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ORIGINAL ARTICLE

Skeletal muscle alterations indicate poor prognosis in cirrhotic patients: a multicenter cohort study in China

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Abstract

Introduction We aimed to determine the diagnostic criteria of myosteatosis in a Chinese population and investigate the effect of skeletal muscle abnormalities on the outcomes of cirrhotic patients.

Methods Totally 911 volunteers were recruited to determine the diagnostic criteria and impact factors of myosteatosis, and 480 cirrhotic patients were enrolled to verify the value of muscle alterations for prognosis prediction and establish new noninvasive prognostic strategies.

Results Multivariate analysis showed age, sex, weight, waist circumference, and biceps circumference had a remarkable influence on the L3 skeletal muscle density (L3-SMD). Based on the cut-off of a mean − 1.28 × SD among adults aged < 60 years, the diagnostic criteria for myosteatosis was L3-SMD < 38.93 Hu in males and L3-SMD < 32.82 Hu in females. Myosteatosis rather than sarcopenia has a close correlation with portal hypertension. The concurrence of sarcopenia and myosteatosis not only is associated with poor liver function but also evidently reduced the overall and liver transplantation-free survival of cirrhotic patients ($p < 0.001$). According to the stepwise Cox regression hazard model analysis, we established nomograms including TBil, albumin, history of HE, ascites grade, sarcopenia, and myosteatosis for easily determining survival probabilities in cirrhotic patients. The AUC is 0.874 (95% CI 0.800–0.949) for 6-month survival, 0.831 (95% CI 0.764–0.898) for 1-year survival, and 0.813 (95% CI 0.756–0.871) for 2-year survival prediction, respectively.

Conclusions This study provides evidence of the significant correlation between skeletal muscle alterations and poor outcomes of cirrhosis, and establishes valid and convenient nomograms incorporating musculoskeletal disorders for the prognostic prediction of liver cirrhosis. Further large-scale prospective studies are necessary to verify the value of the nomograms.

Keywords Skeletal muscle abnormalities · Sarcopenia · Myosteatosis · L3 skeletal muscle index · L3 skeletal muscle density · Hepatic venous pressure gradient · Portal hypertension · Child–Pugh score · Noninvasive prognostic strategies · Nomograms

Abbreviations

HE	Hepatic encephalopathy
L3-SMI	L3 skeletal muscle index
L3-SMD	L3 skeletal muscle density
CT	Computed tomography
MRI	Magnetic resonance imaging
MELD	The Model for End-Stage Liver Disease
HVPG	Hepatic venous pressure gradient
TIPS	Transjugular intrahepatic portosystemic shunts

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EASL	European Association for the Study of the Liver
BMI	Body mass index
WHVP	Wedged hepatic venous pressure
FHVP	Free hepatic venous pressure
CSPH	Clinically significant portal hypertension
HU	Hounsfield units
VATD	Visceral adipose tissue density
SATD	Subcutaneous adipose tissue density
IMATD	Intermuscular adipose tissue density
SMA	Skeletal muscle area
VATA	Visceral adipose tissue area
SATA	Subcutaneous adipose tissue area
VATI	Visceral adipose tissue index
SATI	Subcutaneous adipose tissue area
SD	Standard deviation
PLT	Blood platelet
TBil	Total bilirubin
GGT	Gamma-glutamyl transferase
PT	Prothrombin time
INR	International normalized ratio
SBP	Spontaneous bacterial peritonitis
RBC	Red blood cell
DBil	Direct bilirubin
EGVB	Esophagogastric variceal bleeding
AKI	Acute kidney injury
HRS	Hepatorenal syndrome
SMCS	Sex-Muscle-Child–Pugh score
AUC	The area under the receiver operating characteristic curve

Introduction

Liver cirrhosis, caused by various injury factors, is characterized as a chronic liver disease that is associated with persistently impaired liver function and a distorted hepatic architecture [1]. This disease is identified by a group of complicated clinical manifestations resulting from liver injury and portal hypertension and is associated with multiple complications [1, 2]. Due to its high morbidity and the absence of effective treatment methods, liver cirrhosis is still one of the leading causes of death and illness worldwide to date and has become a high burden for patients and healthcare systems [2]. Thus, it is crucial to precisely identify the poor prognostic factors for making appropriate therapeutic schedules and improving the outcomes of cirrhosis.

