Title page

Factors associated with the progression of myosteatosis in patients with cirrhosis

Running head: Factors that worsen myosteatosis in cirrhotic patients

Yoji Ishizu, MD, PhD[1], Masatoshi Ishigami, MD, PhD[1], Takashi Honda, MD, PhD[1], Norihiro Imai, MD, PhD[1], Takanori Ito, MD, PhD[1], Kenta Yamamoto, MD, PhD[1], Shinya Yokoyama, MD, PhD[1], Tetsuya Ishikawa, MD, PhD[1], Mitsuhiro Fujishiro, MD, PhD[1]

[1] Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya, 466-8550 Japan

Authorship

YI and MI were involved in the conception and design of the study. Generation, collection, assembly, analysis, and interpretation of data were handled by YI, MI, TH, NI, TI, KY, SY, TI and MF. Drafting or revision of the manuscript was the responsibility of YI and MI. All the authors read and approved the final version of the manuscript.

A word count: 3110 words

The total number of figures and tables:

Three figures, one supplementary figure, and five tables

Corresponding Author:

Yoji Ishizu, MD, PhD

Department of Gastroenterology and Hepatology,

Nagoya University Graduate School of Medicine

65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2169

Fax: +81-52-744-2178

E-mail: y-ishizu@med.nagoya-u.ac.jp

ORCID: 0000-0002-1255-5201

Abstract

Background & Aims: The presence of myosteatosis is a poor prognostic factor for patients with cirrhosis; however, the factors contributing to worsening myosteatosis are unknown. We aimed to clarify the changes in myosteatosis and the factors involved in these changes.

Methods: One-hundred-seventy-eight cirrhotic patients who underwent computed tomography twice were enrolled to measure changes in skeletal muscle attenuation (SMA) at the L3 level. Factors associated with SMA and those associated with changes in SMA were examined.

Results: Using linear multiple regression analysis, age (B = –0.22), skeletal muscle index (SMI; skeletal muscle area divided by height squared; B = 0.25), and visceral and subcutaneous fat indices (VFI and SFI; the visceral and subcutaneous fat areas at the umbilical level divided by height squared; B = –0.08, B = –0.06, respectively) were identified as associated with SMA. The 100-day change in SMA was –0.21 ± 1.29 Hounsfield units (HU). Changes in SMI and SMA were positively associated (R = 0.183, P = 0.014), whereas those in VFI and SMA were negatively associated (R = –0.172, P = 0.022). No association was noted between the 100-day changes in SFI and SMA. In patients whose SMI increased and VFI decreased, the 100-day change in SMA was 0.24 ± 1.82 HU, which was marginally different from that in patients whose SMI decreased and VFI increased (–0.44 ± 1.32 HU, P = 0.077).

Conclusions: In cirrhotic patients, myosteatosis progressed, and decreases in SMI and increases in VFI were correlated with its progression.

Keywords: skeletal muscle, myosteatosis, progression, visceral fat accumulation, cirrhosis

Abbreviations

BMI, body mass index; CI, confidence interval; CT, computed tomography; HCC, hepatocellular carcinoma; HR, hazard ratio; HU, Hounsfield unit; L3, third lumbar vertebra; MELD, Model for End-Stage Liver Disease; SFI, subcutaneous fat index; SMA, skeletal muscle attenuation; SMI, skeletal muscle index; VFI, visceral fat index

Main text

Introduction

Patients with liver cirrhosis can easily lose skeletal muscle mass due to malnutrition and chronic inflammation, and loss of skeletal muscle mass is a poor prognostic factor in cirrhotic patients [1]. In general, the amount of skeletal muscle mass correlates with muscle strength [2]. However, a study on elderly people has revealed that muscle strength decreases even if muscle mass is maintained [3], and this led to a focus on the quality of skeletal muscle in addition to the amount of skeletal muscle. As for the quality of skeletal muscle, myosteatosis (a condition in which fat is infiltrated into the skeletal muscle) was observed to be associated with muscle strength [4] and physical performance [5], indicating that myosteatosis may be an indicator of skeletal muscle quality [6].

