Fat-free muscle index predicts overall survival in mass-forming intrahepatic cholangiocarcinoma patients: a sex-stratified analysis

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Abstract

Introduction: Sarcopaenia is associated with adverse outcomes in patients with malignancies, and it remains unclear whether the sex discrepancy of sarcopaenia or muscle loss leads to different prognoses in patients with mass-forming intrahepatic cholangiocarcinoma (MICC).

Material and methods: Patients who were pathologically diagnosed with MICC and underwent partial hepatectomy between 2012 and 2019 were recruited. Fat-free muscle areas (FFMA) were defined as areas of bilateral erector spinae muscles on dual-echo, T1-weighted, gradient-recalled-echo images at the level of the radix of the superior mesenteric artery. Fat-free skeletal muscle index (FFMI) was calculated by dividing the FFMA by the individual's height squared. The prognostic value of FFMI was investigated using the Kaplan-Meier method and multivariable Cox regressions in both the entire cohort and in sex-specific subgroups.

Results: A total of 157 patients were finally included. Cut-off values for the definition of low FFMI were 14.19 cm^2/m^2 in males and 11.07 cm^2/m^2 in females. Patients with low FFMI had significantly shorter overall survival (OS) than those with high FFMI in the entire cohort (19.42 vs. 35.29 months, $p = 0.0067$) and male patients (17.25 vs. 37.19 months, $p = 0.006$), but not in females. Multivariate analyses showed that low FFMI was a significant predictor of OS in the entire cohort (HR = 1.725, 95% CI: 1.054–2.821, $p = 0.030$) and in male patients (HR = 2.145, 95% CI: 1.113–4.133, $p = 0.023$). No association between FFMI and disease-free survival was found in both the entire cohort and sex-specific subgroups.

Conclusions: Preoperative FFMI measured by MRI is a prognostic biomarker for OS in MICC patients, and it is more sensitive in males than in females.

Key words: disease-free survival, magnetic resonance imaging, prognosis, sarcopaenia.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most frequent form of primary hepatic malignant tumour [1]. Generally, ICC can be clas-

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sified into 3 types according to the macroscopic appearance of a tumour: the mass-forming type, the periductal infiltrating type, and the intraductal growing type [2]. Among these, the mass-forming intrahepatic cholangiocarcinoma (MICC) is the most common and accounts for 85% to 94% of all ICCs [3, 4]. Partial hepatectomy is the only possible cure for ICC [1, 4]. However, the prognosis of these patients is discouraging; the 5-year survival rate after surgery is only 21–35% [3, 5]. Multiple factors, such as tumour size, positive resection margins, and lymph node metastasis, are associated with a poor prognosis of ICC after resection [3, 6]. In addition, the patient's conditions such as skeletal muscle status and fat distribution may influence prognosis after surgery [7, 8].

Sarcopaenia, defined as the loss of skeletal muscle mass and strength [9], is currently a hot research topic due to its high prevalence and association with adverse outcomes in patients with various malignancies [7, 8, 10, 11]. The cross-sectional images of computerized tomography (CT) and magnetic resonance imaging (MRI) are now considered standards for muscle mass evaluation [12]. Because CT has drawbacks such as radiation exposure [12], and nowadays MRI is increasingly used in the screening and evaluation of liver diseases, MRI can be utilized to assess muscle quantity precisely in liver cancer patients without additional costs [8, 13].

Moreover, there are sex differences in human skeletal muscle gene expression, as well as hormone regulation, skeletal muscle mass, and fibre composition [14–16]. The amount and rate of muscle mass loss due to aging and cancer also showed differences between males and females [17, 18]. While the impact of muscle loss/sarcopaenia on cancer mortality has received increasing attention in recent years, sex differences in this syndrome are rarely investigated in prognostic studies of cancers [8, 19]. To date, it remains unclear whether this sex discrepancy in sarcopaenia or muscle loss leads to different prognoses in MICC patients.

