International Journal of Surgery 30 (2016) 136–142

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Adverse impact of low skeletal muscle index on the prognosis of hepatocellular carcinoma after hepatic resection

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HIGHLIGHTS

- Skeletal muscle index (SMI) was measured in HCC patients by using preoperative CT.
- Low-SMI was an independent prognostic factor for RFS in patients with BMI $\geq$ 22.
- Body mass index and visceral fat area was not associated with prognosis.
- CT is a simple and useful tool for predicting prognosis.

ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form
31 March 2016
Accepted 28 April 2016
Available online 4 May 2016

Keywords:
Hepatocellular carcinoma
Body composition
Sarcopenia
Prognosis

ABSTRACT

Background: Skeletal muscle depletion predicts poor prognosis of patients with certain cancers. However, the correlation between low skeletal muscle index (SMI) and the prognosis of hepatocellular carcinoma (HCC) is not well understood.

Methods: To determine their influence on prognosis, skeletal muscle index (SMI) and visceral fat area (VFA) were measured using computed tomography at the level of the third lumbar vertebra of 195 patients who underwent primary hepatectomy for hepatocellular carcinoma (HCC). We defined sarcopenia using cutoff values for SMI as 43.75 cm^2/m^2 and 41.10 cm^2/m^2 for males and females, respectively.

Results: Sarcopenia was present in 89 of 195 (45.6%) patients and correlated significantly ($P < 0.001$) with female sex, low body mass index (BMI), low subcutaneous fat area, low VFA, and low serum albumin levels. There was a trend indicating the association of sarcopenia with poor cumulative recurrence rate (CRR) ($P = 0.13$). In patients with BMI $\geq$22, CRR was significantly different between patients with or without sarcopenia (19.0 or 35.2 months, respectively, $P = 0.03$). In contrast, there was no significant difference in patients with BMI $\geq$22 as a function of VFA ($P = 0.47$). When the cohort was limited to patients with BMI $\geq$22, multivariate analysis showed that sarcopenia was a significant independent risk factor for recurrence (hazard ratio = 1.6; 95% confidence interval, 1.1–2.5; $P = 0.02$).

Conclusions: Low-SMI was an independent adverse prognostic factor for CRR in patients with BMI $\geq$22. Therefore, preventing muscle wasting may improve the CRR of patients with HCC.

1. Introduction

Hepatocellular carcinoma (HCC) causes approximately 740,000 deaths annually and is the second most frequent cause (after lung cancer) of cancer deaths worldwide [1]. Despite recent developments in diagnostic technologies and sophisticated surgical techniques [2], the recurrence rate of HCC after curative resection remains high, because 80–90% of HCCs develop from chronic hepatitis or cirrhosis caused by infection with hepatitis B or hepatitis C viruses. Therefore, simple, novel clinical prognostic indicators for HCC apart from genetic diagnosis [3–6] are required to

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http://dx.doi.org/10.1016/j.ijsu.2016.04.049
1743-9191/

predict and, if possible, prevent recurrence.

Prognostic factors based on assessment of body composition and inflammation attract the attention of clinicians, because these factors are significantly associated with the short- and long-term outcomes of certain cancers [7–11]. Among these factors, sarcopenia, generally defined as muscle mass ≤ two standard deviations below the mean muscle mass characteristic of healthy persons <40 years of age, indicates low functional capacity and is associated with a higher risk of falling and bone fractures of elderly people [12].

Moreover, sarcopenia is a predictor of poor prognosis of patients with cancers of digestive organs and those undergoing liver transplantation due to liver cirrhosis and hepatocellular carcinoma [13–17]. Similarly, in patients with HCC, evidence indicates that sarcopenia is an independent adverse prognostic factor [13,18,19]. In contrast, there is debate regarding whether high visceral fat area (VFA) predicts survival of patients with HCC [18,20]. In the area of liver disease, fatty patients might be more likely to have early recurrence of HCC from fatty liver. Conversely, we expected that the patients with low VFA are generally undernourished and may suffer from poor prognosis. However, most previous studies evaluating the impact of body composition on the prognosis of patients with HCC investigated only one parameter of many parameters of body composition [13,19–21].

