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Original article

Concurrent low skeletal muscle mass and fat area may predict poor survival in patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab therapy

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SUMMARY

Background & aims: Combination immunotherapy is the standard first-line treatment for hepatocellular carcinoma. Body composition may affect treatment outcomes; however, the prognostic relevance of skeletal muscle and adipose tissue during immunotherapy remains unclear. We aimed to determine whether integrating skeletal muscle and adipose tissue measurements stratifies survival outcomes in patients with hepatocellular carcinoma receiving atezolizumab plus bevacizumab therapy.
Methods: In this retrospective cohort study, conducted at nine institutions, body composition was assessed using the body mass index, skeletal muscle index at the L3 level, and total fat area at the umbilical level. L3 skeletal muscle index was dichotomized using sex-specific cutoffs, and body mass index and total fat area were dichotomized at the cohort median values.
Results: Japanese patients (n = 445, 74 years median age; 80.4% men) were included. In this cohort, median body mass index, L3 skeletal muscle index (men/women), and total fat area were 23.3, 44.0/37.6 cm^2/m^2, and 262.8 cm^2, respectively. The response rate was 33.0%; the median progression-free and overall survival were 8.4 and 25.1 months, respectively. Low body mass index, L3 skeletal muscle index, and total fat area were associated with poorer overall survival. In the L3 skeletal muscle index × total fat area analysis, the low muscle/low fat group had the poorest overall survival. Per multivariable analysis, this body composition was an independent predictor of poor prognosis.

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Conclusions: Concurrent low skeletal muscle mass and fat area may predict poor prognosis in patients with hepatocellular carcinoma receiving atezolizumab plus bevacizumab therapy. Baseline body composition profiling may aid in risk stratification of these patients.

1. Introduction

Hepatocellular carcinoma (HCC) has high incidence and mortality rates worldwide and often develops in the context of chronic liver disease progression [1]. Systemic therapy for HCC was previously dominated by molecular targeted agents such as sorafenib and lenvatinib; however, in recent years, combination immunotherapy based on immune checkpoint inhibitors (ICIs) has become the cornerstone of first-line treatment [2]. The leading first-line combinations in clinical practice are currently PD-1/PD-L1 antibodies paired with either VEGF inhibitors or CTLA-4 antibodies [2]. Atezolizumab plus bevacizumab therapy (Atezo/Bev) [3] and durvalumab plus tremelimumab therapy (Durva/Treme) [4], as well as nivolumab plus ipilimumab therapy [5], are the recommended first-line regimens. The European Society for Medical Oncology guidelines assign a high recommendation level to Atezo/Bev and Durva/Treme [6]. Atezo/Bev was the first combination immunotherapy to demonstrate a significant overall survival (OS) benefit over sorafenib [3,7], making it the most widely used first-line regimen, supported by approximately 5 years of real-world experience.

However, the epidemiological patterns of HCC etiology have recently changed. Advances in antiviral therapy have reduced the proportion of viral HCC due to hepatitis B and C, whereas that of non-viral HCC, such as that associated with alcohol-related liver disease and metabolic dysfunction-associated steatohepatitis, has increased [8,9]. Additionally, the patient population is aging, making comprehensive assessment of tumor factors, hepatic reserve capacity, systemic conditions, and body composition increasingly important in treatment decision-making. As the liver is a central organ for nutrition and metabolism, the evaluation of the clinical significance of body composition markers in HCC treatment is highly relevant. Height and weight are simple indicators of body composition, while body mass index (BMI) is widely used to assess obesity or underweight status. Obesity has been reported as a carcinogenic risk factor, including for HCC [10,11]. However, some studies have suggested that older patients and those with certain chronic comorbidities may have better survival at high BMI, a phenomenon known as the “obesity paradox” [12–15]. This highlights the complex relationship between body composition and cancer prognosis.

Body weight is largely determined by skeletal muscle and adipose tissue, which differ substantially in their metabolic functions. Muscle depletion is associated with poor survival not only in patients receiving molecular targeted therapies, such as sorafenib and lenvatinib [16–20], but also in patients receiving immunotherapy [21,22]. On the other hand, reports on adipose tissue in immunotherapies are rare. Thus, a comprehensive assessment of body composition incorporating skeletal muscle mass and fat area may provide new insights into predicting immunotherapy efficacy. This study aimed to clarify the impact of skeletal muscle mass and fat area on treatment efficacy and prognosis in patients with unresectable HCC receiving the Atezo/Bev therapy.

2. Materials & methods

2.1. Study design

This multicenter, retrospective study included nine institutions that participated in a domestic multicenter collaborative research group (Yamaguchi University Hospital, Okayama University Hospital, Kurume University Hospital, Kagawa University Hospital, Nagoya University Hospital, Nagasaki University Hospital, Kawasaki Medical School Hospital, Gunma Saiseikai Maebashi Hospital, and Takasaki General Medical Center). Body composition marker data were collected at all institutions. All patients were staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system. The up-to 7 criteria [23] was calculated as the sum of the maximum tumor diameter (in cm) and the number of tumors; patients with a sum of $\leq$7 were classified as “in,” whereas those with a sum of >7 were classified as “out.” The treatment evaluation criteria included imaging assessment based on the RECIST criteria ver. 1.1 [24] and OS/progression free survival (PFS). Body composition markers consisted of BMI, third lumbar spine skeletal muscle index (L3-SMI) calculated as the skeletal muscle area at the L3 level on pre-treatment computed tomography (CT) scans divided by height squared [25], and total fat area (FA) defined as the sum of visceral (VFA) and subcutaneous fat (SFA) at the umbilical level [26].

