RESEARCH ARTICLE

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Sarcopenia as a Predictive Factor for Recurrence of Hepatocellular Carcinoma Following Radiofrequency Ablation

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Abstract

Background: Sarcopenia is a skeletal muscle mass deficiency and a potential prognostic factor for the recurrence of hepatocellular carcinoma (HCC). **Objective:** To determine whether sarcopenia correlates with the recurrence rate of HCC after curative radiofrequency ablation (RFA) in early and very early HCC. **Methods:** We retrospectively reviewed 669 HCC patients who underwent their first curative RFA at Siriraj hospital from 2011 to 2020. Fifty-six patients who were diagnosed with HCC by triple-phase CT scan and had complete response on follow-up CT were included. All patients underwent skeletal muscle index (SMI) assessment at level L3 vertebra and sarcopenia was defined by the cut-off values of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women. We compared patients with and without sarcopenia. Time to recurrence was evaluated by the Kaplan-Meier method. Univariate and multivariate Cox regression analysis was performed. **Results:** Sarcopenia was present in 37 of 56 patients (66.1%). There was no significant difference between groups except body mass index (BMI) (P<0.001) and serum alanine aminotransferase (ALT) (P=0.035). There was a promising result indicating the difference of time to recurrence between each group (P=0.046) and potential association of sarcopenia with HCC recurrence (HR=2.06; P=0.052). The Child-Pugh score and tumor number were independent risk factors for HCC recurrence (HR=2.04; P=0.005 and HR=2.68; P=0.017, respectively). **Conclusion:** Sarcopenia is a potential prognostic factor for recurrence of HCC in Thai patients who underwent RFA. A larger study is required to properly confirm this association.

Keywords: Sarcopenia- hepatoma- Low muscle mas- muscle atrophy- skeletal muscle index- HCC- RFA

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Introduction

Hepatocellular carcinoma (HCC) was one of the most common cause of cancer-related death in the Asia-Pacific region and one with the highest mortality rate worldwide (Kew, 2010; Zhu et al., 2016). There are many new treatment options in the Barcelona Clinic Liver Cancer (BCLC) guideline that have helped improve survival rates. (Bruix et al., 2005; Bruix et al., 2011; Bruix et al., 2016) Selection of the most appropriate treatment regimen is determined by disease factors (number and size of the HCC as well as portal vein thrombosis and metastasis), liver capacity factors (serum bilirubin, portal hypertension), and patient's performance factor. The computed tomography (CT) and magnetic resonance imaging (MRI) are powerful tools to diagnose, stage, and guide treatment decisions in HCC. Radiofrequency ablation (RFA) is a treatment of choice in very early and early stage HCC patients that have preserved liver function.

Sarcopenia is a condition of decreased skeletal muscle mass two standard deviations below healthy adults (Baumgartner et al., 1998; Prado et al., 2008; Fearon et al., 2011). The condition is associated with many adverse outcomes such as physical disability (Janssen et al., 2002; Kim et al., 2016), falls in the elderly (Landi et al., 2012), osteoporosis (Ahedi et al., 2014), prolonged hospital stay and re-admission (Gariballa and Alessa, 2013), and poor quality of life (Boutin et al., 2015). Sarcopenia is often observed in cancer patients and the elderly (Cruz-Jentoft et al., 2010; Cruz-Jentoft et al., 2014). Studies have suggested that sarcopenia is an independent predictor of survival in esophageal, gastric, pancreatic, lung, breast, and urinary bladder cancer. Furthermore, sarcopenia is associated with poor post-treatment outcome such as post-operative complications, post-treatment infection and delayed recovery (Prado et al., 2008; Gibson et al., 2015; Jones et al., 2015; Shachar et al., 2016; Deng et al., 2018; Simonsen et al., 2018).

Sarcopenia can be measured using the middle upper arm muscle by anthropometry (Fearon et al., 2011) or appendicular skeletal muscle area by dual energy X-ray absorptiometry (DXA) (Prado et al., 2008; Fearon et al.,

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2011; Shepherd, 2016; Buckinx et al., 2018; Scafoglieri and Clarys, 2018; Walowski et al., 2020). In addition, the European Working Group on Sarcopenia in Older People (EWGSOP) suggests that sarcopenia is not only low muscle mass but also low muscular strength because of the non-linear the relationship between muscle mass and strength (Cruz-Jentoft et al., 2010). The EWGSOP group have classified sarcopenia into pre-sarcopenia, sarcopenia, and severe sarcopenia, reflecting the severity of pathology in muscle mass, strength, and physical performance (Cruz-Jentoft et al., 2010; Sergi et al., 2016).

Kamachi et al., (2016) reported a correlation between sarcopenia measured by CT scan and the recurrence of HCC in patients with hepatitis C-related cirrhosis after curative resection or RFA. Sarcopenia and high pre-operative α-fetoprotein (AFP) (>40 ng/mL) were independent risk factors for the recurrence of HCC. Similarly, Kobayashi et al., (2019) found that pre-operative sarcopenic obesity and advanced stage of the HCC were independent risk factors for HCC recurrence and death after hepatectomy. Moreover, a meta-analysis by Chang et al., (2018) also reported a significant association between sarcopenia and tumor recurrence and all-cause mortality.