Skeletal muscle alterations, including sarcopenia and myosteatosis, are characterized by a decline in muscle mass, muscle strength, and muscle quality, and reflect complicated nutrition disorders [3]. Previous studies have documented the substantial impact of skeletal muscle abnormalities on the prognosis of cardio-cerebrovascular disease, malignancy, and even all-cause mortality in the general population [4–7]. At present, the role of muscle alterations in the development and outcomes of chronic liver diseases also becomes a major concern for hepatologists [8, 9].

Sarcopenia, the muscle alteration representing low muscle mass and poor muscle strength, is regarded as a common complication of liver cirrhosis [8, 9]. Increasing evidence indicates that sarcopenia has a close association with the occurrence of infections, hepatic encephalopathy (HE), ascites, and poor outcomes in cirrhotic patients [8–14]. Myosteatosis, the muscle disorder defined as an anomalous ectopic fatty infiltration within skeletal muscle, is considered a distinct disease entity from sarcopenia and reflects poor muscle quality. Recently, the influence of myosteatosis on the overall survival and post-transplantation mortality in cirrhotic patients was preliminarily explored [15–17]. In addition, a study found that myosteatosis increased the risk of HE [10]. Hence, it is believed that both sarcopenia and myosteatosis are independent risk factors for poor prognosis in cirrhotic patients [8, 18]. However, it remains unclear whether muscle alterations have effects on portal hypertension, and there is still little evidence for incorporating sarcopenia and myosteatosis into the prognostic prediction strategies of liver cirrhosis.

With the development of imaging examination and applications of computer image procession and analysis technology, it becomes easy and convenient to obtain the image parameters for skeletal muscle alterations evaluation. At present, the L3 skeletal muscle index (L3-SMI) and the L3 skeletal muscle density (L3-SMD) based on computed tomography (CT) or magnetic resonance imaging (MRI) images were recommended for the assessment of sarcopenia and myosteatosis, respectively [3, 19, 20]. Recently, we established diagnostic criteria for sarcopenia based on the L3-SMI in Chinese patients and revealed that cirrhotic patients with sarcopenia had poor liver function and a high prevalence of cirrhosis-related complications. Importantly, our observation showed that the two-year survival exponentially declined in the event of sarcopenia, and the trend even strengthened in patients with Child–Pugh C class and a Model for End-Stage Liver Disease (MELD) score > 14 [21]. Nevertheless, unlike sarcopenia, the standardized diagnostic approach and cut-off values for myosteatosis have not been well established and the evidence of the impact of myosteatosis on chronic liver diseases in the Chinese population is limited [14].

In the current study, we aimed to establish the diagnostic criteria for myosteatosis based on the L3-SMD in the Chinese population, investigate the prevalence of myosteatosis, and elucidate the effect of skeletal muscle alterations on the episodes of the complications and the outcomes of cirrhotic patients. Ultimately, we attempted to construct a

novel simple noninvasive model including skeletal muscle alterations for the prognostic prediction of liver cirrhosis.

Patients and methods

See supporting methods for some detailed methods.

Study population and design

All procedures that were performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and in accordance with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was reviewed and approved by the Institutional Ethics Committee of Shanghai Changzheng Hospital (2012SL018). Informed consent was obtained from all of the volunteers and patients.