Nine institutions participated in this study, and several CT scanner models were used (SOMATOM go.Top, SOMATOM Force, SOMATOM Definition Flash, SOMATOM Drive, and NAEOTOM Alpha [Siemens Healthineers, Munich, Germany]; Aquilion Prime SP-i, Aquilion Precision, Aquilion ONE, Aquilion ONE INSIGHT, Aquilion ONE ViSION Edition, Aquilion Prime SP, and Aquilion Serve SP [Canon Medical Systems, Tokyo, Japan]; Revolution CT, Revolution Apex, and Optima CT660 [GE Healthcare, Buckinghamshire, England]; and Brilliance CT Scanners [Koninklijke Philips N.V., Amsterdam, the Netherlands]). To minimize inter-scanner variability in body composition measurements, slice thickness was limited to $\leq$5 mm, and CT acquisition and reconstruction parameters were standardized across scanners as much as possible. Tube voltage (100–120 kVp) and automatic tube current modulation were adjusted for each patient according to body habitus and clinical indication. All scans were performed with patients in the supine position during end-inspiratory breath-hold. Body composition parameters were obtained using non-contrast CT images. We selected the slice that best visualized the transverse process of the L3 vertebral body and umbilical depression. Skeletal muscle and fat areas were measured using SYNAPSE VINCENT (Fujifilm Healthcare Corporation, Tokyo, Japan). Skeletal muscle and adipose tissue were identified using Hounsfield Unit (HU) thresholds (skeletal muscle: −29 to +150 HU; adipose tissue: −190 to −30 HU; Fig. S1) [27,28]. L3-SMI and FA data obtained at each institution were compiled at Yamaguchi University. CT data were compiled at Yamaguchi University for institutions that could not perform CT assessments. At the central site, a single trained researcher (M.E.; hepatologist) measured 172 cases from five institutions. In the remaining four institutions,

measurements were performed by 1–2 trained researchers (hepatologists or radiologic technologists) per site. We examined the associations between body composition factors and clinical outcomes. The data collection cut-off date was November 30, 2024. All clinical data were anonymized, collected at Yamaguchi University, and analyzed.

2.2. Patients

Among 764 patients in the research group who received Atezo/Bev for unresectable HCC between October 2020 and April 2024, those treated with Atezo/Bev as a first-line systemic therapy were eligible for inclusion. From this cohort, 445 Japanese patients were analyzed after excluding individuals without imaging evaluation, those without a CT scan within 1 month prior to treatment initiation (preventing the assessment of body composition), those with a performance status (PS) of ≥3, and those with Child–Pugh class C (Fig. S2).

2.3. Treatment

The treatment protocol for combination immunotherapy followed the dosage regimen used in a previous clinical trial [3]. Atezo/Bev was administered intravenously every 3 weeks as atezolizumab 1200 mg/body and bevacizumab 15 mg/kg. Dose reduction, interruption, or adjustment of the dosing interval was permitted based on the patient's clinical condition. The initial evaluation was performed at week 6 using contrast-enhanced CT or contrast-enhanced magnetic resonance imaging scans, followed by subsequent evaluations every 6–12 weeks. The treatment was continued until disease progression or uncontrollable adverse events occurred.

2.4. Ethical statement

This study was conducted as an exploratory analysis of a clinical database, in accordance with the "Guidelines for Clinical Research" by the Ministry of Health, Labor and Welfare, and was approval by the ethics committees of Kurume University School of Medicine (approval code 23153) and all participating institutions. The study design followed the principles of the Declaration of Helsinki. Research information was publicly disclosed on the institutional websites, allowing patients and other stakeholders to opt out.

2.5. Statistical analysis

Continuous variables are expressed as medians (interquartile range) and were compared using nonparametric tests. Categorical variables are expressed as frequencies (%) and were compared using the chi-square test. The objective response rate (ORR) was defined as complete response (CR) plus partial response (PR) divided by the total number of CR, PR, stable disease (SD), and progressive disease (PD) cases. OS was defined as the time from treatment initiation to death or last follow-up. PFS was defined as the time from treatment initiation to disease progression or death. Prognosis was evaluated using the Kaplan–Meier curves and compared using the log-rank test. Multicollinearity among body composition variables was assessed using the Correlation of Estimates, an index that evaluates linear dependence among regression coefficients. Cutoff values for body composition markers were set as follows: 42/38 cm^2/m^2 for L3-SMI (men/women) based on the Japanese criteria [25], while BMI and FA were dichotomized using their median values. Prognostic factors were analyzed using the Cox proportional hazards model. All statistical analyses were performed using the JMP software (ver. 17.0; SAS Institute, Cary, NC, USA), with statistical significance set at $p < 0.05$.

3. Results

3.1. Patients

Patients' background characteristics are summarized in Table 1. The median age was 74 years, and 358 (80.4%) patients were men. The etiologies were hepatitis B virus (positive for hepatitis B surface antigen) in 44 (9.9%) patients, hepatitis C virus (positive for hepatitis C virus antibody) in 147 (33.0%) patients, and non-viral (negative for both hepatitis B surface antigen and hepatitis C virus antibody) in 254 (57.1%) patients. Liver function was classified as Child–Pugh class A in 404 (90.8%) patients and class B in 41 (9.2%) patients. The BCLC stage was A in 25 (5.6%) patients, B in 195 (43.8%) patients, and C in 225 (50.6%) patients. Median baseline body composition indices were as follows: BMI, 23.3 kg/m^2; L3-SMI, 44.0 cm^2/m^2 in men and 37.6 cm^2/m^2 in women; FA, 262.8 cm^2 (VFA 125.3 cm^2 and SFA 125.6 cm^2).

