

# Management of Systemic Therapies and Hepatic Arterial Infusion Chemotherapy in Patients with Advanced Hepatocellular Carcinoma Based on Sarcopenia Assessment

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## Keywords

Sarcopenia · Advanced hepatocellular carcinoma · Systemic therapy · Hepatic arterial infusion chemotherapy

## Abstract

**Background:** Sarcopenia, defined as the loss of skeletal muscle mass (MM), physical performance, and strength, has been associated with poor clinical outcomes in hepatocellular carcinoma (HCC) patients treated with several therapies. As systemic therapies, including molecular targeted agents, have a strong impact on sarcopenia, we aimed to review the impact of sarcopenia in patients receiving systemic therapies, especially sorafenib and hepatic arterial infusion chemotherapy (HAIC). **Summary:** Several studies have demonstrat-

ed that sarcopenia is associated with poor clinical outcomes in patients receiving sorafenib or lenvatinib, while HAIC has no association with overall survival (OS) and sarcopenia. Furthermore, based on our previous study, we developed the management of sorafenib score (MS score) to stratify patients' survival according to the positivity of three parameters (skeletal MM, disease control of sorafenib, and post-sorafenib therapy), ranging from 0 to 3. Patients with an MS score  $\geq 2$  (median survival time [MST], 16.4 months) showed significantly longer survival than those with an MS score  $\leq 1$  (MST, 8.4 months) ( $p < 0.001$ ). This result indicates that patients need at least two positive parameters to prolong OS.

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Although performance status (PS) has been used in the Barcelona Clinic Liver Cancer staging system, we consider that the assessment of sarcopenia has the potential to replace PS.

**Key Messages:** Sarcopenia is associated with poor clinical outcomes in patients of HCC receiving sorafenib or lenvatinib. The MS score, based on the positivity of three prognostic factors, including skeletal MM, in patients receiving sorafenib, can be a reliable indicator of prolonged survival.

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## Introduction

Sarcopenia, defined as muscle depletion due to aging by Rosenberg [1, 2], is also known as primary sarcopenia. In contrast, secondary sarcopenia is a disorder caused by liver cirrhosis (LC) and hepatocellular carcinoma (HCC) [3, 4]. Sarcopenia has been defined as the loss of skeletal muscle mass (MM), physical performance (walking speed), and strength, according to diagnostic criteria in Europe and Asia [5, 6]. The Japan Society of Hepatology (JSH) proposed sarcopenia assessment criteria for patients with chronic liver disease [7], which consists of the measurements for handgrip strength (HGS) and skeletal MM by computed tomography (CT) or bioelectrical impedance analysis (BIA); however, the assessment of walking speed has not been adopted for use in the criteria. As there are differences in physical constitution among various regions and races, the respective definition of sarcopenia should be applied to each region and race.

Previous studies demonstrated that sarcopenia is associated with poor clinical outcomes in patients with HCC treated with several therapies [8, 9]. In particular, as skeletal MM significantly decreases after the induction of molecular targeted agents (MTAs) [10, 11], sarcopenia can have a strong impact on the clinical outcomes in patients with advanced HCC treated with systemic therapies, including MTAs. Here, we review the impact of sarcopenia in patients with advanced HCC treated with systemic therapies and discuss the treatment strategies based on sarcopenia outcomes and their association with the overall survival (OS) in these patients.

## Sarcopenia Diagnostic Criteria

As shown in online supplementary Table 1 (see [www.karger.com/doi/10.1159/000522389](http://www.karger.com/doi/10.1159/000522389) for all online suppl. material), several academic society groups have pub-

lished diagnostic criteria for sarcopenia. The European Working Group on Sarcopenia in Older People (EWG-SOP) and the Asian Working Group for Sarcopenia (AWGS) published these criteria in 2010 and 2014, respectively [12, 13]. Recently, these criteria have been updated to EWG-SOP2 and AWGS2019 [5, 6]. The criteria of the JSH defined sarcopenia-related chronic liver diseases as “loss of muscle mass plus low muscle strength” regardless of older age [7]. However, the assessment of physical performance, such as walking speed, was not considered. As it has been reported that slow walking speed overlaps with low HGS in patients with HCC [14], a physical performance evaluation might not be needed for diagnosing sarcopenia in patients with chronic liver disease. The cut-off values of the JSH criteria for low MM were defined as a skeletal muscle index (SMI)  $<42 \text{ cm}^2/\text{m}^2$  in men and  $<38 \text{ cm}^2/\text{m}^2$  in women, using CT imaging, and  $<7.0 \text{ kg}/\text{m}^2$  in men and  $<5.7 \text{ kg}/\text{m}^2$  in women, by BIA. However, as optimal cut-off values for SMI, which are the equivalent to those for BIA based on AWGS criteria [13], were calculated using a receiver operating characteristic curve analysis in 149 patients with LC or HCC, these cut-off values are provisional. In contrast, the cut-off values for low HGS were  $<26 \text{ kg}$  in men and  $<18 \text{ kg}$  in women, which are the same as the AWGS criteria. However, the cut-off value of the AWGS2019 criteria for low HGS in men changed to  $<28 \text{ kg}$  [6]. The JSH has also revised the cut-off value of low HGS in men to  $<28 \text{ kg}$  in the second edition of the JSH criteria report, but the cut-off values for low MM remained the same as that in the first edition of the JSH criteria [15]. This update needs to be considered for sarcopenia diagnosis in patients with HCC.

