Original Article

Skeletal muscle index and muscle attenuation with liver cirrhosis as survival prognosticators by sex

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Background and Objectives: It has been proven that skeletal muscle index (SMI) and muscle attenuation (MA) are correlated with outcomes in liver cirrhosis. However, whether there are sex differences in these factors remains unknown. We aimed to analyze the predictive ability of SMI and MA for the prognosis of cirrhotic patients of different sexes and promote computed tomography (CT) use in body composition assessment. **Methods and Study Design:** CT images taken at the 3rd lumbar vertebra from 223 patients were quantified for body composition. A Cox regression model was used to assess associations between mortality and body composition. Time-dependent receiver operating characteristic curves were calculated to evaluate the predictive ability of SMI and MA for the 1-, 3- and 5- year mortality of cirrhotic patients. **Results:** The majority of patients with liver cirrhosis were male (64.6%), and there was a weak linear correlation between SMI and MA in males (r=0.33, p<0.001). In the sex stratified multivariate Cox regression analysis, SMI in males (HR=0.95; 95% CI, 0.91-0.98; p=0.002) and MA in females (HR=0.91; 95% CI, 0.87-0.96; p<0.001) were independently associated with mortality. The areas under the curve (AUCs) of SMI (AUC=0.718) and MA (AUC=0.705) were similar in the 5-year mortality prediction of males, while in females, MA (AUC=0.797) had a stronger predictive ability than SMI (AUC=0.541). **Conclusions:** SMI in males and MA in females are independent prognostic factors for liver cirrhosis. For females, MA may be a more sensitive indicator of mortality prediction than SMI, while in males, they are equivalent.

Key Words: liver cirrhosis, body composition, skeletal muscle index, muscle attenuation, computed tomography

INTRODUCTION

Liver cirrhosis is one of the leading causes of disability and mortality worldwide,[1] accounting for approximately 2 million deaths per year worldwide.[2] In recent years, a growing number of studies have shown that skeletal muscle consumption is not only a common feature of cirrhosis and contributes significantly to worse outcomes, such as infections,[3] hepatic encephalopathy (HE) and ascites,[4,5] but also an independent predictor of survival in cirrhosis and post liver transplantation.[6-8] Muscle mass is an important predictor of liver cirrhosis.

Muscle mass has been estimated according to a variety of methods. Patients with liver cirrhosis are prone to ascites and edema, which limit the application of traditional skeletal muscle assessment methods, such as bioelectrical impedance and calf circumference measurement. Computed tomography (CT) imaging analysis is gradually being used in the muscle evaluation of patients with cirrhosis due to its objectivity, accuracy and availability. Moreover, the skeletal muscle index (SMI) is also used as a prognostic indicator for patients with liver cirrhosis, and the cutoff values for males and females are different.[9,10]

In previous studies that analyzed males and females separately, SMI was predictive of mortality in males but not in females.[6,11,12] Unfortunately, the prognostic value of SMI was predominantly evaluated in male patients, but its predictive effect in females may be obscured. Researchers have stated that skeletal muscle consumption should be interpreted differently between male and female patients with cirrhosis.[13] Therefore, a more effective indicator for assessing the prognosis of female patients with cirrhosis is needed at present.

Muscle attenuation (MA), which is measured by CT

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and expressed in Hounsfield units (HU), is associated with skeletal muscle lipid content and provides insights into pathophysiology.[14,15] Current findings suggest that MA has prognostic value in predicting overt HE and mortality in patients with cirrhosis.[16,17] Therefore, we aimed to assess the association between SMI and MA in patients with cirrhosis. Furthermore, the capability of SMI and MA to predict mortality in cirrhotic patients of different sexes is evaluated in this research.

METHODS

Study populations

Adult patients (18-80 years) who were diagnosed with liver cirrhosis by imaging examinations or biopsy results were consecutively enrolled from the Affiliated Hospital of Qingdao University between January 2015 and April 2016. Our study was performed in accordance with the Declaration of Helsinki (2000) and was approved by the ethics committee of the Affiliated Hospital of Qingdao University (QYFY WZLL 26501). A total of 898 patients were reviewed, and patients were excluded if they: (1) had primary liver carcinoma or other malignant tumors (n=560); (2) lacked CT scans within 2 weeks on index hospitalization (n=84); (3) had other chronic wasting diseases (n=11); (4) underwent liver transplantation performed during the follow-up period (n=8) or (5) were lost to follow-up (n=12). Ultimately, 223 cirrhotic patients were enrolled in this study (Figure 1).

Clinical data collection

Data for the clinical features and inspection results of all included patients, including sex, age, body mass index (BMI), etiology of cirrhosis, presence of decompensated events (ascites, HE, infection and variceal bleeding), liver function tests, coagulation tests, platelet counts and serum sodium concentration, were collected. The severity of liver disease was assessed by the model for the end-stage liver disease (MELD) score[18] and Child-Pugh score.[19] The interval between laboratory tests acquisition and CT scanning was less than 2 weeks. The primary outcome was mortality before April 30, 2021.

Evaluation of CT imaging

A plain CT scan of the abdomen is a routine examination for patients with liver cirrhosis, which can provide plentiful important information on body composition. Two sequential transverse CT images extended from L3 toward the iliac crest were analyzed using Slice-O-Matic V5.0 software (Cosmovision, Montreal, Quebec, Canada), which enables specific tissue demarcation by using HU thresholds. The CT HU thresholds were -29 to +150 for skeletal muscle area,[20] -190 to -30 for subcutaneous adipose tissue and -150 to -50 for visceral adipose tissue.[21,22] The cross-sectional area of muscle and adipose tissue was normalized for height in squared meters (cm^2/m^2), and these values were referred to as SMI, subcutaneous adipose tissue index (SATI) and visceral adipose tissue index (VATI). The visceral-to-subcutaneous ratio (VSR) was simply calculated as the visceral adipose tissue area (cm^2)/subcutaneous adipose tissue area (cm^2), which explores the distribution of abdominal adipose tissue. In addition, MA measured the mean HU of the entire skeletal muscle area,[23] which is associated with skeletal muscle lipid content.[14] All CT images were analyzed by two trained observers. For difficult cases, several specialists reached a consensus through discussion. Ultimately, the intraobserver coefficient of variation was approximately 2.3%.

