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Relationship of Atezolizumab plus Bevacizumab Treatment with Muscle Volume Loss in Unresectable Hepatocellular Carcinoma Patients: Multicenter Analysis

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Abstract

Background/Aim: There is no known report regarding the relationship of atezolizumab plus bevacizumab (Atez/Bev) treatment with muscle volume loss (MVL) in unresectable hepatocellular carcinoma (u-HCC) patients. This study aimed to elucidate the clinical relationship between MVL and Atez/Bev. ***Materials/Methods:*** From September 2020 to December 2021, 229 u-HCC patients treated with Atez/Bev and with muscle volume data obtained by computed tomography at the baseline available were analyzed (median age, 74 years; males, 186 (81.2%); ECOG PS 0/1, 221 (96.5%); HCV:HBV:alcohol:others = 81:33:40:75; Child-Pugh A, 212 (92.6%); modified albumin-bilirubin (mALBI) grade 1:2a:2b = 79:60:90; BCLC 0:A:B:C = 1:24:87:117; median observation period, 6.8 months). Japan Society of Hepatology criteria were used for definition of MVL and prognostic factors were retrospectively evaluated. ***Results:*** Multivariate Cox-hazard analysis of prognostic factors for progression-free survival (PFS) showed elevated alpha-fetoprotein (AFP) (≥100 ng/mL) (HR 1.848, 95% CI 1.264–2.702, $p = 0.002$), mALBI grade (≥2a) (HR 1.563, 95% CI 1.035–2.359, $p = 0.034$), and MVL (HR 1.479, 95% CI 1.020–2.144, $p = 0.039$) as significant factors. For overall survival (OS), significant factors included elevated AFP (≥100 ng/mL) (HR 3.564, 95% CI 1.856–6.844, $p < 0.001$), mALBI grade (≥2a) (HR 3.451, 95% CI 1.580–7.538, $p = 0.002$), and MVL (HR 2.119, 95% CI 1.150–3.904, $p = 0.016$). Patients with MVL (MVL group, $n = 91$) showed worse PFS than those without (non-MVL group, $n = 138$) (median PFS 5.3 vs. 7.6 months, $p = 0.025$), while the MVL group showed worse OS ($p = 0.038$), though neither reached the median survival time. ***Conclusion:*** MVL may be a clinical factor related to poor prognosis in patients receiving Atez/Bev treatment for u-HCC.

Introduction

Hepatocellular carcinoma (HCC) is a major malignancy and reported to be fifth most common worldwide [1]. Additionally, recurrence is well known to often occur following curative treatment (e.g., surgical resection, radiofrequency ablation [RFA]), with the tumor often finally showing an unresectable state, even if hepatic reserve function is maintained. Furthermore, patients with chronic liver disease often have HCC occurrence, while muscle abnormalities such as sarcopenia, muscle volume loss (MVL), and muscle strength decline are not uncommon in these cases [2].

MVL has been reported to be a negative prognostic factor for survival not only in patients with portal hypertension [3] but also in those with an unresectable HCC (u-HCC) who received treatment with sorafenib [4–7] or lenvatinib [8, 9]. Although atezolizumab plus bevacizumab treatment (Atez/Bev) has recently been developed and shown to be an effective systemic treatment method for u-HCC [10], and is now used in clinical practice [11–15], no known study has evaluated the clinical relationship between MVL and Atez/Bev in u-HCC cases. The present investigation aimed to elucidate the clinical relationship of MVL with Atez/Bev in patients with u-HCC.

Materials and Methods

From September 2020 to December 2021, 399 u-HCC patients were treated with Atez/Bev at our affiliated hospitals. Of those, 229 with computed tomography (CT) data obtained at the baseline (within 1 month of introduction of Atez/Bev) available were assessed regarding muscle volume after exclusion of Barcelona Clinic Liver Cancer stage (BCLC)-D ($n = 3$) [16].