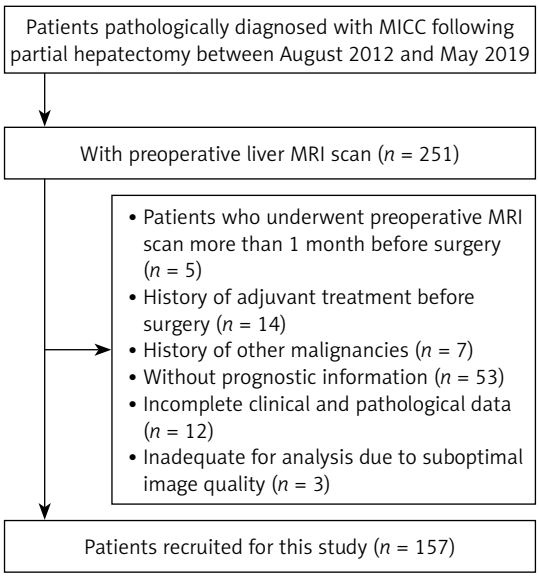

Figure 1. Flow chart of inclusion and exclusion criteria

The purpose of this study was to assess the prognostic value of the fat-free skeletal muscle index (FFMI) measured by preoperative MRI on overall survival (OS) in patients with MICC following partial hepatectomy, and to explore the potential sex differences in the relationship between muscle mass and prognosis.

Material and methods

Study population

The institutional review board approved this retrospective study (TJ-IRB20221317), and the requirement for informed consent was waived due to its retrospective nature. All patients who had preoperative liver MRI scans and were diagnosed with MICC pathologically after partial hepatectomy in our institution between August 2012 and May 2019 were consecutively included. Detailed exclusion criteria are shown in Figure 1.

Clinical characteristics, laboratory examination results, histopathologic parameters, and postoperative therapy were reviewed from electronic medical records. The histopathologic characteristics of tumours included the presence of macrovascular and microvascular invasion, histologic differentiation, histologic subtypes [20], lymph node metastasis, tumour-node metastasis (TNM) staging [21], and surgical margin status. Radical lymphadenectomy, regional lymph node resection, and/or lymph node biopsy were performed depending on the patients' personal situations during surgery. Body mass index (BMI) was calculated as weight/height squared.

MR imaging protocol

MR imaging was performed using a commercially available clinical 3.0-Tesla MR imaging system (Discovery MR750, GE Medical Systems; Magnetom Skyra, Siemens Medical Solutions) or a 1.5-T system (Optima MR360, GE Medical Systems). Dual-echo T1-weighted 3D gradient-recalled-echo (GRE) sequence, a routine sequence for liver MR examination, was based on a 2-point Dixon fat/water separation scheme, which allows divergences from exact in-phase and out-phase echo times, and therefore could provide water and fat images automatically [22]. Exemplary sequence parameters for 1.5 T were repetition time: 6.18 ms; echo time: 2.08/4.17 ms; flip angle: 15°;

acquisition matrix: 256 × 160; section thickness: 5 mm; intersection gap: 0 mm; field of view: 360 × 288 mm.

Assessment of skeletal muscle area in MRI

T1-weighted 3D GRE images for each patient were used to quantify skeletal muscle mass. Fat-free muscle areas (FFMA) were analysed on cross-section images at the level of the radix of the superior mesenteric artery using Slice-Omatic (version 5.0; Tomovision, https://tomovision.com) [23]. One abdominal radiologist (Reader 1, with 8 years of experience) segmented bilateral erector spinae muscles semi-automatically using the mathematical morphology functions in the Morpho mode on fat-only images (Figure 2). FFMA was semi-automatically quantified using a threshold algorithm that depended on the differences in signal intensity between striated muscle and macroscopic adipose tissue within the total muscle area, i.e. hypointense for striated muscle and hyperintense for fat. To evaluate the inter-observer repeatability for each skeletal muscle variable, 20 cases were randomly selected and segmented again by another abdominal radiologist (Reader 2, with 2 years of experience). The fat-free skeletal muscle index (FFMI) was calculated by dividing the FFMA by individual's height squared.