Therefore, we aimed to explore the association between sarcopenia and the recurrence of HCC after RFA.

Materials and Methods

This study was a retrospective observational study approved by the Siriraj Institutional Review Board (IRB).

Patient Samples and data collection

We searched the electronic database to identify 669 HCC patients who were treated with radiofrequency ablation for the first time at the Siriraj Center of Interventional Radiology (SiCIR), Siriraj hospital between January, 2011 and August, 2020.

Inclusion criteria

All HCC patients who underwent RFA during January, 2011 to August, 2020 and has all of the following conditions were included:

1. Complete data of CT scan of the upper abdomen/liver prior to RFA procedure in the patient archiving and communication system (PACS) system of Siriraj hospital. The time between the CT study and RFA is less than 120 days.

2. All patients were classified as very early or early stages according to the BCLC prior to RFA (Bruix et al., 2005; Bruix et al., 2011; Bruix et al., 2016; Omata et al., 2017; European Association for the Study of the Liver. Electronic address and European Association for the Study of the, 2018).

3. Complete response in the follow up imaging (CT scan or MR scan of the upper abdomen/liver) performed 4-8 weeks after the procedure. Complete response is defined as no detectable intratumoral arterial enhancement (no viable tumor) and no new evidence of HCC in another liver segment by CT or MRI (Vincenzi et al., 2015; Liver, 2019).

4. Follow-up CT or MRI every 3-6 months, as appropriate. Tumor progression or recurrence is defined according to the mRECIST criteria (Eisenhauer et al., 2009; Lencioni and Llovet, 2010; Liver, 2015; Vincenzi et al., 2015; Liver, 2019).

Exclusion criteria

1) History of other cancer types

2) History of prior treatment other than RFA such as liver transplant or transarterial chemoembolization

3) Incomplete clinical data in the electronic medical record

4) No obtainable CT images before or after RFA

5) Significant CT artifact which could obscure interpretation or interfere with the analysis of skeletal muscle area

After the inclusion and exclusion criteria were applied, 56 patients were included. A total of 610 cases were excluded due to following conditions; presence of other cancer (60 cases), no pre-treatment imaging (180 cases), underwent other treatment prior to radiofrequency ablation (356 cases), no available follow-up imaging (4 cases), incomplete/inadequate radiofrequency ablation or had residual tumor after treatment (12 cases), and poor pretreatment imaging quality due to metallic artifact (1 case).

The subjects were divided into sarcopenic and non-sarcopenic groups according to their skeletal muscle areas (SMI of less than 52.4 cm^2/m^2 in male and 38.5 cm^2/m^2 in female measured by CT at the L3 vertebral body level).

The electronic medical record of each subject was reviewed for patient demographic data, performance status, laboratory findings, disease parameters, radiologic examination details, treatment, and post-treatment information. Time to recurrence/progression was defined as the interval from the date of curative RFA (complete response) to date of detectable radiological tumor recurrence.

Treatment procedure: RFA

The patients underwent RFA according to the BCLC classification and the Thailand guidelines for management of hepatocellular carcinoma 2019 (Bruix et al., 2005; Bruix et al., 2011; Liver, 2015; Bruix et al., 2016; Liver, 2019). RFA was performed using the 15-cm LeVeen (Boston Scientific) or StarBurst Talon (Balmer Medical) radiotherapeutic needle electrode with a 2.0- to 5.0-cm ablation zone diameter fit for each lesion under local anesthesia and an intravenous sedation. An electrode was inserted percutaneously into the lesion assisted by ultrasonography or CT. Then, thermal power was delivered and adjusted according to the standard protocol until the target impedance was reached or echogenic cloud was observed. Before the procedural termination, an adequate ablative safety margin of at least 5 mm away from the tumor border was confirmed to assure complete tumor necrosis (Goldberg et al., 2003; Kim et al., 2006; Nakazawa et al., 2007; Teng et al., 2015).

Image analysis

Skeletal muscle area evaluation

The CT images data were acquired via the eFilm Workstation 3.1 and then analyzed in semi-automatic manner using Siriraj hospital's SiSarcopenia 3.0. Axial CT slice with 1.25-mm to 1.5-mm thickness was chosen at 3rd lumbar vertebral level. The target muscle area consists of psoas muscles, paraspinal muscles (erector spinae, multifidus, and quadratus lumborum), and abdominal wall muscles (transversus abdominis, external and internal obliques, and rectus abdominis). Semi-automated outlining of the aforementioned muscle areas was done by including the pixel with attenuation range of -29 to +150 HU for muscular selection (Harimoto et al., 2013; Kamachi et al., 2016; Yabusaki et al., 2016; Chang et al., 2018). Manual exclusion was done to make the perfect outline of the abdominal and back muscles as shown in Figure 1. Automatic calculation into cross-sectional area in cm2 was made. The skeletal muscle index was then obtained by the following equation.

$$\text{Skeletal muscle index (SMI) } (cm^2/m^2) = \frac{\text{Lean tissue area at L3 vertebral level } (cm^2)}{\text{Height } (m^2)}$$

Sarcopenia was defined as an SMI of less than 52.4 cm^2/m^2 in male and 38.5 cm^2/m^2 in female.