After obtaining written informed consent from each patient, intravenous Atez/Bev treatment, composed of 1,200 mg of Atez/Bev at 15 mg/kg of body weight, was given every 3 weeks [10], based on the guidelines for Atez/Bev treatment provided by the manufacturer. Treatment was discontinued following observation of any unacceptable or serious adverse event (AE), or clinical tumor progression. Each was examined using upper gastrointestinal endoscopy for surveillance of esophago-gastric varices within 6 months of introduction of Atez/Bev. When bleeding was detected or in cases with high risk (esophago-gastric varices F2 or more, or positive for red-color sign), the patient was treated by endoscopic treatments (endoscopic variceal ligation or endoscopic injection sclerotherapy and ligation) before introducing Atez/Bev.

Underlying Liver Disease

Positive anti-HCV findings were considered to indicate that HCC was due to hepatitis C virus (HCV), whereas HCC due to hepatitis B virus (HBV) was determined when the HBV surface antigen was positive. For patients with a history of alcohol abuse (≥60 g/day) [17, 18], underlying liver disease was judged as related to alcohol. Patients with a known history of autoimmune disease were not treated with Atez/Bev.

Response Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) package, ver. 1.1 [19], was used for evaluation of therapeutic response (complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]). The initial assessment of the effect of therapy was performed using dynamic-CT results obtained at approximately 6 weeks after introduction of Atez/Bev whenever possible, then additional dynamic-CT examinations were performed as needed depending on patient condition, even before 6 weeks in some cases. After the initial

6 weeks, dynamic-CT examinations were performed again every 6 weeks and then every nine to 12 weeks after the first 6 months.

Liver Function Assessment

Child-Pugh classification [20], albumin-bilirubin (ALBI) grade [21, 22], and modified ALBI (mALBI) grade [23], for which ALBI grade 2 was divided into two sub-grades (mALBI 2a and 2b) using an ALBI score of −2.27 as the cut-off value, were used for hepatic reserve function assessment.

HCC Diagnosis and Treatment

HCC diagnosis was based on an increasing course of alpha-fetoprotein (AFP), as well as dynamic-CT [24], magnetic resonance imaging [25, 26], and/or pathological findings obtained during the clinical course. BCLC stage [16] was used for evaluations of tumor progression.

Muscle Volume Evaluation and Definition of MVL

CT data at the baseline (within 1 month of introduction of Atez/Bev) were sent to Ehime Prefectural Central Hospital (EPCH). The muscle area at the middle of the L3 level was evaluated using a Synapse Vincent 3D image analysis system, ver. May 5, 0007 (FUJIFILM Corporation, Tokyo, Japan), by AH of EPCH, with skeletal muscle index (muscle area [cm^2] calculated based on the middle of L3/height $[m]^2$). MVL was defined as 42 cm^2/m^2 or less in males and 38 or less cm^2/m^2 in females [27]. The measuring process and results were confirmed by TTan of EPCH.

Assessment of AEs during Atez/Bev Treatment

The National Cancer Institute Common Terminology Criteria for Adverse Events, ver. 5.0 [28], was used for assessment of AEs. At the time of Atez/Bev discontinuation, introduction of the next treatment was determined by the attending physician.

After receiving official approval, this study was conducted as a retrospective analysis of database records based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures were done in accordance with the declaration of Helsinki. Written informed consent was received from each of the enrolled patients.

Statistical Analysis

Continuous variables are expressed as median values (interquartile range [IQR]). For statistical analyses, Student's *t* test, Welch's *t* test, a Mann-Whitney U test, the Kaplan-Meyer method, and a log-rank test were used. Univariate and multivariate analyses were conducted using Cox-hazard analysis to identify prognostic factors associated with progression-free survival (PFS) and overall survival (OS). Used variables included age (≥75 years), gender, etiology (nonviral), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (≥2), AFP (≥100 ng/mL), mALBI grade (≥2a), BCLC-C, line of use of Atez/Bev (first-line or later line), and existence of MVL. *p* values <0.05 were considered to indicate statistical significance. Easy-R (EZR), ver. 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [29], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used to perform all of the statistical analyses.