Follow-up

After the patients were discharged from the hospital, routine outpatient visits were performed every 6 months, and abdominal ultrasound or CT examinations, liver function tests, tumor marker tests and other examinations were performed. Telephone interviews were regularly performed by the investigators to assess the general situation of each included patient. Survival time was defined as the interval between the first admission to our hospital for cirrhosis and death or the cutoff date (April 30, 2021), whichever came first.

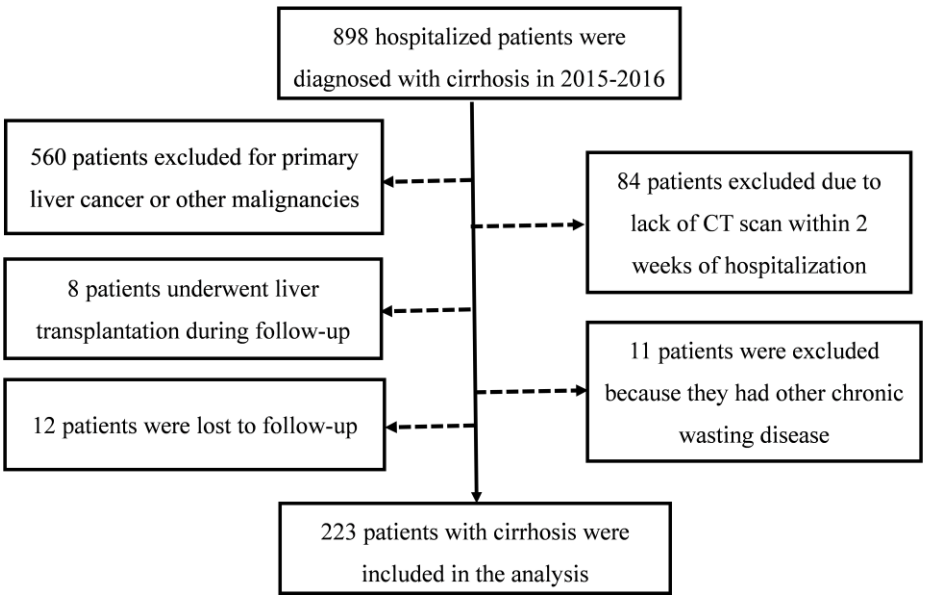

Figure 1. Flowchart of patients excluded/included in this cohort.

Statistical analysis

Data are presented as the mean standard deviation or median interquartile range (IQR), as appropriate. Differences between groups were analyzed using Wilcoxon's test for continuous variables and Pearson's χ^2 test for categorical data. Correlations between SMI, MA and age were assessed by Pearson's correlation coefficient analysis.

Univariate and multivariate analyses of overall survival were performed using Cox regression models, and the results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Backward stepwise elimination (p>0.1) was performed to derive a more parsimonious model to identify variables that were independently associated with the outcome.

Based on the different performances of SMI and MA in male and female patients, we used time-dependent receiver operating characteristic (ROC) curves[24] to analyze the predictive value of SMI and MA for the 1-, 3- and 5-year mortality of the patients in this cohort. The area under the curve (AUC) was used to estimate the ability of the indicator to predict mortality, and the Delong test was used to compare the AUCs.[25] The optimal value of each indicator was determined by Youden's index, and MA was divided into low-MA and high-MA groups by the cutoff value in different sexes. Cumulative mortality curves were constructed using the Kaplan-Meier procedure, and the log-rank test was utilized to compare the mortality curves of the two groups.

The statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and Medals version 18.2.1 (Ostend, Belgium). A p value <0.05 (2 sided) was considered statistically significant.

RESULTS

Baseline characteristics of the enrolled patients

Among the 223 patients who met the inclusion criteria, 144 were male (64.6%) with a mean age of 51.5±10.6 years, and 79 were women (35.4%) with an average age of 54.6±11.6 years. Hepatitis B virus (HBV) infection was the main etiology, followed by autoimmune liver disease (AILD) (20.2%) and alcohol abuse (15.7%) (Table 1).

During the hospitalization period, 125 (56.1%), 97 (43.5%), 95 (42.6%), and 45 (20.2%) patients were diagnosed with ascites, variceal bleeding, infection and HE, respectively, and there were no significant differences between males and females. The median follow-up time of the study was 65.1 (IQR, 34.7-70.9) months, and the five-year mortality rates for men and women were 38.2% and 38.0%, respectively.

Differences in body composition status according to sex

In this study, we performed sex stratification and compared baseline body composition compartments of patients with cirrhosis, including BMI, SMI, MA, VATI, SATI and VSR (Table 1). Although BMI and VATI values were not significantly different between male and female patients, SMI (51.6±8.1 vs 40.9±7.0, p<0.001), MA (39.5±7.9 vs 30.3±9.8, p<0.001) and VSR (0.90 [IQR, 0.65-1.38] vs 0.51 [IQR, 0.36-0.76], p<0.001) values were significantly higher in male than female patients. In contrast, the SATI value in male patients was significantly lower than that in female patients (30.0 [IQR, 19.1-43.65] vs 52.8 [IQR, 32.0-66.9], p<0.001).