Follow-up

Follow-up was performed within 3 months of surgery, and then at an interval of 3–6 months. OS was calculated from the date of surgery to the date of death or the date of last contact. Disease-free survival (DFS) was calculated from the date of surgery to the first date of local recurrence or distant metastasis, death, or the date of last contact.

Statistical analysis

Mann-Whitney U tests were used to compare continuous variables and χ^2 test for categorical variables. There are no previously recognized threshold values defining abnormal ranges regarding FFMI for patients with MICC. Hence, the sex-specific median values were used as cut-off points. Kaplan-Meier survival curves were plotted, and the log-rank test was used to compare DFS and OS between different groups. The effects of clinicopathological factors and FFMI on survival were assessed using univariable and multivariable cox regression analysis. Age and variables with $p < 0.05$ at univariable analysis were included in multivariable Cox regression analysis after confirmation of the proportional hazard assumption. Interobserver agreement for FFMA assessment was studied using the intraclass correlation coefficient

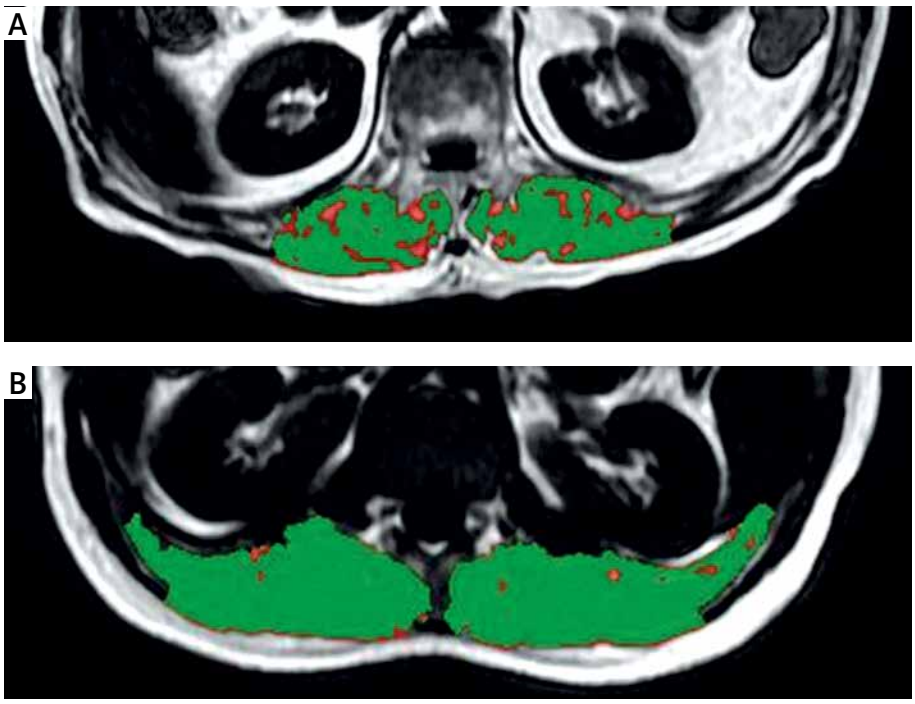

Figure 2. Skeletal muscle measurements of bilateral erector spinae muscles via cross-sectional images (fat-only images derived from dual-echo, T1-weighted, 3D gradient-recalled-echo sequences) on the level of the radix of the superior mesenteric artery. Individual with low fat-free muscle index showed FFMA (green areas in Figure 2 **A**) of 26.85 cm^2 and FFMI of 9.29 cm^2/m^2. Individual with high fat-free muscle index, showed FFMA (green areas in Figure 2 **B**) of 53.76 cm^2 and FFMI of 17.16 cm^2/m^2

FFMA – fat-free muscle areas, FFMI – fat-free muscle index.