There were two cohorts included in this study (Fig. 1). In cohort 1, CT imaging data at the L3 level were collected from 1236 volunteers in two centers from March 2018 to May 2018. All the volunteers performed chest or abdomen CT scans during the routine physical examinations or due to acute abdominal pain and had available distinct images at the L3 level. Those individuals who had diseases or conditions affecting nutritional status or limb function were eliminated, including paralysis, long-term bedridden status, severe burns and trauma, hyperthyroidism, hypothyroidism, inflammatory bowel diseases, and so on. Those subjects who had undergone gastrointestinal surgery, were treated with glucocorticoids or immunosuppressive agents, or had an evident history of cardio-cerebrovascular diseases, liver cirrhosis or dysfunction, chronic renal and/or respiratory insufficiency, confirmed or strongly suspected diagnosis of malignant tumors were excluded too. The detailed eligibility and exclusion criteria were listed in a previous study [21]. Totally 911 subjects aged 20–80 years who were consistent with the inclusion criteria and were not in accordance with the exclusion criteria were enrolled to explore the impact factors of the L3-SMD in the general Chinese population. The CT images of the 665 adults younger than 60 years (365 males, 296 females) were used to establish the reference range for the imaging parameters and determine the diagnostic criteria of myosteatosis.

In cohort 2, 480 cirrhotic patients (286 male and 184 female) were enrolled to further determine the role of skeletal muscle alterations on the outcomes of liver cirrhosis in 3 centers from January 2013 to December 2017. All the patients were aged between 18 and 80 year, and diagnosed with liver cirrhosis on the basis of typical clinical manifestations, laboratory tests, imaging characteristics, and/or representative pathology results according to the guideline of the European Association for the Study of the Liver (EASL) and Chinese Society of Hepatology [22, 23]. All patients were hospitalized, and abdominal CT scans were performed during their hospitalizations. The detailed inclusion and exclusion criteria and the data for the basic characteristics of these patients were reported previously [21]. These data were also used to establish the new noninvasive model for the prediction of the prognosis in liver cirrhosis. Among the 480 cirrhotic patients in cohort 2, 182 individuals who underwent a hepatic venous pressure gradient (HVPG) measurement within 1 month before or after an abdominal CT scan were included to investigate the impact of muscle alterations on portal hypertension. The patients whose HVPG measurement was inaccurate or could not reflect portal vein pressure properly were excluded. The main exclusion criteria were as follows: (i) underwent an operation that included transjugular intrahepatic portosystemic shunts (TIPS), hepatectomy or liver transplantation; (ii) the presence of a severe intrahepatic venous shunt, a hepatic arteriovenous shunt or an intrahepatic arterial-portal fistula; (iii) unstable occlusive disease or thrombosis within the hepatic, portal or mesenteric veins; (iv) a confirmed or suspected diagnosis of malignant tumors. Ultimately, 168 patients were included.

Anthropometric measurements and clinical assessments

The strategies for anthropometric measurements and clinical assessments were reported in a previous study [21]. All the enrolled individuals in the 3 cohorts performed a detailed assessment Their medical history, demographic information, and anthropometric variables were collected, including age, height, weight, comorbidities, body mass index (BMI), waist circumference, biceps circumference, triceps skinfold thickness, abdominal skinfold thickness, subscapular skinfold thickness, dominant hand grip strength, and non-dominant hand grip strength, etc. All cirrhotic patients in cohort 2 and 3 were followed for at least 2 years or until death. The Child–Pugh score and classification and the MELD score were calculated at baseline and at the end of follow-up, respectively.