HCC recurrence evaluation

Recurrence of HCC was made according to the tumor progression definition from the mRECIST criteria (Eisenhauer et al., 2009; Lencioni and Llovet, 2010; Liver, 2015; Vincenzi et al., 2015; Liver, 2019). This was a condition when new intrahepatic or extrahepatic HCC is found after RFA in this study. The diagnosis of HCC recurrence was based on imaging or pathology result (if any). By radiologic diagnosis, the lesion must have had a longest diameter of at least 1 cm and an arterial enhancement pattern typical of HCC with washout in portal venous or late venous phase. In addition, a highly suspicious lesion that led to further treatment including surgery or RFA was counted as recurrent disease. If the lesion did not show characteristic enhancement of HCC, interval increase in size of at least 1 cm was also considered as disease recurrence. A suspicious finding that did not meet any of the aforementioned recurrence criteria was counted as an equivocal lesion.

Statistical analysis

Descriptive statistics were used to summarize demographic data such as age, sex, comorbidities, BMI, laboratory findings as well as tumor stage, size, and number. For categorical variables including sex, comorbidities, tumor stage, tumor size, and tumor number, Pearson's Chi-squared test or Fisher's exact test was used. The obtained data were presented as frequency and percentage. Continuous data with normal distribution such as age, BMI, albumin, and prothrombin time were evaluated with independent-samples T-test and shown as mean ± S.D. The Mann-Whitney U test was used to assess continuous data with non-normal distribution such as AST, ALT, AFP, and total bilirubin which were demonstrated in median and range. The Cox proportional hazards model was used to analyze associations between variables. Time to recurrence was evaluated using the Log–rank or Breslow test (Kaplan-Meier method). Any variables identified as significant (p value <0.05) or showing a value of P <0.10 in univariate analysis with the abovementioned tests were deemed as candidates for multivariate Cox regression analysis and the results were displayed as hazard ratios (HRs) with 95% confidence interval (CI). All statistical analyses were performed using SPSS version 18.0. A P value that is less than 0.05 was considered statistically significant.

Results

Patient characteristics

The patients' characteristics, laboratory data, and other associated information are shown in Table 1. Among the 56 patients, 37 (66.1%) had sarcopenia and 19 patients (33.9%) did not. The distribution of skeletal muscle index is shown in Figure 2. No significant difference is observed between these two groups in terms of age, sex, comorbidities, and laboratory findings. Only the BMI and serum ALT level were significantly different

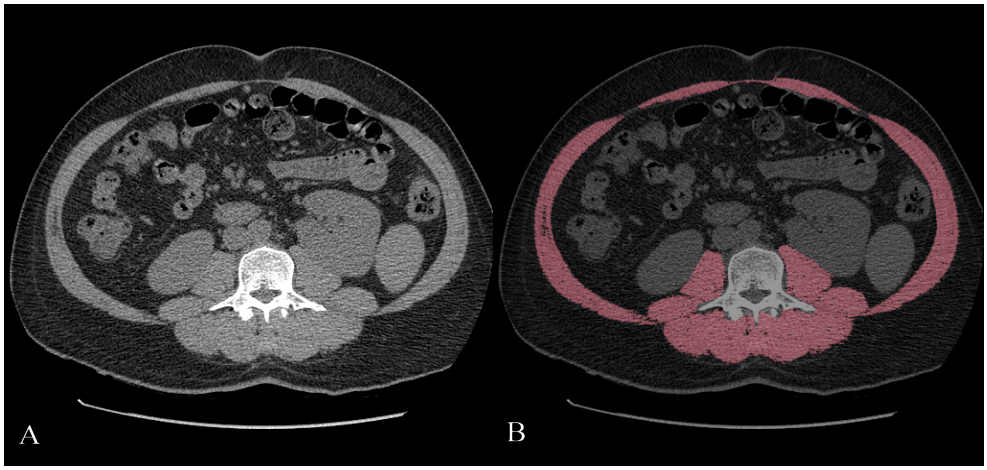

Figure 1. Skeletal Muscle Mass Evaluation before (A) and after (B) Cross-Sectional Muscular Delineation. The skeletal muscle mass including psoas, paraspinal, and abdominal wall muscles were manually outlined and calculated at the L3 vertebral level using a range of -29 to +150 HU.