Table 1. Baseline characteristics and body compositions in cirrhosis

Characteristics	Total (N=223)	Male (n=144)	Female (n=79)	*p*
Age, y	52.7±11.6	51.5±10.6	54.6±11.6	0.358
Etiology, n (%)				<0.001
HBV	127 (57.0)	89(61.8)	38(48.1)	
AILD	45 (20.2)	9(6.3)	37(46.8)	
Alcohol	35 (15.7)	34(23.6)	0(0.0)	
Cryptogenic/others†	16 (7.2)	12 (8.3)	4 (5.1)	0.840
Ascites, n (%)	125 (56.1)	80 (55. 6)	45 (57.0)	0.840
HE, n (%)	45 (20.2)	28 (19.4)	17 (21.5)	0.712
Variceal bleeding, n (%)	97(43.5)	66(45.8)	31(39.2)	0.342
Infection, n (%)	95 (42.6)	53 (36.8)	42 (53.2)	0.018
MELD score	11.8±4.4	12.1±4.4	11.2±4.6	0.059
Child-Pugh class, N (%)				0.976
A	79 (35.4)	51 (35.4)	28 (35.4)	
B	100 (44.8)	64 (44.4)	36 (45.6)	
C	44 (19.7)	29 (20.1)	15 (19.0)	
Albumin, g/L	31.8±7.0	32.4±7.2	30.6±6.4	0.083
Bilirubin, mmol/L	25.0 (16.5, 44.9)	25.3 (16.8, 43.8)	22.8 (16.1, 44.9)	0.921
Sodium, mmol/L	141 (139, 143)	141 (138, 143)	142 (139, 143)	0.096
Platelet, 10^9/L	89 (57, 132)	91 (55, 139)	84 (61, 123)	0.870
Body composition variables				
BMI	23.9±3.4	24.2±3.2	23.4±3.6	0.082
SMI (cm^2/m^2)	47.8±9.3	51.6±8.1	40.9±7.0	<0.001
MA (HU)	36.3±9.7	39.5±7.9	30.3±9.8	<0.001
VATI (cm^2/m^2)	25.5 (13.6, 46.4)	25.7 (13.4, 46.8)	24.1 (14.1, 43.8)	0.957
SATI (cm^2/m^2)	35.1 (22.7, 54.1)	30.0 (19.1, 43.7)	52.8 (32.0, 66.9)	<0.001
VSR	0.77 (0.47, 1.25)	0.90 (0.65, 1.38)	0.51 (0.36, 0.76)	<0.001

HBV: hepatitis B virus; AILD: autoimmune liver disease; HE: hepatic encephalopathy; MELD: model for end-stage liver disease; BMI: body mass index; SMI: skeletal muscle index; MA: muscle attenuation; VATI: visceral adipose tissue index; SATI: subcutaneous adipose tissue index; VSR: visceral to subcutaneous adipose tissue area ratio.

†Others include non-alcoholic steatohepatitis, hepatitis C virus, Wilson disease and Budd-Chiari syndrome.

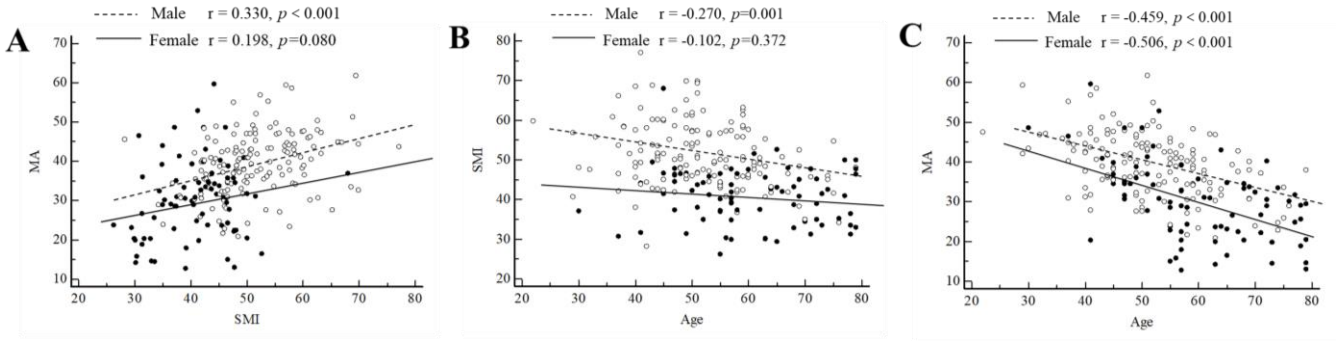

Figure 2. Scatter graphs depicting the correlations between skeletal muscle index (SMI), muscle attenuation (MA), and age according to sex.