To identify the features of body composition that may have a powerful impact on the prognosis of patients with HCC, we investigated the relationship between various body composition components, clinical factors, and outcomes of patients with HCC who underwent hepatic resection.

2. Methods

2.1. Patients

We enrolled 195 consecutive patients who underwent primary and curative hepatectomy for hepatocellular carcinoma (HCC) at the Department of Gastroenterological Surgery, Nagoya University Hospital, between July 2003 and October 2014. We confirmed the histological diagnosis of HCC for all patients. Written informed consent for inclusion in the study, as required by the Institutional Review Board of Nagoya University, was obtained from all patients.

2.2. Surgical procedure

Major and minor hepatectomies were defined as the resection of ≥4 or <4 Couinaud segments, respectively. Measurement of the rate of disappearance of indocyanine green from plasma and volumetric computed tomography (CT) were always performed to evaluate future functional liver reserves. Postoperative complications were graded according to the Clavien-Dindo classification [22], and postoperative complications were defined as Clavien-Dindo grade IIIa or higher. Tumor stage was categorized according to the guidelines of the Liver Cancer Study Group of Japan (The 5th Edition, Revised Version) [23].

2.3. Follow-up strategy

After discharge from the hospital, patients were examined once each month for 6 months and every 3 months thereafter. None of the patients received adjuvant chemotherapy. Blood tests, including serum α-fetoprotein and protein induced by vitamin K absence or antagonist- II, were performed each month. Abdominal ultrasonography was performed every 3 months, and dynamic contrast-enhanced CT scans were performed every 6 months. Cumulative recurrence rate (CRR) was calculated as the time between curative resection of HCC and confirmation of recurrence of disease.

2.4. Image analysis

Total skeletal muscle and fat tissue areas (cm^2) were evaluated from a single preoperative CT image acquired at the 3rd lumber vertebra (L3), using Hounsfield unit thresholds of −29 to +150 for skeletal muscle and −200 to −50 for visceral and subcutaneous fat tissues. All CT images were analyzed using SYNAPSE VINCENT software version 4.0 (Fuji Film, Tokyo, Japan). The cross-sectional skeletal muscle area (cm^2) was normalized using the square of the height (m^2) to obtain the L3 skeletal muscle index (SMI, cm^2/m^2). Cutoff values for skeletal muscle were defined as 43.75 cm^2/m^2 and 41.10 cm^2/m^2 for males and females, respectively [13,16]. Cutoff values for VFAs (cm^2) were 103 cm^2 and 69 cm^2 for males and females, respectively, which are recognized by physicians practicing in Japan [24]. We assigned patients to low-SMI or high-SMI groups and high-VFA or low-VFA groups according to these cutoff values.

2.5. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and range. Correlations between clinicopathological variables and skeletal muscle index (SMI) were analyzed using the χ^2 and Fisher's exact tests. Overall survival (OS) and CRR were calculated using the Kaplan–Meier method, and the differences in survival curves were analyzed using the log-rank test. The multivariate Cox proportional hazard model was used to determine independent risk factors associated with CRR. Data were analyzed using JMP v10 software (JMP, SAS Institute, Cary, NC, USA). The level of statistical significance was defined as $P < 0.05$.

3. Results

Patient demographics and clinical characteristics are listed in Table 1. The median follow-up period was 1121 days (range, 37–3622 days), and 67 (34.4%) patients died by the end of the follow-up period. Patients' mean age was 66 years, and the male to female ratio was 157:38. The mean BMI (kg/m^2) was 23.2 kg/m^2. The TNM stages of patients' cancers were as follows: stage I ($n = 20$), stage II ($n = 112$), stage III ($n = 42$), stage IVA ($n = 19$), and stage IVB ($n = 2$). Sixty-two (31.8%) patients underwent major hepatectomy, and 133 (68.2%) underwent minor hepatectomy or non-anatomical resection. Postoperative complications were present in 41 (21.0%) patients.