The degree of myosteatosis can be assessed using computed tomography (CT) based on the fact that fatty infiltration into skeletal muscle decreases the attenuation of skeletal muscle [4, 7]. Additionally, in patients with cirrhosis, the presence of myosteatosis diagnosed by CT has been reported to be a factor associated with worse prognosis [8] and development of complications after liver transplantation [9].

Although the mechanism of myosteatosis remains to be elucidated, the degree of myosteatosis has been shown to be negatively associated with skeletal muscle mass and positively associated with visceral fat accumulation [10]. However, it is also unclear how the degree of myosteatosis changes

over time and how these changes are related to changes in skeletal muscle mass, as well as visceral and subcutaneous fat mass.

Therefore, the purpose of this study was to evaluate the changes in the degree of myosteatosis over time and to identify the factors associated with the progression of myosteatosis in patients with cirrhosis.

Materials and Methods

Patients

We retrospectively reviewed 1330 adult patients who underwent CT at our hospital from January 1, 2010, to December 31, 2016, and were diagnosed radiologically as having cirrhosis. Radiologists made a diagnosis of cirrhosis based on the following findings: irregularity of the surface of the liver, atrophy of the right lobe of the liver, enlargement of the left lobe of the liver, splenomegaly, and the development of collateral vessels of the portal vein. Patients with a history of hepatocellular carcinoma (HCC) (n = 626), liver transplantation (n = 4), incurable malignancy other than HCC (n = 63), severe chronic respiratory or heart disease (n = 23), nephrotic syndrome (n = 3), active ulcerative colitis (n = 1), and rare liver disease (n = 35), as well as patients without a detailed examination of liver disease (n = 88) or sufficient data (n = 130), were excluded. Moreover, to evaluate longitudinal changes in skeletal muscle attenuation (SMA), we obtained the data of SMA from the second CT performed >6 months after the first CT. Thus, patients without a second CT

performed >6 months after the first CT were excluded (n = 179). Finally, 178 patients were enrolled for analysis (Supplementary Figure 1). Patients' characteristics are shown in Table 1. Etiology of liver disease was as follows: alcoholic liver disease (n = 31), active viral hepatitis (hepatitis B virus [n = 3] and hepatitis C virus [n = 32]) with no antiviral treatment during the observation period, inactive or treated viral hepatitis by antiviral treatment against hepatitis B virus (n = 10) or hepatitis C virus (n = 48) before or during the observation period, non-alcoholic steatohepatitis (n = 14), autoimmune hepatitis (n = 11), primary biliary cholangitis (n = 13), and cryptogenic liver disease (n = 16). The mean Model for End-Stage Liver Disease (MELD) score was 9 ± 3. Six patients had a history of variceal bleeding, 16 had mild ascites, and 12 had a history of hepatic encephalopathy. The requirement for informed consent was waived due to the retrospective nature of the study; anonymous clinical data were analyzed.

Data collection

Clinical and laboratory data at the time of CT imaging were collected retrospectively. CT was performed to assess the presence of the hepatocellular carcinoma and the degree of ascites. A transverse CT image without contrast media at the level of the third lumbar vertebra (L3) was used for the measurement of the muscle area and that at the umbilical level was used for the evaluation of the visceral and subcutaneous fat area. Muscle and abdominal fat areas were calculated using SYNAPSE VINCENT software (Fujifilm Co., Tokyo, Japan), which enables