## Relationship between HGS and Skeletal MM

Hanai et al. [16] reported that in patients with LC, including HCC ( $n = 563$ ), HGS was moderately correlated with MM ( $r = 0.35$ ) in men, while the correlation in women was weak ( $r = 0.17$ ). Another report also showed a moderate correlation between HGS and MM ( $r = 0.38$ ) in patients with HCC ( $n = 107$ ) [14]. We measured these parameters in 53 patients with HCC [17] and found that the correlation coefficients in men and women were 0.35, and 0.20, respectively (data not shown). Therefore, the correlation between HGS and MM was weak to moderate in the previous reports, including ours.

We collected four articles in which both HGS and MM were evaluated in patients with HCC [14, 17, 18] or LC/

HCC [16]. We divided the patients into four groups according to the JSH criteria [7]. As shown in online supplementary Figure 1, of the 786 total patients (HCC, 620 [78.9%]; LC, 166 patients), 269 (34%) had normal HGS and normal MM, 202 (26%) had normal HGS and low MM, 124 (16%) had low HGS and normal MM, and 191 (24%) had low HGS and low MM; of the total patients, 24% (191/786) were diagnosed with sarcopenia. Recently, Nishikawa et al. [19] reported the prevalence of four groups classified by HGS and MM in patients with chronic liver diseases ( $n = 1,624$ ; HCC, 626 patients [38.5%]) in a large-scale multicenter study (normal HGS and normal MM, 830 [51.1%]; normal HGS and low MM, 250 [15.4%]; low HGS and normal MM, 319 [19.6%]; and low HGS and low MM, 225 [13.9%]). The difference between the data from online supplementary Figure 1 and the data from Nishikawa et al. [19] may be due to differences in the proportion of patients with HCC. As there were a few reports in which both HGS and MM were assessed, the impact of either low HGS or low MM remains unclear, and further studies are required in this field to generate strong evidence.

### Impact of HGS

Two research groups, including ours, have demonstrated low HGS, but not skeletal muscle depletion, as an independent unfavorable prognostic factor for survival in patients with HCC treated with lenvatinib [17, 18] (Table 1). However, these were single-center studies with a small number of patients and short observation periods. Therefore, further multicenter studies with larger populations are needed. Currently, there are no studies available regarding the effect of HGS in patients with HCC treated with other MTAs, including sorafenib. According to a recent report [19], low HGS was an independent unfavorable prognostic factor in patients with chronic liver diseases, including HCC (HCC, 626 patients [38.5%]; without HCC, 998 patients [61.5%]), whereas skeletal MM was not a significant factor. Furthermore, patients with HCC with low HGS showed significantly shorter survival than those with normal HGS. In the future, the impact between HGS and skeletal MM needs to be evaluated in patients with HCC treated with other MTAs and immunotherapies including a combination of atezolizumab and bevacizumab.

### Impact of Skeletal MM on Survival among Patients Treated with Different Systemic Therapies and Hepatic Arterial Infusion Chemotherapy

#### *Sorafenib*

Sorafenib was approved as a first-line systemic therapy for advanced HCC in 2007 [20]. Most previous studies have only evaluated skeletal MM without assessing HGS in patients with HCC treated with sorafenib [10, 11, 21–32]. As shown in Table 1, skeletal muscle depletion (low MM) is a poor prognostic factor for OS in most studies [10, 22–24, 26, 28, 31, 32], while there was no significant difference in others [11, 27, 29]. The subgroup analyses showed that the OS of patients who had two or more negative prognostic factors (albumin  $\leq 3.5$  g/dL, alpha-fetoprotein  $\geq 100$  ng/mL, lesions in bilateral hepatic lobes, or major portal vein invasions) with low MM was significantly shorter than in those with high MM [27], and the combined presence of low MM and low total adipose tissue index was significantly associated with worse OS [29]. Although a few reports have evaluated progression-free survival or time to progression regarding the impact of skeletal MM [23, 24, 29, 31], there have been few studies regarding the relationship between skeletal MM and post-progression survival (PPS). A recent report indicated that PPS was significantly correlated with pre-sarcopenia (transverse psoas muscle thickness per height  $< 16.8$  mm/m) at the time of disease progression in patients with HCC treated with sorafenib [30]. On the other hand, in a multicenter study, we demonstrated that a high skeletal MM before sorafenib treatment is a significant predictor of PPS in patients with HCC [31].

