)	0.0815		
History of TACE	1.29 (0.65–2.56)	0.4609		
Temporary drug suspension or drug reduction	1.10 (0.55–2.17)	0.7819		
Sarcopenia	2.75 (1.36–5.58)	0.0048	1.93 (0.93–4.00)	0.0744
Best response (modified-RECIST): PD or SD (*vs* CR or PR)	2.47 (1.22–4.97)	0.0112	2.13 (1.04–4.35)	0.0371

AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; DCP, des-gamma-carboxyprothrombin; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HR, hazard ratio; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TACE, transcatheter arterial chemoembolization.
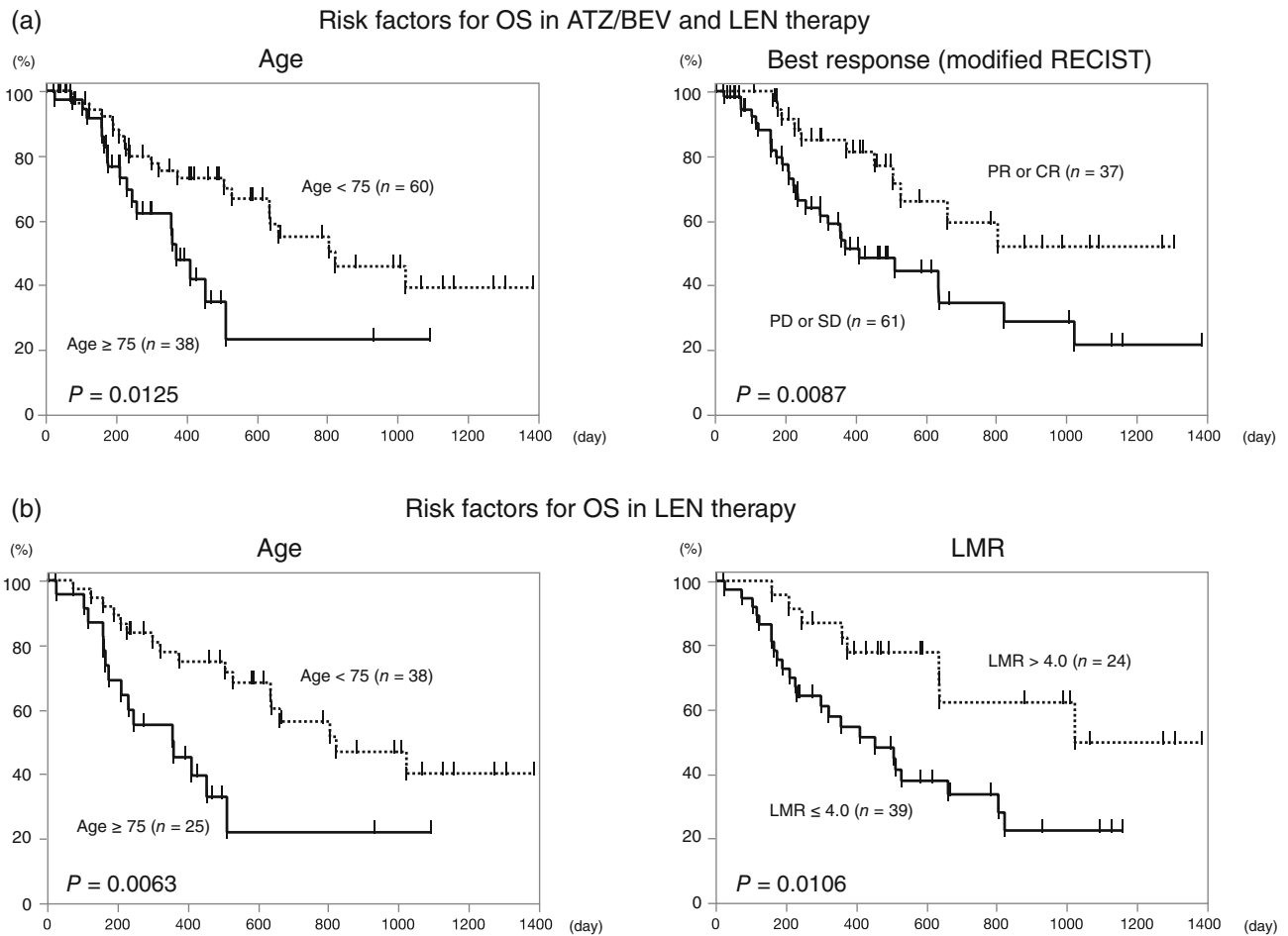
(a) Risk factors for OS in ATZ/BEV and LEN therapy