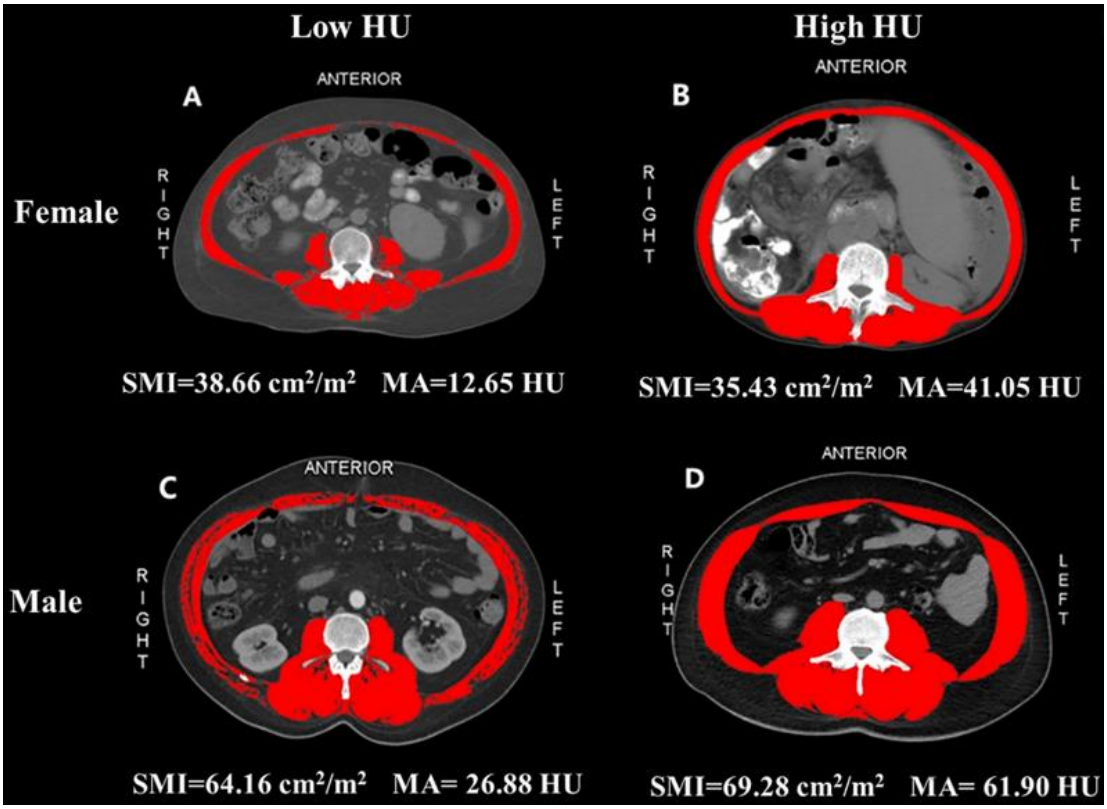

Figure 3. Comparison of two female (A, B) and two male (C, D) patients with cirrhosis. Abdominal CT images taken at the third lumbar vertebra. The red shadows show the skeletal muscle areas from -29 to +150 HU. Images A and B, images C and D have similar skeletal muscle index (SMI) values, but the muscle attenuation (MA) values are obviously different.

The correlation between SMI and MA in different sexes

There was a significant linear (p<0.001) and weak (r=0.33) relationship between SMI and MA in male patients, while a linear correlation between SMI and MA was not observed in females (Figure 2A). As shown in Figure 3, two female and two male cirrhotic patients had similar SMI values, whereas their MA values were significantly different. These results suggested that MA and SMI were two different metrics for assessing skeletal muscle, and they cannot replace each other.

Age is a known risk factor for skeletal muscle wasting. Therefore, we analyzed the correlation between SMI, MA and age. As shown in Figure 2B and 2C, in male patients, SMI (r=-0.270, p=0.001) and MA (r=-0.459, p<0.001) were negatively correlated with age. In female patients, only MA (r=-0.506, p<0.001) was negatively correlated with age.

Univariate and multivariate analyses of mortality

To quantify the effects of SMI and MA on mortality, we conducted Cox proportional hazard regression analysis, and the results from univariate and multivariate analyses are summarized in Table 2. In female patients with cirrhosis, univariate analysis indicated a correlation between MA and mortality (HR=0.91; 95% CI, 0.87-0.96; p<0.001), but SMI did not show an association with mortality (HR=0.97; 95% CI, 0.92-1.02; p=0.264). After adjusting for confounding factors, MA was still an independent factor influencing the survival of female patients (HR=0.91; 95% CI, 0.87-0.96; p<0.001). For males, MA (HR=0.93; 95% CI, 0.90-0.96; p<0.001) and SMI (HR=0.91; 95% CI, 0.87-0.96; p<0.001) were significantly associated with mortality in the univariate analysis. In multivariate Cox regression analysis, only SMI (HR=0.95; 95% CI, 0.91-0.98; p=0.002) was independently associated with mortality.

Table 2. Mortality associated factors by univariate and multivariate cox proportional-hazards analysis in female and male cirrhotic patients

Characteristics	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Female patients				
Age, y	1.06 (1.02, 1.09)	0.001		
MELD score	1.20 (1.12, 1.30)	<0.001	1.22 (1.12, 1.33)	<0.001
Bilirubin, mmol/L	1.00 (1.00, 1.01)	0.002		
Sodium, mmol/L	0.96 (0.84, 1.09)	0.526		
INR	6.05 (2.83, 12.94)	<0.001		
Albumin, g/L	0.93 (0.88, 0.99)	0.016		
Ascites	2.14 (0.98, 4.65)	0.055		
HE	3.57 (1.72, 7.39)	0.001	2.51 (1.15, 5.49)	0.021
Infection	2.81 (1.29, 6.11)	0.009	3.01 (1.35, 6.70)	0.007
Variceal bleeding	1.22 (0.60, 2.48)	0.581	2.42 (1.11, 5.28)	0.027
SMI (cm^2/m^2)	0.97 (0.92, 1.02)	0.264		
MA(HU)	0.92 (0.88, 0.96)	<0.001	0.91 (0.87, 0.96)	<0.001
SATI (cm^2/m^2)	1.00 (0.98, 1.01)	0.694		
VATI (cm^2/m^2)	1.01 (1.00, 1.03)	0.078		
VSR	5.20 (1.90, 14.26)	0.001		
Male patients				
Age, y	1.04 (1.02, 1.07)	0.001	1.04 (1.02, 1.07)	0.001
MELD score	1.20 (1.13, 1.27)	<0.001	1.16 (1.09, 1.23)	<0.001
Bilirubin, mmol/L	1.00 (1.00, 1.01)	0.322		
Sodium, mmol/L	0.93 (0.87, 0.99)	0.029		
INR	3.67 (2.03, 6.63)	<0.001		
Albumin, g/L	0.94 (0.91, 0.98)	0.003		
Ascites	2.42 (1.36, 4.32)	0.003		
HE	2.86 (1.64, 4.97)	<0.001	1.99 (1.09, 3.64)	0.025
Infection	2.58 (1.53, 4.35)	<0.001	1.75 (0.98, 3.15)	0.061
Variceal bleeding	1.55 (0.92, 2.61)	0.099		
SMI (cm^2/m^2)	0.93 (0.90, 0.96)	<0.001	0.95 (0.91, 0.98)	0.002
MA(HU)	0.93 (0.90, 0.96)	<0.001		
SATI (cm^2/m^2)	0.99 (0.97, 1.00)	0.072		
VATI (cm^2/m^2)	1.00 (0.99, 1.01)	0.717		
VSR	2.26 (1.42, 3.60)	0.001		

HR: hazard ratio; MELD: model for end-stage liver disease; INR: international normalized ratio; HE: hepatic encephalopathy; SMI: skeletal muscle index; MA: muscle attenuation; SATI: subcutaneous adipose index; VATI: visceral adipose tissue index; VSR: visceral to subcutaneous adipose tissue area ratio.