[24]. Statistical analysis was performed with R software (version 4.0.3, R Project for Statistical Computing, www.r-project.org). All *p*-values were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients

In total, 157 patients including 96 males (mean age: 56.1 ±10.2 years) and 61 females (mean age: 56.0 ±9.2 years) were recruited for this study. The clinical and pathological characteristics of MICC patients are summarized in Table I. Viral hepatitis (n = 125, 79.6%) was common in our cohort, and cirrhosis was presented in 56 (35.7%) patients. About one-third of patients (n = 55, 35.0%) had lymph node metastasis, and 44 (28.0%) patients showed macrovascular invasion. Most patients (n = 99, 63.1%) were diagnosed with TNM I or II stage. Most patients (n = 151, 96.2%) received margin-negative resection. Adjuvant chemotherapy was administrated in 53 (33.8%) patients. Transhepatic arterial chemotherapy and embolization (TACE), and ablation, were applied to 12 (7.6%) patients with postoperative relapse.

The median follow-up time was 26.3 months (range: 3.6–61.1 months). At the end of follow-up, 75 of 157 (47.8%) patients died, and the median OS was 24.3 months (95% CI: 19.6 to 37.2 months). A total of 111 patients (70.7%) had a recurrence, with a median DFS of 9.1 months (95% CI: 7.8–11.8 months).

Interobserver agreement of the measurements of FFMA between the 2 radiologists was excellent, with a high intraclass correlation coefficient of 0.980 (95% CI: 0.951–0.991, $p < 0.0001$).

Comparison of characteristics in high and low FFMI groups

Sex-specific median values (14.19 cm^2/m^2 in males and 11.07 cm^2/m^2 in females) were used to distinguish high and low FFMI. Patients with low FFMI had significantly lower body weight (61.01 ±9.38 vs. 65.27 ±9.75 kg, $p = 0.006$) and BMI (21.99 ±2.68 vs. 23.74 ±2.71 kg/m^2, $p < 0.001$) compared to patients with high FFMI. Patients with low FFMI were older (57.78 ±9.20 vs. 54.29 ±10.07 years, $p = 0.025$) and had a higher percentage of lymph node metastasis (43.6% vs. 26.6%, $p = 0.039$) (Table I, Supplementary Table SI).

Analysis of variables on OS and DFS in the entire patient cohort

Kaplan-Meier analysis indicated that patients with low FFMI had significantly lower OS compared to patients with high FFMI (median: OS 19.42 vs. 35.29 months, $p = 0.0067$; Figure 3 A) but not in survival curves of DFS (median OS 8.64 vs. 11.20 months, $p = 0.170$; Figure 3 B). In the univariate model, CA19-9, tumour diameter, multifocal tumour, macrovascular invasion, major resection, radical lymphadenectomy, positive surgical margins, TNM stage, and low FFMI were found to be associated with OS (Supplementary Table SII). In the multivariate model, low FFMI (HR = 1.725, 95% CI: 1.054–2.821, $p = 0.030$) and macrovascular invasion (HR = 2.017, 95% CI: 1.145–3.553, $p = 0.015$) remained significant predictors of OS in MICC patients (Table II).

Sex-stratified analysis

Male patients showed a trend of survival curves that was similar to the entire cohort, i.e. patients with low FFMI had significantly worse survival (median OS: 17.25 vs. 37.19 months, $p = 0.006$, Figure 4 A). However, female patients with low FFMI had no significantly different OS outcomes compared with those with high FFMI (median OS: 20.53 vs. 35.29 months, $p = 0.350$, Figure 4 B) on Kaplan-Meier analysis. Also, FFMI was not associated with DFS in male (median DFS: 8.38 vs. 11.89 months, $p = 0.093$) or in female (median DFS; 9.00 vs. 8.84 months, $p = 0.950$) sub-groups (Figures 4 C, D).