Table 1. Clinicopathological Characteristics of Patients with and without Sarcopenia

Characteristics	Non-sarcopenia, n=19	Sarcopenia, n=37	p value
Patient characteristics and profiles			
Age, years, mean ± S.D.	59.6 ± 8.6	62.1 ± 11.7	0.419
Male: Female, n (%)	12 (63.2%): 7 (36.8%)	28 (75.7%): 9 (24.3%)	0.326
Comorbidities			
Cirrhosis, n (%)	15 (78.9%)	33 (89.2%)	0.423
Hepatitis B infection, n (%)	11 (57.9%)	14 (37.8%)	0.153
Hepatitis C infection, n (%)	4 (21.1%)	14 (37.8%)	0.203
Diabetes mellitus, n (%)	7 (36.8%)	9 (24.3%)	0.326
BMI, kg/m^2, mean ± S.D.	28.6 ± 3.3	23.2 ± 3.1	<0.001
Albumin, g/dL, mean ± S.D.	3.9 ± 0.6	4.0 ± 0.5	0.743
Total bilirubin, mg/dL, median (range)	0.8 (0.2-3.9)	0.7 (0.3-2.7)	0.597
AST, U/L, median (range)	50 (30-155)	41.5 (16-315)	0.344
ALT, U/L, median (range)	41 (15-119)	27 (10-204)	0.035
PT, second, mean ± S.D.	13.5 ± 1.4	13.5 ± 1.4	0.948
AFP, IU/mL, median (range)	9.2 (1.1-989.8)	6.8 (0.8-2519.0)	0.734
Disease parameters before treatment			
BCLC stage, n (%)			0.61
0	8 (42.1%)	13 (35.1%)	
A	11 (57.9%)	24 (64.9%)	
Tumor number, n (%)			1
Single	16 (84.2%)	31 (83.8%)	
Two	3 (15.8%)	6 (16.2%)	
Tumor size, n (%)			0.703
≤ 30 mm	17 (89.5%)	31 (83.8%)	
> 30 mm	2 (10.5%)	6 (16.2%)	

AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, the Barcelona Clinic Liver Cancer; BMI, body mass index (kg/m^2); PT, prothrombin time (second)

between the sarcopenic and non-sarcopenic groups (P<.001 and P=0.035, respectively). The means of the BMI were 23.2 kg/m^2 and 28.6 kg/m^2 and the median for the serum ALT were 27 U/L in sarcopenic and 41 U/L in the non-sarcopenic groups. The pre-treatment disease parameters involving BCLC stage, tumor number, and tumor size, revealed no significant difference between these two groups (p value>0.56).

Recurrence of HCC

Throughout the 10-year observational interval, there were 39 patients who had recurrent cancer and 17 who did not (recurrent rate of 69.6 percent). The means and standard deviations of the skeletal muscle index in male patients with and without HCC recurrence are 48.26 ± 9.38 cm^2/m^2 and 47.36 ± 7.68 cm^2/m^2, respectively. The means and standard deviations of the skeletal muscle index in

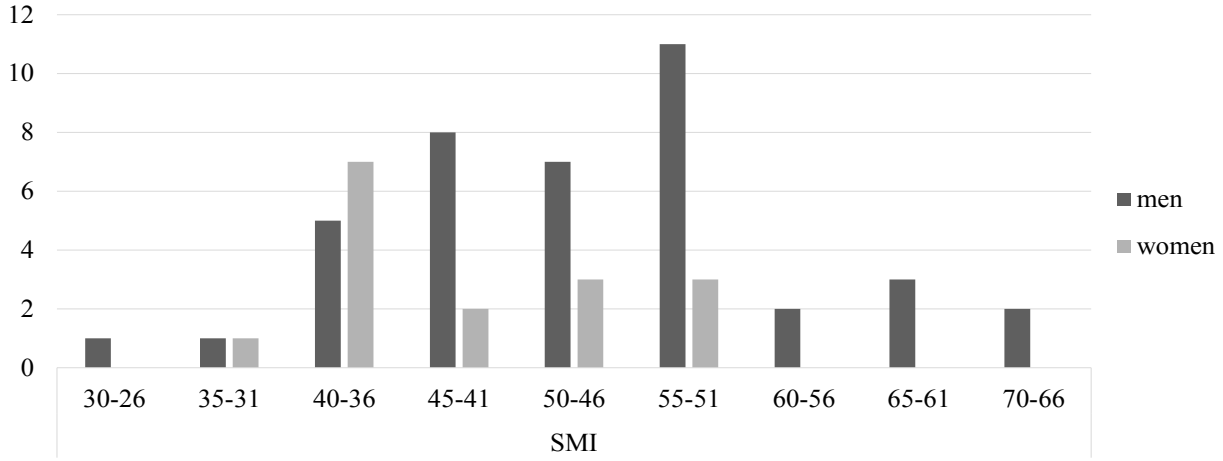

Figure 2. Distribution of Skeletal Muscle Index (cm^2/m^2) at the L3 Vertebral Level

Table 2. Univariate and Multivariate Cox Proportional Hazard Models for Recurrence of HCC