3.2. Relationship among body composition markers

First, we examined simple correlations among body composition variables. Strong correlations were observed between BMI and L3-SMI ($r = 0.683$) and between BMI and FA ($r = 0.800$). In contrast, the correlation between L3-SMI and FA was moderate ($r = 0.477$; Fig. 1A–C). Second, we assessed multicollinearity within the multivariable regression model, which reflects linear dependence among predictors after adjustment for other covariates. Under the assumption of linear dependence, the regression estimates for BMI showed notable correlations with those for FA (−0.738) and L3-SMI (−0.571). In contrast, the correlation

Table 1
Patient characteristics.

	Total ($n = 445$)
Age, median (IQR)	74 (69–80)
Sex, *n (%)*	
Men	358 (80.4)
Etiology, *n (%)*	
HBV	44 (9.9)
HCV	147 (33.0)
Non-viral	254 (57.1)
ECOG-PS, *n (%)*	
0	350 (78.7)
1	77 (17.3)
2	18 (4.0)
Child-Pugh class, *n (%)*	
A	404 (90.8)
B	41 (9.2)
BCLC stage, *n (%)*	
A	25 (5.6)
B	195 (43.8)
C	225 (50.6)
Macrovascular invasion, *n (%)*	112 (25.2)
Extrahepatic spread, *n (%)*	131 (29.4)
BMI [kg/m^2]	23.3 (21.0–25.9)
L3-SMI [cm^2/m^2]	
Men	44.0 (39.2–49.2)
Women	37.6 (33.1–41.6)
FA [cm^2]	262.8 (179.1–334.3)
VFA [cm^2]	125.3 (78.1–171.9)
SFA [cm^2]	125.6 (86.1–167.6)

HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; L3-SMI, third lumbar spine skeletal muscle index; FA, fat area; VFA, visceral fat area; SFA, subcutaneous fat area.

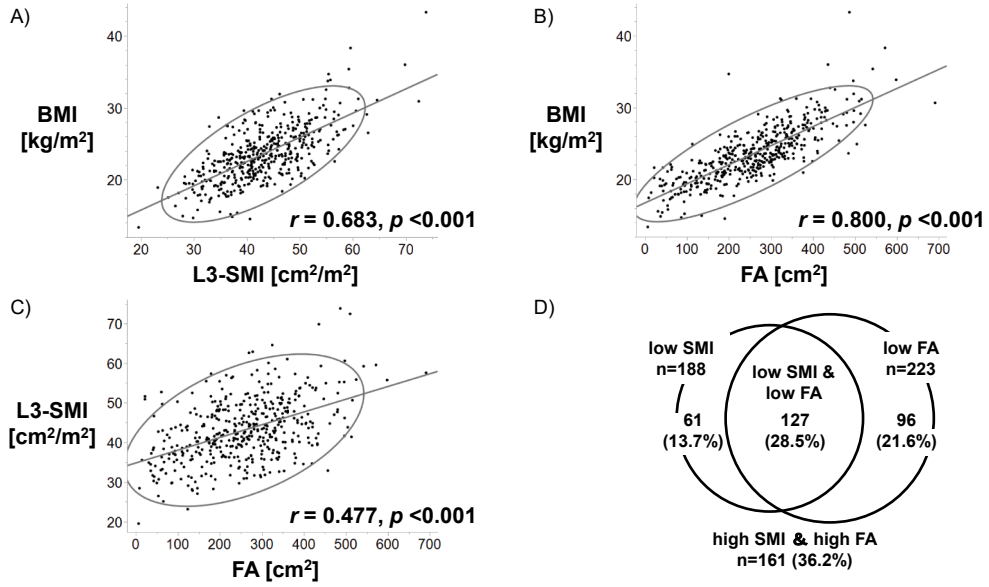

Fig. 1. Relationship among body composition factors
A) Body mass index (BMI) vs. the third lumbar spine skeletal muscle index (L3-SMI). B) BMI vs. total fat area (FA). C) L3-SMI vs. FA. D) Venn diagram of the relativity of L3-SMI and FA.

between the regression estimates for L3-SMI and FA was low (0.157), suggesting that not all variables exhibited strong collinearity. In a standard least-squares model, the standard errors (SEs) of the regression estimates did not show abnormal inflation (BMI: 0.691 [SE 0.265], L3-SMI: −0.143 [SE 0.089], FA: −0.004 [SE 0.007]). These findings indicate that the estimates remained stable and that dichotomization of L3-SMI and FA effectively minimized multicollinearity among the continuous variables. Based on these findings, we concluded that using categorical variables combining L3-SMI and FA prevents multicollinearity from influencing the multivariable analyses. Classification using pre-defined cutoff values (FA: 263.0 cm^2 and sex-specific L3-SMI thresholds) showed that 42.2% and 50.1% of the patients were classified as having "low" L3-SMI and FA, respectively, indicating an approximately even distribution. A Venn diagram summarizing the prevalence of each factor (Fig. 1D) showed that 28.5% of the patients had low values for both SMI and FA (low SMI and low FA; LL), 36.2% had high values for both SMI and FA (high SMI and high FA; HH), and 35.3% had low values for only one of the two indicators (high SMI and low FA or low SMI and high FA; mixed [MX]).

