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

Katsuya Toshida, Shinji Itoh, Takahiro Tomiyama, Akinari Morinaga, Yukiko Kosai, Takahiro Tomino, Takeshi Kurihara, Yoshihiro Nagao, Kazutoyo Morita, Noboru Harada and Tomoharu Yoshizumi

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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.

Key words
atezolizumab plus bevacizumab, hepatocellular carcinoma, lenvatinib, sarcopenia.

Accepted for publication 14 May 2022.

Correspondence
Shinji Itoh, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashiku, Fukuoka 812-8582, Japan.
Email: itoh.shinji.453@m.kyushu-u.ac.jp

Declaration of conflict of interest: The authors have no conflict of interest.

Author contribution: Katsuya Toshida participated in the study conception and design, analysis, and drafting of the article. Shinji Itoh participated in the study conception and design, and in the critical revision of the manuscript. Takahiro Tomiyama, Akinari Morinaga, Yukiko Kosai, Takahiro Tomino, Katsuya Toshida, Yoshihiro Nagao, Kazutoyo Morita, and Noboru Harada participated in the data acquisition, analysis, and interpretation. Tomoharu Yoshizumi participated in the critical revision of the manuscript.

Financial support: This study was supported by the Medical Research Encouragement Prize from the Japan Medical Association and by JSPS KAKENHI grant number JP-19K09198. The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the article for publication.

Funding support: JSPS KAKENHJP-19K09198

Funding support: The Medical Research Encouragement Prize from The Japan Medical Association

Introduction

Hepatocellular carcinoma (HCC) is a common cancer in patients with chronic liver disease and is the leading cause of cancer mortality. While surgery is selected as a curative treatment for HCC, many patients are not eligible because of rapid disease progression. 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 resection7,8 but also in systemic therapy with sorafenib (SOR) and lenvatinib (LEN).9,10 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 performed11,12 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.13

**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%) | 11 (28.9%) | 0.3518 |
| HCV-Ab positive | 1 (2.6%) | 1 (2.6%) | 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 (2.4–4.8) | 0.0003 |
| Prothrombin time (%) | 90 (37–122) | 89 (33–117) | 0.4563 |
| Platelet count (10⁴ μL) | 16.5 (7.1–30.3) | 15.1 (5.6–40.8) | 0.3233 |
| AST (IU/L) | 29 (16–139) | 38 (16–186) | 0.0823 |
| ALT (IU/L) | 21 (7–108) | 22 (7–127) | 0.8350 |
| NLR | 2.31 (0.80–4.65) | 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 | 10/2/0 | 10/4/6 | 0.0209 |
| AFP (ng/mL) | 6.5 (0.9–29 100) | 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 (51.6%) | 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 | 28/7/1/4 | 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 |
| AEIs (any grade) | 32 (84.2%) | 46 (85.1%) | 0.8980 |
| AEIs (≥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).

AEIs, 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. 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, body mass index [BMI], hepatitis B surface-antigen [HBV-Ag]-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, extrapleural 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 χ² 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/m²)                                  | 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 (10⁴ 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                            | 2/1/2                   | 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                                  | 4/47                    | 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; HBV-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 ($P=0.0023$), 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

| 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                    | 21/9                | 0.0003    |
| BMI (kg/m²)                                  | 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 (10⁴ 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    |
| AE(s) any Grade                              | 21 (91.3%)              | 31 (91.1%)          | 0.9866    |
| AE(s) ≥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, transcatheater 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              |
|                               |                     |                      |
| Age ≥75 (years)               | 2.26 (1.17–4.33)    | 0.0148               |
| 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 (IU/L)                    | 1.01 (0.99–1.01)    | 0.0980               |
| ALT (IU/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               |
| ALBI grade, 2 or 3 (vs 1)     | 2.60 (1.21–5.58)    | 0.0143               |
| 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    | 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     | 1.10 (0.55–2.17)    | 0.7819               |
| Sarcopenia                    | 2.75 (1.36–5.58)    | 0.0048               |
| Best response (modified-RECIST): PD or SD (vs CR or PR) | 2.47 (1.22–4.97) | 0.0112               |

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.