3.1. Correlation between body composition and clinicopathological factors

There was a significant positive correlation between BMI and SMI in males and females (Supplementary Fig. 1) ($P < 0.001$ for males, $P = 0.04$ for females). The mean SMI values were 45.3 cm^2/m^2 (range, 30.8–67.8) for males and 38.0 cm^2/m^2 (range, 29.2–66.6) for females. Similarly, there was a significant correlation between BMI and VFA in males and females (Supplementary Fig. 2) ($P < 0.001$, respectively). The mean VFAs were 136.2 cm^2/m^2 (range, 12.5–356) for males and 84.5 cm^2/m^2 (range, 11.4–298.5 cm^2) for females.

When the cutoff values for SMI were applied (43.75 cm^2/m^2 and 41.10 cm^2/m^2 for males and females, respectively), the cohort was divided into 89 (45.6%) and 106 (54.4%) patients with low and high-SMI. The comparisons of clinicopathological features of HCC patients with low or high-SMI are shown in Table 2. Females were more likely to have low-SMI compared with males ($P < 0.001$). The patients with low-SMI had significantly lower BMIs, VFAs, and

Table 1
Patient demographics and clinical characteristics.

Variables	n = 195
Age (years)	66 (22–80)
Sex (male/female)	157 (80%)/38 (20%)
BMI (kg/m^2)	23.2 (14.3–37.3)
Etiology (HBV/HCV/HBV + HCV/others)	50(26)/88(45)/1(0.5)/56(28.5%)
Child Pugh classification (A/B)	182 (93%)/13 (7%)
Tumor size (cm)	3.5 (0.1–17.5)
Number of tumors (solitary/multiple)	150 (77%)/45 (23%)
Tumor differentiation (well/moderate/poor)	38(19)/144(74)/12(6%)
TNM stage (I/II/III/IVA/IVB)	20(10)/112(57)/42(21)/19(11)/2(1%)
Microvascular invasion (yes/no)	30(15%)/165(85%)
Hepatectomy (major/minor)	62(31.8%)/133(67.2%)
Operation time (min)	330 (96–792)
Intraoperative blood loss (ml)	711 (3–17090)
Intraoperative blood transfusion	42 (21.5%)
Postoperative complication	41 (21.0%)
90-days mortality	5 (2.6%)

Values are median (range).
BMI body mass index, *HBV* hepatitis B virus, *HCV* hepatitis C virus.
TNM tumor node metastasis.

Table 2
Clinicopathological factors in patients with, and without sarcopenia.

	Low-SMI (n = 89)	High-SMI (n = 106)	*P*-value
Age (years)	66.2 ± 10.1	63.8 ± 10.1	0.1
Sex (male/female)	57(64%)/32(36%)	100(94%)/6(6%)	<0.001*
Skeletal muscle index (cm^2/m^2)	37.1 ± 3.6	49.5 ± 4.9	<0.001*
BMI (kg/m^2)	21.8 ± 2.6	24.3 ± 3.5	<0.001*
Visceral fat area (cm^2)	100.5 ± 72.2	147.6 ± 71.1	<0.001*
Subcutaneous fat area (cm^2)	88.1 ± 49.3	104.6 ± 46.0	0.02*
Albumin (g/dl)	3.7 ± 0.6	4.0 ± 0.4	<0.001*
Total bilirubin (mg/dl)	0.8 ± 0.8	0.7 ± 0.2	0.12
Platelet count ($\times 10^4$/mm^3)	17.0 ± 0.8	16.4. ± 0.8	0.62
Prothrombin time (%)	93.4 ± 12.5	94.6 ± 13.7	0.51
ICGR15 (%)	12.6 ± 7.3	12.7 ± 10.6	0.96
Child Pugh grade (A/B)	81(91%)/8(9%)	101(95%)/5(5%)	0.23
Tumor size (cm)	4.8 ± 3.5	4.1 ± 3.2	0.12
Number of tumors (solitary/multiple)	75(84%)/14(16%)	75(71%)/31(29%)	0.02*
Tumor differentiation (well/moderate/poor)	15(17)/69(77)/5(6%)	23(22)/75(71)/7(7%)	0.39
AFP (ng/ml)	11.8 (0.8–70632)	14 (1–82730)	0.21
PIVKA-II (mAU/ml)	96 (3–91960)	53 (10–103910)	0.46
TNM stage (I/II/III/IVA/IVB)	6(7)/58(65)/18(20)/7(8)/0(0%)	14(13)/54(51)/24(23)/12(11)/2(2%)	0.14
Microvascular invasion (yes/no)	11(12%)/78(88%)	19(18%)/87(82%)	0.45
Hepatectomy (major/minor)	25(28%)/64(72%)	37(35%)/69(65%)	0.31
Operation time (min)	333 ± 126	361 ± 133	0.13
Intraoperative blood loss (ml)	1229 ± 2149	1301 ± 1551	0.79
Intraoperative blood transfusion	21(23.6%)	21(19.8%)	0.52
Postoperative complication	18(20.2%)	23(21.7%)	0.8
90-days mortality	2(2.2%)	3(2.8%)	0.8