3.3. Treatment efficacy with a focus on body composition

The overall maximum anti-tumor effects were CR, PR, SD, PD in 12 (2.7%), 135 (30.3%), 209 (47.0%), and 89 (20.0%) patients, respectively. The median OS was 25.1 months (95% confidence interval [CI]: 22.8–30.5), and median PFS was 8.4 months (95% CI: 7.0–9.7; Fig. 2A, B). The ORR did not differ between patients with high and low body compositions (high vs. low BMI, ORR: 32.5 vs. 33.7%, p = 0.794; high vs. low SMI, 32.7 vs. 33.5%, p = 0.855; high vs. low FA, 35.1 vs. 30.9%, p = 0.347). OS was well-stratified by the cutoff values of each body composition marker: BMI, SMI, and FA (high vs. low BMI, median OS: 29.8 vs. 22.1 months, p = 0.009; high vs. low SMI, 26.3 vs. 22.7 months, p = 0.046; high vs. low FA, 31.3 vs. 22.7 months, p = 0.023; Fig. 3A–C). Similarly, PFS showed a favorable trend in the high-value groups for BMI, SMI, and FA, although no statistically significant differences were observed compared with OS (high vs. low BMI; median PFS 9.1 vs. 7.5 months, p = 0.133; high vs. low SMI; 9.1 vs. 7.2 months, p = 0.067; high vs. low FA; 10.0 vs. 7.2 months, p = 0.146; Fig. 3D–F). The analysis combining L3-SMI and FA factors into four groups (HH vs. high SMI & low FA vs. low SMI & high FA vs. LL) revealed a median OS of 29.8, 26.3, 32.7, and 19.1 months (p = 0.051), respectively (Fig. S3). Survival curves for groups with low SMI or low FA (high SMI & low FA or low SMI & high FA) were similar (p = 0.821) and were grouped as MX. When comparing the prognosis among the three body composition groups (HH vs. MX vs. LL), the LL group showed the poorest OS (Fig. 4A). Furthermore, the LL group had a poorer OS than that of the other (HH plus MX) group (19.1 vs. 28.5 months, p = 0.009, Fig. 4B).

3.4. Analysis of factors contributing to OS

Univariate and multivariable analyses were performed to identify the factors contributing to OS, including body composition. Univariate analysis identified PS (p = 0.003), Child–Pugh class (p < 0.001), BCLC stage (p < 0.001), macrovascular invasion (p = 0.005), extrahepatic spread (p = 0.019), up-to 7 (p = 0.029), BMI (p = 0.010), L3-SMI (p = 0.047), and FA (p = 0.024) as prognostic factors, along with LL (p = 0.007: vs. HH) as a clearly poor survival factor (Table 2). Furthermore, we performed multivariable analysis using seven factors considering the potential collinearity among significant factors in the univariate analysis. Four factors (Child–Pugh class, macrovascular invasion, extrahepatic spread, and body composition; LL) were selected as factors contributing to OS. The LL group showed a poorer prognosis than that of the HH (hazard ratio [HR] = 1.464, 95% CI: 1.012–2.119, p = 0.043) and MX (HR = 1.461, 95% CI: 1.014–2.106, p = 0.042) groups. However, no significant differences were observed between the MX and HH groups (HR = 1.002; 95% CI: 0.682–1.457; p = 0.991).

3.5. Characteristics of the LL group

A comparison of patient backgrounds between the LL and other groups (HH and MX) revealed that the LL group had a higher proportion of patients with viral HCC (LL vs. others; 52.8% vs.

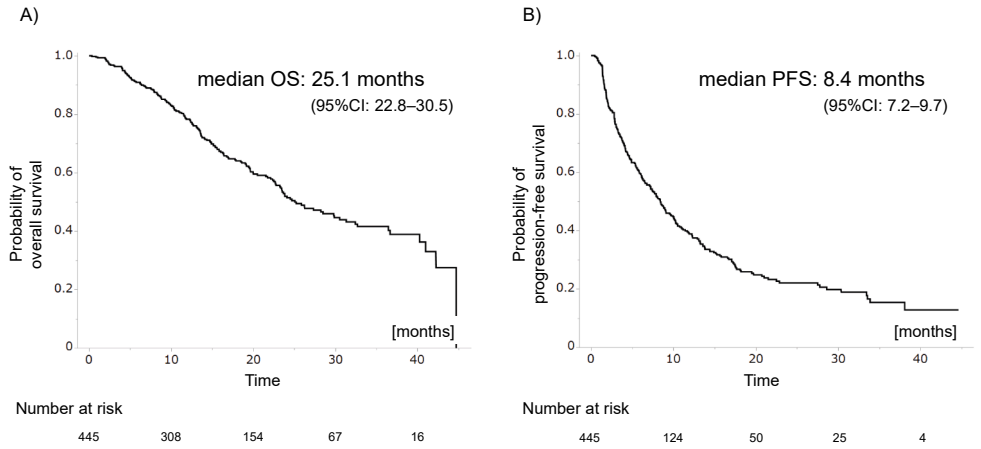

Fig. 2. Cumulative survival curves
A) Overall survival (OS). B) Progression-free survival (PFS).