© 2022 The Authors. JGH Open published by Journal of Gastroenterology and Hepatology Foundation and John Wiley & Sons Australia, Ltd.
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. 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. The association between sarcopenia and alcohol and diabetes itself has, of course, been reported, 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. 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.

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, but others show that it has no effect on prognosis. 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
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 ICI. 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 ICI 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.4,28 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 a significant predictor of survival in patients with LEN but not ATZ/BEV.29 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.

Table 5 Risk factors associated with overall survival in lenvatinib therapy

| Factors                                                                 | Univariate analysis | Multivariate analysis |
|------------------------------------------------------------------------|---------------------|-----------------------|
|                                                                       | HR (95% CI)         | P value               |
| Age ≥ 75 (years)                                                      | 2.64 (1.28–5.45)    | 0.0062                |
| Sex, female                                                           | 2.30 (1.08–9.43)    | 0.0308                |
| HBs-Ag positive                                                       | 2.38 (0.72–7.87)    | 0.1540                |
| HCV-Ab positive                                                       | 1.06 (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 (μ/L)                                                             | 1.00 (0.99–1.01)    | 0.0505                |
| ALT (μ/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                |
| ALBI grade, 2 or 3 (vs 1)                                             | 2.63 (1.20–5.75)    | 0.0153                |
|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                |
| Best response (modified-RECISt): PD or SD (vs CR or PR)               | 2.20 (1.04–4.66)    | 0.0389                |

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.
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, and this treatment approach can be expected to

Acknowledgment
We thank H. Nikki March, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