Figure 2 (a) Kaplan–Meier curves for overall survival (OS) in the two groups according to age and best response in patients with atezolizumab plus bevacizumab (ATZ/BEV) and lenvatinib (LEN) therapy. (b) Kaplan–Meier curves for OS in the two groups according to age and lymphocyte–monocyte ratio (LMR) in patients with LEN therapy. CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

of ATZ/BEV therapy are shown in Figure S2. Kaplan–Meier analysis revealed no significant differences in PFS and OS in the viral and non-viral subgroups. The Kaplan–Meier curves of LEN therapy are shown in Figure S3. In the viral subgroup, Kaplan–Meier analysis revealed a trend towards significantly impaired PFS ($P = 0.0100$) and OS ($P = 0.0423$) in the sarcopenia group, while in the non-viral subgroup, Kaplan–Meier curves revealed a trend towards significantly impaired OS ($P = 0.0067$) in the sarcopenia group.

Discussion

This retrospective study demonstrated that the presence of sarcopenia affects the prognosis of patients treated with LEN but not those treated with ATZ/BEV.

Sarcopenia occurs with the decline in performance status of patients with various diseases, in particular carcinoma, and has received much attention.[5] The number of patients with liver disease and cirrhosis has recently been increasing worldwide, and non-viral hepatitis cases with a background of alcohol and diabetes are on the rise.[19] The association between sarcopenia and alcohol and diabetes itself has, of course, been reported,[20,21] but chronic liver disease and cirrhosis cause sarcopenia because of the inability of muscles to synthesize protein as a result of the consumption of branched-chain amino acids in muscles.[22] Most HCC patients basically have chronic liver disease or liver cirrhosis in the background, with a high rate of sarcopenia, or a precursor to sarcopenia, and thus the recognition, prevention, and treatment of these conditions are essential.[22]

As we mentioned in the Introduction section, no association between sarcopenia and prognosis in patients with ATZ/BEV therapy has been reported. In other cancer types, there are reports that sarcopenia leads to worse prognosis in patients with ICI therapy,[14,23] but others show that it has no effect on prognosis.[24,25] There are differences in the molecular mechanisms among carcinomas, and in sarcopenia, in particular, there are reports of associations with the patient's immune status and other factors. Thus, large-scale studies and exploration of biomarkers associated with sarcopenia in HCC patients with ATZ/BEV therapy are needed in the future. Either way, to our

Table 5 Risk factors associated with overall survival in lenvatinib therapy

	Univariate analysis		Multivariate analysis	
Factors	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥ 75 (years)	2.64 (1.28–5.45)	0.0082	2.31 (1.05–5.05)	0.0362
Sex, female	2.30 (1.08–4.93)	0.0308	1.06 (0.42–2.64)	0.8910
HBs-Ag positive	2.38 (0.72–7.87)	0.1540		
HCV-Ab positive	1.05 (0.50–2.19)	0.8863		
Total bilirubin (mg/dL)	1.00 (0.98–1.02)	0.2853		
Prothrombin time (%)	1.00 (0.99–1.01)	0.7024		
AST (U/L)	1.00 (0.99–1.01)	0.0505		
ALT (U/L)	1.00 (0.98–1.01)	0.4564		
Platelet count (10^4 µL)	0.99 (0.93–1.05)	0.8587		
NLR ≥ 3.0	1.45 (0.71–2.96)	0.2969		
LMR ≤ 4.0	2.73 (1.22–6.11)	0.0142	2.40 (1.05–5.46)	0.0365
ALBI grade, 2 or 3 (*vs* 1)	2.63 (1.20–5.75)	0.0153	1.91 (0.81–4.51)	0.1361
AFP ≥ 400 (ng/mL)	1.93 (0.88–4.23)	0.1157		
DCP ≥ 1000 (mAU/mL)	1.77 (0.81–3.84)	0.1467		
Maximum tumor size (cm)	1.04 (0.93–1.14)	0.3774		
Number of tumors, multiple (*vs* none/single)	1.01 (0.46–2.19)	0.9777		
Macroscopic vascular invasion	2.34 (0.99–5.51)	0.0512		
Extrahepatic metastasis	1.27 (0.62–2.62)	0.5014		
BCLC, C (*vs* A or B)	1.79 (0.89–3.60)	0.1023		
History of systemic therapy	4.84 (0.66–35.5)	0.1205		
History of TACE	1.28 (0.60–2.72)	0.5137		
Temporary drug suspension or drug reduction	1.17 (0.52–2.65)	0.6969		
Sarcopenia	3.96 (1.72–9.11)	0.0012	2.86 (1.11–7.33)	0.0288
Best response (modified-RECIST): PD or SD (*vs* CR or PR)	2.20 (1.04–4.66)	0.0389	1.77 (0.81–3.86)	0.1460

AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; DCP, des-gamma-carboxyprothrombin; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HR, hazard ratio; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TACE, transcatheter arterial chemoembolization.

knowledge, this is the first study to evaluate the effect of sarcopenia on the prognosis of patients while complying with the established guidelines in u-HCC patients treated with ATZ/BEV. Our study showed that sarcopenia did not affect PFS/OS and safety in patients treated with ICIs. Furthermore, approximately half of the patients treated with ATZ/BEV in this study had a history of systemic therapy such as LEN or SOR, and approximately 30% had a history of TACE, as shown in Table 2. Moreover, it was recently reported that older age was not associated with worse OS or PFS in ATZ/BEV therapy.[26] These results and this study suggest that ATZ/BEV therapy may be administered relatively safely, not only as first-line therapy for HCC but also in patients with a history of systemic therapy or TACE.

SOR and LEN were used as the mainstay of systemic therapy for u-HCC until ATZ/BEV was approved, and sarcopenia has often been reported to be an independent risk factor for worse prognosis in SOR and LEN therapies, with similar results in this study.[9–12] Moreover, patients treated with ICIs for advanced solid malignancies have a lower risk of developing AEs, and the proportion of patients with serious AEs above grade III is significantly lower (16.5 *vs* 41.0%) compared with traditional systemic therapy.[27] In these SOR or LEN therapies, the reduced activation of the phosphatidylinositol 3-kinase–AKT–mammalian target of rapamycin pathway, which promotes protein synthesis, is involved with sarcopenia.[28] Several

recent reports suggested that sarcopenia was associated with the presence of systemic inflammation and activation of the immune system, but the molecular mechanisms related to ICI and sarcopenia are not fully understood. Regarding HCC, the overall incidence of AEs was the same in the REFLECT and IMbrave150 trials, but AEs such as anorexia (34 *vs* 17.6%), weight loss (31 *vs* 11.2%), and fatigue (31 *vs* 20.4%) were higher in LEN compared with ATZ/BEV.[4,29] With respect to the reasons why sarcopenia affected the prognosis of patients with LEN but not ATZ/BEV, we consider that this may have had a direct impact on the patients with sarcopenia, in particular worsening their general condition and tolerance of chemotherapy. Moreover, this study showed that high NLR was not an independent predictor of OS, contradicting previous reports, but low LMR was.[30] Lower LMR may increase monocyte-derived cells in the HCC microenvironment and cytokine expression by immune cells, and this was reported to a be a prognostic biomarker of hepatic resection,[31] but there are no reports of the prognostic effect of low LMR on patients. It must be examined on a large scale and comprehensive biomarkers are needed.

This study had a couple of limitations. First, it was a single-center retrospective study with a relatively small study cohort. Second, the observation period was not very long. Therefore, this study should be validated in many patients at multiple centers over a longer period.

In conclusion, in ATZ/BEV therapy, sarcopenia is not a prognostic factor, and this treatment approach can be expected to be effective even in patients with sarcopenia. Sarcopenia is a poor prognostic factor in LEN treatment and should be considered when using LEN. Further cases are required to verify these results.

Acknowledgment

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1A. Kaplan–Meier curves for PFS and OS in the sarcopenia and nonsarcopenia group in patients with ATZ/BEV and LEN therapy whose background liver disease were viral.

Figure S1B. Kaplan–Meier curves for PFS and OS in the sarcopenia and nonsarcopenia group in patients with ATZ/BEV and LEN therapy whose background liver disease were non-viral.

Figure S2A. Kaplan–Meier curves for PFS and OS in the sarcopenia and nonsarcopenia group in patients with ATZ/BEV therapy whose background liver disease were viral.

Figure S2B. Kaplan–Meier curves for PFS and OS in the sarcopenia and nonsarcopenia group in patients with ATZ/BEV therapy whose background liver disease were non-viral.

Figure S3A. Kaplan–Meier curves for PFS and OS in the sarcopenia and non-sarcopenia group in patients with LEN therapy whose background liver disease were viral.

Figure S3B. Kaplan–Meier curves for PFS and OS in the sarcopenia and nonsarcopenia group in patients with LEN therapy whose background liver disease were non-viral.