HVPG measurement

HVPG was measured using the standard catheterization method with the balloon wedge technique by 3 designated intervention professionals [24]. Under fluoroscopic guidance, a 5.5-French compliant balloon-tipped catheter (Edwards Lifesciences Fogarty 12TLW805F35, USA) was guided into the right or middle hepatic vein through the right internal jugular vein for wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) measurements. WHVP was determined when the balloon could completely occlude the hepatic vein,

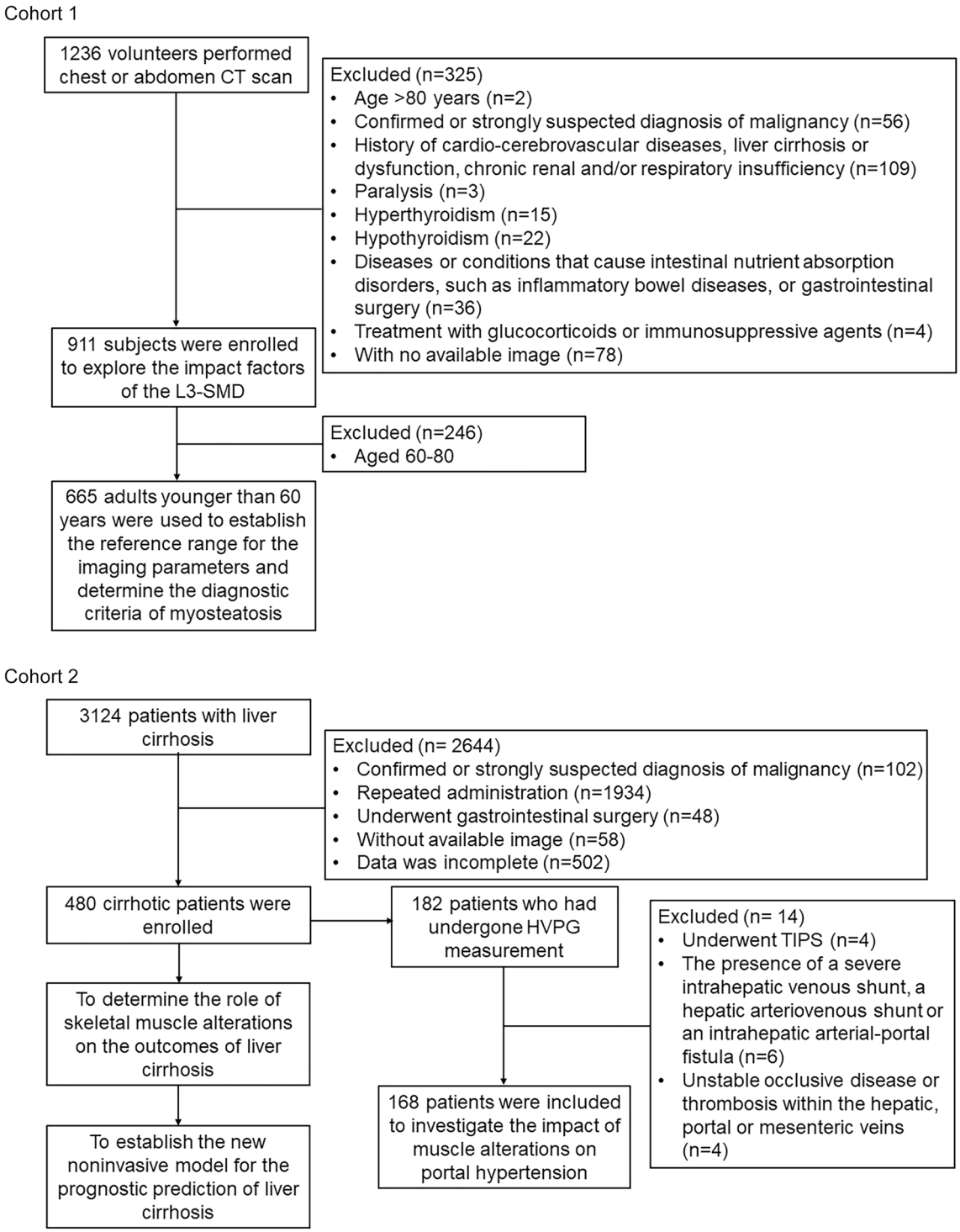

Fig. 1 Cohorts for the study

and FHVP was performed approximately 3 cm from the opening of the hepatic vein into the inferior vena cava until the tracing remained stable. All measurements were carried out at least in triplicate, and the average values were obtained. Then, HVPG was calculated with the following formula: HVPG = WHVP – FHVP. Clinically significant portal hypertension (CSPH) was defined as HVPG ≥ 10 mmHg.