specific tissue demarcation by using the Hounsfield unit (HU) thresholds. Muscles, visceral fat, and subcutaneous fat were quantified within the HU ranges of –29 to +150 HU, –150 to –50 HU, and –190 to –30 HU, respectively [8], and tissue boundaries were manually corrected as needed. All analyses were performed by the same person who was blinded to the outcome variables. The skeletal muscle index (SMI) was calculated as the total area of all skeletal muscle mass (cm^2) divided by the square of the height (m^2). The degree of myosteatosis was evaluated by using the mean CT attenuation value of all skeletal muscle mass at L3. The visceral fat index (VFI) and subcutaneous fat index (SFI) were calculated as the visceral and subcutaneous fat areas (cm^2), respectively, divided by the square of the height (m^2). The time between the first and second CT differed among the patients. To normalize the results, the differences between the first and second CT were calculated for the amounts of skeletal muscle, subcutaneous fat, and visceral fat, as well as for the CT attenuation of skeletal muscle, subsequently divided by the number of days between the first and second CT, and finally multiplied by 100 to calculate the change per 100 days. Height data were obtained within 5 years and weight data within 30 days before and after the time of CT scanning. Body mass index (BMI) was calculated as body weight (kg) divided by the square of the height (m^2).

Definition of skeletal muscle depletion and visceral fat deposition

In accordance with the Japan Society of Hepatology guidelines [11], skeletal muscle depletion was

defined as an SMI of <42 (cm^2/m^2) in men and <38 (cm^2/m^2) in women. Visceral fat deposition was defined as a visceral fat area of ≥100 cm^2 [12]. Myosteatosis was defined as follows: radiation attenuation of skeletal muscle at L3 of <41 HU for patients with a BMI of ≤24.9 kg/m^2 and that of <33 HU for patients with a BMI of ≥25 kg/m^2 [13].

Statistical analysis

Quantitative variables were compared using the Student's t-test. We used analysis of variance and the Bonferroni post hoc test for multiple comparisons. Correlations were determined using Pearson's correlation coefficients. A multiple linear regression analysis was used to study the linear relationships between SMA and the variables. Patients were followed-up from the date of the CT performed for the evaluation of skeletal muscle and fat mass to the date of death, liver transplantation, or last visit, and competing risk analysis using the Fine and Gray model was used to identify risk factors for mortality. Values with $P < 0.05$ were considered to be statistically significant. Data were statistically analyzed using EZR on R commander (Version 1.38) [14] and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Ethics

The Ethics Committee at Nagoya University Hospital approved this study (approval no. 2018-0291), which was conducted in accordance with the principles of the Declaration of Helsinki (1975).

Results

Factors associated with SMA

Factors associated with SMA were examined using data acquired at the time of the first CT. The SMI showed a weak positive correlation with SMA ($R = 0.34$, $P < 0.001$), whereas age showed a moderate negative correlation ($R = –0.46$, $P < 0.001$); VFI and SFI showed weak negative correlations (VFI, $R = –0.21$, $P = 0.004$; SFI, $R = –0.20$, $P = 0.02$) with SMA. MELD score, albumin level, and BMI were not correlated with SMA (Table 2). The mean SMA was significantly lower in female patients than in male patients (31.6 ± 7.2 vs 37.2 ± 6.6 HU, $P < 0.001$). No significant difference in the mean SMA was observed among patient groups with different etiologies. Multiple linear regression was calculated to predict SMA based on age, sex, SMI, VFI, and SFI. A significant regression equation was observed ($F = 19.3$, $P < 0.01$), with an adjusted R^2 of 0.40. Age (B = –0.22), SMI (B = 0.25), VFI (B = –0.08), and SFI (B = –0.06) were significant predictors of SMA (Table 3). Next, we divided the study population into four groups according to the presence of skeletal muscle depletion and visceral fat deposition and compared the SMA among the four groups. The SMA was observed to be the lowest in patients with skeletal muscle depletion and visceral fat accumulation (30.4 ± 7.1 HU) and was significantly lower than that in patients without both skeletal muscle depletion and visceral fat accumulation (36.2 ± 8.5 HU, $P = 0.026$; Table 4).