Results

For all 399 patients treated during the study period (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000527402), median PFS was 6.7 months (95% CI: 6.1–8.0) (1-year PFS rate: 30.4%) and median OS was nonestimable (NE) (95% CI: 14.3-not applicable [NA]) (1-year survival rate: 68.3%) (online suppl. Fig. 1a,b). Analyses of median PFS and OS according to mALBI grade showed 8.8 months and NE, respectively, for mALBI 1, 6.7 months and NE, respectively, for mALBI 2a, 6.0 months and NE, respectively, for mALBI 2b, and 3.3 and 7.3 months, respectively, for mALBI 3 ($p = 0.003$ and $p < 0.001$, respectively) (online suppl. Fig. 2a,b).

Of the total 399 patients, 229 could be assessed for muscle volume using CT data obtained at the baseline after exclusion of BCLC-D (median age 74 years [IQR: 68–80 years], male:female = 186:43, ECOG PS 0:1:2 = 179:42:8, HCV:HBV:alcohol:others = 81:33:40:75, Child-Pugh score 5:6:7:8 = 135:77:11:6, mALBI grade 1:2a:2b = 79:60:90, median ALBI score: −2.36 [IQR: −2.06 to −2.68], BCLC-0:A:B:C = 1:24:87:117, AFP [≥100 ng/mL] 95 [41.5%], median observation period 6.8 months [IQR: 3.6–10.2 months]). Patients in the MVL group ($n = 91$) showed worse PFS as compared to the non-MVL group ($n = 138$) (median PFS 7.6 months [95% CI: 6.2-NA] versus 5.3 months [95% CI: 4.5–8.0], $p = 0.025$), while OS was also worse in the MVL group (NE [95% CI: 14.3-NA] versus NE [95% CI: 10.2-NA], $p = 0.038$) (Fig. 1a, b). In addition, the frequencies of non-viral patients and body mass index values were lower in the MVL as compared to the non-MVL group, while there were no significant differences between the groups for other clinical factors, including BCLC stage, mALBI grade, and past history of previous systemic treatments with other tyrosine kinase inhibitors (TKI) or molecular targeting agents (MTA) (Table 1), or AE profiles (Table 2).

When assessment regarding therapeutic response was performed with RECIST, ver. 1.1, there were no significant differences between the groups for initial response evaluation (non-MVL: CR:PR:SD:PD = 3:24:78:18, objective response rate (ORR)/disease control rate (DCR) = 21.9%/85.4%; MVL: CR:PR:SD:PD = 2:15:47:22, ORR/DCR = 19.7%/74.4%, $p = 0.264$) and for best response judged by the attending physician (non-MVL: CR:PR:SD:PD = 5:23:68:18, ORR/DCR = 24.6%/84.2%; MVL: CR:PR:SD:PD = 2:17:43:23, ORR/DCR = 22.6%/73.8%, $p = 0.291$).