#### *Lenvatinib*

Lenvatinib had been recommended as a first-line systemic therapy for advanced HCC until the introduction of atezolizumab plus bevacizumab [33–36] and has been used since March 2018 in Japan, earlier than in the rest of the world. The first report on the relationship between skeletal MM and clinical outcome was described in 2020, when Uojima et al. [37] demonstrated that low MM was significantly associated with worse time to treatment failure and worse OS. Thereafter, two reports were published at the same time in which skeletal muscle depletion was not found associated with OS, unlike in a previous report [17, 18]. In contrast, Hiraoka et al. [38] recently reported that low MM was a significant prognostic factor. However, the results leave room for further investigation because of the small population size and short follow-up periods.

**Table 1.** Studies related with sarcopenia in HCC patients receiving systemic therapies and HAIC

Author [ref]	Region	Therapy	Patients' number	Method	Cut-off value	Low MM, n (%)	Outcome
Mir et al. [21]	France	Sorafenib	40	L3-SMI	M: <55.4 cm <sup>2</sup> /m <sup>2</sup> F: <38.9 cm <sup>2</sup> /m <sup>2</sup>	11 (27.5)	Predictor of dose limiting toxicities
Imai et al. [22]	Japan	Sorafenib	40	L3-SMI	<39.2 cm <sup>2</sup> /m <sup>2</sup>	15 (37.5)	Low MM: poor OS
Hiraoka et al. [23]	Japan	Sorafenib	93	PSI	M: <4.24 cm <sup>2</sup> /m <sup>2</sup> F: <2.50 cm <sup>2</sup> /m <sup>2</sup>	20 (21.5)	Low MM: poor OS Not significant for TTP and TTF
Nishikawa et al. [24]	Japan	Sorafenib	232	L3-SMI	M: <36.2 cm <sup>2</sup> /m <sup>2</sup> F: <29.6 cm <sup>2</sup> /m <sup>2</sup>	151 (65.1)	Low MM: poor OS and poor PFS
Yamashima et al. [25]	Japan	Sorafenib	40	ΔTPMT/height	≥0.59 mm/m	ND	ΔTPMT/height ≥0.59: poor OS but not significant for PFS
Saeki et al. [10]	Japan	Sorafenib	100	L3-SMI	M: <42 cm <sup>2</sup> /m <sup>2</sup> F: <38 cm <sup>2</sup> /m <sup>2</sup>	46 (46)	Low MM: poor OS
Takada et al. [27]	Japan	Sorafenib	214	L3-SMI	M: <42 cm <sup>2</sup> /m <sup>2</sup> F: <38 cm <sup>2</sup> /m <sup>2</sup>	123 (57)	No muscle depletion with high visceral fat: favorable OS Low MM: not significant for OS (p = 0.16)
Antonelli et al. [26]	Italy	Sorafenib	96	L3-SMI	M: <53 cm <sup>2</sup> /m <sup>2</sup> (BMI ≥25) <43 cm <sup>2</sup> /m <sup>2</sup> (BMI <25) F: <41 cm <sup>2</sup> /m <sup>2</sup>	47 (49)	Low MM: poor OS Low MM: poor TTF
Labeur et al. [29]	The Netherlands	Sorafenib	278	L3-SMI	M: <53 cm <sup>2</sup> /m <sup>2</sup> (BMI ≥25) <43 cm <sup>2</sup> /m <sup>2</sup> (BMI <25) F: <41 cm <sup>2</sup> /m <sup>2</sup>	145 (52)	Low MM: not significant for OS (p = 0.145) Low MM: poor TTP
Imai et al. [28]	Japan	Sorafenib	61	L3-SMI	M: ≤117.4 cm <sup>2</sup> (median) F: ≤96.9 cm <sup>2</sup> (median)	25 (41)	Low MM + low TATI: poor OS Low MM: poor OS
				ΔL3-SMI	ΔL3-SMI > -5.73 cm <sup>2</sup> /m <sup>2</sup> /120 days		ΔL3-SMI > -5.73: poor OS
				ΔSFMI	ΔSFMI > -5.33 cm <sup>2</sup> /m <sup>2</sup> /120 days		ΔSFMI > -5.33: poor OS
				ΔVFMI	ΔVFMI > -3.95 cm <sup>2</sup> /m <sup>2</sup> /120 days		ΔVFMI: not significant for OS

