Retrospective Cohort Study

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Impact of sarcopenia on clinical outcomes for patients with resected hepatocellular carcinoma: a retrospective comparison of Eastern and Western cohorts

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Background: Patient fitness is important for guiding treatment. Muscle mass, as a reflection thereof, can be objectively measured. However, the role of East–West differences remains unclear. Therefore, we compared the impact of muscle mass on clinical outcomes after liver resection for hepatocellular carcinoma (HCC) in a Dutch [the Netherlands (NL)] and Japanese [Japan (JP)] setting and evaluated the predictive performance of different cutoff values for sarcopenia.

Method: In this multicenter retrospective cohort study, patients with HCC undergoing liver resection were included. The skeletal muscle mass index (SMI) was determined on computed tomography scans obtained within 3 months before surgery. The primary outcome measure was overall survival (OS). Secondary outcome measures were: 90-day mortality, severe complications, length of stay, and recurrence-free survival. The predictive performance of several sarcopenia cutoff values was studied using the concordance index (C-index) and area under the curve. Interaction terms were used to study the geographic effect modification of muscle mass.

Results: Demographics differed between NL and JP. Gender, age, and body mass index were associated with SMI. Significant effect modification between NL and JP was found for BMI. The predictive performance of sarcopenia for both short-term and long-term outcomes was higher in JP compared to NL (maximum C-index: 0.58 vs. 0.55, respectively). However, differences between cutoff values were small. For the association between sarcopenia and OS, a strong association was found in JP [hazard ratio (HR) 2.00, 95% CI [1.230–3.08], $P = 0.002$], where this was not found in NL (0.76 [0.42–1.36], $P = 0.351$). The interaction term confirmed that this difference was significant (HR 0.37, 95% CI [0.19–0.73], $P = 0.005$).

Conclusions: The impact of sarcopenia on survival differs between the East and West. Clinical trials and treatment guidelines using sarcopenia for risk stratification should be validated in race-dependent populations prior to clinical adoption.

Keywords: effect modification, hepatocellular carcinoma, liver resection, muscle mass, overall survival, sarcopenia

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HIGHLIGHTS

- Various commonly used cutoff values for sarcopenia had a similar predictive performance.
- Variables associated with sarcopenia were the same in the Eastern and Western populations, although the impact of body mass index differed.
- The effect of sarcopenia on overall survival is region-dependent, with only a strong association in the East.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third most frequent cause of cancer-related death worldwide[1,2]. Its incidence has risen over the past decades by more than 75% and is expected to keep rising[1,3]. Despite its worldwide presence, it is showing a significant geographical imbalance, with 85% of the cases in the Asia-Pacific and African regions[4]. This is partially explained by the fact that

HCC is most often appearing after years of chronic liver disease and these chronic liver diseases are markedly different across regions[1]. In Asia, HCC is more often following hepatitis B and C infections (HBV, HCV), whereas in Europe and the U.S., an increasing proportion of cases are now attributable to nonalcoholic steatohepatitis[3]. These proportions are also likely to change over time as obesity is also increasing in Asia, and antiviral therapies are showing widespread success[3,5]. Furthermore, cultural differences in terms of diet and physical activity are evident. In addition, the treatment protocols are more aggressive in Asia. For example, vascular invasion is not a contraindication for surgical resection in the Japanese, Chinese, and Hong Kong guidelines in contrast to the EASL-EORTC (European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer) and AASLD (American Association for the Study of Liver Diseases) guidelines[6].

Nevertheless, in all treatment selection algorithms, there is a movement to extend beyond the classical tumor and liver function variables. The general fitness of a patient is important in guiding treatment, although it might be severely impacted by East–West differences as described above. As an indicator of general fitness, low muscle mass, also known as sarcopenia, is shown to be an important predictor of both short-term and long-term clinical outcomes in various malignant and nonmalignant diseases[7–9]. However, the vast majority of studies investigating sarcopenia in patients with resected HCC are based on Eastern cohorts[10]. It is often questioned if inferences and conclusions on sarcopenia as a prognostic variable generalize[11]. Furthermore, the definition of sarcopenia itself is ambiguous due to the use of many different cutoff values with unclear impact. Therefore, our aim is to compare the impact of muscle mass on clinical outcomes in an Eastern and Western setting and evaluate if the use of different cutoff values for sarcopenia is justified.

Method

The protocol for this study was registered at the UMIN clinical trial registry (UMIN000049970, Supplement 1, Supplemental Digital Content 1, http://links.lww.com/JS9/A516). It adhered to the Declaration of Helsinki and was approved by the Medical Ethics Committee of Erasmus MC, Erasmus University Medical Centre, Rotterdam, the Netherlands (MEC-2018-1544), and by the Okayama University Hospital, Okayama, Japan. The reporting of this multicenter retrospective observational cohort study fulfills the STROCSS (Strengthening the Reporting of Cohort, cross-sectional and case–control Studies in Surgery) criteria (Supplemental Digital Content 2, http://links.lww.com/JS9/A517) and adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines (Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/A518)[12,13].