In univariate and multivariate Cox proportional hazards regression models, the performance of SMI and MA in male and female patients with liver cirrhosis was different, which was an interesting discovery.

The predictive ability of SMI and MA for mortality in patients with cirrhosis

In view of the differences between SMI and MA in different sexes, we used time-dependent ROC curves to examine the predictive effectiveness of SMI and MA in predicting the 1-, 3- and 5-year mortality of cirrhotic patients of different sexes (Figure 4).

In the time-dependent ROC analysis of all 223 patients, the AUC of MA was consistently larger than that of SMI, but a significant difference was not shown until the 5-year mortality prediction (p=0.047). In males, the AUC of SMI was slightly larger than that of the MA in predicting 1-, 3- or 5-year mortality, but there was no significant difference between the two indicators. For females, the AUC of MA showed a gradually increasing trend as the observation time increased, while the AUC of SMI decreased, and the p value of these two parameters gradually decreased. The predictive ability of MA is significantly better than that of SMI for the mortality of female patients with cirrhosis.

According to the cutoff values of the ROC curves in the 5-year mortality of the different sexes, in females, MA less than 30.73 HU was defined as low-MA, with an AUC of 0.797 (95% CI, 0.692-0.879), while in males, MA <39.83 HU was defined as low MA, with an AUC of 0.705 (95% CI, 0.623-0,778).

Cumulative mortality curves were constructed using the Kaplan-Meier method (Figure 5). The mortality of the low-MA group was higher than that of the high-MA group in all patients with liver cirrhosis. In males, the 1-year, 3-year and 5-year probabilities of mortality were 19.7%, 36.6% and 54.9% in patients with low MA, compared to 6.8%, 11.0% and 21.9% with high MA, respectively. For females, the 1-, 3- and 5-year estimated mortality probabilities in patients with low and high MA were 30.0% and 2.6%, 52.5% and 5.1%, 65.0% and 10.3%, respectively (all p<0.001 by log-rank tests). Hence, patients with low MA had a higher risk of mortality.

DISCUSSION

Numerous patients with liver cirrhosis are faced with increased energy consumption, decreased appetite, and protein synthesis dysfunction, causing an imbalance in protein synthesis and consumption in the body,[26] which consequently leads to skeletal muscle consumption. Muscle tissue is more often affected in male patients, while adi-

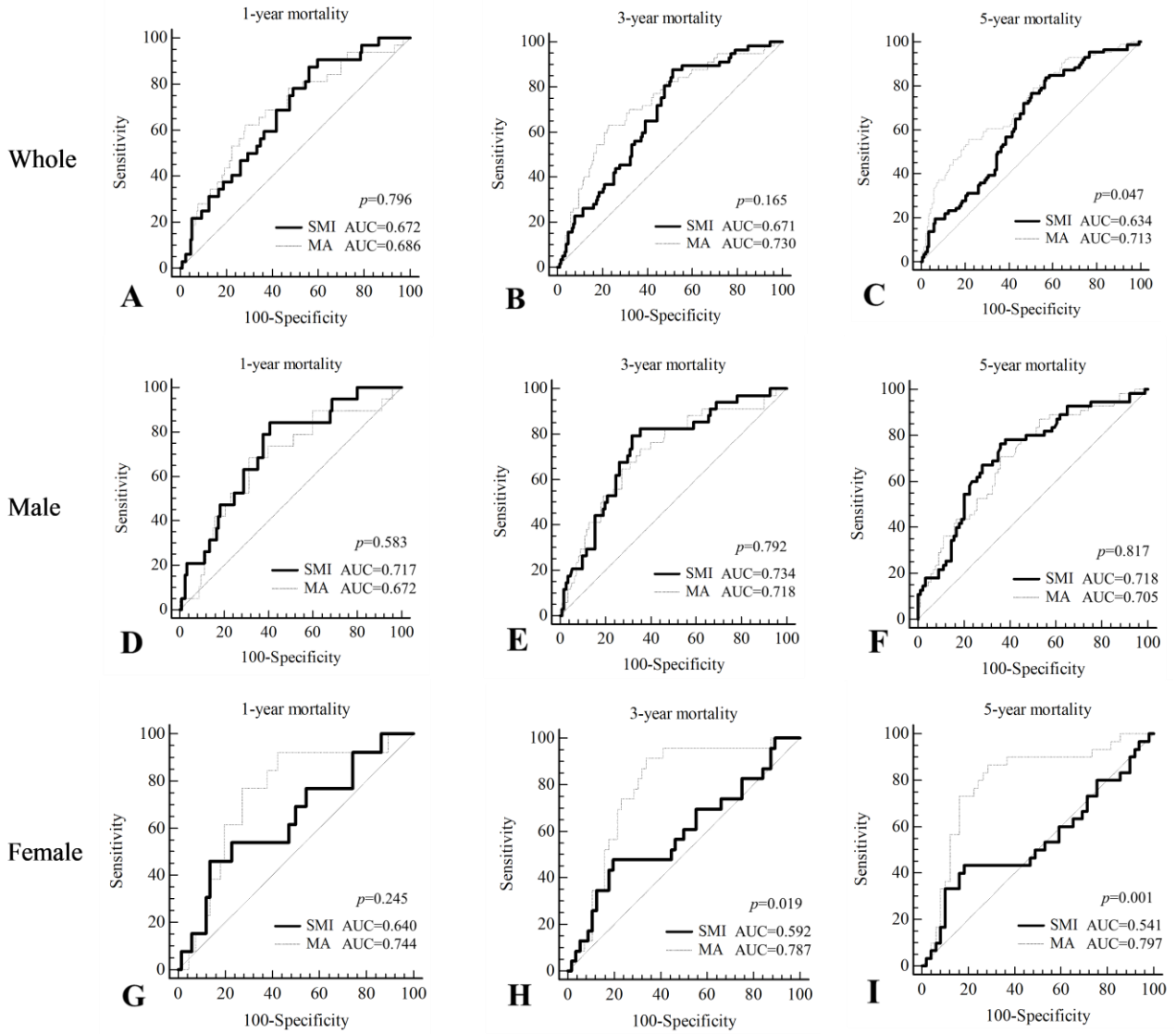

Figure 4. Predictive value of skeletal muscle index (SMI) and muscle attenuation (MA) in predicting 1-, 3- and 5-year mortality of liver cirrhosis patients in this cohort; utility of SMI and MA for predicting the prognosis of patients with cirrhosis, as determined by comparing the areas under the ROC curve.