FFMI was used as a continuous variable in the Cox regression modes to explore the association between FFMI and OS in male and female subgroups, respectively. For male patients, albumin levels, tumour diameter, macrovascular invasion, large duct subtype, major resection, TNM stage, and FFMI were predictors of OS in univariate analysis (Supplementary Table SIII.). In multivariate analysis, FFMI (HR = 0.845, 95% CI: 0.753–0.947, $p = 0.004$), tumour diameter (HR = 1.016, 95% CI: 1.002–1.03, $p = 0.025$), and large duct subtype (HR = 2.283, 95% CI: 1.123–4.64, $p = 0.023$) were independently associated with OS (Table III). For females, univariate cox regression analysis showed that only radical lymphadenectomy, macrovascular invasion, and positive surgical margins were associated with OS (Supplementary Table SIII).

Similar results were observed when FFMI was included as a dichotomous variable in the Cox regression modes. Low FFMI was independently associated with OS (HR = 2.145, 95% CI: 1.113–4.133, $p = 0.023$) in males but not in females (HR = 0.802, 95% CI: 0.378–1.702, $p = 0.565$) (Supplementary Table SIV).

Discussion

In this study, we analysed the association between preoperative skeletal muscle mass and survival outcomes in patients with MICC following partial hepatectomy. Patients with low FFMI

Table I. Patient characteristics and skeletal muscle parameters in the low and high fat-free muscle index groups

Characteristics	Low FFMI (n = 78)	High FFMI (n = 79)	P-value
Clinical characteristics:			
Age [years]	57.78 ±9.2	54.29 ±10.07	0.025
Sex (female)	30 (38.5%)	31 (39.2%)	1.000
Height [cm]	166.35 ±7.84	165.62 ±7.75	0.565
Weight [kg]	61.01 ±9.38	65.27 ±9.75	0.016
BMI [kg/m$^{2]}$	21.99 ±2.68	23.74 ±2.71	< 0.001
FFMA [cm$^{2]}$	30.63 ±7.13	42.70 ±9.85	< 0.001
FFMI [cm^2/m^2]	10.96 ±1.94	15.41 ±2.66	< 0.001
History of HBV infection	60 (76.9%)	65 (82.3%)	0.526
history of cholelithiasis	12 (15.4%)	16 (20.3%)	0.556
Cirrhosis	26 (33.3%)	30 (38.0%)	0.660
CA19-9 [U/ml]	1158.32 ±2314.65	374.47 ±812.86	0.233
Albumin [g/l]	38.89 ±6.06	40.33 ±4.07	0.196
Serum total bilirubin [mg/dl]	17.91 ±22.59	19.76 ±28.83	0.895
Child Pugh score:			0.746
A	71 (91.0%)	74 (93.7%)	
B	7 (9.0%)	5 (6.3%)	
Tumour characteristics:			
Multifocal tumour	16 (20.5%)	18 (22.8%)	0.879
Tumour diameter [mm]	52.28 ±23.14	50.80 ±21.88	0.628
Macrovascular invasion	24 (30.8%)	20 (25.3%)	0.560
Microvascular invasion	29 (37.2%)	25 (31.6%)	0.574
Histologic subtype:			0.168
Large duct	34 (43.6%)	25 (31.6%)	
Small duct	44 (56.4%)	54 (68.4%)	
Histologic differentiation:			0.696
Well or moderate	34 (43.6%)	31 (39.2%)	
Poor	44 (56.4%)	48 (60.8%)	
Surgical margin status (R1)	4 (5.1%)	2 (2.5%)	0.666
Lymph node metastasis	34 (43.6%)	21 (26.6%)	0.039
Metastases	1 (1.3%)	2 (2.5%)	1.000
T stage:			0.674
T1a	25 (32.1%)	31 (39.2%)	
T1b	16 (20.5%)	13 (16.5%)	
T2	35 (44.9%)	33 (41.8%)	
T3	1 (1.3%)	0	
T4	1 (1.3%)	2 (2.5%)	
Treatment:			
Extension of hepatectomy:			0.121
Minor resection	44 (56.4%)	55 (69.6%)	
Major resection	34 (43.6%)	24 (30.4%)	
Radical lymphadenectomy	29 (37.2%)	31 (39.2%)	0.919
Adjuvant therapy	28 (35.9%)	25 (31.6%)	0.693
TACE	3 (3.8%)	9 (11.4%)	0.139
Ablation therapy	6 (7.7%)	6 (7.6%)	1.000