Population

All consecutive patients that had HCC and had received their first liver resection with curative intent in the period between January 2000 and January 2020 at one of the tertiary care centers were included. Patients were excluded if: HCC was not confirmed upon histopathological examination or if no preoperative computed tomography (CT) scan was available within 3 months prior to the resection. The CT scan had to enable analysis for muscle mass at the level of the third lumbar vertebra (L3). Lastly, patients were excluded if data concerning height or weight was missing. Both centers used a standardized template for data extraction that encompassed: patient demographics, etiology of liver disease, liver function, cancer stage at diagnosis, alpha-fetoprotein (AFP), locoregional therapies, operative findings, length of stay, complications, date of recurrence, and date of death which was last evaluated on the 3 February 2022. Patients from the Netherlands represented the Western cohort, whereas patients from Japan represented the Eastern cohort.

Skeletal muscle mass

Skeletal muscle mass area and muscle density were measured on CT scans. These scans were part of the preoperative diagnosis and workup for each patient. The total cross-sectional skeletal muscle area (cm^2) was measured manually by the authors with the initials B.R.B. and K.T. at the L3 level on a slice that showed both transverse processes. Using a validated software package FatSeg v4 developed by the Biomedical Imaging Group Rotterdam, the psoas, the paraspinal, transverse abdominal, external oblique, internal oblique, and rectus abdominis were manually outlined using Hounsfield units (HU) thresholds (i.e. – 30 to + 150 HU)[14,15]. This area was then normalized by the patient's squared height (m^2), resulting in the L3 skeletal muscle mass index (SMI; cm^2/m^2). Sarcopenia was defined based on the current study population. For each country, patients were stratified into four strata based on their gender and whether their body mass index (BMI) was greater or equal to 25 kg/m^2. For each stratum, the patients in the lowest tertial of the SMI distribution were classified as being sarcopenic (Supplementary Table 2, Supplemental Digital Content 3, http://links.lww.com/JS9/A518)[16].

Outcome parameters

The primary outcome was overall survival (OS), defined as the time in days between the date of resection and the date of death or last follow-up. Furthermore, we investigated short-term outcome measures: recurrence-free survival (RFS), length of hospital stay, complications with Clavien–Dindo grade (CD) at least 3 within a period of 90 days after surgery[17], and 90-day mortality. RFS was defined as the time in days between the date of resection and the date of recurrence or the date of the last scan showing no recurrence.

Statistical analysis

For descriptive statistics, discrete data was represented in absolute numbers and percentages. Continuous data was represented using the mean, the standard deviation, the first, second, and third quartiles, and the range. For the included data, the characteristics were compared between the Western and Eastern cohorts. Differences were tested using the Chi-squared (χ^2) or Mann–Whitney U test where appropriate. A complete case analysis was performed. Univariable and multivariable association with SMI was researched by means of a linear regression model with the variables: Western center, Male, Age, BMI, HCV, HBV, transarterial chemoembolization (TACE), radiofrequency ablation (RFA), American Society of Anesthesiologist physical status (ASA), Diabetes, Hypertension, Cardiac comorbidity, Cerebral comorbidity Child–Pugh score, Albumin–bilirubin score (ALBI), Microvascular invasion, and Log_{10}(AFP), tumor number, and

tumor size at radiology. In which tumor size was defined as the diameter of the largest tumor in cm. For each variable, effect modification by geographical region was investigated by means of interaction terms. The distribution of the residuals for each regression was assessed with a normal Q–Q plot and the Jarque–Bera test. For sarcopenia, the predictive performance of seven definitions and cutoff values were compared between the two countries for the outcomes: OS, RFS, 90-day mortality rate, complication rate, and length of stay (LOS)[16,18–23]. The specifications of the definitions are provided in Supplementary Table 3 (Supplemental Digital Content 3, http://links.lww.com/JS9/A518). For the outcome measures OS and RFS, a Cox proportional hazard model was used, and the predictive performance was assessed using the Harrel C-index. For the binary outcome measures 90-day mortality rate and complication rate, a logistic regression was used, and the predictive performance was assessed using the area under the receiver operating characteristic (AUC). Lastly, for the LOS, a Poisson regression model was used and predictive performance was assessed using the deviance. In the univariable analysis, Sarcopenia was the only variable included. In the multivariable analysis, the variables Sarcopenia, Male, Age, BMI, HCV, HBV, TACE, RFA, ASA score, Diabetes, Hypertension, Cardiac comorbidity, Cerebral comorbidity, Child–Pugh score, ALBI score, Tumor number, Tumor size, MVI, Log_{10}(AFP), and Western center were included.

To investigate if the impact of muscle mass, measured as SMI or as sarcopenia, changes between the East and West, several regressions were performed for each of the outcome variables. For OS, first a univariable survival model with sarcopenia was run for all data combined and for each region separately. Whereafter appropriate interaction terms of the variable Western center were added. Kaplan–Meier curves stratified for region and sarcopenia status were used to visualizing potential effect modification. Analogous multivariable regressions were performed in which the following control variables were added: Male, Age, BMI, HCV, HBV, TACE, RFA, ASA score, Diabetes, Hypertension, Cardiac comorbidity, Cerebral comorbidity, Child–Pugh score, ALBI score, Tumor number, Tumor size, Microvascular invasion, Log_{10}(AFP), Western center. The statistical script is provided in Supplement 2 (Supplemental Digital Content 4, http://links.lww.com/JS9/A519). The analysis was performed in R version 4.0.3.