Impact of myosteatosis on the prognosis of patients with cirrhosis

Ninety-seven of 178 patients (54.5%) had myosteatosis. During the observation period (1831 ± 793 days), 33 patients died, and 2 received liver transplantation. In the univariate analysis, etiology of active viral hepatitis ($P = 0.004$), a higher MELD score ($P < 0.001$), lower albumin levels ($P < 0.001$), and the presence of myosteatosis were associated with mortality ($P = 0.047$; Table 5 and Figure 1). The multivariate analysis showed that the MELD score (hazard ratio [HR], 1.147; 95% confidence interval [CI], 1.038–1.266; $P = 0.007$) and albumin levels (HR, 0.338; 95% CI, 0.154–0.743; $P = 0.007$) were significantly associated with mortality, and etiology of active viral hepatitis (HR, 1.943; 95% CI, 0.952–3.970; $P = 0.068$) and presence of myosteatosis (HR, 1.916; 95% CI, 0.900–4.082; $P = 0.092$) were marginally associated with mortality (Table 5).

Factors associated with the deterioration of SMA

SMA decreased in 55.6% of patients (99/178) during the period between the dates of the first and second CT (480 ± 376 days), and the change per 100 days was –0.21 ± 1.29 HU. Then, we evaluated the correlations between 100-day changes in SMA and those in SMI, VFI, and SFI. The 100-day changes in SMI were positively and weakly associated with those in SMA ($R = 0.183$, $P = 0.014$), whereas those in VFI were negatively and weakly ($R = –0.172$, $P = 0.022$) associated with those in SMA (Figure 2a, 2b). No association was noted between the 100-day changes in SFI and those in SMA (Figure 2c). Next, we divided our cohort into four groups according to an increase or a decrease

in SMI and VFI at the second time point. The SMA was decreased in patients whose SMI and VFI decreased (n = 49, –0.20 ± 1.10 HU/100 days), SMI and VFI increased (n = 39, –0.30 ± 0.63 HU/100 days), and SMI decreased and VFI increased (n = 54, –0.44 ± 1.32 HU/100 days). Conversely, in patients whose SMI increased and VFI decreased, the 100-day change in SMA was 0.24 ± 1.82 HU/100 days, which was marginally different from that in patients whose SMI decreased and VFI increased (P = 0.077, Figure 3).

Discussion

Cross-sectional studies have reported that the degree of myosteatosis is positively correlated with aging and visceral fat accumulation and negatively correlated with skeletal muscle mass [10, 15, 16], which is consistent with the results of this study. We also conducted a longitudinal study and observed that SMA decreased by 0.21 ± 1.29 HU per 100 days in patients with cirrhosis, and the amount of change was positively correlated with the 100-day decrease in SMI and negatively correlated with the 100-day increase in VFI. This indicates that the decrease in skeletal muscle mass and increase in visceral fat mass contribute to the worsening of myosteatosis.

Regarding longitudinal changes in myosteatosis in patients with cirrhosis, a previous study involving patients on the transplant waiting list reported that SMA decreased by 2.9 HU over a median period of 9.6 months [17]. The reason for quicker worsening of myosteatosis in the patients in the previous report compared to those in this study might be that the SMI decreased by 2.0 ±

4.9 cm^2/m^2 over a median of 9.6 months in the previous report, whereas the SMI decreased by only 0.49 ± 3.1 cm^2/m^2 over 1 year in this study.

Although the mechanism of myosteatosis remains unclear, the degeneration of the skeletal muscle cell progenitors into adipocytes [18] and ectopic deposition of excess lipids in the skeletal muscle [19] are thought to be possible causes of the onset and progression of myosteatosis; the finding that decreased skeletal muscle mass was associated with worsening of myosteatosis in this study supports the former hypothesis, and the finding that increased visceral fat was associated with worsening of myosteatosis supports the latter hypothesis. However, patients with cirrhosis are in a condition where their skeletal muscle is easily metabolized due to malnutrition, hyperendotoxemia, and hyperammonemia [20, 21]. Therefore, it is necessary to elucidate the basic mechanisms underlying the development of myosteatosis in these patients.