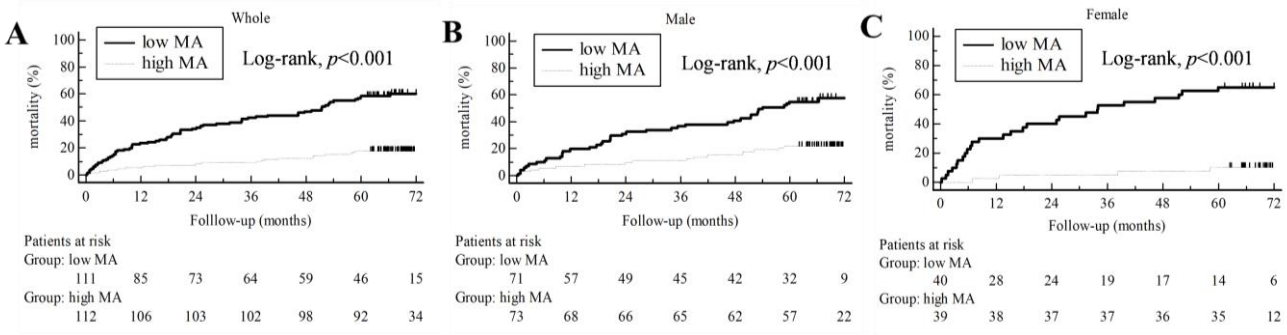

Figure 5. Kaplan-Meier curves indicating the mortality of patients with low muscle attenuation (MA) and high MA in whole (A), male (B) and female (C) patients with cirrhosis.

pose tissue is depleted more severely in females. In addition to body composition, sex differences exist for other clinical features of liver disease, such as etiology and creatinine concentration.[27] Unfortunately, sex-specific differences are often ignored in many disease studies despite obvious variability in hormonal profiles, body composition phenotype changes, differential etiologies and liver metabolism,[28-32] which emphasizes the need for sex classification in cirrhosis associated mortality studies.

By sex stratification, SMI was independently associated with mortality in male patients with cirrhosis, but this finding was inconsistent with that in female patients,[11,12] which is in line with our current results. However, the mechanism that causes sex differences in its ability to predict the mortality of cirrhotic patients is complex, but

may be related to hormone concentration. As an androgen, testosterone plays an important role in muscle synthesis. Clinical trials of testosterone have proven that the dose-dependent increases in muscle mass extend well into the supraphysiological range.[33] At the cellular level, testosterone affects the differentiation and proliferation of myocytes and regulates muscle protein turnover.[34] Serum testosterone is reduced in up to 90% of men with liver cirrhosis, and decreases with the progression of liver disease.[35] In females, the serum testosterone concentration is only one-tenth that of males, and has little effect on the production and decomposition of skeletal muscle. Therefore, it is not difficult to understand that SMI is more sensitive to the mortality prediction of male patients.

SMI and MA are two independent muscle assessment indicators, and no obvious linear correlation between them has been found in recent studies,[36] which is in line with our current findings. There are some similarities between them, and a lack of unified assessment criteria in muscle assessment makes it inevitable that some people confound the two. According to some studies, SMI and MA are defined as dichotomous variables as sarcopenia and myosteatosis, respectively.[37,38] In our analysis of 223 patients with liver cirrhosis, the AUC of MA was larger than that of SMI, although the significant differences between the two parameters did not appear until the fifth year. MA may be a better indicator than SMI, especially in long-term mortality prediction. Of note, the majority of patients with liver cirrhosis are male, furthermore, the early death caused by acute liver failure and acute gastrointestinal bleeding may influence the ability of SMI and MA to predict mortality. In the subsequent sex-stratified analyses, MA showed fine mortality prediction ability in both males and females. A recent study related to orthotopic liver transplantation (OLT) also found that myosteatosis may be a useful parameter for predicting the perioperative prognosis of OLT patients, supporting the role of myosteatosis.[39] Similar findings were disclosed in studies of other diseases. For instance, Vedder et al[40] demonstrated that myosteatosis is a stronger predictor of survival than sarcopenia in peripheral arterial occlusive disease (PAOD) in a single-center retrospective cohort study of 686 PAOD patients. In another retrospective cohort study of 228 patients with pancreatic cancer, Rollins et al[41] suggested that the presence of myosteatosis was significantly associated with systemic inflammation and reduced survival rates, while sarcopenia alone did not have a bearing on survival. In summary, MA may be a better indicator for predicting disease prognosis.

Some research has concluded that pathological variation in MA is directly associated with the accumulation of lipids,[14,42] however, little is known about the exact composition of muscle lipid components. What is known thus far is that muscle lipids comprise a variety of lipid species, including free fatty acids, diacylglycerol, triacylglycerol and phospholipids. Moreover, it may be not only the content but also the proportion of these components that may be important in the pathological effects of fat accumulation. Recent studies have revealed that the composition of lipid components in muscle may be as important as the total amount of fat per se in promoting muscle loss (both in pathology and function). For example, accumulation of diacylglycerols instead of triacylglycerol is associated with insulin resistance in non-adipose tissues.[43,44] In addition, the pathogenesis of fatty muscle infiltration has not yet been fully elucidated. The accumulation of fat in skeletal muscle is not only the result of age and continuous consumption of disease but also may be a concentrated response to the overall poor condition of patients. Excess muscle fat may be seen as stored fat to meet or predict future metabolic needs, or as fat toxicity and its cascading toxic effects (such as IR, oxidative stress, inflammation, impaired regeneration, altered protein balance).[45] Therefore, lipid composition and the mechanism of intermuscular fat deposition still need to be studied in cirrhotic patients of different sexes.