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Patient characteristics and profiles				
Age > 75 years	1.47 (0.52-4.16)	0.474		
Men	1.35 (0.65-2.80)	0.425		
BMI > 25 kg/m^2	0.68 (0.36-1.29)	0.234		
Diabetes mellitus	0.46 (0.20-1.05)	0.065		
Albumin < 3.5 g/dL	1.63 (0.76-3.47)	0.207		
Total bilirubin > 1.0 mg/dL	1.63 (0.84-3.17)	0.149		
AST > 35 U/L	1.03 (0.50-2.14)	0.935		
ALT > 40 U/L	1.30 (0.69-2.46)	0.42		
PT	1.09 (0.86-1.39)	0.473		
AFP	1.0 (0.99-1.00)	0.408		
Child-Pugh score	1.75 (1.10-2.77)	0.018	2.04 (1.23-3.36)	0.005
Disease parameters (before treatment)				
Tumor size > 30 mm	1.30 (0.54-3.15)	0.558		
Tumor number	2.52 (1.14-5.55)	0.022	2.68 (1.20-5.99)	0.017
BCLC stage A	1.17 (0.60-2.28)	0.639		
Sarcopenia parameter				
Sarcopenia	1.68 (0.85-3.32)	0.137	2.06 (0.99-4.27)	0.052

AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, the Barcelona Clinic Liver Cancer; BMI, body mass index (kg/m^2); PT, prothrombin time (second)

female patients with and without HCC recurrence are 38.10 ± 7.59 cm^2/m^2 and 38.65 ± 5.54 cm^2/m^2, respectively. There is no significant difference between recurrent and non-recurrent groups (P=0.777 for men; P=0.879 for women).

Time to recurrence

The median time to recurrence of HCC was 17.6 months (95% CI, 7.2-28.0 months) in sarcopenic patients and 36.7 months (95% CI, 33.7-39.6 months) in non-sarcopenic patients (P=0.046). (Figure 3) Recurrence rates after 1, 3, and 5 years were 43.0%, 61.4%, and 100%, respectively, for patients with sarcopenia, and 21.1%, 49.5%, and 88.0%, respectively, for those without sarcopenia. The Child-Pugh score (P=0.018) and tumor number (P=0.022) were significantly associated with recurrence of HCC. After multivariate analysis, only the Child-Pugh score (HR, 2.04; 95% CI, 1.23-3.36;

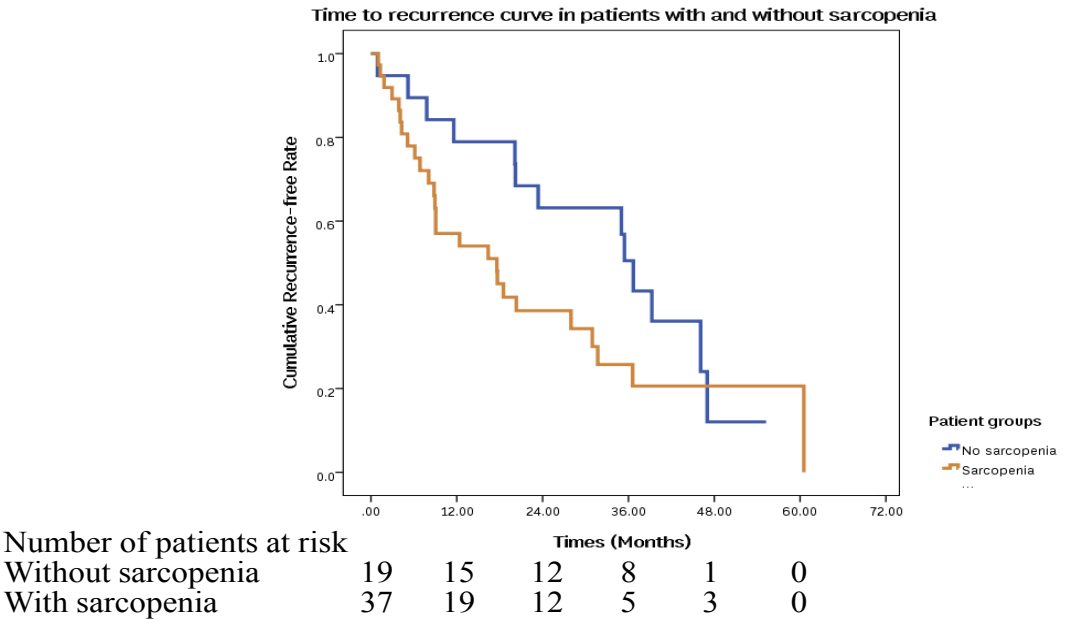

Figure 3. Time to Recurrence after Curative Radiofrequency Ablation of Patients with and without Sarcopenia

P=0.005) and tumor number (HR, 2.68; 95% CI, 1.20-5.99; P=0.017) were significantly and independently associated with recurrence of HCC (Table 2).

Discussion

We observed a high incidence of sarcopenia in patients with early stage HCC (37 in 56 patient or 66.1 percent) compared with a report by Prado et al., (2008) (15%). Our result is consistent with a study in HCC patients by Kamachi et al. (2016) (61/92; 66.3 percent). Using the sarcopenia cut-off values of 52.4 cm^2/m^2 in male and 38.5 cm^2/m^2 in female, we observed no significant difference in recurrence rate between sarcopenic and non-sarcopenic groups (HR 2.06; P=0.052). Multivariate Cox analysis suggested that sarcopenia may be associated with HCC recurrence in Thai patients (P=0.052). This could be due to insufficient sample size to demonstrate the substantial difference between these two groups. However, the calculated p values for sarcopenia are only near the cut-off point of statistical significance. Nevertheless, sarcopenia is a promising factor of becoming independent risk factor for HCC recurrence in Thai population.