Previous studies have reported that the presence of myosteatosis worsened the prognosis of patients with cirrhosis [8, 22]. Similarly, in this study, the presence of myosteatosis tended to be associated with poor prognosis, albeit not significantly. In addition to being a poor prognostic factor, myosteatosis is also reported to be associated with the development of hepatic encephalopathy [23, 24] and complications after liver transplantation [9]. Thus, the presence of myosteatosis is an important factor affecting the clinical course of patients with cirrhosis. Based on our findings that the progression of myosteatosis is related to skeletal muscle mass loss and visceral fat mass increase, it is possible that the progression of myosteatosis can be reduced by increasing

skeletal muscle mass and reducing visceral fat accumulation. Exercise therapy, which can help increase skeletal muscle mass and reduce visceral fat mass, has been demonstrated to improve myosteatosis in the elderly and obese [25]. Regarding nutritional therapy, in a study of obese older adults, weight loss was shown to reduce the amount of fat in skeletal muscle, but also reduced skeletal muscle mass [26]. Patients with cirrhosis can easily lose skeletal muscle mass [20, 21]. Therefore, weight loss by restricting calories is undesirable. However, excessive calorie and fat intake has been reported to worsen myosteatosis [27]. Therefore, exercise therapy under proper nutritional management is considered necessary to prevent the progression of myosteatosis.

There are several limitations in this study. First, this was a single-center, retrospective study. In addition, since no previous study has examined the changes in SMA and the factors that contribute to these changes in patients with cirrhosis, our study was an exploratory one; therefore, it was not possible to determine the appropriate sample size. A multicenter, prospective study with a larger patient population needs to be conducted to validate our results. Second, the degree of myosteatosis was evaluated by using SMA on CT only and not pathologically. Although muscle biopsy findings are well correlated with SMA results on CT, a muscle biopsy is an invasive procedure. Furthermore, pathological deposition of lipid in the muscle was previously reported on CT [7]; therefore, SMA can be used as a surrogate marker for the evaluation of myosteatosis as evidenced by previous studies [4, 7-10, 16-18]. Third, we used BMI-adjusted cutoff values to diagnose myosteatosis. This study included patients with ascites, which may have affected their BMI. However, in several

studies on myosteatosis in patients with cirrhosis, the cutoff value used was adjusted for BMI [8, 10, 16, 17]; therefore, the same criteria were used in this study. Cutoff values suitable for patients with ascites need to be determined in future studies.

Conclusion

In patients with cirrhosis, myosteatosis progressed, and a decrease in SMI and an increase in VFI were correlated with its progression.

References

[1] Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: Sarcopenia in cirrhosis - Aetiology, implications and potential therapeutic interventions. Aliment Pharmacol Ther 2016;43:765–77. https://doi.org/10.1111/apt.13549.

[2] Newman AB, Haggerty CL, Goodpaster B, Harris T, Kritchevsky S, Nevitt M, et al. Strength and muscle quality in a well-functioning cohort of older adults: The health, aging and body composition study. J Am Geriatr Soc 2003;51:323–30. https://doi.org/10.1046/j.1532-5415.2003.51105.x.

[3] Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz A V, et al. The loss of skeletal muscle strength, mass, and quality in older adults: The health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006;61:1059–64. https://doi: 10.1093/gerona/61.10.1059.

[4] Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The health ABC study. J Appl Physiol 2001;90:2157–65. https://doi.org/10.1152/jappl.2001.90.6.2157.

[5] Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: The health, aging and body composition study. J Am Geriatr Soc 2002;50:897–904. https://doi.org/10.1046/j.1532-5415.2002.50217.x.

[6] Correa-de-Araujo R, Harris-Love MO, Miljkovic I, Fragala MS, Anthony BW, Manini TM. The need for standardized assessment of muscle quality in skeletal muscle function deficit and other aging-related muscle dysfunctions: A symposium report. Front Physiol 2017;8:87. https://doi.org/10.3389/fphys.2017.00087.