Results

In total, 720 patients were screened. One hundred fifty-three patients from the Western cohort and 13 patients from the Eastern cohort were excluded, as no CT scan in the period of 3 months prior to resection was available. One patient from the Western cohort was excluded as weight was not recorded. Ultimately, 553 patients were included and analyzed in the current study, of which 174 were from the Western cohort and 379 from the Eastern cohort (Fig. 1). Of the included patients, descriptive statistics between the Western and Eastern cohorts were markedly different in terms of demographic composition (Table 1). In the Eastern cohort, patients were more often male (West vs. East: 70 vs. 79%, $P = 0.027$), had a lower BMI (West vs. East: 27 vs. 24, $P < 0.001$), and were older of age (West vs. East: mean 63 vs. 67, $P < 0.001$). In terms of etiology, HCV was more prominent in the East compared to the West (West vs. East 10 vs. 47%, $P < 0.001$). Patients in the Eastern cohort received significantly more often preoperative TACE (West vs. East: 3 vs. 50%, $P < 0.001$), but less often a major resection (West vs. East: 49 vs. 37%, $P = 0.011$) (Supplementary Table 4, Supplemental Digital Content 3, http://links.lww.com/JS9/A518). Patients in the Western cohort had lower liver function according to the ALBI score (West vs. East: mean −3 vs. −2.7, $P < 0.001$). In addition, patients in the Western cohort had a larger tumor size (West vs. East: mean 7 vs. 5 cm, $P < 0.001$) and tumors had more often microvascular invasion at histopathological examination (West vs. East 56 vs. 29%, $P < 0.001$). With regard to SMI, the distributions of the two regions were largely overlapping with no significant differences (West vs. East median (IQR) 47 (40–54) vs. 45 (39–51), $P = 0.476$). The median OS was larger in the Eastern cohort (West vs. East: median in years [95% CI] 5.7 [5.2–10.2] vs. 11 [9.2 to NA(not applicable)], $P < 0.001$). In addition, the proportion of patients alive at 5 years after surgery was in the West at 0.59, 95% CI [0.52–0.68] and in the East at 0.69, 95% CI [0.64–0.74]. Furthermore, in the Western cohort, there was a higher 90-day mortality, and more severe complications, while the length of stay was shorter.

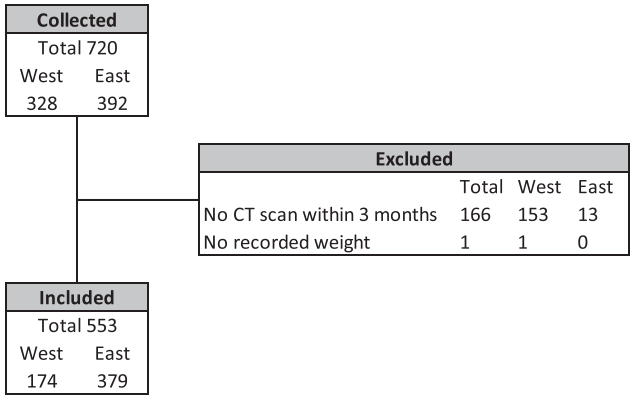

Figure 1. Flowchart of inclusions and exclusions. CT, computed tomography.

The Q–Q plots of the residuals of the linear regression models did not show significant deviation from the normal distribution. This was confirmed by the Jarque–Bera test with all P values greater than 0.05. Univariable correlation with SMI showed that the male gender and a higher BMI were significantly associated with a higher SMI. Whereas older age, increased tumor number, and higher AFP values were significantly associated with a lower SMI (Supplementary Table 5, Supplemental Digital Content 3, http://links.lww.com/JS9/A518). Between the Eastern and Western regions, significant effect modification of several univariable correlations with SMI was found (Supplementary Table 6, Supplemental Digital Content 3, http://links.lww.com/JS9/A518). More specifically, the interaction term for age implied that the SMI of a patient that lives in a Western region compared to a patient living in an Eastern region at age 60 is, on average, 0.104 units higher, whereas at age 70, the average SMI at the Western region is 1.845 units higher [coefficient (Coef) 0.19, 95% CI [0.07–0.32], $P = 0.003$]. The interaction term regarding HCV showed an increase in SMI of 3.70 units if HCV was present for the Western cohort, whereas for the Eastern cohort, a decrease in SMI of −1.11 was found (Coef 4.68, 95% CI [0.31–9.31], $P = 0.037$). For every extra unit in BMI, the SMI

Table 1

Descriptive statistics stratified by region.