The Child-Pugh score and tumor number of HCC were confirmed to be independently associated with HCC recurrence (P=0.005 and P=0.017, respectively), consistent with a 1973 study by Pugh et al. (1973) stating the Child-Pugh score as a prognostic predictor in cirrhotic patients. The score reflects both clinical and laboratory conditions that are important factors in determining treatment outcome. Increasing in number of HCC to more than one is one of the critical features in distinguishing between the very early and early stages according to BCLC classification. Our study confirms the higher recurrence rate (HR, 2.68; P=0.017). The result also correlates well with several studies which show connection of higher stage and poorer outcome under the concept of the larger/more number of the tumor, the poorer outcome (Llovet et al., 1999; Sala et al., 2005; Colecchia, 2014; Kao et al., 2015; Forner et al., 2018). Despite the association of tumor number with HCC recurrence, other features such as tumor size of more than 3 cm or BCLC stage A were not associated with tumor recurrence in this study (P=0.558 and P=0.639, respectively). This could be due to advancement in RFA technique which could be done safely in case of tumor size of more than 3 cm without a change in prognosis.

Consistent with many studies, we observed that higher BMI is significantly correlated with the absence of sarcopenia (P<0.001) (Harimoto et al., 2013; Levolger et al., 2015; Voron et al., 2015; Kamachi et al., 2016; Yabusaki et al., 2016; Ha et al., 2018). In general, BMI varies directly with body weight (kg), but inversely with height squared (m^2). Therefore, such calculation tells us roughly how the patient might look like in general. However, caution is still needed in this regard since the mentioned body weight can represent both fat and muscle or even ascites. Because muscular mass weighs more than fat, a person with a high BMI can be muscular with short stature or fat with tall stature. In our study, the high BMI in HCC patients might reflect the higher muscular mass patient (BMI, 28.6 ± 3.3 kg/m^2 in non-sarcopenia and 23.2 ± 3.1 kg/m^2 in sarcopenia; P<0.001).

The association between serum ALT and low muscle mass has been a topic of research interest (Le Couteur et al., 2010; Vespasiani-Gentilucci et al., 2018; Bekkelund and Jorde, 2019). A study by Vespasiani-Gentilucci et al. (2018) that utilized a different criteria of sarcopenia at the leg reported that decreased ALT level is associated with frailty, disability, and sarcopenia in elderly. Though ALT is mainly found in hepatocytes, it is also aggregated in muscle, heart, adipose tissue, intestines, prostate, and brain (Panteghini, 1990; Ozer et al., 2008; Liu et al., 2014). Thus, we postulate that low ALT is probably due to reduced quantities released from muscles into the bloodstream in the presence of sarcopenia. Another possible explanation is that lower BMI in sarcopenic patients portrays reduced risk of developing fatty liver disease (Fan et al., 2018), and so does the probability of increased ALT level (Chen et al., 2008; Miyake et al., 2013; Wang et al., 2013; Loomis et al., 2016; Wang et al., 2016). Le Couteur et al. examined elderly men and found a dissimilar relationship between serum ALT and lean body mass measured by DXA (Le Couteur et al., 2010). We suspect that this discrepancy could in part be from different population groups in each study, including genders and underlying diseases or the method of sarcopenia measurement.

This retrospective study has several limitations. It was conducted in a single institution using a small sample size. This reduced our ability to detect meaningful associations among the variable of interest. There are several different definitions of sarcopenia, including the one used in this study. To the best of our knowledge, there is no consensus definition of sarcopenia in the Thai population. So, we decided to use the cut-off values of 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women, which have been used in the Japanese population. Finally, we did not evaluate muscle function or strength.

In conclusion, sarcopenia measured by skeletal muscle index (SMI) (cm^2/m^2) in CT scan is a potential risk factor for recurrence of HCC in patients who underwent radiofrequency ablation. To confirm this association, larger studies are required.

Author Contribution Statement

Jaruvongvanich V: Conceptualization, methodology, data curation, investigation, resources, validation, visualization, writing - original draft, review & editing; Thamtorawat S: Methodology, validation, visualization, writing – review & editing, supervision; Saiviroonporn P: Conceptualization, validation; Pisanuwongse A: Validation, proofreading; Siriwanarangsun P: Conceptualization, methodology, data curation, investigation, resources, validation, visualization, writing - original draft, review & editing, supervision.

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analysis.

Approval

The research was not approved by any scientific body or a part of student thesis.

Ethical declaration

The study was approved by the Siriraj Institutional Review Board (IRB) with certificate of approval (COA) Si 092/2020.

Availability of data

The datasets analyzed during this study are not publicly available due to privacy and ethical concerns

Any conflict of interest

The authors declare that they have no potential conflicts of interest.