References
1 Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391: 1301–14.
2 Itoh S, Yoshizumi T, Yugawa K et al. Impact of immune response on outcomes in hepatocellular carcinoma: association with vascular formation. Hepatology. 2020; 72: 1987–99.
3 Vogel A, Saborowski A. Medical therapy of HCC. J. Hepatol. 2021; 76: 208–10.
4 Finn RS, Qin S, Ikeda M et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. New Engl. J. Med. 2020; 382: 1894–905.
5 Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. J. Lab. Clin. Med. 2001; 137: 231–43.
6 Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. Eur. J. Cancer. 2016; 57: 58–67.
7 Itoh S, Shirabe K, Matsumoto Y et al. Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. Ann. Surg. Oncol. 2014; 21: 3063–8.
8 Itoh S, Yoshizumi T, Sakata K et al. Slow gait speed is a risk factor for complications after hepatic resection. J. Gastrointest. Surg. 2019; 23: 1810–6.
9 Takada H, Kurosaki M, Nakanishi H et al. Impact of pre-sarcopenia in sorafenib treatment for advanced hepatocellular carcinoma. PLoS One. 2018; 13: e0198812.
10 Endo K, Kuroda H, Kanazawa J et al. Impact of grip strength in patients with unresectable hepatocellular carcinoma treated with lenvatinib. Cancer. 2020; 12: 2146.
11 Uozima H, Chuma M, Tanaka Y et al. Skeletal muscle mass loss after hepatic resection in patients with hepatocellular carcinoma. Liver Cancer. 2020; 9: 193–206.
12 Hiraoka A, Kumada T, Kariyama K et al. Clinical importance of muscle volume in lenvatinib treatment for hepatocellular carcinoma: analysis adjusted with inverse probability weighting. J. Gastroenterol. Hepatol. 2021; 36: 1812–9.
13 Takada K, Yoneshima Y, Tanaka K et al. Clinical impact of skeletal muscle area in patients with non-small cell lung cancer treated with anti-PD-1 inhibitors. J. Cancer Res. Clin. Oncol. 2020; 146: 1217–25.
14 Loosen SH, Bosch V v d, Gorgulho J et al. Progressive sarcopenia correlates with poor response and outcome to immune checkpoint inhibitor therapy. J. Clin. Med. 2021; 10: 1361.
15 Kudo M, Kawamura Y, Hasegawa K et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. Liver Cancer. 2021; 10: 181–223.
16 Itoh S, Yoshizumi T, Tomiyama T et al. Impact and risk factors for skeletal muscle mass loss after hepatic resection in patients with hepatocellular carcinoma. JGH Open. 2021; 5: 785–92.
17 Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol. Res. 2016; 46: 951–63.
18 Toshida K, Itoh S, Yoshizumi T et al. Retrospective evaluation of the effect of Ninjin’yoeito in hepatocellular carcinoma patients treated with lenvatinib. Surg. Today. 2022; 52: 441–8.
19 European Association for the Study of the Liver, Merli M, Berzigotti A et al. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J. Hepatol. 2018; 70: 172–93.
20 Izzo A, Massimino E, Riccardi G, Pepa GD. A narrative review on sarcopenia in type 2 diabetes mellitus: prevalence and associated factors. Nutrients. 2021; 13: 183.
21 Anand AC. Nutrition and muscle in cirrhosis. J. Clin. Exp. Hepatol. 2017; 7: 340–57.
22 Dasarathy S. Consilience in sarcopenia of cirrhosis. J. Cachexia. Sarcopenia Muscle. 2012; 3: 225–37.
23 Cortellini A, Bozzetti F, Palumbo P et al. Weighing the role of skeletal muscle mass and muscle density in cancer patients receiving PD-1/PD-L1 checkpoint inhibitors: a multicenter real-life study. Sci. Rep. 2020; 10: 1456.
24 Haik L, Gonthier A, Quivy A et al. The impact of sarcopenia on the efficacy and safety of immune checkpoint inhibitor monotherapy for pretreated patients with advanced non-small cell lung cancer. World J. Oncol. 2020; 11: 9–22.
25 Minami S, Ihara S, Tanaka T, Komuta K. Sarcopenia and visceral adiposity did not affect efficacy of immune-checkpoint inhibitor monotherapy for pretreated patients with advanced non-small cell lung cancer. World J. Oncol. 2020; 11: 9–22.
26 Tada T, Kumada T, Hiraoka A et al. Safety and efficacy of atezolizumab plus bevacizumab in elderly patients with hepatocellular carcinoma: a multicenter analysis. Cancer Med. 2022; online ahead of print.
27 Magee DE, Hird AE, Klaassen Z et al. Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: a systematic review and meta-analysis of randomized clinical trials. Ann. Oncol. 2020; 31: 50–60.
28 Filbin MG, Dabrjal SK, Pazynra-Murphy MF et al. Coordinate activation of Shh and PI3K signaling in PTEN-deficient glioblastoma: new therapeutic opportunities. Nat. Med. 2013; 19: 1518–23.
29 Kudo M, Finn RS, Qin S et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018; 391: 1163–73.
30 Tada T, Kumada T, Hiraoka A et al. Neutrophil-to-lymphocyte ratio is associated with survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib. Liver Int. 2020; 40: 968–76.
31 Itoh S, Yugawa K, Shimokawa M et al. Prognostic significance of inflammatory biomarkers in hepatocellular carcinoma following hepatic resection. BJS Open. 2019; 3: 500–8.

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 sarcoopenia and nonsarcoopenia 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 sarcoopenia and nonsarcoopenia 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 sarcoopenia and nonsarcoopenia group in patients with ATZ/BEV therapy whose background liver disease were viral.

Figure S2B. Kaplan–Meier curves for PFS and OS in the sarcoopenia and nonsarcoopenia 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.

**Table S1.** Risk factors associated with PFS in ATZ/BEV and LEN therapy

**Table S3.** Risk factors associated with PFS in LEN therapy.

**Table S2.** Risk factors associated with PFS in ATZ/BEV therapy

**Table S4.** Risk factors associated with OS in ATZ/BEV therapy.