		West	East	*P*
n		174	379	
Male, *n* (%)	*n* (%)	122 (70)	300 (79)	0.027*
Age (years)	Mean (SD)	63 (13)	67 (10)	0.009*
	q1 | q2 Iq3	58 | 67 | 72	61 | 68 | 74	
	Range	17–87	33–86	
BMI (kg/m^2)	Mean (SD)	27 (4)	24 (4)	< 0.001*
	q1 | q2 Iq3	24 | 26 | 29	21 | 23 | 26	
	Range	18–44	13–40	
Height (m)	Mean (SD)	1.73 (0.09)	1.62 (0.08)	< 0.001*
	q1 | q2 Iq3	1.67 | 1.73 | | 1.79	1.57 | 1.63 | 1.68	
	Range	1.5–2	1.4–1.84	
Weight (kg)	Mean (SD)	80 (16)	63 (12)	< 0.001*
	q1 | q2 Iq3	68 | 80 | 90	55 | 62 | 70	
	Range	44–135	34–114	
HCV	*n* (%)	18 (10)	180 (47)	< 0.001*
HBV	*n* (%)	27 (16)	105 (28)	0.003*
Pretreatment, *n* (%)	TACE	5 (3)	191 (50)	< 0.001*
	RFA	3 (2)	31 (8)	0.006*
ALBI score	Missing (%)	9 (5)	0 (0)	
	Mean (SD)	− 3 (0.5)	− 2.7 (0.4)	< 0.001*
Tumor number	Mean (SD)	1 (1)	2 (1)	0.007*
Tumor size (cm)	Mean (SD)	7 (5)	5 (4)	< 0.001*
	q1 | q2 Iq3	4 | 6 | 10	2 | 4 | 6	
	Range	1–30	0–27	
Log_{10}(AFP) (log_{10}(ng/ml))	Missing (%)	9 (5)	0 (0)	
	Mean (SD)	1.4 (1.5)	1.4 (1.2)	0.456
	q1 | q2 Iq3	0.5 | 0.9 | 2.1	0.6 | 1 | 1.9	
	Range	− 4 to 6.4	− 0.2 to 6.3	
Microvascular invasion	Missing (%)	8 (5)	0 (0)	
	n (%)	98 (56)	109 (29)	< 0.001*
Major resection	*n* (%)	85 (49)	140 (37)	0.011*
Positive margin	*n* (%)	20 (11)	10 (3)	< 0.001*
SMI (L3-muscle area/Height^2)	Mean (SD)	47 (9)	46 (8)	0.116
	q1 | q2 Iq3	40 | 47 | 54	39 | 45 | 51	
	Range	24–76	23–72	
Length of stay (days)	Missing (%)	1 (1)	0 (0)	
	Mean (SD)	11 (11)	23 (19)	< 0.001*
	q1 | q2 Iq3	6 | 7 | 13	15 | 18 | 25	
	Range	1–85	2–266	
Clavien–Dindo score, *n* (%)	Missing (%)	5 (3)	34 (9)	
	0	70 (12)	93 (21)	< 0.001*
	1	21 (12)	78 (21)	
	2	34 (20)	123 (32)	
	3	22 (13)	42 (11)	
	4	8 (5)	1 (0)	
	5	14 (8)	8 (2)	
Recurrence, *n* (%)		85 (49)	189 (50)	0.896
Death, *n* (%)		79 (45)	126 (33)	0.008*
90-day mortality, *n* (%)		16 (9)	15 (4)	0.016*
Median follow-up [95% CI] (years)		5.6 [5.0–6.1]	5.9 [5.5–6.4]	0.329
Median RFS [95% CI] (years)		2.6 [1.9–4.3]	4.2 [3.0–6.3]	0.080
Median OS [95% CI] (years)		5.7 [5.2–10.2]	11 [9.2 to NA]	< 0.001*

Main characteristics stratified by region. Tumor number and size were measured at radiology. Meld score, ALBI score, and AFP are the last measurements prior to liver transplantation.

AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ASA, American Society of Anesthesiologist physical status; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; OS, overall survival; RFA, radiofrequency ablation; RFS, recurrence-free survival; SMI, L3 skeletal muscle mass index; TACE, transarterial chemoembolization.

* Highlights *p* values < 0.05.

increased on average by 1.004 units in the Western region, where this was 1.348 in the Eastern region (Coef − 0.34, 95% CI [− 0.65 to 0.04], $P = 0.027$). Lastly, also interaction terms with diabetes (Coef 4.94, 95% CI [1.65–8.23], $P = 0.003$) and hypertension (Coef 3.39, 95% CI [0.33–6.45], $P = 0.030$) were significant. Upon multivariable regression with SMI as the dependent variable, only Male gender (Coef 9.43, 95% CI [8.03–10.82], $P < 0.001$), Age (Coef − 0.13, 95% CI [− 0.19 to − 0.07], $P < 0.001$), BMI (Coef 1.01, 95% CI [0.85–1.16], $P < 0.001$), and HCV (Coef 1.46, 95% CI [0.01–2.92], $P = 0.049$) remained significant (Supplementary Table 7, Supplemental Digital Content 3, http://links.lww.com/JS9/A518). Effect modification remained in the multivariable case for Age with a coefficient of − 0.17, 95% CI [− 0.25 to − 0.10] and an interaction term Age × Western center of 0.10, 95% CI [< 0.01–0.21]. BMI with a coefficient of 1.22, 95% CI [1.02–1.41] and an interaction term BMI × Western center of − 0.50, 95% CI [− 0.79 to − 0.21] and for HCV with coefficient 0.20, 95% CI [− 1.40 to 1.80] and a coefficient for the HCV × Western center interaction term of 6.07, 95% CI [2.69–9.44] (Supplementary Table 8, Supplemental Digital Content 3, http://links.lww.com/JS9/A518).