Values are mean ± SD, median (range).
BMI body mass index, *ICGR15* indocyanine green dye retention test at 15 min, *AFP* α-fetoprotein, *PIVKA-II* vitamin K absence or antagonist- II, *TNM* tumor node metastasis.

subcutaneous fat areas compared with those with high-SMI. Although serum albumin levels in the low-SMI group were significantly lower compared with those of the high-SMI group ($P < 0.001$), except for the number of tumors, no differences were noted between the two groups in liver function, tumor factors, and surgical factors. There was no difference in the incidence of postoperative complications and 90-day mortality between the two groups. Because we intended to analyze only patients who are indicated for hepatectomy in this study, the patients with extremely poor liver function such as Child C were excluded. Indeed, liver damage status of most patients had been at the level of Child A as shown in Table 2 (Low-SMI: 91%, High-SMI: 95%). The patients enrolled in this study were only those who underwent hepatectomy for the first time, and whose ASA physical status were only Class 1 or Class 2 The patient backgrounds were as follows; Class 1: 82 patients in high-SMI and 70 in low-SMI, Class 2: 24 in high-SMI and 19 in low-SMI ($P = 0.82$). When the cohort was limited to the patients with stage I and II, there was a trend for low SMI that correlated with shorter CRR (Median survival time (MST); 20.4 months and 42.4 months for patients with low and high-SMI, respectively, $P = 0.20$). The results were similar when the cohort was limited to the patients with stage III and IV (MST; 9.1 months and 23.1 months for patients with low and high-SMI, respectively, $P = 0.07$).

3.2. Association of the components of body composition and patient survival

Of the 195 patients, 67 died during the study for the reasons as follows: $n = 55$, cancer progression; $n = 3$, liver failure; $n = 5$,

surgery; and $n = 4$, diseases unrelated to the liver. Tumors recurred in 107 patients (88 males, 19 females). Deceased patients not clearly associated with recurrence of HCC and those with another disease were excluded from the calculation of CRR. We did not detect a significant relationship between OS and BMI ($P = 0.52$) (Supplementary Fig. 3). The same result was obtained when we applied a different cutoff value of BMI (data not shown). Further, there was no significant relationship between CRR and BMI ($P = 0.87$, data not shown). The OS of patients according to SMI and VFA is shown in Fig 1. There was no significant correlation between OS and SMI, and VFA ($P = 0.72$ and $P = 0.34$, respectively). Fig. 2 shows the correlation between CRR with SMI or VFA. There was no significant correlation between CRR and SMI or RMS and VFA ($P = 0.13$ and $P = 0.29$, respectively).