[7] 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 2000;89:104–10. https://doi.org/10.1152/jappl.2000.89.1.104.

[8] Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CMM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle 2016;7:126–35. https://doi.org/10.1002/jcsm.12039.

[9] Czigany Z, Kramp W, Bednarsch J, 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. https://doi.org/10.1111/ajt.15577.

[10] Tachi Y, Kozuka A, Hirai T, Ishizu Y, Honda T, Kuzuya T, et al. Impact of myosteatosis on skeletal muscle volume loss in patients with chronic liver disease. J Gastroenterol Hepatol 2018;33:1659–66. https://doi.org/10.1111/jgh.14133.

[11] Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol Res 2016;46:951–63.

https://doi.org/10.1111/hepr.12774.

[12] The Examination Committee of Criter. New Criteria for `Obesity Disease' in Japan. Circ J 2002;66:987–92. https://doi.org/10.1253/circj.66.987.

[13] Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013;31:1539–47. https://doi.org/10.1200/JCO.2012.45.2722.

[14] Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant 2013;48:452–8. https://doi.org/10.1038/bmt.2012.244..

[15] Larsen B, Bellettiere J, Allison M, McClelland RL, Miljkovic I, Vella CA, et al. Muscle area and density and risk of all-cause mortality: The multi-ethnic study of atherosclerosis. Metabolism 2020;111:154321. https://doi.org/10.1016/j.metabol.2020.154321.

[16] Kiefer LS, Fabian J, Rospleszcz S, Lorbeer R, Machann J, Storz C, et al. Assessment of the degree of abdominal myosteatosis by magnetic resonance imaging in subjects with diabetes, prediabetes and healthy controls from the general population. Eur J Radiol 2018;105:261–8. https://doi.org/10.1016/j.ejrad.2018.06.023.

[17] Bhanji RA, Takahashi N, Moynagh MR, Narayanan P, Angirekula M, Mara KC, et al. The evolution and impact of sarcopenia pre- and post-liver transplantation. Aliment Pharmacol Ther 2019;49:807–13. https://doi.org/10.1111/apt.15161.

[18] Hamrick MW, McGee-Lawrence ME, Frechette DM. Fatty infiltration of skeletal muscle: Mechanisms and comparisons with bone marrow adiposity. Front Endocrinol (Lausanne) 2016;7:1–7. https://doi.org/10.3389/fendo.2016.00069.

[19] Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med 2014;371:1131–41. https://doi.org/10.1056/nejmra1011035.

[20] Tsiaousi ET, Hatzitolios AI, Trygonis SK, Savopoulos CG. Malnutrition in end stage liver disease: Recommendations and nutritional support. J Gastroenterol Hepatol 2008;23:527–33. https://doi.org/10.1111/j.1440-1746.2008.05369.x.

[21] Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol 2016;65:1232–44. https://doi.org/10.1016/j.jhep.2016.07.040.

[22] Correa-de-Araujo R, Addison O, Miljkovic I, Goodpaster BH, Bergman BC, Clark R V., et al. Myosteatosis in the context of skeletal muscle function deficit: An interdisciplinary workshop at the National Institute on Aging. Front Physiol 2020;11:963. https://doi.org/10.3389/fphys.2020.00963.

[23] Nardelli S, Lattanzi B, Merli M, Farcomeni A, Gioia S, Ridola L, et al. Muscle alterations are associated with minimal and overt hepatic encephalopathy in patients with liver cirrhosis. Hepatology 2019;70:1704–13. https://doi.org/10.1002/hep.30692.

[24] Bhanji RA, Moctezuma-Velazquez C, Duarte-Rojo A, Ebadi M, Ghosh S, Rose C, et al. Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis.

Hepatol Int 2018;12:377–86.https://doi.org/10.1007/s12072-018-9875-9.