**Table 1** (continued)

Author [ref]	Region	Therapy	Patients' number	Method	Cut-off value	Low MM, n (%)	Outcome
Uchikawa et al. [11]	Japan	Sorafenib/ lenvatinib	67 (sorafenib, 49; lenvatinib, 18)	L3-SMI	M: <42 cm <sup>2</sup> /m <sup>2</sup> F: <38 cm <sup>2</sup> /m <sup>2</sup>	49 (73.1)	Not significant for OS (p = 0.437)
Cheng et al. [30]	Taiwan	Sorafenib	385	TPMT/height at the time of sorafenib failure	16.8 mm/m	249 (64.7)	Low MM: poor PPS
Saeki et al. [31]	Japan	Sorafenib	356	L3-SMI	M: <45 cm <sup>2</sup> /m <sup>2</sup> F: <38 cm <sup>2</sup> /m <sup>2</sup>	175 (49.2)	Low MM: poor OS and poor PPS but not significant for TTP
Wu et al. [32]	Taiwan	Sorafenib	137 (M, 120; F, 17)	L3-SMI	M: <39.1 cm <sup>2</sup> /m <sup>2</sup> F: no optimal cut-off	18 (15)	Low MM in men: poor OS
Uojima et al. [37]	Japan	Lenvatinib	100	L3-SMI	M: <42 cm <sup>2</sup> /m <sup>2</sup> F: <38 cm <sup>2</sup> /m <sup>2</sup>	59 (59)	Low MM: poor OS Low MM: poor TTF
Kotoh et al. [17]	Japan	Lenvatinib	53	HGS	M: <26 kg F: <18 kg	25 (47.2)	Low HGS: poor OS
Endo et al. [18]	Japan	Lenvatinib	63	Sarcopenia HGS	JSH criteria M: <26 kg F: <18 kg	15 (28.3) 21 (33.3)	Sarcopenia: poor OS Low HGS: poor OS and poor PPS but PFS not significant
Hiraoka et al. [38]	Japan	Lenvatinib	151	PSI	M: <4.24 cm <sup>2</sup> /m <sup>2</sup> F: <2.50 cm <sup>2</sup> /m <sup>2</sup>	41 (27.2)	Low MM: poor OS and poor PFS
Saeki et al. [45]	Japan	HAIC/ sorafenib	133 (HAIC, 55; sorafenib, 78)	L3-SMI	M: <42 cm <sup>2</sup> /m <sup>2</sup> F: <38 cm <sup>2</sup> /m <sup>2</sup>	56 (42.1)	Low MM: poor OS of sorafenib but not significant for OS of HAIC (p = 0.121)

L3, third lumbar vertebra; SMI, cross-sectional areas of skeletal muscle (cm<sup>2</sup>)/patient's height (m<sup>2</sup>); PSI, psoas muscle area at level of middle of third lumbar vertebra (cm<sup>2</sup>/height (m<sup>2</sup>); TPMT/height, transversal psoas muscle thickness (mm)/height (m); VFA, visceral fat area (m<sup>2</sup>); TATI, total adipose tissue index (m<sup>2</sup>); ΔTPMT/height, change in TPMT (mm)/height (m); ΔL3-SMI, change in third lumbar vertebra skeletal muscle index; ΔSFMI, change in subcutaneous fat mass index; ΔVFI, change in visceral fat mass index; OS, overall survival; TTP, time to progression; TTF, time to treatment failure; PFS, progression-free survival; PPS, post-progression survival; ND, not done; HGS, handgrip strength; HAIC, hepatic arterial infusion chemotherapy; M, male; F, female.

### Hepatic Arterial Infusion Chemotherapy

Hepatic arterial infusion chemotherapy (HAIC) has been widely used throughout Asia, especially in Japan. However, HAIC is not recommended as a standard systemic therapy for advanced HCC according to several guidelines, except in Japan [33–36]. Subgroup analyses of the SILIUS study, which compared sorafenib plus HAIC (using 5-fluorouracil and cisplatin [CDDP]) with sorafenib alone in a randomized, open-label, phase III study, demonstrated that sorafenib plus HAIC showed survival benefits in patients with advanced HCC with main portal vein invasion [39]. Another randomized, open-label, phase III study in China also showed that sorafenib plus HAIC (using oxaliplatin, 5-fluorouracil, and leucovorin) improved the survival compared with sorafenib alone in patients with HCC plus portal vein invasion [40]. In addition, both a retrospective cohort study with a large population (2,006 patients; 541 HAIC patients, 1,465 sorafenib patients) [41] and a systematic review [42] indicated that HAIC is superior to sorafenib in patients with HCC plus vascular invasion. Therefore, HAIC might be a potential first-line systemic therapy in a subpopulation of patients with advanced HCC plus vascular invasion without extrahepatic spread (EHS). Furthermore, it is possible to perform HAIC in advanced HCC with Child-Pugh class B, unlike MTAs [43, 44].

We observed no relationship between skeletal MM and survival in patients with HCC receiving HAIC [45]. As there have been no reports since then, this result requires further validation. The different results of survival according to skeletal MM between HAIC and sorafenib are worthy of notice when considering the management of systemic therapies.