References

Ahedi H, Aitken D, Scott D, et al (2014). The association between hip muscle cross-sectional area, muscle strength, and bone mineral density. *Calcif Tissue Int*, **95**, 64-72.

Baumgartner RN, Koehler KM, Gallagher D, et al (1998). Epidemiology of Sarcopenia among the Elderly in New Mexico. *Am J Epidemiol*, **147**, 755-63.

Bekkelund SI, Jorde R (2019). Alanine Aminotransferase and Body Composition in Obese Men and Women. *Dis Markers*, **2019**, 1695874.

Boutin RD, Yao L, Canter RJ, et al (2015). Sarcopenia: Current Concepts and Imaging Implications. *AJR Am J Roentgenol*, **205**, W255-66.

Bruix J, Reig M, Sherman M (2016). Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology*, **150**, 835-53.

Bruix J, Sherman M, American Association for the Study of Liver D (2011). Management of hepatocellular carcinoma: an update. *Hepatology*, **53**, 1020-2.

Bruix J, Sherman M, Practice Guidelines Committee AAftSoLD (2005). Management of hepatocellular carcinoma. *Hepatology*, **42**, 1208-36.

Buckinx F, Landi F, Cesari M, et al (2018). Pitfalls in the measurement of muscle mass: a need for a reference standard. *J Cachexia Sarcopenia Muscle*, **9**, 269-78.

Chang KV, Chen JD, Wu WT, et al (2018). Association between Loss of Skeletal Muscle Mass and Mortality and Tumor Recurrence in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. *Liver Cancer*, **7**, 90-103.

Chen ZW, Chen LY, Dai HL, et al (2008). Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. *J Zhejiang Univ Sci B*, **9**, 616-22.

Colecchia A (2014). Prognostic factors for hepatocellular carcinoma recurrence. *World J Gastroenterol*, **20**, 5935.

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al (2010). Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*, **39**, 412-23.

Cruz-Jentoft AJ, Landi F, Schneider SM, et al (2014). Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing*, **43**, 748-59.

Deng CY, Lin YC, Wu JS, et al (2018). Progressive Sarcopenia in Patients With Colorectal Cancer Predicts Survival. *AJR Am J Roentgenol*, **210**, 526-32.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.

European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L (2018). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*, **69**, 182-236.

Fan R, Wang J, Du J (2018). Association between body mass index and fatty liver risk: A dose-response analysis. *Sci Rep*, **8**, 15273.

Fearon K, Strasser F, Anker SD, et al (2011). Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*, **12**, 489-95.

Forner A, Reig M, Bruix J (2018). Hepatocellular carcinoma. *Lancet*, **391**, 1301-14.

Gariballa S, Alessa A (2013). Sarcopenia: prevalence and prognostic significance in hospitalized patients. *Clin Nutr*, **32**, 772-6.

Gibson DJ, Burden ST, Strauss BJ, et al (2015). The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review. *Eur J Clin Nutr*, **69**, 1079-86.

Goldberg SN, Charboneau JW, Dodd GD, et al (2003). Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. *Radiology*, **228**, 335-45.

Ha Y, Kim D, Han S, et al (2018). Sarcopenia Predicts Prognosis in Patients with Newly Diagnosed Hepatocellular Carcinoma, Independent of Tumor Stage and Liver Function. *Cancer Res Treat*, **50**, 843-51.

Harimoto N, Shirabe K, Yamashita YI, et al (2013). Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg*, **100**, 1523-30.

Janssen I, Heymsfield SB, Ross R (2002). Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc*, **50**, 889-96.

Jones KI, Doleman B, Scott S, et al (2015). Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal Dis*, **17**, O20-6.

Kamachi S, Mizuta T, Otsuka T, et al (2016). Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment. *Hepatol Res*, **46**, 201-8.

Kao WY, Chao Y, Chang CC, et al (2015). Prognosis of Early-Stage Hepatocellular Carcinoma: The Clinical Implications of Substages of Barcelona Clinic Liver Cancer System Based on a Cohort of 1265 Patients. *Medicine (Baltimore)*, **94**, e1929.

Kew MC (2010). Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. *Pathol Biol (Paris)*, **58**, 273-7.

Kim H, Suzuki T, Saito K, et al (2016). Long-term effects of exercise and amino acid supplementation on muscle mass, physical function and falls in community-dwelling elderly Japanese sarcopenic women: A 4-year follow-up study. *Geriat Gerontol Int*, **16**, 175-81.

Kim YS, Rhim H, Cho OK, et al (2006). Intrahepatic recurrence after percutaneous radiofrequency ablation of hepatocellular carcinoma: analysis of the pattern and risk factors. *Eur J Radiol*, **59**, 432-41.

Kobayashi A, Kaido T, Hamaguchi Y, et al (2019). Impact of Sarcopenic Obesity on Outcomes in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma. *Ann Surg*, **269**, 924-31.