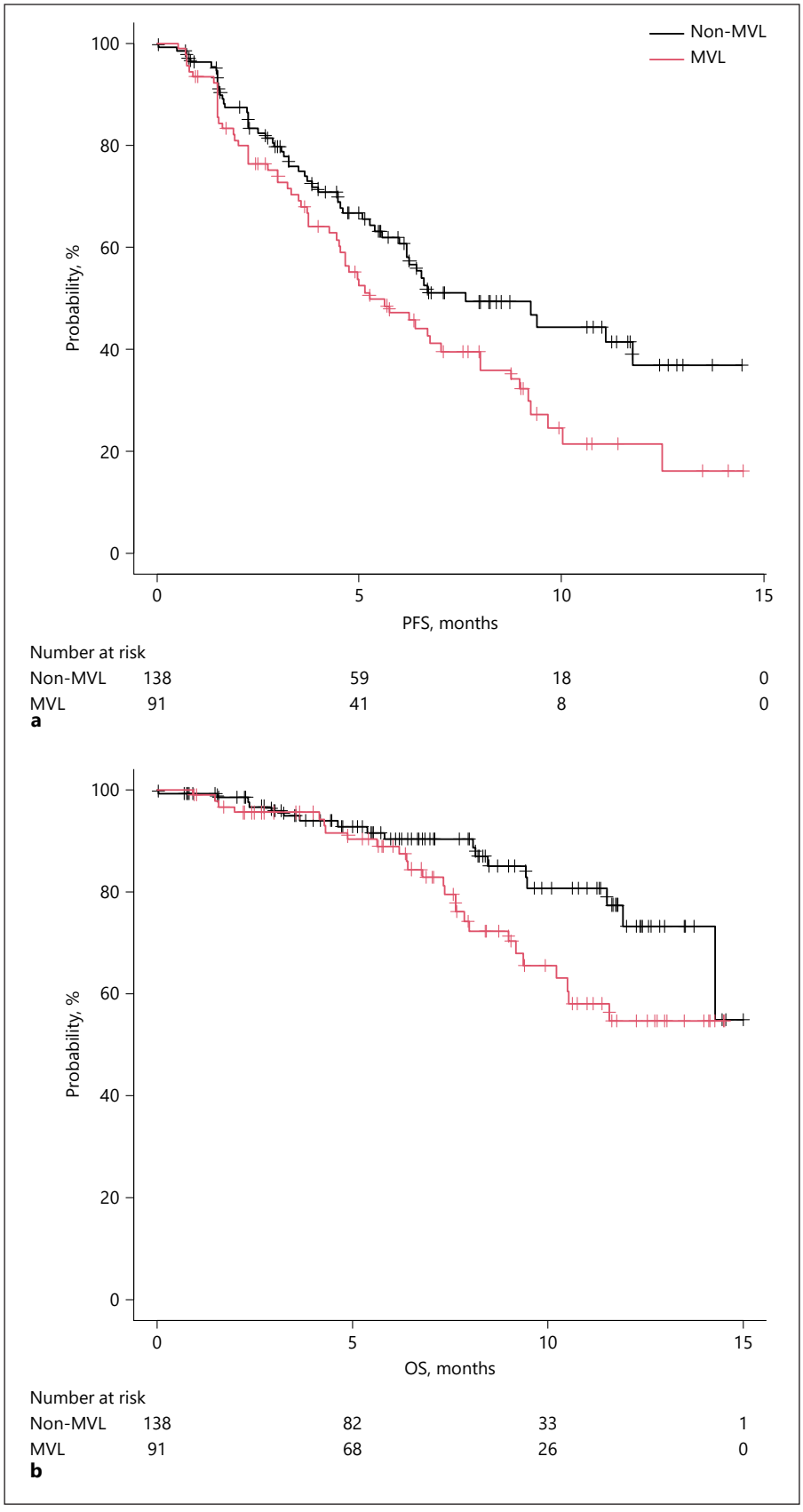

Fig. 1. Progression-free and overall survival in patients with and without muscle volume loss. **a** Patients with muscle volume loss (MVL group, n = 91) showed worse progression-free survival (PFS) than those without (non-MVL group, n = 138) (median PFS 7.6 (95% CI: 6.2-not applicable [NA]) versus 5.3 months (95% CI: 4.5–8.0), p = 0.025). **b** Overall survival was worse in the MVL group as compared to the non-MVL group (nonestimable (NE) (95% CI: 14.3-NA) vs. NE (95% CI: 10.2-NA), p = 0.038).