### Skeletal Muscle Change during Systemic Therapy and HAIC

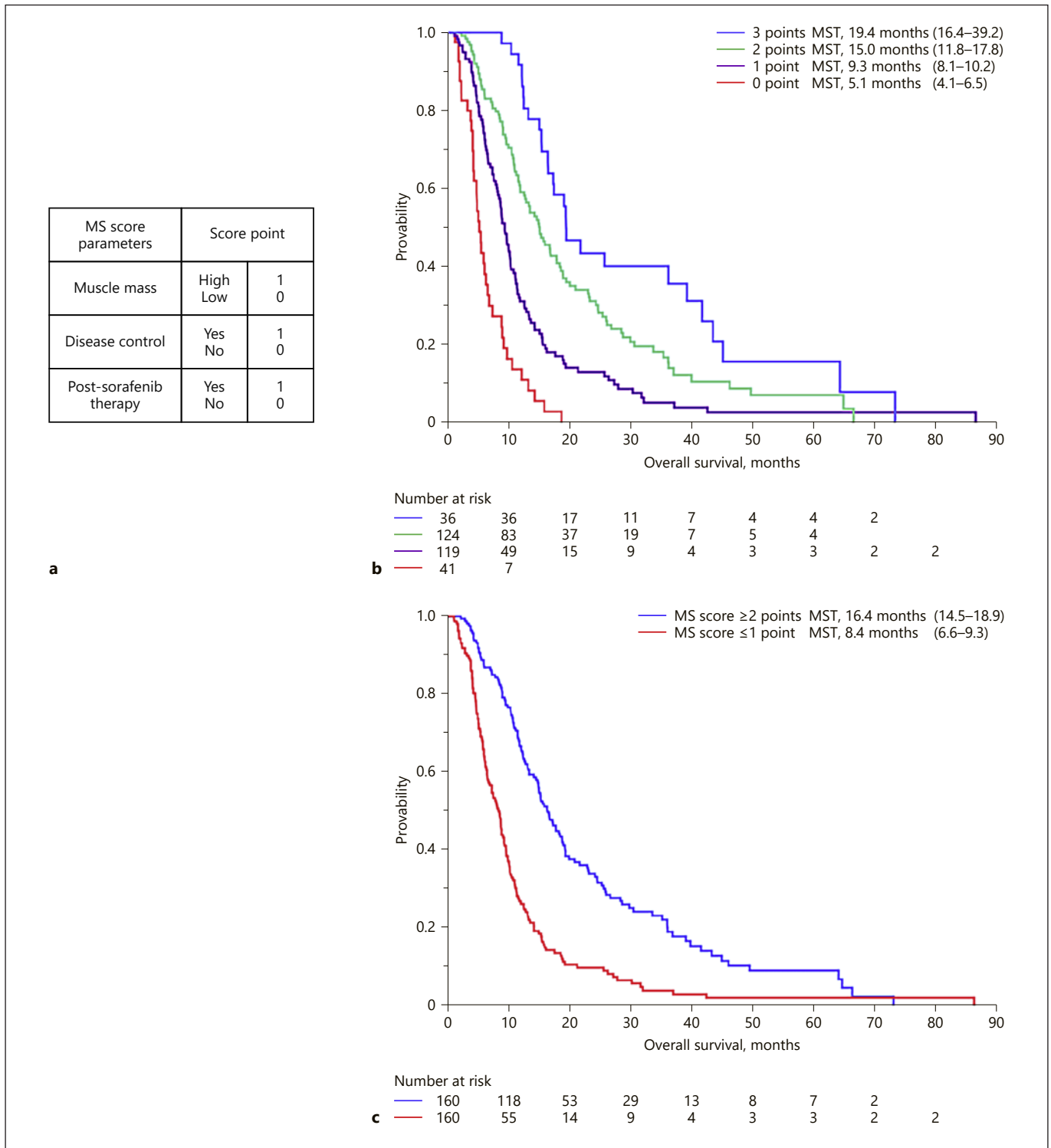
In cirrhotic patients, the annual rates of skeletal MM decline were 1.3% for Child-Pugh A, 3.5% for Child-Pugh B, and 6.1% for Child-Pugh C [46]. Our previous study showed that skeletal MM decreased by 7.2% and 2.7% at 3 months after therapy in patients receiving sorafenib and HAIC, respectively [45]. The skeletal muscle change in the sorafenib group tended to decrease rapidly ( $p = 0.095$ ), indicating that sufficient skeletal MM is required in patients designated to be treated with sorafenib. Uchikawa et al. [11] demonstrated a significant depletion of skeletal MM, regardless of disease progression, hepatic reserve, or type of MTAs (sorafenib or lenvatinib). In addition, it has

been reported that rapid skeletal muscle depletion ( $\Delta L3-SMI > -5.73 \text{ cm}^2/\text{m}^2/120 \text{ days}$ ) was an independent predictor of survival in patients with HCC treated with sorafenib [28].