According to the receiver operating characteristic (ROC) curve for BMI and sarcopenia, the optimal cutoff value for BMI was 21.3 (sensitivity, 48.3% and specificity, 84.0%) (data not shown). Therefore, we applied an approximate value of 22, which was considered the standard value [25]. When patients were classified according to BMI ($\geq$22 or <22 kg/m^2) (Fig. 3) there was a significant difference in CRR (MST: 19.0 months and 35.2 months for patients with low and high-SMI, respectively, $P = 0.03$) only in the group with BMI $\geq$22. In contrast, there was no significant difference between the groups as a function of VFA for patients with BMI $\geq$22 ($P = 0.47$) and <22 ($P = 0.29$), respectively. When the cohort was limited to males there was a trend for low-SMI and low-VFA that correlated with shorter CRR ($P = 0.05$ and $P = 0.17$, respectively) (Supplementary Fig. 4).

3.3. Sarcopenia as a predictor of HCC recurrence

When the cohort was limited to patients with BMI $\geq$22, univariate analysis of CRR using the Cox proportional hazards model identified the prognostic factors as follows: poorly differentiated tumor cells, microvascular invasion, serum α-fetoprotein ($\geq$20 ng/ml), and low-SMI. The results of multivariate analysis revealed that poorly differentiated tumor cells, microvascular invasion, and low-SMI were independently associated with increased risk of recurrence (hazard ratio = 1.6; 95% confidence interval, 1.1–2.5; $P = 0.02$) (Table 3).

4. Discussion

The concept of sarcopenic obesity is associated with poor survival of patients with malignant or nonmalignant disease [26,27]. In our present study of HCC patients, multivariate analysis revealed that low-SMI was an independent adverse prognostic factor for CRR of patients with HCC with BMI $\geq$22. Although previous studies found that sarcopenia obesity is an adverse prognostic factor for several cancers [15,18,26], in the present study, low-SMI was an independent prognostic factor in patients with normal body weight. Although some authors define obesity as BMI >25–30, we set a cutoff value of BMI = 22 here, because there were only 47 of 195 patients with BMI $\geq$25.

Many Japanese people have slimmer bodies than Westerners and patients with digestive cancers tend to lose weight. In contrast, SMI did not influence OS, likely because there are many effective therapeutic options after recurrence, such as repeat surgery, transcatheter arterial chemoembolization, radiofrequency ablation, and chemotherapy that includes sorafenib. The marked changes in body composition after primary surgery might provide another explanation.

Patients with low-SMI have significantly lower BMI values compared with those with high-SMI [13,15,16,18], and the serum albumin levels of such patients are generally lower [28]. Albumin is a negative acute-phase protein that decreases in concentration with ongoing systemic inflammation, poor health, and malnutrition [29]. Because these unfavorable conditions lead to depletion of skeletal muscle mass, low albumin concentrations might reflect low-SMI. The results of the present study are consistent with these findings and indicate that low serum albumin levels may serve as an early warning sign of sarcopenia [30].

Ohki et al. [31]. limited the patients with NASH only, whereas approximately 70% patients had viral hepatitis in this study as shown in Table 1. The cause of NASH is thought to be fatty liver due to the metabolic syndrome, and that the increase in visceral fat could become risk factor of the recurrence from fibrosis of the liver. Our result that the patients with high VFA had better prognosis was near to that of Itoh et al. [20]. In this study, VFA was not related to tumor factors but was significantly correlated with patients' factors including BMI ($P < 0.001$) and SMI ($P < 0.001$). Although the result was not significant this time, the patients with high-VFA were weakly associated with the better prognosis than that of those with low-VFA.

Nutritional support and exercise therapies improve the outcomes of patients with cirrhosis [32]. Therefore, preventing muscle wasting might represent an effective strategy for improving the