Categorical variables were presented as numbers (percentage) and continuous variables were presented as mean (standard deviation). BMI – body mass index, CA19-9 – carbohydrate antigen 19-9, FFMA – fat-free muscle area, FFMI – fat-free skeletal muscle index, HBV – hepatitis B virus, TACE – transhepatic arterial chemotherapy and embolization.

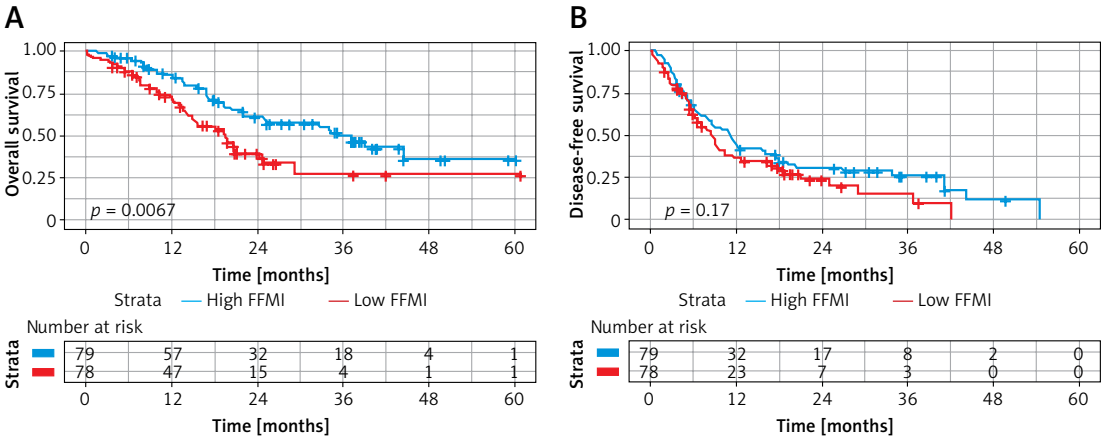

Figure 3. Kaplan-Meier survival analyses of overall survival (**A**) and disease-free survival (**B**) for patients stratified by the dichotomized fat-free muscle index in the entire patient cohort

Table II. Multivariable Cox regression analysis for overall survival in the entire patient cohort

Characteristics	HR	95% CI	*P*-value
Age (> 65 years)	1.104	0.605 –2.014	0.748
Low FFMI	1.725	1.054 –2.821	0.030
CA19-9 (> 1000 U/ml)	1.350	0.715 –2.548	0.355
Multifocal tumour	1.419	0.814 –2.473	0.217
Tumour diameter [mm]	1.001	0.991 –1.012	0.791
Macrovascular invasion	2.017	1.145 –3.553	0.015
Surgical margin status (R1)	2.308	0.766 –6.957	0.137
TNM stage (3, 4 vs. 1, 2)	1.331	0.791 –2.239	0.281
Major resection	1.159	0.667 –2.013	0.602
Radical lymphadenectomy	1.322	0.784 –2.228	0.295

Age and variables with a p-value < 0.05 identified on univariable analysis were selected for the multivariable analysis. CA19-9 – carbohydrate antigen 19-9, FFMI – fat-free muscle index, HR – hazard ratio, 95% CI – 95% confidence intervals.

showed a significantly shortened OS compared to patients with high FFMI, and low FFMI remained an independent risk factor for poor survival after adjusting for other clinical and pathological variables in the entire cohort. In sex-stratified analysis, FFMI was shown to be an independent prognostic factor only in male patients.