### Management of Sorafenib Based on an Assessment of Skeletal MM

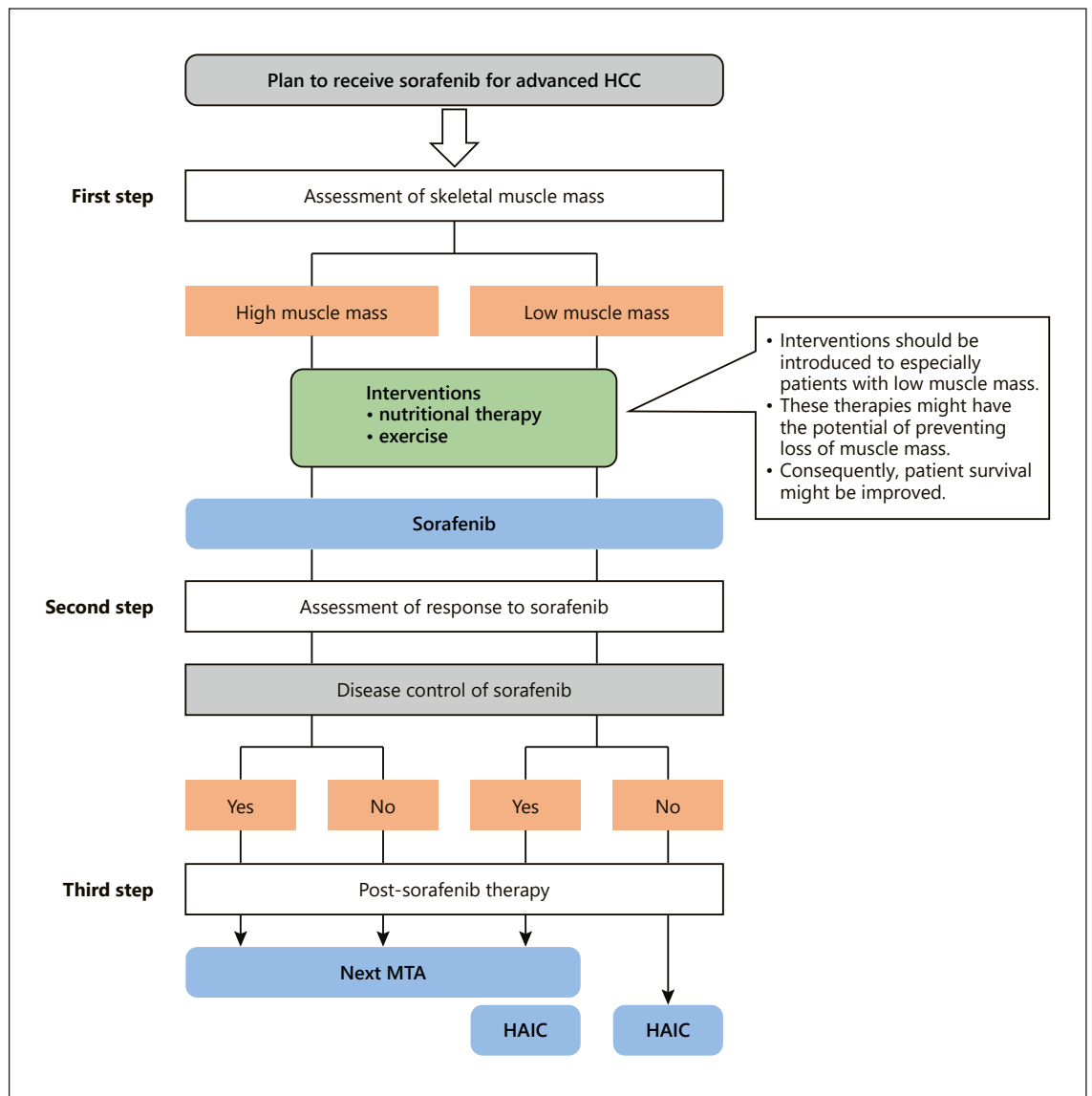
#### MS Score

Recently, we reported a multicenter cohort study of patients with HCC treated with sorafenib [31]. We retrospectively enrolled 356 patients with HCC and analyzed the impact of skeletal MM on clinical outcomes. This multicenter study protocol was approved by the Institutional Review Board of the Yamaguchi University Hospital (H30-042) and those of the other institutions in accordance with the ethical principles of the 1975 Declaration of Helsinki. Informed consent was not obtained due to the retrospective study design. In this study, the median values of SMI in men and women were used as cut-off values; skeletal muscle depletion was defined as an SMI less than  $45 \text{ cm}^2/\text{m}^2$  in men and less than  $38 \text{ cm}^2/\text{m}^2$  in women. Consequently, we demonstrated that low MM was an unfavorable predictor of PPS and OS. Subgroup analyses of prognostic factors (age, sex, body mass index, performance status (PS), Child-Pugh class, tumor number, tumor size, macrovascular invasion, EHS, skeletal MM, disease control, and post-sorafenib therapy) for OS showed that six factors – male sex (hazard ratio [HR], 0.717;  $p = 0.037$ ), tumor number  $< 8$  (HR, 0.615;  $p < 0.001$ ), EHS (HR, 0.684;  $p = 0.004$ ), high MM (HR, 0.545;  $p < 0.001$ ), disease control-yes (HR, 0.398;  $p < 0.001$ ), and post-sorafenib therapy-yes (HR, 0.610;  $p < 0.001$ ) – were identified as independent prognostic factors on multivariate analysis. To establish a new assessment score for managing sorafenib, we selected three parameters with favorable HRs: skeletal MM, disease control with sorafenib, and post-sorafenib therapy. Tumor characteristics such as tumor number and EHS were unchanged at the time of sorafenib therapy and, hence, were not included in the new score. We developed a management of sorafenib score (MS score, ranging from 0 to 3) according to the frequency of the three positive parameters. The MS score was calculated as the sum of the scores for the following: skeletal MM (high = 1, low = 0), disease control (yes = 1, no = 0), and post-sorafenib therapy (yes = 1, no = 0) (Fig. 1a). The median survival times of patients with MS scores 0 ( $n = 41$ ), 1 ( $n = 119$ ), 2 ( $n = 124$ ), and 3 ( $n = 36$ ) points were 5.1, 9.3, 15.0, and 19.4 months, respectively ( $p < 0.001$ ,