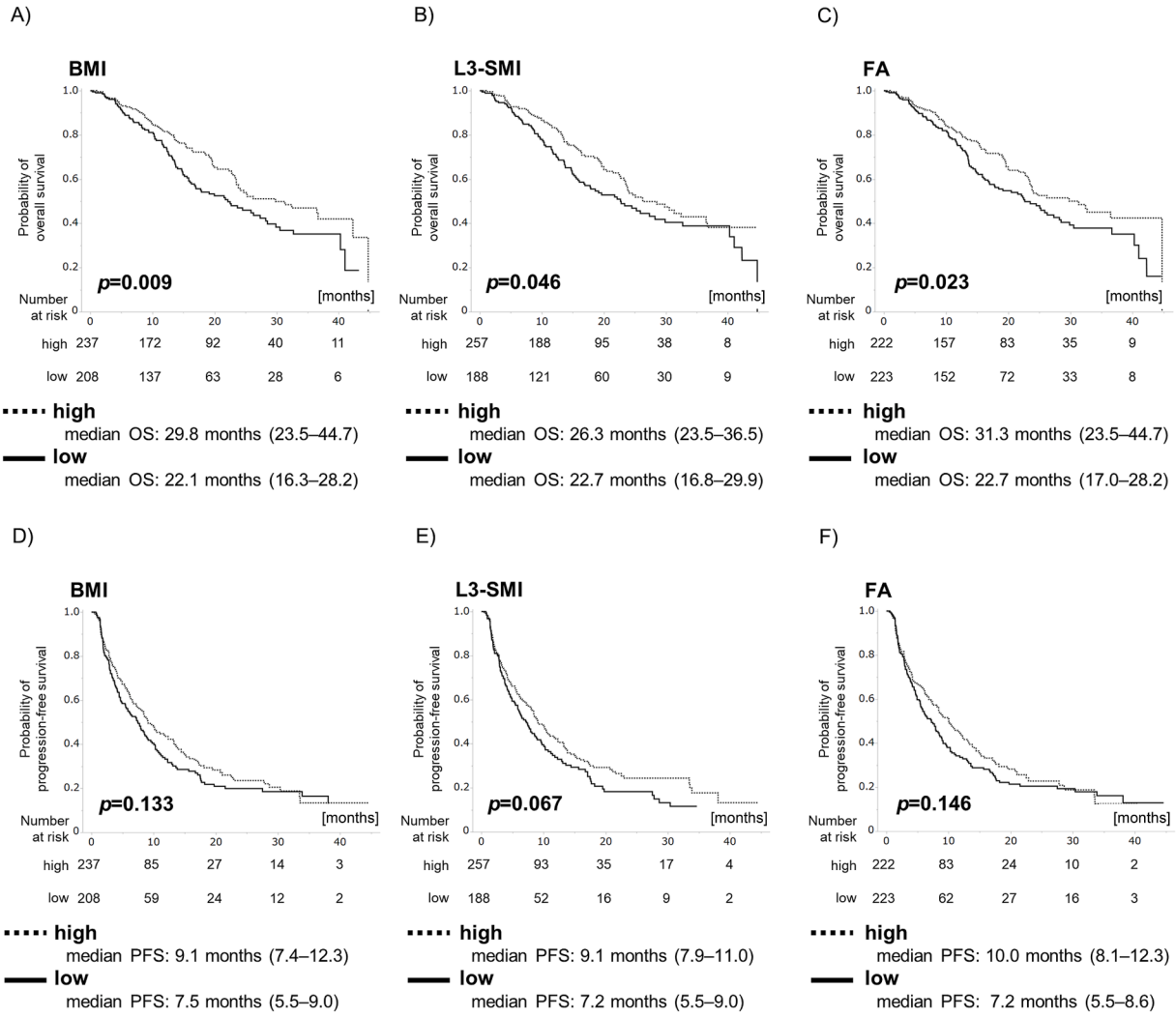

Fig. 3. Cumulative survival curve stratified by body composition
A) Overall survival (OS) stratified by body mass index (BMI). B) OS stratified by the third lumbar spine skeletal muscle index (L3-SMI). C) OS stratified by total fat area (FA). D) Progression-free survival (PFS) stratified by BMI. E) PFS stratified by L3-SMI. F) PFS stratified by FA.

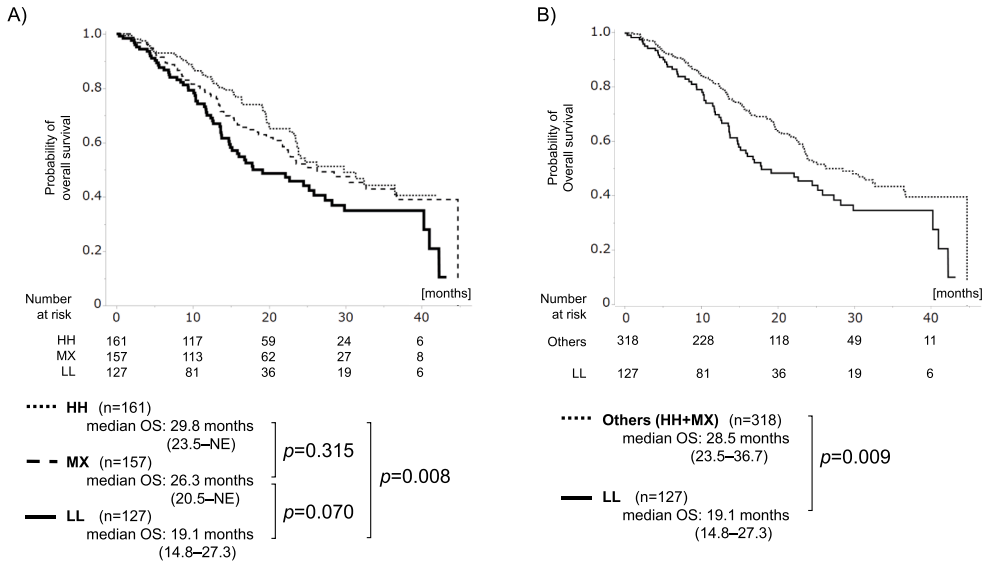

Fig. 4. Cumulative overall survival curve stratified sub-group analysis
A) Stratified three-group analysis: high skeletal muscle index (SMI)/high fat area (FA) (HH) group, mix with high SMI/low FA and low SMI/high FA (MX) group, and low SMI/low FA (LL) group. B) Stratified two-group analysis: low SMI/low FA (LL) group and others.

Table 2
Univariate and multivariable analyses of factors contributing to overall survival.