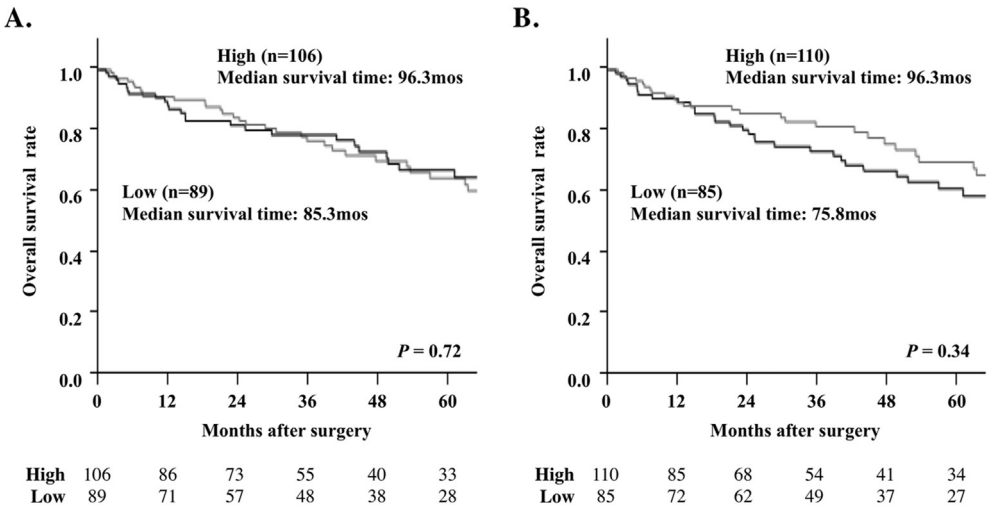

Fig. 1. There was no significant correlation between OS, SMI, and VFA. (A) $P = 0.72$. (B) $P = 0.34$, log-rank test.

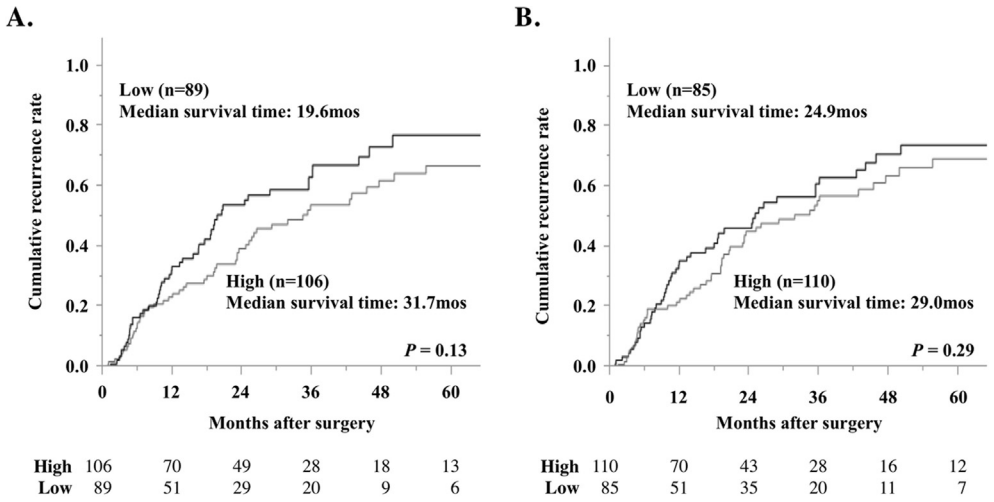

Fig. 2. There was no significant correlation between CRR, SMI, and VFA. (A) $P = 0.13$. (B) $P = 0.29$, log-rank test.