**Fig. 1.** OS according to the MS score. **a** The MS score is calculated as the sum of the score for the following: skeletal MM (high = 1, low = 0), disease control (yes = 1, no = 0), and post-sorafenib therapy (yes = 1, no = 0), ranging from 0 to 3. The MSTs of patients with MS scores of 0 ( $n = 41$ ), 1 ( $n = 119$ ), 2 ( $n = 124$ ), and 3 ( $n = 36$ ) points were 5.1, 9.3, 15.0, and 19.4 months, respectively ( $p <$

0.001, **b**). When the cut-off value of the MS score was set as 2 points, the patients with scores  $\geq 2$  ( $n = 160$ ) showed a significantly longer survival than those with scores  $\leq 1$  ( $n = 160$ ) (MST: 16.4 vs. 8.4 months,  $p < 0.001$ , **c**). MST, median survival time; MS score, management of sorafenib score.



**Fig. 2.** A draft proposal of the treatment strategy for advanced HCC patients who plan to receive sorafenib therapy, based on the MS score. HCC, hepatocellular carcinoma; MTA, molecular targeted agent; HAIC, hepatic arterial infusion chemotherapy.

Fig. 1b). Furthermore, there were no significant differences in OS among subgroups with the same scores (online suppl. Fig. 2). When the cut-off value of the MS score was set as 2 points, the patients with scores  $\geq 2$  ( $n = 160$ ) showed a significantly longer survival than those with scores  $\leq 1$  ( $n = 160$ ) (median survival time: 16.4 vs. 8.4 months,  $p < 0.001$ ; Fig. 1c). Therefore, these results indicate that patients with HCC receiving sorafenib need at least two positive MS score parameters to prolong OS, and the MS score may be a useful tool for prolonged survival in ad-

vanced HCC. For patients with high MM without achieving disease control, it is necessary to switch to other MTAs immediately. For patients with low MM who achieve disease control, it is important to appropriately determine the timing of conversion to post-progression treatment. In this study, post-sorafenib therapy, such as transcatheter arterial chemoembolization (TACE) and HAIC, was performed because only regorafenib was approved in Japan until the study period. In the TACE procedure, although the impact of skeletal MM remains controversial, two re-



ports from Japan demonstrated no significant association between skeletal MM and OS [9], similar to the HAIC procedure [45]. In an era of MTAs, sequential therapy using MTAs might decrease skeletal MM markedly, more than the first-line MTA therapy. In the future, we have even more room to investigate whether the MS score can be adopted directly for the sequential therapy using MTAs.

#### *Treatment Strategy for Advanced HCC through the MS Score*

The combination therapy of atezolizumab with bevacizumab was significantly superior to sorafenib in terms of OS, progression-free survival, and response rate in unresectable HCC [47]. Consequently, this combination therapy was approved for unresectable HCC in the USA and Japan in May 2020 and September 2020, respectively. Therefore, combination therapy is considered as the first-line therapy for advanced HCC, and the previous first-line (sorafenib and lenvatinib) and second-line (regorafenib, ramucirumab, and cabozantinib) therapies shift to second- and third-line therapies, respectively [48]. Thus, the choice of second- and third-line therapies after failure of atezolizumab plus bevacizumab is crucial. Based on the MS score, we present a draft proposal of a treatment strategy for patients with advanced HCC who plan to receive sorafenib therapy (Fig. 2). This strategy consists of three steps. In the first step, skeletal MM is assessed and divided into two groups, high MM or low MM. Thereafter, sorafenib is administered. Interventions, such as nutritional therapies (including branched-chain amino acid supplementation and L-carnitine) and exercise (cancer rehabilitation) [9], should be introduced especially to patients with low MM because interventions might have the potential of preventing loss of MM [49–52]. For even patients with a high MM, these interventions are required to maintain MM because progression of muscle loss was observed regardless of having skeletal MM in patients receiving sorafenib [10]. Exercise with branched-chain amino acid treatment has been shown to help maintain MM in patients with HCC [49], and exercise has also been shown to help increase MM in patients with HCC treated with TACE [52]. L-Carnitine has been shown to suppress the progression of MM depletion in cirrhotic patients including patients with HCC [50, 51]. However, the evidence regarding management of sarcopenia in patients with HCC receiving several treatments including systemic therapies and HAIC are lacking, and thus further studies will be needed in the future. When these interventions improve sarcopenia in patients with HCC receiving sorafenib, patient survival might be improved. For the