Factor	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*	HR	95%CI	*p*
Age (years)						
<75	1		0.109	1		0.065
≥75	1.267	0.948–1.693		1.340	0.981–1.830	
Sex						
Men	1		0.610			
Women	1.095	0.773–1.549				
Etiology						
Viral	1		0.490			
Non-viral	1.109	0.827–1.486				
ECOG-PS						
0	1		0.003	1		0.106
≥1	1.637	1.181–2.271		1.330	0.942–1.878	
Child-Pugh class						
A	1		<00.001	1		<00.001
B	2.355	1.563–3.549		2.141	1.391–3.295	
BCLC						
A or B	1		<00.001			
C	1.902	1.417–2.552				
Macrovascular invasion						
	1		0.005	1		0.038
+	1.575	1.144–2.168		1.456	1.022–2.076	
Extrahepatic spread						
	1		0.019	1		0.003
+	1.442	1.063–1.957		1.625	1.175–2.248	
Up-to-seven						
in	1		0.029	1		0.142
out	1.432	1.037–1.979		1.283	0.920–1.788	
BMI						
<23	1		0.010			
≥23	0.683	0.512–0.912				
L3-SMI						
<42/38 cm^2/m^2	1		0.047			
≥42/38 cm^2/m^2	0.746	0.558–0.996				
FA						
<263 cm^2	1		0.024			
≥263 cm^2	0.715	0.535–0.956				
Body composition						
HH	1			1		
MX	1.187	1.106–2.033	0.345	1.002	0.689–1.457	0.991
LL	1.637	1.143–2.344	0.007	1.464	1.012–2.119	0.043

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; L3-SMI, third lumbar spine skeletal muscle index; FA, fat area; HH, high SMI and high FA group; MX, high SMI and low FA, or low SMI and high FA groups; LL, low SMI and low FA group.

39.0%, p = 0.008). No differences were observed between the two groups in terms of other tumor or liver function factors (Table 3). The ORR was nearly equivalent in both groups (31.5% vs. 33.7%, p = 0.663).

3.6. Subgroup analysis of body composition factors contributing to OS by patient characteristics

We examined the impact of SMI and FA on OS in subgroups defined by the following patient characteristics: age, sex, etiology, Child–Pugh class, and BCLC stage (Table 4, Fig. 5). Sex and etiology showed particularly characteristic results in the host-factor subgroups. Low SMI in men (HR = 1.421; 95% CI: 1.023–1.974; p = 0.036) and low FA in women (HR = 2.098; 95% CI: 1.094–4.025; p = 0.026) were significantly poor predictors of OS (Fig. S4A–D). Low FA in patients with viral HCC (HR = 1.821; 95% CI: 1.093–3.032; p = 0.021) and low SMI in those with non-viral HCC (HR = 1.801; 95% CI: 1.229–2.637; p = 0.003) were significant poor prognostic factors of OS (Fig. S4E–H).

4. Discussion

In recent years, primary systemic therapy for HCC has shifted from molecular targeted agents to combination immunotherapy [2], and validating the significance of body composition is essential. Skeletal muscle is not merely a motor organ; it secretes various myokines and plays a role in regulating immune cell function and inflammatory responses [29]. Consequently, muscle depletion is thought to contribute to reduced immune response and treatment resistance. Accordingly, multiple meta-analyses have demonstrated that muscle depletion is a poor prognostic factor in patients with cancer receiving immunotherapy [30,31]. However, adipose tissue exerts both negative and positive effects on immunotherapy, and evidence remains inconsistent [13]. Obesity is associated with T-cell dysfunction and exhaustion and has been linked to a favorable response to ICIs [32]. Moreover, adipose tissue functions as a buffer enabling the body to adapt to various stresses, such as inflammation, stress, and fluctuations in nutritional intake. This critical tissue is depleted during the early stages of cachexia [33]. In this study, patients with unresectable HCC treated with Atezo/Bev who belonged to the LL group, characterized by low SMI and low FA, exhibited poor prognosis, independent of tumor and liver function factors. This suggests that body composition directly or indirectly influences the OS in patients undergoing immunotherapy. We focused on patients who received Atezo/Bev, in whom PFS was strongly influenced by direct treatment response. However, because body composition does not contribute to treatment response, a significant difference in PFS was absent. Instead, body composition appeared to strongly influence the prognosis following sequential treatments after Atezo/Bev and after the completion of drug therapy.

Furthermore, a key finding of our study is that the effect of body composition varied depending on the background factors identified in the sub-analysis. Specifically, L3-SMI strongly correlated with prognosis in men, whereas FA strongly correlated with prognosis in women. Additionally, FA was strongly associated with prognosis in patients with viral HCC, whereas L3-SMI was strongly associated with non-viral HCC. These findings suggest that differences in metabolic, endocrine, and inflammatory environments based on etiology or sex may be reflected in prognostic factors. Collectively, these results indicate that the effect of body composition on OS varies depending on the underlying condition, highlighting the importance of body composition assessment when initiating Atezo/Bev therapy. While tumor and liver function factors have traditionally been key factors in treatment decisions, incorporating body composition into a comprehensive evaluation may be desirable. Particularly, in patients in the LL group, combination immunotherapy alone may not yield sufficient efficacy; combining it with nutritional therapy and rehabilitation may enhance treatment outcomes. Accordingly, exercise interventions have been reported to potentially enhance tumor immunity [34,35], and improving the body composition may lead to enhanced immunotherapeutic efficacy.

Table 3
Comparison of baseline characteristics between the LL and other groups.