Table 1. Characteristics of non-MVL and MVL groups

	Non-MVL (n = 138)	MVL (n = 91)	p value
Age, years*	74 (68–80)	73 (70–79)	0.957
Gender, male:female	112:26	74:17	1.0
ECOG PS, 0/1:2	133:5	88:3	0.087
Body mass index, kg/m^2*	24.5 (22.2–26.6)	20.6 (19.1–22.6)	<0.001
Etiology, HCV:HBV:alcohol:others (viral:nonviral)	43:13:27:55 (56:82)	38:20:13:20 (58:33)	0.003 (0.001)
AST, U/L*	40 (27–58)	42 (31–59)	0.267
ALT, U/L*	27 (19–38)	31 (20–38)	0.554
Platelets, 10^4/μL*	13.4 (10.2–18.4)	14.2 (11.5–20.7)	0.077
T-bilirubin, mg/dL*	0.72 (0.52–1.00)	0.80 (0.60–1.00)	0.372
Albumin, g/dL*	3.7 (3.4–4.0)	3.7 (3.2–4.0)	0.248
Prothrombin time, %*	89.0 (80.0–98.0)	93.4 (85.0–100)	0.106
Creatinine, mg/dL*	0.82 (0.72–1.03)	0.79 (0.71–0.92)	0.147
eGFR, mL/min/1.73 m^2*	65.2 (51.4–0.1)	71.2 (59.2–77.6)	0.062
ALBI score at baseline*	−2.37 (−2.12 to −2.7)	−2.34 (−1.99 to −2.67)	0.231
mALBI 1:2a:2b	46:40:52	33:20:38	0.427
Child-Pugh score 5:6:7:8	84:46:4:4	51:31:7:2	0.399
Maximum intrahepatic tumor size, cm*	2.9 (1.7–5.7)	3.0 (1.6–5.9)	0.657
BCLC-0:A:B:C	1:16:55:66	0:8:32:51	0.588
AFP (≥100 ng/mL) (%)	50 (36.2%)	45 (49.5%)	0.055
Use line of Atez/Bev, First-line:later line	89:49	47:44	0.177
Died (%)	18 (13.0%)	26 (28.6%)	0.006
Observation period, months*	6.3 (3.1–9.64)	7.6 (5.1–10.6)	0.047

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCV, hepatitis C virus; HBV, hepatitis B virus; AST, aspartate transaminase; ALT, alanine aminotransferase; ALBI score, albumin-bilirubin score; mALBI grade, modified ALBI grade; BCLC, Barcelona Clinic Liver Cancer stage; AFP, alpha-fetoprotein; Atez/Bev, atezolizumab plus bevacizumab treatment. * Median. Values in parentheses show interquartile range, unless otherwise indicated.

Table 2. AEs in non-MVL and MVL groups (all grades: ≥10%)

	All (n = 229)	Non-MVL (n = 138)	MVL (n = 91)	p value
General fatigue (grade 0:1:2:3)	174:36:15:4	107:17:12:2	67:19:3:2	0.133
Appetite loss (grade 0:1:2:3)	177:27:16:9	110:14:9:5	67:13:7:4	0.719
Hypertension (grade 0:1:2:3)	183:14:19:13	114:11:8:5	69:3:11:8	0.062
Protein urine (grade 0:1:2:3)	184:25:11:9	117:6:8:7	67:19:3:2	0.107
Hepatic function abnormality (grade 0:1:2:3:4)	203:14:6:5:1	124:9:3:1:1	79:5:3:4:0	0.346

MVL, muscle volume loss. There were no significant differences in fever (G0:1:2:3 = 125:3:8:2 vs. 82:3:5:1. p = 0.969), bleeding (G0:1:2:3:4:5 = 132:2:0:1:2:1 vs. 88:0:1:2:0:0, p = 0.433), and skin reaction (G0:1:2 = 132:3:3 vs. 87:3:1, p = 0.780) between the MVL- and non MVL-groups.

In Cox-hazard analysis of prognostic factors for PFS, ECOG PS (≥2) (HR 3.641, 95% CI: 1.580–8.394, p = 0.002), elevated AFP (≥100 ng/mL) (HR 2.108, 95% CI: 1.454–3.056, p < 0.001), mALBI grade (≥2a) (HR 1.640, 95% CI: 1.092–2.415, p = 0.017), BCLC-C (HR 1.549, 95% CI: 1.061–2.261, p = 0.024), and existence of MVL (HR 1.516, 95% CI: 1.048–2.194, p = 0.027) were found to be significant prognostic factors in univariate analysis, while elevated AFP (≥100 ng/mL) (HR 1.848, 95% CI: 1.264–2.702, p = 0.002), mALBI grade (≥2a) (HR 1.563, 95% CI: 1.035–2.359, p = 0.034), and existence of MVL (HR 1.479, 95% CI: 1.020–2.144, p = 0.039) were significant in multivariate analysis results (Table 3). Furthermore, in Cox-hazard analysis of prognostic factors for OS, elevated AFP (≥100 ng/mL) (HR 3.453, 95% CI: 1.806–6.599, p < 0.001), mALBI grade (≥2a) (HR 3.123, 95% CI:

Table 3. Cox-hazard analyses of PFS and OS

a PFS	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (≥75 years)	1.256	0.865–1.823	0.231			
Female	0.637	0.370–1.097	0.104			
Etiology (nonviral)	1.118	0.772–1.619	0.556			
ECOG PS (≥2)	3.641	1.580–8.394	0.002	2.332	0.988–5.509	0.053
AFP (≥100 ng/mL)	2.108	1.454–3.056	<0.001	1.848	1.264–2.702	0.002
mALBI grade (≥2a)	1.640	1.092–2.465	0.017	1.563	1.035–2.359	0.034
BCLC-C	1.549	1.061–2.261	0.024	1.341	0.909–1.977	0.140
Use of Atez/BemALBI'mALBIv (later line)	0.954	0.657–1.384	0.803			
Existence of MVL	1.516	1.048–2.194	0.027	1.479	1.020–2.144	0.039
b OS	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (≥75 years)	1.034	0.569–1.879	0.913			
Female	0.611	0.240–1.557	0.302			
Etiology (nonviral)	0.805	0.444–1.460	0.475			
ECOG PS (≥2)	2.046	0.631–6.613	0.234			
AFP (≥100 ng/mL)	3.453	1.806–6.599	<0.001	3.564	1.856–6.844	<0.001
mALBI grade (≥2a)	3.123	1.446–6.750	0.004	3.451	1.580–7.538	0.002
BCLC-C	1.172	0.637–2.156	0.611			
Use of Atez/Bev (later line)	1.023	0.562–1.862	0.941			
Existence of MVL	1.869	1.024–3.409	0.042	2.119	1.150–3.904	0.016

PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AFP, alpha-fetoprotein; mALBI, modified albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer stage; Atez/Bev, atezolizumab plus bevacizumab treatment; MVL, muscle volume loss.

1.446–6.750, $p = 0.004$), and existence of MVL (HR 1.869, 95% CI: 1.024–3.409, $p = 0.042$) were significant prognostic factors in univariate analysis, while elevated AFP (≥100 ng/mL) (HR 3.564, 95% CI: 1.856–6.844, $p < 0.001$), mALBI grade (≥2a) (HR 3.451, 95% CI: 1.580–7.538, $p = 0.002$), and existence of MVL (HR 2.119, 95% CI: 1.150–3.904, $p = 0.016$) were significant prognostic factors in multivariate analysis results (Table 3).

After exclusion of patients treated with Atez/Bev as beyond PD treatment after progression confirmation, reasons of discontinuation of Atez/Bev were PD ($n = 42$, 76.4%) and AE including 1 immunoreactive AE (interstitial pneumonia) ($n = 21$, 38.2%), and hepatic failure ($n = 4$, 7.3%) in discontinuation of Atez/Bev patients of the non MVL-group ($n = 55$) (There are duplicate cases), while PD ($n = 41$, 75.9%), AE including 3 immunoreactive AE (2 hepatic function abnormality, and 1 colitis), ($n = 10$, 18.5%), and hepatic failure ($n = 5$, 9.3%) in those of the MVL-group ($n = 54$). Migration rates to posttreatment after discontinuation of Atez/Bev were 60.0% (TKI/MTA:interventional radiology = 24:6) and 68.0% (TKI/MTA:interventional radiology = 23:9) in non-MVL group and in the MVL-group ($p = 0.659$).

Discussion

In the present study, existence of MVL at the time of introduction of Atez/Bev was found to be a significant prognostic factor for poor PFS and OS in u-HCC patients. Atez/Bev is the first combination of an immune-check point inhibitor (ICI) and anti-vascular endothelial growth factor (anti-VEGF) developed for treating u-HCC, though no known report has shown a relationship between Atez/Bev and MVL. Although some previous studies have found that MVL is a negative prognostic factor

in patients receiving sorafenib [4–7] or lenvatinib [8, 9], to the best of our knowledge, this is the first investigation to evaluate the relationship between MVL and Atez/Bev in patients with u-HCC. Results of meta-analysis reported by Chang et al. [30] showed that MVL has a large prognostic role in regard to recurrence following curative resection (crude HR = 1.85, 95% CI: 1.44–2.37; adjusted HR = 1.76, 95% CI: 1.27–2.45), as well as OS in patients treated with either a curative or palliative method (crude HR = 2.04, 95% CI: 1.74–2.38; adjusted HR = 1.95, 95% CI: 1.60–2.37). Furthermore, those authors described stratified analysis findings showing that inclusion of body mass index or body weight in the Cox regression model did not modify either of those clinical outcomes.