Predictive performance of various definitions for sarcopenia showed that sarcopenia, as the sole predictor in a model for OS or RFS, performs better in the East compared to the West, regardless of the definition (Table 2). Excluding the definition of Toshima, which defined sarcopenia as the lowest sex-dependent 5th percentile[23], differences between the definitions are small (West vs. East C-index range for OS: 0.51–0.55 vs. 0.56–0.58). The addition of BMI in the definition of sarcopenia did not lead to a clear improvement in predictive performance. However, both in the Eastern and Western cohorts, definitions using percentiles as relative cutoffs attain slightly higher predictive performance overall outcome measures compared to those using absolute cutoff values. Differences in the definition of sarcopenia had even fewer implications when sarcopenia was absorbed into a multivariable model (Supplementary Table 9, Supplemental Digital Content 3, http://links.lww.com/JS9/A518).

The impact of both SMI and Sarcopenia on outcomes OS and RFS was overall bigger for the East compared to the West. In the multivariate regression for OS, the interaction term was significant with a hazard ratio (HR) 0.37, 95% CI [0.19–0.73], and $P = 0.005$ (Table 3 and Fig. 2). However, for RFS, the interaction term at multivariate regression did not attain significance (HR

Table 2

Predictive performance sarcopenia definitions per region.

Sarcopenia definition			West					East				
Author (year)	Variables	Cutoff	Sarcopenia, %	OS (C-index)	RFS (C-index)	90d mort (AUC)	CD ≥3 (AUC)	LOS (Deviance)	Sarcopenia, %	OS (C-index)	RFS (C-index)	90d mort (AUC)	CD ≥3 (AUC)	LOS (Deviance)
1. Martin *et al.*, 2013[18]	Gender + BMI	Absolute	53	0.55	0.49	0.62	0.59	1173.05	52	0.57	0.54	0.61	0.52	3270.48
2. Caan *et al.*, 2017[19]	Gender + BMI	Absolute	63	0.52	0.51	0.6	0.55	1186.59	72	0.56	0.51	0.53	0.55	3238.9
3. Prado *et al.*, 2008[20]	Gender	Absolute	56	0.53	0.5	0.64	0.58	1181.86	72	0.56	0.51	0.53	0.54	3237.13
4. Carey *et al.*, 2017[21]	Gender	Absolute	51	0.52	0.5	0.6	0.61	1159	63	0.58	0.54	0.52	0.58	3231.5
5. Englesbe *et al.*, 2010[22]	Gender	Tertile	33	0.51	0.52	0.52	0.61	1090.5	33	0.57	0.55	0.6	0.54	3271.82
6. Beumer *et al.*, 2022[16]	Gender + BMI	Tertile	33	0.51	0.5	0.52	0.61	1136.9	33	0.58	0.55	0.6	0.59	3230.59
7. Toshima *et al.*, 2015[23]	Gender	5th perc	19	0.52	0.51	0.57	0.55	1193.77	13	0.53	0.51	0.5	0.54	3273.04

Predictive performance of a univariate model containing only sarcopenia as a predictor, with the columns presenting different outcome measures and the rows presenting various cutoff values to define sarcopenia.
90d mort, 90-day mortality; AUC, area under the receiver operating curve; CD, Clavien–Dindo score; LOS, length of stay; OS, overall survival; RFS, recurrence-free survival.

0.68, 95% CI [0.36–1.27], $P = 0.222$). Furthermore, only in the Eastern cohort was sarcopenia a significant predictor in both univariable and multivariable survival analyses. In particular, for OS at univariable analysis, the HR for sarcopenia was 1.89, 95% CI [1.33–2.69] with $P < 0.001$ corresponding to a 5-year survival of 75%, 95% CI [69–81] for patients without sarcopenia and 56%, 95% CI [47–67], for patients with sarcopenia. At multivariable analysis a HR for sarcopenia was similar with 2.00, 95% CI [1.230–3.08] with P value 0.002. For the perioperative outcome measures, 90-day mortality, and severe complications, there was no significant geographic effect modification (Supplementary Table 10, Supplemental Digital Content 3, http://links.lww.com/JS9/A518). For the length of stay, effect modification was found for both SMI (univariable −0.02, 95% CI [−0.02 to −0.01], $P < 0.001$; multivariable −0.02, 95% CI [−0.03 to −0.01], $P < 0.001$) and Sarcopenia (univariable 0.22, 95% CI [0.12–0.32], $P < 0.001$, multivariable 0.19, 95% CI [0.07–0.30], $P < 0.001$). For the univariable case, this would translate into an average difference of 4.35 days between sarcopenia and nonsarcopenia in the West and a difference of 3.43 days in the East.

Discussion

In this study, we compared the impact of muscle mass on clinical outcomes in an Eastern and Western setting. Additionally, we evaluated the impact of different cutoff values for sarcopenia with regard to its predictive performance. We found marked differences in terms of demographics, etiology, and outcome measures. However, the variables associated with muscle mass, such as Age, Gender, and BMI, were the same. Of these, the effect of BMI on SMI was significantly different in the two cohorts, with an increase in BMI in the West correlating with a lower gain in muscle mass compared to the East. With regard to a collection of frequently used cutoff values for sarcopenia, we found no difference in predictive performance for any of the outcome measures. It was, however, evident that the predictive performance of sarcopenia was higher in the East compared to the West for OS, RFS, 90-day mortality rate, severe complication rate, and length of stay. Focusing on the association between sarcopenia and OS, we observed a strong and significant association in the East, where this was not significant in the West. Moreover, the interaction term upon multivariable regression indicated significant differences. Therefore, we conclude that the impact of sarcopenia and an increase in muscle mass on survival differs between the East and West. Hence, we advise clinical trials regarding interventions to reverse sarcopenia and treatment guidelines using sarcopenia for risk stratification to be locally validated prior to clinical adoption.