second step, the assessment of the response to sorafenib is performed. In the third step, post-sorafenib therapy is considered. For patients with low MM without disease control, HAIC may be considered because there is no association between OS and low MM [45], while the next MTA is considered for patients with high MM without disease control. For patients with disease control, the next MTA is considered when sorafenib is discontinued. For patients with disease control who have low MM, HAIC may also be considered. In addition, HAIC might be considered as a frontline treatment choice in patients with macrovascular invasion without EHS or with Child-Pugh class B, regardless of skeletal MM [39–44, 53, 54]. Although it has been reported that the assessment of skeletal MM at the time of disease progression (so-called before post-sorafenib therapy) was significantly associated with PPS [30], we demonstrated that patients with high MM before sorafenib therapy was a significant favorable predictor of PPS [31]. We consider that the assessment of skeletal MM before post-sorafenib therapy is not essential to predict PPS. However, this assessment might be required for the borderline patients between low MM and high MM before sorafenib therapy.

#### **Future Perspectives**

As described above, most of the evidence regarding the relationship between sarcopenia and systemic therapies related to sorafenib therapy came from Eastern studies. Furthermore, the measurement of skeletal MM using CT, without the assessment of HGS, has been used as “sarcopenia” in most of the previous studies. Therefore, there are some future directions for research in this area: (1) the definition of sarcopenia should be established for each region and race; (2) an alternate procedure for the measurement of skeletal MM using BIA needs to be established because the current procedure is a time-consuming method and involves radiation exposure; (3) as it has been reported that HGS was lost 2–5 times faster than skeletal MM [55], HGS might be a potential early predictor for OS in patients with HCC treated with MTAs, compared to skeletal MM. Further studies are required on this topic because of the limited number of reports [17–19]; and (4) the assessment of skeletal muscle changes in patients with HCC treated with sequential therapy using MTAs is required to prolong survival. Moreover, there is a need to assess the contribution of nutritional therapy and/or cancer rehabilitation to maintaining skeletal MM during sequential therapy using MTAs.

## Conclusion

Several studies have demonstrated that sarcopenia is associated with poor clinical outcomes in patients with HCC treated with MTAs, especially sorafenib. Therefore, assessment of MM is important for the management of systemic therapies in patients with advanced HCC. However, there are several issues that need to be addressed, such as assessment methods for sarcopenia with different cut-offs. The criteria for sarcopenia should be established based on a nationwide survey with a large population. Although PS has been used in the Barcelona Clinic Liver Cancer staging system [56], we consider that the assessment of sarcopenia has the potential to replace PS. Further studies are required to clarify this issue.

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## Statement of Ethics

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Yamaguchi University Hospital (H30-042) and two other institutions (Chiba University Hospital; No. 3253, Hiroshima University Hospital; E-1382). Informed consent was not obtained due to the retrospective study design.

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## Conflict of Interest Statement

H. Aikata received honoraria from Eisai and Bayer. S. Ogasawara received grant support, advisory fees, and honoraria from Bayer and Eisai. K. Chayama has received honoraria from AbbVie, MSD, Gilead Sciences Inc., Bristol Myers Squibb (BMS), Sumitomo Dainippon Pharma, Otsuka, and Tanabe Mitsubishi and grants and research funding from Sumitomo Dainippon Pharma. N. Kato received grant support, advisory fees, and honoraria from Bayer and Eisai. The authors declare no conflicts of interest.

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## Author Contributions

Takahiro Yamasaki, Issei Saeki, and Yurika Yamauchi designed the study. The literature search was performed by Takahiro Yamasaki, Issei Saeki, Yurika Yamauchi, Toshihiko Mastumoto, and Yutaka Suehiro. Data curation was performed by Issei Saeki, Yurika Yamauchi, Tomokazu Kawaoka, Shinsuke Uchikawa, Akira Hiramatsu, Hiroshi Aikata, Kazufumi Kobayashi, Takayuki Kondo, Sadahisa Ogasawara, and Tetsuhiro Chiba. Formal analysis was performed by Takahiro Yamasaki, Issei Saeki, and Yurika Yamauchi. Takahiro Yamasaki, Issei Saeki, and Yurika Yamauchi wrote the original draft of the manuscript. Taro Takami, Kazuaki Chayama, Naoya Kato, and Isao Sakaida reviewed and edited the manuscript. All authors read and approved the final manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this manuscript and its online supplementary material. Further inquiries can be directed to the corresponding author.

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