As for cases other than HCC, a prognostic relationship between ICI and MVL has been reported. MVL was found to be a prognostic marker for worse PFS and OS in patients receiving ICI treatment for non-small cell lung cancer (MVL vs. non-MVL, PFS: 2.1 vs. 6.8 months, p = 0.004) [31] and advanced cancers, such as NSCLC, melanoma, renal cell carcinoma, and others (shorter OS: HR 2.19, 95% CI: 1.31–3.64, p = 0.0026) [32]. Also, a meta-analysis to examine the relationship between ICI treatment and MVL in NSCLC patients revealed that MVL was a prognostic factor not only for PFS (HR 1.61, 95% CI: 1.24–2.10) but also for OS (HR 1.98, 95% CI: 1.32–2.97) [33], while meta-analysis findings of patients with malignancy and treated with ICI showed that MVL was related with poor ORR (OR 0.46, 95% CI: 0.28–0.74, p = 0.001), DCR (OR 0.44, 95% CI: 0.31–0.64, $p < 0.0001$), PFS (HR 1.46, 95% CI: 1.20–1.78, $p = 0.0001$), and OS (HR 1.73, 95% CI: 1.36–2.19, $p < 0.0001$) [34]. Although the reasons of discontinuation of Atez/Bev were similar in both groups and migration rates to post treatment of Atez/Bev discontinuation did not show significant difference between both group, analysis of the present results indicated that MVL also has a large role as an important prognostic factor in Atez/Bev treatment for u-HCC as well as in ICI treatment for other malignancies.

MVL has been defined as pre-sarcopenia status by the European Working Group on Sarcopenia in Older People [35]. Additionally, Khaddour et al. mentioned that there is an enough production of IL-15, which connect with receptors of natural killer cell and T-cell and enhance activities of antitumor effect in status without sarcopenia, while reduction of IL-15 production of muscle and chronic inflammatory by IL-6 and TGF-β are observed and inhibiting mTOR as a result of them makes functions of natural killer cell and T-cell dysfunction in status with sarcopenia [36]. Thus, MVL is thought to be very important biological prognostic marker for poorer prognosis in ICI treatment also against u-HCC as well as other malignancies.

Cheng et al. [36] reported that MVL was related to post-progression outcome in advanced HCC cases after sorafenib failure. When considering post-progression treatment, MVL is an important factor. Terashima et al. [37] reported that post-progression survival is more important than PFS for prolonging the prognosis of u-HCC patients. Following Atez/Bev failure in u-HCC patients, it is considered that TKI and MTA, i.e., sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib, each available in Japan at December 2021, will have increasingly vital roles to improve prognosis and sequential systemic treatments increased importance. Since Child-Pugh class A patients have been shown to have a greater percentage of post-progression survival in OS as compared to Child-Pugh class B (54.4 ± 17.6% vs. 32.0 ± 11.6%, p = 0.015) [37], it is important to keep in mind introduction of such treatments as TKI/MTA as a later line after Atez/Bev in cases showing better hepatic reserve function. Although mALBI grade could stratify for PFS and OS in u-HCC patients treated with Atez/Bev, the prognostic importance of mALBI grade in relation to Atez/Bev might be slightly different from that in relation to TKI/MTA treatments because there was no difference in OS between u-HCC patients with mALBI 1 and mALBI 2a in lenvatinib treatment (median PFS: 9.8 months vs. 8.0 months, and median OS: 21.0 months vs. 20.0 months) [38]. The present results showed that mALBI grade 1 (ALBI 1) had an overwhelming prognostic impact in Atez/Bev in contrast to TKI/MTA cases. On the other hand, patients with mALBI grade 1 or 2a, which is a more detailed assessment tool than Child-Pugh classification, are considered a minimum requirement to obtain better prognosis in TKI/MTA therapy. There might be a difference TKI/MTA monotherapy and Atez/Bev combination treatment cases regarding the clinical role of hepatic reserve function. Although Atez/Bev has a limited negative influence on hepatic function, with the majority of patients maintaining liver reserve during the course of Atez/Bev treatment [11, 39], it is important to maintain nutritional status in patients undergoing that treatment because introducing in the condition with better hepatic function (mALBI 1 or 2a) is considered to be important in TKI/MTA treatments [40–43] to improve prognosis when sequential treatment using TKI/MTA drugs are given as post-progression therapy following Atez/Bev failure. Presently, it is not clear that the reason of the relationship between mALBI grade and prognosis is slightly