Landi F, Liperoti R, Russo A, et al (2012). Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. *Clin Nutr*, **31**, 652-8.
Le Couteur DG, Blyth FM, Creasey HM, et al (2010). The association of alanine transaminase with aging, frailty, and mortality. *J Gerontol Series A Biol Sci Med Sci*, **65**, 712-7.
Lencioni R, Llovet JM (2010). Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*, **30**, 52-60.
Levolger S, van Vledder MG, Muslem R, et al (2015). Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. *J Surg Oncol*, **112**, 208-13.
Liu Z, Que S, Xu J, et al (2014). Alanine aminotransferase-old biomarker and new concept: a review. *Int J Med Sci*, **11**, 925-35.
Liver TAftSot (2015). Thailand Guideline for Management of Hepatocellular Carcinoma 2015, Nonthaburi, Thai Association for the Study of the Liver.
Liver TAftSot (2019). Thailand Guideline for Management of Hepatocellular Carcinoma 2019, Nonthaburi, Thai Association for the Study of the Liver.
Llovet JM, Brú C, Bruix J (1999). Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*, **19**, 329-38.
Loomis AK, Kabadi S, Preiss D, et al (2016). Body Mass Index and Risk of Nonalcoholic Fatty Liver Disease: Two Electronic Health Record Prospective Studies. *J Clin Endocrinol Metabolism*, **101**, 945-52.
Miyake T, Kumagi T, Hirooka M, et al (2013). Body mass index is the most useful predictive factor for the onset of nonalcoholic fatty liver disease: a community-based retrospective longitudinal cohort study. *J Gastroenterol*, **48**, 413-22.
Nakazawa T, Kokubu S, Shibuya A, et al (2007). Radiofrequency ablation of hepatocellular carcinoma: correlation between local tumor progression after ablation and ablative margin. *AJR Am J Roentgenol*, **188**, 480-8.
Omata M, Cheng AL, Kokudo N, et al (2017). Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int*, **11**, 317-70.
Ozer J, Ratner M, Shaw M, et al (2008). The current state of serum biomarkers of hepatotoxicity. *Toxicology*, **245**, 194-205.
Panteghini M (1990). Aspartate aminotransferase isoenzymes. *Clin Biochem*, **23**, 311-9.
Prado CMM, Lieffers JR, McCargar LJ, et al (2008). Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*, 9, 629-35.
Pugh RN, Murray-Lyon IM, Dawson JL, et al (1973). Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*, **60**, 646-9.
Sala M, Forner A, Varela M, et al (2005). Prognostic prediction in patients with hepatocellular carcinoma. *Semin Liver Dis*, **25**, 171-80.
Scafoglieri A, Clarys JP (2018). Dual energy X-ray absorptiometry: gold standard for muscle mass?. *J Cachexia Sarcopenia Muscle*, **9**, 786-7.
Sergi G, Trevisan C, Veronese N, et al (2016). Imaging of sarcopenia. *Eur J Radiol*, **85**, 1519-24.
Shachar SS, Williams GR, Muss HB, et al (2016). Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *Eur J Cancer*, **57**, 58-67.
Shepherd J (2016). Evaluation of Sarcopenia by DXA. *Clin Rev Bone Mineral Metabolism*, **14**, 45-9.
Simonsen C, de Heer P, Bjerre ED, et al (2018). Sarcopenia and Postoperative Complication Risk in Gastrointestinal Surgical Oncology: A Meta-analysis. *Ann Surg*, **268**, 58-69.
Teng W, Liu KW, Lin CC, et al (2015). Insufficient ablative margin determined by early computed tomography may predict the recurrence of hepatocellular carcinoma after radiofrequency ablation. *Liver Cancer*, **4**, 26-38.
Vespasiani-Gentilucci U, De Vincentis A, Ferrucci L, et al (2018). Low Alanine Aminotransferase Levels in the Elderly Population: Frailty, Disability, Sarcopenia, and Reduced Survival. *J Gerontol A Biol Sci Med Sci*, **73**, 925-30.
Vincenzi B, Di Maio M, Silletta M, et al (2015). Prognostic Relevance of Objective Response According to EASL Criteria and mRECIST Criteria in Hepatocellular Carcinoma Patients Treated with Loco-Regional Therapies: A Literature-Based Meta-Analysis. *PLoS One*, **10**, e0133488.
Voron T, Tselikas L, Pietrasz D, et al (2015). Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma. *Ann Surg*, **261**, 1173-83.
Walowski CO, Braun W, Maisch MJ, et al (2020). Reference Values for Skeletal Muscle Mass - Current Concepts and Methodological Considerations. *Nutrients*, **12**.
Wang L, Guo J, Lu J (2016). Risk factor compositions of nonalcoholic fatty liver disease change with body mass index in males and females. *Oncotarget*, **7**, 35632-42.
Wang Z, Xu M, Peng J, et al (2013). Prevalence and associated metabolic factors of fatty liver disease in the elderly. *Exp Gerontol*, **48**, 705-9.
Yabusaki N, Fujii T, Yamada S, et al (2016). Adverse impact of low skeletal muscle index on the prognosis of hepatocellular carcinoma after hepatic resection. *Int J Surg*, **30**, 136-42.
Zhu RX, Seto WK, Lai CL, et al (2016). Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. *Gut Liver*, **10**, 332-9.