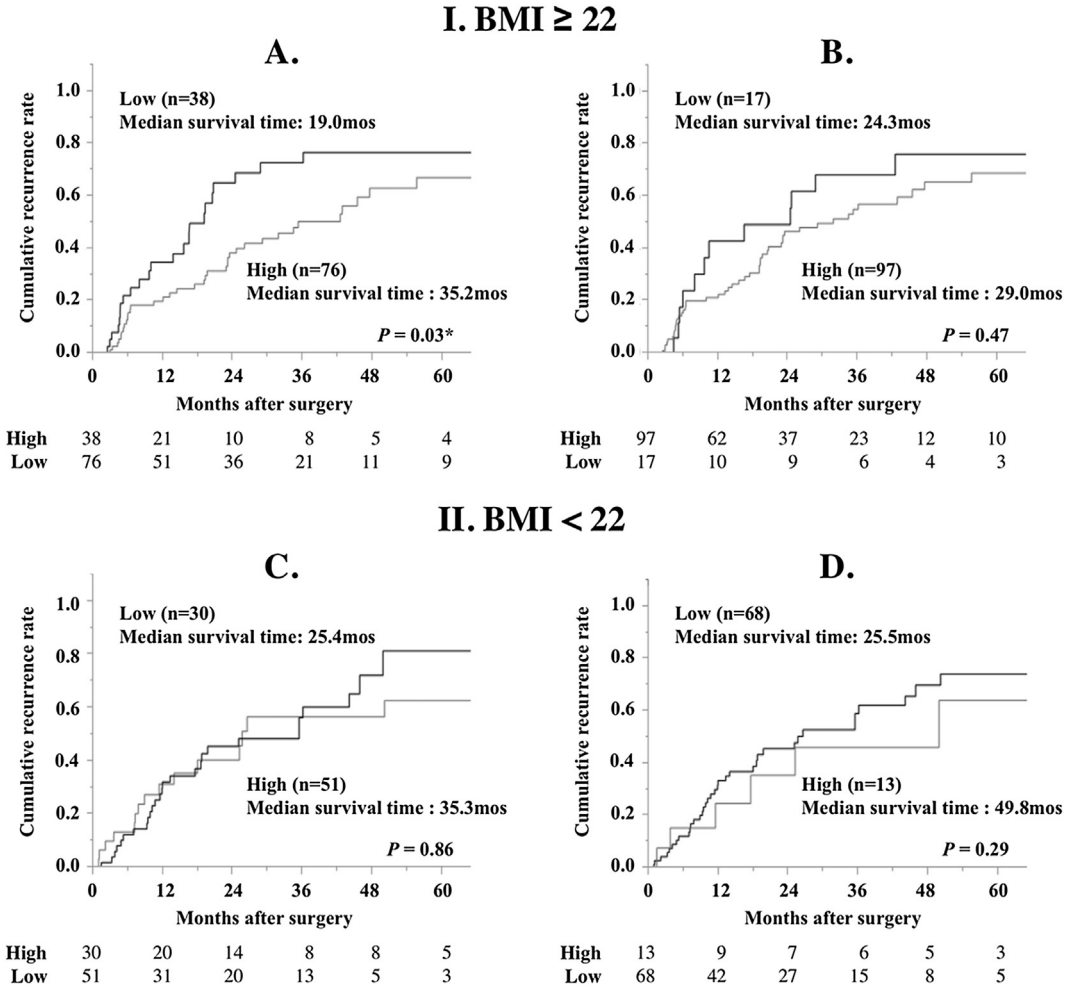

Fig. 3. In the BMI ≥22 group, patients with low-SMI had significantly worse prognoses compared with those of patients with high-SMI ($P = 0.03$) but not with those of the BMI <22 group ($P = 0.86$). There was no significant difference between the groups as a function of VFA (BMI ≥22, $P = 0.47$; BMI <22, $P = 0.29$). (A) $P = 0.03$. (B) $P = 0.47$. (C) $P = 0.86$. (D) $P = 0.29$, log-rank test.

prognosis of patients with HCC patients. Branched-chain amino acids (BCAAs) and vitamin D (VD) are two of the most important components of nutritional therapy [33]. For example, perioperative nutritional therapy using BCAAs increases significantly the overall survival of patients with cirrhosis and sarcopenia who undergo liver transplantation [17]. Low serum levels of VD are associated

Table 3
Univariate and multivariate analyses of possible factors for recurrence-free survival in patients with hepatocellular carcinoma (BMI ≥ 22).