To the best of our knowledge, this is the first study to analyze the predictive ability of SMI and MA by time-dependent ROC in patients with liver cirrhosis, and we used body parameters as continuous variables for analysis to avoid the loss of information. Furthermore, evaluating the body composition of cirrhotic patients through CT imaging is objective as well as accessible, and makes it possible to simultaneously avoid the interference of fluid retention, which is also the main advantage of this study. Nonetheless, it should be noted that this is a retrospective study in a single institution, making it difficult to evaluate the preadmission diet and physical activity of these cirrhotic patients, which are also factors affecting skeletal muscle. Therefore, further research of a well-designed multicentric prospective cohort is needed in the future.

Conclusion

SMI in males and MA in females are independent prognostic factors of liver cirrhosis. For females, MA may be a more sensitive indicator of mortality prediction than SMI, especially regarding long-term prognosis, while in males, they are equivalent. Therefore, there may be a great need to pay more attention to intermuscular fat deposition in female patients with liver cirrhosis when performing body composition assessment.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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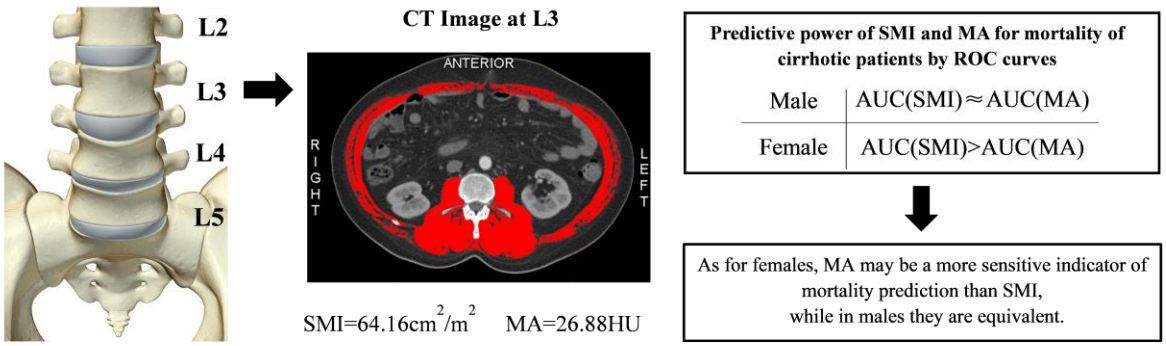
REFERENCES

1. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053): 1459-544. doi: 10.1016/S0140-6736(16)31012-1.

2. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70:151-71. doi: 10.1016/j.jhep.2018.09.014.
3. Ooi PH, Hager A, Mazurak VC, Dajani K, Bhargava R, Gilmour SM, Mager DR. Sarcopenia in chronic liver disease: impact on outcomes. Liver Transpl. 2019;25:1422-38. doi: 10.1002/lt.25591.
4. Chang KV, Chen JD, Wu WT, Huang KC, Lin HY, Han DS. Is sarcopenia associated with hepatic encephalopathy in liver cirrhosis? A systematic review and meta-analysis. J Formos Med Assoc. 2019;118:833-42. doi: 10.1016/j.jfma.2018.09.011.
5. Kim TY, Kim MY, Sohn JH, Kim SM, Ryu JA, Lim S, Kim Y. Sarcopenia as a useful predictor for long-term mortality in cirrhotic patients with ascites. J Korean Med Sci. 2014;29:1253-9. doi: 10.3346/jkms.2014.29.9.1253.
6. Montano-Loza AJ, Meza-Junco J, Prado CMM, Lieffers JR, Baracos VE, Bain VG, Sawyer MB. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol. 2012;10:166-73. doi: 10.1016/j.cgh.2011.08.028.
7. Kalafateli M, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. J Cachexia Sarcopenia Muscle. 2017;8:113-21. doi: 10.1002/jcsm.12095.
8. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211:271-8. doi: 10.1016/j.jamcollsurg.2010.03.039.
9. Carey EJ, Lai JC, Sonnenday C, Tapper EB, Tandon P, Duarte-Rojo A et al. A North American expert opinion statement on sarcopenia in liver transplantation. Hepatology. 2019;70:1816-29. doi: 10.1002/hep.30828.
10. Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, Dunn MA. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl. 2017;23:625-33. doi: 10.1002/lt.24750.
11. Ebadi M, Tandon P, Moctezuma-Velazquez C, Ghosh S, Baracos VE, Mazurak VC, Montano-Loza AJ. Low subcutaneous adiposity associates with higher mortality in female patients with cirrhosis. J Hepatol. 2018;69:608-16. doi: 10.1016/j.jhep.2018.04.015.
12. DiMartini A, Cruz RJ, Dew MA, Myaskovsky L, Goodpaster B, Fox K, Kim KH, Fontes P. Muscle mass predicts outcomes following liver transplantation. Liver Transpl. 2013;19:1172-80. doi: 10.1002/lt.23724.
13. Merli M, Durand F. Muscle mass vs. adipose tissue to predict outcome in cirrhosis: Which matters and in which patients? J Hepatol. 2018;69:567-9. doi: 10.1016/j.jhep.2018.06.005.
14. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol (1985). 2000;89:104-10. doi: 10.1152/jappl.2000.89.1.104.
15. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, Mazurak VC. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf). 2014;210:489-97. doi: 10.1111/apha.12224.
16. Bhanji RA, Moctezuma-Velazquez C, Duarte-Rojo A, Ebadi M, Ghosh S, Rose C, Montano-Loza AJ. Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis. Hepatol Int. 2018;12:377-86. doi: 10.1007/s12072-018-9875-9.
17. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CMM, Sawyer MB, Beaumont C, Esfandiari N, Ma M, Baracos VE. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle. 2016;7:126-35. doi: 10.1002/jcsm.12039.
18. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464-70. doi: 10.1053/jhep.2001.22172.
19. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-9. doi: 10.1002/bjs.1800600817.
20. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85:115-22. doi: 10.1152/jappl.1998.85.1.115.
21. Kvist H, Sjöström L, Tylén U. Adipose tissue volume determinations in women by computed tomography: technical considerations. Int J Obes. 1986;10:53-67.
22. Vehmas T, Kairemo KJ, Taavitsainen MJ. Measuring visceral adipose tissue content from contrast enhanced computed tomography. Int J Obes Relat Metab Disord. 1996;20:570-3.
23. Goodpaster BH, Thaete FL, Kelley DE. Composition of skeletal muscle evaluated with computed tomography. Ann N Y Acad Sci. 2000;904:18-24. doi: 10.1111/j.1749-6632.2000.tb06416.x.
24. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. BMC Med Res Methodol. 2017;17:53. doi: 10.1186/s12874-017-0332-6.
25. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-45.
26. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol. 2019;70:172-93. doi: 10.1016/j.jhep.2018.06.024.
27. Mariante-Neto G, Marroni CP, Fleck Junior AM, Marroni CA, Zanotelli ML, Cantisani G, Brandão ABM. Impact of creatinine values on MELD scores in male and female candidates for liver transplantation. Ann Hepatol. 2013;12:434-9.
28. Pramfalk C, Pavlides M, Banerjee R, McNeil CA, Neubauer S, Karpe F, Hodson L. Sex-specific differences in hepatic fat oxidation and synthesis may explain the higher propensity for NAFLD in men. J Clin Endocrinol Metab. 2015;100:4425-33. doi: 10.1210/jc.2015-2649.
29. Della Torre S, Mitro N, Meda C, Lolli F, Pedretti S, Barcella M et al. Short-term fasting reveals amino acid metabolism as a major sex-discriminating factor in the liver. Cell Metab. 2018;28. doi: 10.1016/j.cmet.2018.05.021.
30. Klein SL, Schiebinger L, Stefanick ML, Cahill L, Danska J, de Vries GJ et al. Opinion: Sex inclusion in basic research drives discovery. Proc Natl Acad Sci U S A. 2015;112:5257-8. doi: 10.1073/pnas.1502843112.
31. Nutritional status in cirrhosis. Italian multicentre cooperative project on nutrition in liver cirrhosis. J Hepatol. 1994;21:317-25.
32. Caregaro L, Alberino F, Amodio P, Merkel C, Bolognesi M, Angeli P, Gatta A. Malnutrition in alcoholic and virus-related cirrhosis. Am J Clin Nutr. 1996;63:602-9. doi: 10.1093/ajcn/63.4.602.

33. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N et al. Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab. 2001;281:E1172-81. doi: 10.1152/ajpendo.2001.281.6.E1172.
34. Sinha-Hikim I, Roth SM, Lee MI, Bhasin S. Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. Am J Physiol Endocrinol Metab. 2003;285:E197-205. doi: 10.1152/ajpendo.00370.2002.
35. Grossmann M, Hoermann R, Gani L, Chan I, Cheung A, Gow PJ, Li A, Zajac JD, Angus P. Low testosterone levels as an independent predictor of mortality in men with chronic liver disease. Clin Endocrinol (Oxf). 2012;77:323-8. doi: 10.1111/j.1365-2265.2012.04347.x.
36. Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol. 2015;63:131-40. doi: 10.1016/j.jhep.2015.02.031.
37. Ahn H, Kim DW, Ko Y, Ha J, Shin YB, Lee J, Sung YS, Kim KW. Updated systematic review and meta-analysis on diagnostic issues and the prognostic impact of myosteatosis: A new paradigm beyond sarcopenia. Ageing Res Rev. 2021;70:101398. doi: 10.1016/j.arr.2021.101398.
38. Martin L, Gioulbasanis I, Senesse P, Baracos VE. Cancer-associated malnutrition and CT-defined sarcopenia and myosteatosis are endemic in overweight and obese patients. JPEN J Parenter Enteral Nutr. 2020;44:227-38. doi: 10.1002/jpen.1597.
39. Czigany Z, Kramp W, Bednarsch J, van der Kroft G, Boecker J, Strnad P et al. Myosteatosis to predict inferior perioperative outcome in patients undergoing orthotopic liver transplantation. Am J Transplant. 2020;20:493-503. doi: 10.1111/ajt.15577.
40. Vedder IR, Levolger S, Dierckx RAJO, Zeebregts CJ, de Vries J-PPM, Viddeleer AR, Bokkers RPH. Effect of muscle depletion on survival in peripheral arterial occlusive disease: Quality over quantity. J Vasc Surg. 2020;72. doi: 10.1016/j.jvs.2020.03.050.
41. Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, Fearon KCH, Lobo DN. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. Clin Nutr. 2016;35:1103-9. doi: 10.1016/j.clnu.2015.08.005.
42. Larson-Meyer DE, Smith SR, Heilbronn LK, Kelley DE, Ravussin E, Newcomer BR. Muscle-associated triglyceride measured by computed tomography and magnetic resonance spectroscopy. Obesity (Silver Spring). 2006;14:73-87. doi: 10.1038/oby.2006.10.
43. Chabowski A, Zendzian-Piotrowska M, Nawrocki A, Górski J. Not only accumulation, but also saturation status of intramuscular lipids is significantly affected by PPARγ activation. Acta Physiol (Oxf). 2012;205:145-58. doi: 10.1111/j.1748-1716.2011.02380.x.
44. Coen PM, Goodpaster BH. Role of intramyocelluar lipids in human health. Trends Endocrinol Metab. 2012;23:391-8. doi: 10.1016/j.tem.2012.05.009.
45. Nachit M, Leclercq IA. Emerging awareness on the importance of skeletal muscle in liver diseases: time to dig deeper into mechanisms! Clin Sci (Lond). 2019;133:465-81. doi: 10.1042/CS20180421.



Graphical abstract. SMI: skeletal muscle index; MA: muscle attenuation; HU: Hounsfield units; AUC: area under the curve.