Sarcopaenia is a common syndrome in the elderly and in patients with chronic diseases [8, 14]. It is speculated tha the quantity of skeletal muscle is linked to the prognosis of patients with tumours through various mechanisms, including increased proinflammatory cytokines, and decreased levels of myokines and growth factors [9, 25–27]. In this study, we indicated that preoperative FFMI is a potential biomarker for overall survival in patients with MICC. Compared with previous studies involving the association between CT-based sarcopaenia and prognosis in cholangiocarcinoma [13, 28], our study adds to the field by precisely evaluating fat-free skeletal muscle areas using Dixon-based MRI, which could obtain fat- and water-signal-only image series according to the difference in chemical shift between hydrogen atoms in water and fat so as to accurately measure the amount of muscle and fat tissue [22]. FFMA was determined by the area of erector spinae muscle at the level of the origin of the superior mesenteric artery [23]. It has a good correlation with skeletal muscle parameters measured at the level of L3 and is demonstrated to be a reliable indicator for the estimation of skeletal muscle both in previous and our studies [23, 29]. Hence, we can measure FFMA and FFMI during routine liver MRI examinations without expending additional medical resources. Moreover, we studied the impact of FFMI on OS only in patients with MICC who underwent similar surgical methods; this more homogeneous population could minimize confounding variables and provide more reliable conclusions.

It is worth noting that there are considerable sex-based differences in skeletal muscle structure and composition, as well as age and/or disease-induced losses in skeletal muscle mass [15, 17, 19], but the sex differences are rarely investigated in prognostic studies of cancers. Our study revealed that low FFMI was associated with increased mortality risk in male patients, but not in