Several independent studies investigated the relationship between sarcopenia and survival in patients receiving hepatectomy for HCC. None focused specifically on geographical differences. They were, however, conducted in various countries, among which several from Asia[24–29] and Europe[30–32]. In a recent meta-analysis by Xu *et al.*, no significant difference between Caucasian and Asian cohorts was found. This might, however, be caused by the fact that in the Caucasian subgroup, only two relatively small studies, with very heterogenous results, were available, rendering the analysis inconclusive[31,32]. Overall, the majority of studies concluded

Table 3

Geographical effect modification of muscle mass on survival.

					L3 skeletal muscle mass index		Sarcopenia	
Outcome	**Model**	**Cohort**	***n***	***n* events**	**HR [95% CI]**	***P***	**HR [95% CI]**	***P***
OS	Univariate[a]	All	553	205	0.99 [0.97–1.01]	0.207	1.54 [1.16–2.04]	0.003*
	Univariate	West	174	79	1.00 [0.98–1.03]	0.797	1.10 [0.69–1.75]	0.686
	Univariate	East	379	126	0.98 [0.96–1.00]	0.057	1.89 [1.33–2.69]	< 0.001*
	Univariate[a]	All	553	205	0.98 [0.96–1.00]	0.057	1.89 [1.33–2.69]	< 0.001*
	Interaction term		553	205	1.02 [0.99–1.06]	0.144	0.58 [0.32–1.05]	0.070
	Multivariate[a]	All	422	175	0.99 [0.97–1.02]	0.676	1.39 [1.00–1.93]	0.052
	Multivariate	West	144	64	1.04 [0.99–1.08]	0.116	0.76 [0.42–1.36]	0.351
	Multivariate	East	278	111	0.97 [0.93–1.01]	0.195	2.00 [1.30–3.08]	0.002*
	Multivariate[a]							
	Interaction term	All	422	175	0.99 [0.96–1.02]	0.451	2.00 [1.33–3.01]	0.001*
			422	175	1.02 [0.97–1.06]	0.453	0.37 [0.19–0.73]	0.005*
RFS	Univariate[a]	All	553	274	1.00 [0.99–1.02]	0.780	1.28 [1.00–1.65]	0.051
	Univariate	West	174	85	1.01 [0.99–1.04]	0.249	1.07 [0.68–1.68]	0.771
	Univariate	East	379	189	1.00 [0.98–1.01]	0.598	1.39 [1.03–1.88]	0.030*
	Univariate[a]	All	553	274	1.00 [0.98–1.01]	0.598	1.39 [1.03–1.88]	0.030*
	Interaction term		553	274	1.02 [0.99–1.05]	0.216	0.77 [0.45–1.32]	0.343
	Multivariate[a]	All	422	227	1.00 [0.97–1.02]	0.861	1.23 [0.91–1.66]	0.174
	Multivariate	West	144	73	1.01 [0.97–1.05]	0.498	0.79 [0.45–1.38]	0.411
	Multivariate	East	278	154	1.00 [0.97–1.04]	0.935	1.30 [0.89–1.9]	0.170
	Multivariate[a]	All	422	227	0.99 [0.96–1.02]	0.572	1.40 [0.98–2.01]	0.066
	Interaction term		422	227	1.02 [0.98–1.05]	0.408	0.68 [0.36–1.27]	0.222

Impact of the L3 skeletal muscle mass index (SMI) and Sarcopenia on the outcomes overall survival (OS); recurrence-free survival (RFS). Each row describes on the left a model for SMI and on the right a model for Sarcopenia. Only the coefficients of the variables SMI, Sarcopenia, and the interaction term with the Western cohort are shown. Control variables in the multivariable models consisted of Male gender, Age, Body mass index, Hepatitis C virus, Hepatitis B virus, Transarterial chemoembolization, Radiofrequency ablation, ASA, Diabetes, Hypertension, Cardiac comorbidity, Cerebral comorbidity, Child–Pugh score, Albumin–Bilirubin score, Tumor number at radiology, Tumor size in cm at radiology, Microvascular invasion, $\log_{10}$Alpha fetoprotein.

[a]Regression stratified per center.

HR, hazard ratio.