different between Atez/Bev treatment and TKI treatment. However, based on the present study, the optimal liver reserve for the introduction of Atez/Bev treatment is considered to be mALBI 1, but considering that Atez/Bev treatment has little effect on liver reserve [11, 39], we need to be aware that it should be introduced at least at mALBI 2a to increase the chance of treatment after progression of Atez/Bev with TKI/MTA drugs.

This study has some limitations, including its retrospective nature. Furthermore, there was no assessment of relative change in skeletal muscle index during Atez/Bev treatment or its influence. Additional studies with a larger number of patients are needed in the near future. In conclusion, the present findings indicate that MVL may be an important clinical factor related to worse prognosis in patients undergoing Atez/Bev treatment for u-HCC.

Statement of Ethics

The entire study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (No. 30–66). After receiving official approval, this study was conducted as a retrospective analysis of database records based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures were done in accordance with the declaration of Helsinki. The data were made anonymous before analysis to protect patient privacy. Written informed consent was obtained from all patients before treatment and this study received ethical approval for use of an opt-out methodology based on low risk to the participants.

Conflict of Interest Statement

Atsushi Hiraoka, MD, PhD: lecture fees; Chugai and Eli Lilly. Takashi Kumada, MD, PhD: lecture fees; Eisai. None of the other authors have potential conflicts of interest to declare. Masatoshi Kudo, MD, PhD – Advisory role: Eiasi, Ono, MSD, Bristol-Myers Squibb, Roche; Lecture fees: Eisai, Bayer, MSD, Bristol-Myers Squibb, Eli Lilly, EA Pharma; Research funding: Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda, Otsuka, EA Pharma, Abbvie, Eisai. Prof. Kudo is the Editor-in-Chief of Liver Cancer and Dr. Nouso an Editorial Board Member of Liver Cancer. None of the other authors have potential conflicts of interest to declare.

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Author Contributions

Atsushi Hiraoka and Takashi Kumada conceived the study, drafted the text, and participated in its design and coordination. Atsushi Hiraoka, Toshifumi Tada, Masashi Hirooka, Kazuya Kariyama, Joji Tani, Masanori Atsukawa, Koichi Takaguchi, Ei Itobayashi, Shinya Fukunishi, Kunihiko Tsuji, Toru Ishikawa, Kazuto Tajiri, Hironori Ochi, Satoshi Yasuda, Hidenori Toyoda, Chikara Ogawa, Takashi Nishimura, Takeshi Hatanaka, Satoru Kakizaki, Noritomo Shimada, Kazuhito Kawata, Atsushi Naganuma, Masaki Kaibori, Takaaki Tanaka, Hideko Ohama, Kazuhiro Nouso, Asahiro Morishita, Akemi Tsutsui, Takuya Nagano, Norio Itokawa, Tomomi Okubo, Taeang Arai, Michitaka Imai, Yohei Koizumi, Shinichiro Nakamura, Kouji Joko, Hiroko Iijima, Hisashi Kosaka, Yoichi Hiasa, and Masatoshi Kudo performed data curation. Atsushi Hiraoka performed statistical analyses and interpretation. All authors have read and approved the final version of the manuscript.

Data Availability Statement

Due to the nature of this research, participants in this study could not be contacted regarding whether the findings could be shared publicly, thus supporting data are not available. The datasets generated and/or analyzed for the current study are not publicly available due to the nature of the research, as noted above. Further inquiries can be directed to the corresponding author.

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