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Sex (male)	1.2	0.7–2.0	0.55			
Age (years)	1.0	1.0–1.1	0.08			
Low-SMI	1.8	1.1–3.0	0.03*	1.6	1.1–2.5	0.02*
Low-VFA	1.3	0.6–2.3	0.48			
The presence of HCV-ab	1.1	0.7–1.9	0.59			
Child Pugh B	1.6	0.5–3.6	0.37			
Albumin<3.5(g/dl)	1.7	0.9–3.1	0.08			
Platelet<10.0 × 10^4/mm^3	1.7	0.8–3.3	0.18			
Liver cirrhousis	0.8	0.5–1.2	0.32			
Tumor size≥3.5 cm	1.0	0.6–1.7	0.94			
TNM stage ≥ III	1.5	0.9–2.6	0.13			
Multiple tumors	1.3	0.8–2.1	0.25			
Poorly differentiation	6.2	2.1–15.0	0.003*	4.7	2.2–9.2	0.002*
Microvascular invasion	2.7	1.5–4.7	0.002*	2.9	1.8–4.5	<0.001*
AFP≥20 (ng/ml)	2.4	1.4–4.0	0.002*	1.1	0.7–1.7	0.73
PIVKA-II≥40 (mAU/ml)	1.3	0.8–2.3	0.36			
Hepatectomy (major)	1.4	0.9–2.1	0.15			
Operation time ≥ 330 (min)	1.1	0.8–1.7	0.52			
Intraoperative blood loss≥700 (ml)	1.4	1.0–2.1	0.07	1.4	0.9–2.1	0.09
Intraoperative blood transfusion	1.0	0.6–1.6	1.0			
Postoperative complication	1.1	0.7–1.8	0.62			

HR hazard ratio, *CI* confidence interval, *VFA* visceral fat area, *HCV-ab* hepatitis C virus antibody, *AFP* α-fetoprotein, *PIVKA-II* vitamin K absence or antagonist- II.

with an increased risk for the depletion of muscle mass [34]. VD signals through the 1,25-hydroxyvitamin nuclear receptor and affects the growth and differentiation of muscle cells [35]. Moreover, VD therapy increases muscle function in people with low serum levels of VD [36]. However, nutritional therapy alone is insufficient to increase skeletal muscle mass and may be more effective in combination with exercise therapy [37].

The present study has several limitations. In our cohort, the relatively low representation of females (19.5%) might have introduced selection bias. In addition, predominance of Stage I/II cancers resulted in lack of correlation between some established prognostic factors with RFS. The definition of sarcopenia varies even among studies conducted in Japan by Japanese researchers [13,18,19]. CT is the standard procedure for quantifying skeletal muscle mass and assessing metabolic activity, and some studies define sarcopenia and obesity using anthropometric measurements of preoperative CT images [8,21,38–40]. In the present study, we defined skeletal muscle mass depletion according to previous studies of Japanese patients who were measured at the L3 level with SMI values ≥43.75 cm^2/m^2 and ≥41.10 cm^2/m^2 for males and females, respectively. Using these definitions, the combined prevalence of low-SMI was 45.6% (36.3% for males and 84.2% for females). Because applying a different definition will likely change the results, the actual prevalence of sarcopenia in Japanese HCC patients may differ.

Another limitation is that some researchers likely disagree with the cutoff value of BMI = 22. Although the BMI cutoff value is usually 25 or 30 [15,26,27], here there were only 7 patients who met the definition of BMI ≥25 and low-SMI. Therefore, we used ROC curve analysis and set the cutoff value of BMI = 22 as an approximation of the optimal value. The last limitation of this retrospective study is that muscle strength and physical performance were not measured. Although the European Working Group on Sarcopenia in Older People recommends that a diagnosis of sarcopenia requires demonstrating decreases in muscle mass and function [41], most reports of sarcopenia measure only muscle mass for descriptive purposes [14,15,18,19,21], and their definitions of sarcopenia vary substantially. Ideally, evaluating sarcopenia requires measuring grip strength and gait speed.

In conclusion, we show here that low-SMI was an independent prognostic factor for CRR of patients with HCC with BMI ≥22, although BMI and VFA did not affect prognosis. Because SMI, rather than BMI and VFA, is important for determining the prognosis of patients with HCC, evaluation of skeletal muscle mass using preoperative CT is a simple and useful tool for predicting prognosis.

Ethical approval

None.

Sources of funding

None.

Author contribution

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Conflicts of interest

The authors have no conflicts of interest to declare.

Guarantor

Tsutomu Fujii.
Suguru Yamada.

Research registration unique identifying number (UIN)

906.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijsu.2016.04.049.

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