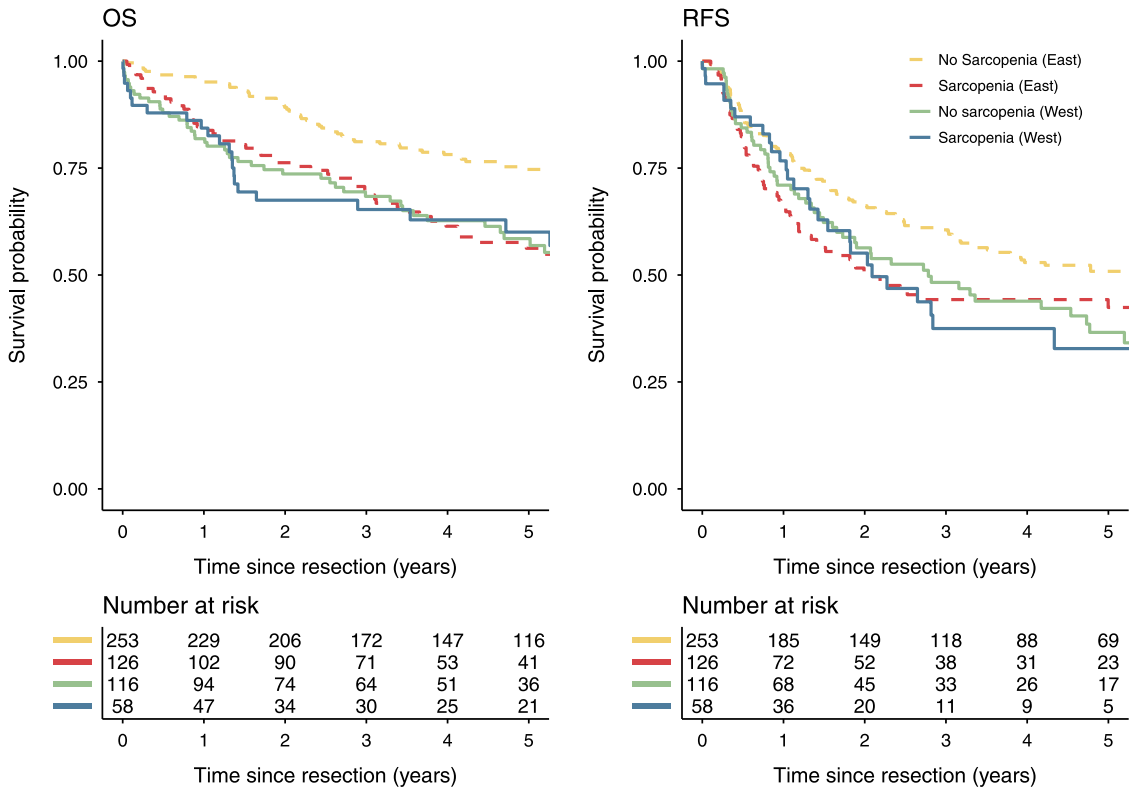

Figure 2. Kaplan–Meier curves of overall survival (OS) and recurrence-free survival (RFS) stratified by region and by sarcopenia status.

that sarcopenia was a strong prognostic factor for a decrease in OS, with point estimates for the HR ranging from 1.57 to 3.19[24–31]. Only a German study by Kroh *et al*.[32], investigating 70 patients reported that significance was not attained, remarking that in their report, the survival curves and the HR from their regression analysis were conflicting. Additionally, studies found that sarcopenia is a prognostic factor for reduced RFS[24,28,29,31]. It remains, however, complicated to compare the results of individual studies as different techniques for measuring muscle mass for sarcopenia were used. This makes it hard to interpret if their differences are structural, an artifact due to a lack of consensus on cutoff values, or normal statistical variation. Our study stands out in that regard as we collected a large body of data using clear predefined variable definitions and analyzed the data simultaneously. In this analysis, interestingly the association of sarcopenia with OS and RFS was much stronger in the East compared to the West with a point estimate of the HR of 1.89 versus 1.10, respectively. Leading to the question of what is causing the association between sarcopenia and impaired survival.

Reasoning backward from the causes of death for HCC patients. A recent study by Kim *et al*. investigating liver cancer patients, of which 83% had HCC, in South Korea found that 92% of the patients died due to their primary liver cancer. Where only 6% of the patients died due to noncancer-related causes, of which 45% were due to liver disease or viral hepatitis[33]. These results were similar to those of an analysis of the SEER database performed by Kumar *et al*.[34]. Therefore, it is important to investigate if sarcopenia accelerates or is a reflection of more aggressive HCC. Although the causes of sarcopenia are multifactorial, one important aspect is that HCC and liver fibrosis cause an accelerated rate of starvation. Increased fatty acid oxidation and gluconeogenesis disrupt the balance between protein synthesis and protein breakdown[35]. More specifically, amino acids are made available by proteolysis of skeletal muscle mass which acts as the major protein store. Furthermore, several mediators that inhibit protein synthesis have been described, such as hyperammonemia, elevated levels of myostatin, increased insulin resistance, decreased availability of branched-chain amino acids due to anorexia, and decreased levels of testosterone[36,37]. Furthermore, imbalances in reactive oxygen species and reduced physical activity also contribute to the loss of muscle mass. In turn, it has been hypothesized that the proinflammatory effect of myokines excreted by skeletal muscle cells, such as myostatin, interleukin 6, follistatin, aggravate liver fibrosis, HCC development, and recurrence[10]. However, in our study, we did not find a strong correlation with RFS, with only a significant univariable association in the Eastern cohort questioning this rationale.