	LL (n = 127)	Others (n = 318)	p
Age, median (IQR)	76 (69–82)	74 (69–79)	0.069
Sex, *n* (%)			
Men	100 (83.3)	258 (81.1)	0.566
Etiology, *n* (%)			
HBV	15 (11.8)	29 (9.1)	0.030
HCV	52 (40.9)	95 (29.9)	
Non-viral	60 (47.2)	194 (61.0)	
ECOG-PS, *n* (%)			
0	94 (74.0)	256 (80.5)	0.292
1	26 (20.5)	51 (16.0)	
2	7 (5.5)	11 (3.5)	
Child-Pugh class, *n* (%)			
A	116 (91.3)	288 (90.6)	0.799
B	11 (8.7)	30 (9.4)	
BCLC stage, n (%)			
A	5 (3.9)	20 (6.3)	0.621
B	57 (44.9)	138 (43.4)	
C	66 (52.0)	160 (50.3)	
Macrovascular invasion, *n* (%)	32 (25.2)	80 (25.2)	0.993
Extrahepatic spread, *n* (%)	40 (31.5)	91 (28.6)	0.547
BMI [kg/m^2]	20.1 (18.6–21.6)	24.6 (22.6–27.0)	<0.001
L3-SMI [cm^2/m^2]			
Men	37.3 (34.1–39.7)	46.6 (43.1–51.0)	<0.001
Women	33.0 (28.4–36.3)	39.9 (37.1–43.7)	<0.001
FA [cm^2]	151.0 (90.5–203.1)	303.1 (243.1–355.5)	<0.001
VFA [cm^2]	72.4 (40.3–103.3)	145.0 (106.6–186.6)	<0.001
SFA [cm^2]	70.3 (44.3–100.4)	144.4 (111.7–188.8)	<0.001

HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; L3-SMI, third lumbar spine skeletal muscle index; FA, fat area; VFA, visceral fat area; SFA, subcutaneous fat area.

Table 4
Subgroup analysis of body composition factors contributing to overall survival by patient characteristics.

		No. of patients	SMI low group relative to high group			FA low group relative to high group		
			Hazard ratio for death	95%CI	p-value	Hazard ratio for death	95%CI	p-value
Age	<75	228	1.250	0.817–1.913	0.305	1.271	0.836–1.931	0.261
	≥75	217	1.386	0.930–2.064	0.109	1.501	0.999–2.253	0.050
Sex	Men	358	1.421	1.023–1.974	0.036	1.250	0.901–1.735	0.182
	Women	87	1.081	0.583–2.004	0.805	2.098	1.094–4.025	0.026
Etiology	Viral	191	1.045	0.665–1.641	0.850	1.821	1.093–3.032	0.021
	Non-viral	254	1.801	1.229–2.637	0.003	1.286	0.878–1.884	0.196
Child-Pugh class	A	404	1.320	0.965–1.806	0.083	1.380	1.009–1.887	0.044
	B	41	2.060	0.953–4.455	0.066	1.132	0.499–2.569	0.766
BCLC stage	AB	220	1.364	0.871–2.136	0.174	1.692	1.079–2.651	0.022
	C	225	1.323	0.905–1.934	0.148	1.136	0.775–1.663	0.514

SMI, skeletal mass index; FA, fat area; BCLC, Barcelona Clinic Liver Cancer.

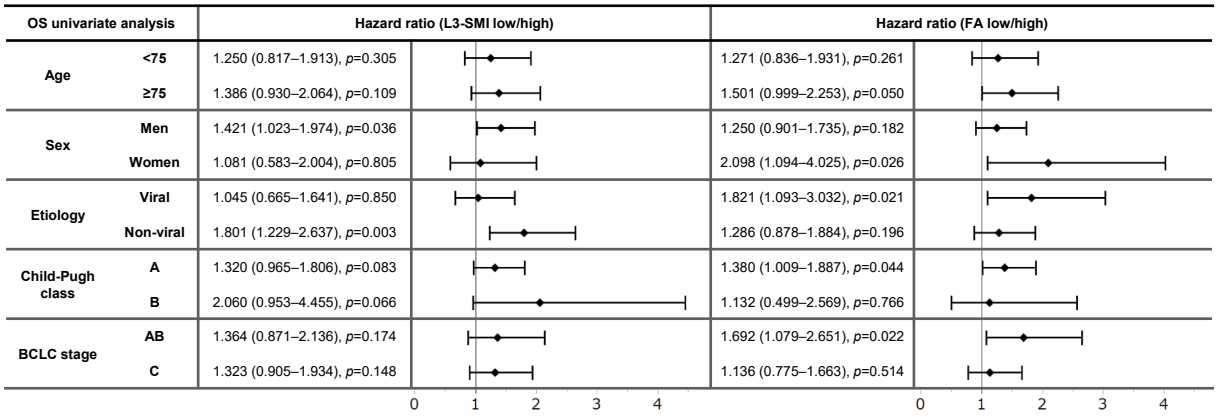

Fig. 5. Subgroup analysis of body composition factors contributing to overall survival (OS) by patient characteristics. BCLC, Barcelona Clinic Liver Cancer; SMI, third lumbar spine skeletal muscle index; FA, total fat area.

However, this study has some limitations. First, this was a retrospective, multicenter exploratory analysis, which introduced biases related to patient selection and treatment choices. Variability in the assessment of body composition may have occurred across institutions, scanner models, and observers. However, all participating centers in this study were high-volume institutions, and the general imaging conditions were standardized. Furthermore, two independent observers (M.E. and I.S.) assessed 50 cases from our institution (Yamaguchi University) to evaluate inter-observer reproducibility. Both L3-SMI and FA demonstrated good reproducibility, as confirmed by intraclass correlation coefficients and Bland–Altman analyses (correlation coefficients A and B, and their corresponding CIs). Furthermore, this study was designed as an exploratory multicenter analysis with the largest feasible sample size, restricted to first-line systemic therapy, to ensure a homogeneous cohort. However, variability in imaging and measurement parameters could not be completely eliminated. To address this limitation, future studies should incorporate prospective designs or validation cohorts utilizing fully standardized imaging protocols.