[25] Ramírez-Vélez R, Ezzatvar Y, Izquierdo M, Garcia-Hermoso A. Effect of exercise on myosteatosis in adults: a systematic review and meta-analysis. J Appl Physiol 2021;130:245–55. https://doi.org/10.1152/japplphysiol.00738.2020.

[26] Shea MK, Nicklas BJ, Marsh AP, Houston DK, Miller GD, Isom S, et al. The effect of pioglitazone and resistance training on body composition in older men and women undergoing hypocaloric weight loss. Obesity (Silver Spring). 2011 ;19(8):1636-46. doi: 10.1038/oby.2010.327.

[27] Ahmed S, Singh D, Khattab S, Babineau J, Kumbhare D. The effects of diet on the proportion of intramuscular fat in human muscle: A systematic review and meta-analysis. Front Nutr 2018;5:7. https://doi.org/10.3389/fnut.2018.00007.

Tables

Table 1

Patients' characteristics

Variable	At the time of the first CT	At the time of the second CT*	Change per 100 days**
Age (years)	64.3 ± 12.2		
Sex (female/male)	86/92		
Body weight (kg)	60.7 ± 14.2		
Body mass index (kg/m^2)	23.7 ± 4.41		
Etiology (alcohol/active viral hepatitis/inactive or treated viral hepatitis/NASH/AIH and PBC/others)	31/35/58/14/24/16		
Presence of PHTN-related complications			
History of variceal bleeding (yes/no)	6/172		

Ascites (no/mild)	162/16		
History of hepatic encephalopathy (yes/no)	12/166		
MELD score	9 ± 3	9 ± 4	0 ± 1
Albumin levels (g/dL)	3.63 ± 0.62	3.64 ± 0.70	0.01 ± 0.15
Skeletal muscle area at L3 level (cm^2)	115.1 ± 31.3	113.2 ± 30.3	–0.38 ± 2.14
SMI at L3 level (cm^2/m^2)	44.7 ± 9.2	44.2 ± 9.2	–0.13 ± 0.84
Radiation attenuation of skeletal muscle (HU)	34.5 ± 7.44	33.6 ± 7.48	–0.21 ± 1.29
Visceral fat area at umbilical level (cm^2)	98.2 ± 51.3	98.5 ± 52.3	–0.13 ± 7.28
VFI at umbilical level (cm^2/m^2)	38.3 ± 19.3	38.6 ± 20.0	–0.03 ± 2.79
Subcutaneous fat area at umbilical level (cm^2)	121.6 ± 76.2	109.4 ± 67.4	–1.99 ± 8.96
SFI at umbilical level (cm^2/m^2)	47.1 ± 28.2	40.6 ± 24.6	–0.77 ± 3.67

*The period between the date of the first CT and the date of the second CT (480 ± 376 days).

**The changes in each variable from the first CT to the second CT were divided by the number of days between the first and second CT and multiplied by 100 to calculate the change per 100 days.

AIH, autoimmune hepatitis; CT, computed tomography; HU, Hounsfield unit; L3, third lumbar vertebra; MELD, Model for End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PHTN, portal hypertension; SFI, subcutaneous fat deposition; SMI, skeletal muscle index; VFI, visceral fat deposition.

SMI, VFI, and SFI were calculated according to the following formulas: SMI = skeletal muscle area [cm^2]/(height [m])^2, VFI and SFI = visceral and subcutaneous fat area [cm^2]/(height [m])^2, respectively.

Data are expressed as the mean ± standard deviation.

Table 2

Correlations between clinical parameters and skeletal muscle attenuation at the time of the first CT

Variable	*R*	*P*
Age (years)	0.46	< 0.001
MELD score	0.02	0.793
Albumin levels (g/dL)	0.09	0.249
Body mass index (kg/m^2)	–0.02	0.801
SMI at L3 level (cm^2/m^2)	0.34	< 0.001
VFI at umbilical level (cm^2/m^2)	–0.21	0.004
SFI at umbilical level (cm^2/m^2)	–0.20	0.020

SMI shows a positive correlation with skeletal muscle attenuation, whereas age, VFI, and SFI show negative correlations with skeletal muscle attenuation.