An alternative theory on how sarcopenia impacts survival is through increased risk of, and a reduced ability to recover from postoperative complications. In an earlier study, the survival difference between sarcopenic and nonsarcopenic patients was largest in the first years after resection[30]. Also in our study, it can be observed that although the slope of the sarcopenia groups and nonsarcopenia group are different at all times, the largest difference in slope is in the first 2 years after surgery (Fig. 1). In concordance with the literature, in our cohort's sarcopenia was strongly associated with length of hospital stay suggesting a reduced ability of sarcopenic patients to recover from the surgical trauma. Interestingly the impact of sarcopenia on length of stay differed between the Eastern and Western cohorts. With regard to complications, in our study, sarcopenia was strongly correlated with severe complications at univariate regression both in the East (OR 2.32, 95% CI [1.27–4.26]) and West (OR 2.56, 95% CI [2.56–5.26]). At multivariate regression, the odds ratio was roughly the same but surrounded with more uncertainty, only reaching significance for the combined cohort (OR 2.20, 95% CI [1.23–3.94]). These results are in line with a recent cohort study by Marasco *et al*.[38] and a meta-analysis by Thorman *et al*.[39]. The latter study described the effect of sarcopenia on severe complications (i.e. complications CD $\geq$ 3) in six small cohorts and found a pooled OR of 1.37, 95% CI [0.61–3.09], and a significant heterogeneity across cohorts with an I^2 of 82%. This suggests that especially the perioperative effects of sarcopenia might be different across geographical regions.

Besides the geographical differences, we also investigated the impact of various cutoff values of sarcopenia. As earlier described, the fact that multiple cutoff values are being used hampers clear communication and comparison. We imagine that one of the reasons why there are so many in circulation is due to the fact that muscle mass varies a lot across age groups, gender, BMI, and regions where people have different diets and physical routines. This makes it harder to define what is normal and when low muscle mass is pathologic. The question arises if we can do without cutoff values altogether, as binarization of a continuous variable also leads to a loss of information. However, cutoff values also define fixed groups of patients for which clinicians can make practical decisions regarding interventions. Furthermore, cutoffs entail a scale transfer; the difference between patients with sarcopenia versus those without is more tangible than a unit increase in SMI. Therefore, we reason that they are, for now, a necessary evil. In this research, we observed that the relative cutoff values using percentiles performed slightly better compared to absolute cutoff values with regard to predictive performance.

Although our research was conducted carefully, we want to point out some limitations of this study. First, although the sample size allowed for comprehensive analysis in terms of control variables, it is known that the interaction terms have low statistical power[40]. Therefore, not attaining statistical significance of the interaction terms should not be seen as proof that the effect of sarcopenia on survival is the same in the East and West. In extension, we would like to point out that we performed multiple analyses, and we did not use a false discovery rate correction as this would further reduce the power of the interaction terms. Secondly, this observational study could potentially be affected by confounders that we could not control for. For example, variables such as type of diet, smoking status, or activity level could affect both muscle mass and survival, potentially biasing our results. Furthermore, although recurrence was assessed by experienced radiologists, over time, radiology guidelines for HCC were subject to minor changes, and a single definition for recurrence would be an incorrect simplification of clinical practice. Additionally, we acknowledge that variations in the reporting quality of complications across regions may affect the reproducibility of our results regarding complications. Lastly, although we screened all consecutive resections in both centers, we only included records in the analysis if patients had undergone a CT scan within 3 months prior to surgery. This could potentially limit the generalizability of our results. We invite future studies to corroborate our results and replicate our analysis with data from other centers, not only from Asia and Europe but also from Africa and America. A molecular analysis studying the

underlying reason why sarcopenia is harming survival and what factors per region change the association are needed and could aid ongoing preclinical efforts to identify novel targets to treat HCC[41–43]. Furthermore, future randomized controlled trials are best equipped to investigate if interventions to increase muscle mass in sarcopenic patients lower their risk of serious complications and improve survival.

Overall, we conclude that the impact of sarcopenia on both short-term and long-term outcomes differs between Eastern and Western cohorts. Clinical trials and guidelines, including sarcopenia as a variable, require local validation. Furthermore, we conclude that there is no clear justification for different sarcopenia definitions in various regional cohorts, and further research is needed to define the best definition to be used worldwide.

Ethical approval

The protocol for this study (MEC-2018-1544) adhered to the Declaration of Helsinki and was approved by the Medical Ethics Committee of Erasmus MC, Erasmus University Medical Centre, Rotterdam, the Netherlands and by the Okayama University Hospital, Okayama, Japan.

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Author contributions

B.R.B., K.T., S.B., J.L.A.v.V., and J.N.M.I.: conceptualization; B.R.B. and K.T.: data curation; B.R.B. and K.T.: project administration; B.R.B.: methodology; B.R.B.: formal analysis; B.R.B., K.T., S.B., Y.U., T.Y., T.F., J.L.A.v.V., and J.N.M.I.: investigation; J.L.A.v.V., and J.N.M.I.: supervision; B.R.B.: original draft; K.T., S.B., Y.U., T.Y., T.F., J.L.A.v.V., and J.N.M.I.: review and editing.

Conflicts of interest disclosure

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Research registration unique identifying number (UIN)

1. Name of the registry: University hospital medical information network clinical trial registry.
2. Unique identifying number or registration ID: Protocol ID UMIN000049970.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000056915

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Data availability statement

Relevant anonymized patient-level data that underlie the results reported in this article will be made available to researchers who provide a methodologically sound proposal. Our results can be replicated using the analytic code supplied in the supplemental files. The data will be available immediately following publication ending 5 years following article publication. Proposals should be directed to j.ijzermans@erasmumc.nl, where data requestors will be asked to sign a data access agreement at each of the participating centers.

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