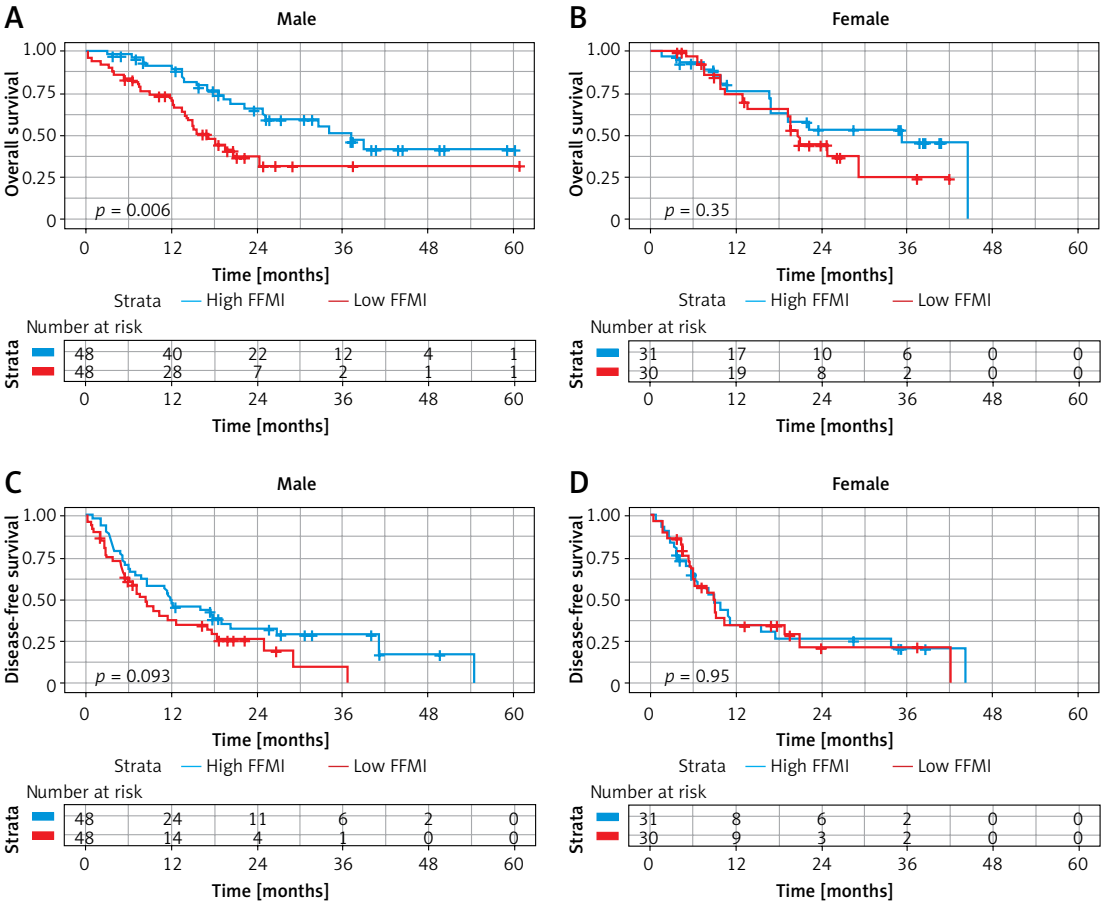

Figure 4. Kaplan-Meier curves of overall survival (OS) (**A**, **B**) and disease-free survival (DFS) (**C**, **D**) stratified according to fat-free muscle index (FFMI) in different sex subgroups

Table III. Multivariable Cox regression analysis for overall survival in male patients

Characteristics	HR	95% CI	*P*-value
Age (> 65 year)	0.470	0.207–1.065	0.071
FFMI [cm²/m²]	0.845	0.753–0.947	0.004
Albumin [g/l]	0.980	0.902–1.064	0.627
Tumour diameter [mm]	1.016	1.002–1.03	0.025
Large duct subtype	2.283	1.123–4.64	0.023
Macrovascular invasion	1.519	0.748–3.081	0.247
TNM stage (3, 4 vs. 1, 2)	1.363	0.677–2.746	0.386
Major resection	1.227	0.612–2.46	0.564

Age and variables with a p-value < 0.05 identified on univariable analysis were selected for the multivariable analysis. FFMI – fat-free muscle index, HR – hazard ratio, 95% CI – 95% confidence intervals.

females, and similar results were also found when using FFMI as a continuous variable. Our finding is in keeping with previous studies on cirrhosis and gastric cancer, which showed that male patients with sarcopaenia are significantly more likely to have a poor prognosis than females [30, 31]. The different impact of low muscle mass on survival between males and females may be explained by decreased sex hormones that occur during aging and the course of chronic diseases such as cancers [17, 19]. Testosterone has an anabolic effect on the maintenance of muscle mass through promotion of protein synthesis and muscular regeneration, while oestrogens have a muscle-protective effect through anti-inflammation and anti-catabolism [16, 32]. With aging and/or other diseases, testosterone deficiency leads to a more robust catabolic response in males than in females [19]. This may result in muscle mass loss in males being greater and faster than in females, and hence the effect of muscle mass loss on health or mortality may be more severe in males [17, 33]. The different prog-

nostic effects of FFMI between males and females illustrate the importance of sex classification in sarcopaenia-associated prognosis studies.

There were several limitations in this study. First, this is a single-centre retrospective study, and prospective multicentre studies are needed to further validate the prognostic value of FFMI. Second, as skeletal muscle mass and the prevalence rate of sarcopaenia varies regarding different geography, ethnicity, and disease status, the generalizability of our findings needs to be substantiated in other populations. Third, MR can estimate fibre architecture on diffusion tensor imaging (DTI) and T2-maps, and analyse the proton density fat fraction (PDFF) in muscle via magnetic resonance spectroscopy or multi-echo DIXON sequences [13, 34]. Utilizing the aforementioned new MR technologies would provide a more accurate evaluation of muscle quality/quantity and would further improve its prognostic accuracy.

In conclusion, preoperative FFMI is a potential prognostic factor for overall survival in patients with MICC after partial hepatectomy, and it is more sensitive in males than in females. Our study suggested that physical exercise therapy, nutritional support, and other measures to improve the muscle mass may be another therapeutic strategy worth considering. Sex differences should be concerned in sarcopaenia-associated prognostic studies.

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Hualing Li and Han Zhang contributed equally to this work.

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