L3, third lumbar vertebra; MELD, Model for End-Stage Liver Disease; SFI, subcutaneous fat deposition; SMI, skeletal muscle index; VFI, visceral fat deposition.

Table 3

Linear multiple regression analysis for variables predicting skeletal muscle attenuation at the time of the first CT

Variable	B	SE B	t
Age (years)	–0.22*	0.04	–5.46
Sex (1, male; 0, female)	0.72	1.32	0.54
SMI	0.25*	0.07	3.42
VFI	–0.08*	0.03	–2.62
SFI	–0.06*	0.02	–3.05
Adjusted R^2		0.40	
F		19.3*	

Age, SMI, VFI, and SFI are significant predictors of skeletal muscle attenuation.

*P< 0.01

SFI, subcutaneous fat index; SMI, skeletal muscle index; VFI, visceral fat index.

Table 4

Difference of skeletal muscle attenuation among patients with or without skeletal muscle depletion and/or visceral fat deposition

Skeletal muscle depletion	Absent	Absent	Present	Present
Visceral fat accumulation	Absent	Present	Absent	Present
Skeletal muscle attenuation (HU)	36.2 ± 8.5	34.7 ± 6.1	33.3 ± 7.1	30.4 ± 7.1*

Skeletal muscle attenuation is lowest in patients with skeletal muscle depletion and visceral fat accumulation, which is significantly lower than that in patients without both skeletal muscle depletion and visceral fat accumulation.

Skeletal muscle depletion was defined as an SMI of < 42 (cm^2/m^2) in men and < 38 (cm^2/m^2) in women. The visceral fat deposition was defined as a visceral fat area of ≥ 100 cm^2.

*P = 0.026 (compared with patients without skeletal muscle depletion and visceral fat accumulation)

HU, Hounsfield unit; SMI, skeletal muscle index.

Data are expressed as the mean ± standard deviation.

Table 5

Factors associated with mortality

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*P* value	HR	95% CI	*P*-value
Age (years)	1.010	0.980–1.040	0.52			
Sex (female)	0.829	0.421–1.631	0.59			
Etiology (active viral hepatitis)	2.822	1.394–5.716	0.004	1.943	0.952–3.970	0.068
MELD score (one score increase)	1.202	1.081–1.337	< 0.001	1.147	1.038–1.266	0.007
Albumin levels (g/dL) (1 g/dL increase)	0.231	0.108–0.496	< 0.001	0.338	0.154–0.743	0.007
Presence of skeletal muscle depletion	1.495	0.738–3.029	0.260			
Presence of visceral fat accumulation	1.501	0.760–2.964	0.240			
Presence of myosteatosis	2.090	1.011–4.322	0.047	1.916	0.900–4.082	0.092

The MELD score and albumin levels are significantly associated with mortality, and etiology of active viral hepatitis and the presence of myosteatosis are marginally associated with mortality.

CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease

Figure legends

Figure 1. Mortality in cirrhotic patients with or without myosteatosis

The gray and black curves show the cumulative mortality in patients with and without myosteatosis, respectively.

Figure 2. Correlations between 100-day changes in skeletal muscle attenuation and those in SMI, VFI, and SFI

Correlations between 100-day changes in skeletal muscle attenuation and those in (a) SMI, (b) VFI, and (c) SFI.

HU, Hounsfield unit; SFI, subcutaneous fat index; SMI, skeletal muscle index; VFI, visceral fat index

Figure 3. Differences in 100-day changes in skeletal muscle attenuation among four groups with an increase or a decrease in SMI and VFI at the time of the second CT

HU, Hounsfield unit; SMI, skeletal muscle index; VFI, visceral fat index

Supplementary Figure 1. Patient selection flowchart