Second, body composition assessment was limited to a single time point before treatment. Consequently, future prospective studies incorporating longitudinal tracking of changes in body composition are necessary. Additionally, verification of the effects of nutritional and exercise therapies on prognostic improvement is desirable.

Third, adipose tissue was analyzed as FA rather than as VFA and SFA separately. This is because VFA and SFA exhibited significant sex-related differences (Fig. S5A and B), which we considered impossible to adjust for in the statistical analysis. We evaluated FA because it integrates VFA and SFA and was well-balanced between men and women (Fig. S5C). Both VFA and SFA may function as important buffers and energy storage sources. We exploratively evaluated their combination as FA and considered dichotomization at the median feasible for a generalized assessment of low-energy state. In real-world clinical practice, therapeutic interventions targeting only VFA or SFA are difficult. Therefore, the evaluation of FA, as in this study, is considered clinically reasonable. Furthermore, we evaluated muscle based solely on quantity but not quality. In recent years, qualitative assessments, such as intramuscular fat [36] and muscle strength itself [37], have also been recognized as important and represent key areas for future research.

Finally, we were unable to perform a detailed etiological classification of non-viral HCC, because we did not collect key information, such as alcohol intake and the presence or absence of steatotic liver disease. Such information is necessary to identify metabolic dysfunction-associated steatotic liver disease. Consequently, our ability to accurately stratify non-viral HCC was limited.

Despite these limitations, the novelty of this study lies in demonstrating that patients with low values for both skeletal muscle and adipose tissue exhibit extremely poor prognosis.

5. Conclusion

Patients in the LL group had significantly poorer outcomes than did those in the MX and HH groups, whereas the outcomes of the MX and HH groups were equivalent. Compared with the other groups, the LL group showed no differences in liver function or

tumor stage and had a median BMI of 20.1, indicating no extremely thin body type. This group is presumed to be indistinguishable from patients in other groups unless body composition is considered. In survival curves dividing patients into four groups based on L3-SMI and FA levels, the LL group showed a poor prognosis. However, the MX group, which maintained either L3-SMI or FA, had better prognosis than that of the LL group. This finding suggests the importance of evaluating skeletal muscle and adipose tissue separately, not just overall weight, and considering the impact of body composition on prognostic factors within subgroups. This approach is crucial for tailoring liver rehabilitation and nutritional therapies to individual patients. A key future research challenge is to verify whether improving body composition prolongs survival in clinical practice.

In conclusion, patients with concurrent low skeletal muscle mass and adipose tissue who were treated with Atezo/Bev had a poor prognosis.

Data availability statement

The data generated in the present study may be requested from the corresponding author.

Ethics approval statement

This study was conducted as an exploratory analysis of a clinical database, in accordance with the Ministry of Health, Labor and Welfare's "Guidelines for Clinical Research," and after obtaining approval from the ethics committees of Kurume University School of Medicine (approval code 23153) and all other institutions. The study design followed the principles of the Declaration of Helsinki. The research information was disclosed on the website, ensuring that the study patients and others had the opportunity to opt out.

Authorship statement

Guarantor of the article: Issei Saeki, MD, PhD.

Specific author contributions: Maho Egusa: Conceptualization, Methodology, Data Curation, Formal Analysis, Writing—Original Draft Preparation; Issei Saeki: Conceptualization, Methodology, Data Curation, Formal Analysis, Writing—Original Draft Preparation; Yasuto Takeuchi: Data Curation; Shigeo Shimose: Conceptualization, Data Curation; Takanori Ito: Data Curation; Joji Tani: Data Curation; Ryu Sasaki: Data Curation; Kyo Sasaki: Data Curation; Takeshi Hatanaka: Data Curation; Takaya Suzuki: Data Curation; Rintaro Kobayashi: Data Curation; Satoru Kakizaki: Data Curation; Norikazu Tanabe: Data Curation; Sohji Nishina: Writing—Review & Editing; Hisamitsu Miyaaki: Writing—Review & Editing; Hideki Kobara: Writing—Review & Editing; Hiroki Kawashima: Writing—Review & Editing; Takumi Kawaguchi: Writing—Review & Editing; Motoyuki Otsuka: Writing—Review & Editing; Takahiro Yamasaki: Writing—Review & Editing; Taro Takami: Writing—Review & Editing. All authors have read and approved the final version of the article, including the authorship list.

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Conflict of interests

I.S.: Lecture fees from Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., and Eisai Co. Ltd.; S.S.: Lecture fees from AstraZeneca K.K. and Eisai Co. Ltd.; T.I.: Lecture fees from Chugai Pharmaceutical Co., AstraZeneca K.K., Eisai Co., Ltd., Bristol Myers Squibb, and Ono Pharmaceutical, and research funding from Chugai Pharmaceutical Co., Ltd.; T.H.: Research funding from CureApp, Inc.; H.M.: Lecture fees from AstraZeneca K.K.; T.K.: Lecture fees from Kowa Company, Ltd., ASKA Pharmaceutical Co., Ltd., AbbVie GK, Taisho Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Sumitomo Pharma Co., Ltd., Eisai Co., Ltd., and Novo Nordisk Pharma Ltd., and research funding from Boehringer Ingelheim Japan, Co., Ltd.; T.T.: Lecture fees from Gilead Sciences, Inc., AbbVie GK., Otsuka Pharmaceutical Co., Ltd., and Chugai Pharmaceutical Co., Ltd. The listed companies were not involved in the design or conduct of the study.

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Appendix A. Supplementary data

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