CT scan and assessment of the imaging parameters

CT scans were taken with a 256-slice spiral CT scanner (Brilliance, Philips Medical Systems, The Netherlands) in accordance with the established standard. The collimating reconstruction thickness was set as 1 mm, and the interval was 1 mm. The scan was performed when the individuals were in the supine position and during the deep inspiration breath-hold to avoid artifacts. The images at the L3 level were analyzed by two independent radiologists using SliceOmatic V5.0 software (Rev-8, Tomovision, Montreal, Quebec, Canada), and data errors were ensured to not exceed 5%. According to previous studies, L3-SMI was the muscle area at the level of L3 (cm^2) normalized for height in meters squared (m^2), subcutaneous and intermuscular adipose tissues were identified on CT images based on HU ranging from − 190 to − 30, and visceral adipose tissue was identified with Hounsfield units (HU) thresholds from − 150 to − 50 [21, 25]. Moreover, tissues with HU ranging from − 29 to + 150 were considered muscle tissues. The L3-SMD was defined as the average radiodensity of the total skeletal muscle at the L3 level cross-section, including the psoas major, erector spinalis, quadratus psoas, external abdominal oblique and internal abdominal oblique on the right and left sides and the transverse abdominis. The L3 visceral adipose tissue density (VATD), subcutaneous adipose tissue density (SATD), and intermuscular adipose tissue density (IMATD) were obtained with similar methods. Then, the L3 skeletal muscle area (SMA), visceral adipose tissue area (VATA), subcutaneous adipose tissue area (SATA) and L3-SMI, visceral adipose tissue index (VATI) and subcutaneous adipose tissue area (SATI) were calculated using the software as previously described [21].

Sample size

We calculated the sample size according to the methods established by Jennen-Steinmetz et al. [26]. In Cohort 1, the sample size was determined with the formula: $n = (1 + 0.5{Z_{1-q*}}^2)\left(\Phi(Z_{1-q*})Z_{(\beta+1)/2}/\delta\right)$. In this formula, $\beta = 0.9$, $q* = 0.05$, $\delta = 0.015, \delta/q* = 0.3$. The estimated sample size for individuals aged < 60 years was $n = 302$. Considering the amount of available CT images in the two centers, we then recruited volunteers who performed chest or abdomen CT scan from March 2018 to May 2018. Ultimately, 911 subjects aged 20–80 years, including 665 adults younger than 60 years, were enrolled in Cohort 1. In addition, the sample size in Cohort 2 was calculated using the following formula: $n = {Z_{1-\alpha/2}}^2 p(1-p)/e^2$. In this formula, α = 0.05, $e = 0.1p, Z_{1-\alpha/2} = 1.96$. Based on the prevalence of previous reports, the estimated prevalence of skeletal muscle alterations is about 45% among cirrhotic patients. The estimated sample size for Cohort 2 was $n = 469$. Then we included 480 cirrhotic patients in 3 centers.

Statistical analysis

The data were analyzed by two independent statistical experts using STATA 16 statistical software (Stata Corporation; College Station, TX, USA), SPSS 22.0 (IBM SPSS, Chicago, IL), and R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are shown as the means ± standard deviations (SDs), and categorical variables are expressed as numbers and percentages. Student's *t*-tests, Mann–Whitney U, Meld Kruskal–Wallis test, or one-way ANOVA tests were used to make comparisons of the continuous parameters. Two-tailed χ^2 tests or Fisher's exact tests were used to compare the categorical parameters. Univariate analysis and multiple linear regression were performed to analyze the factors influencing the L3-SMD or HVPG. A Pearson correlation coefficient analysis was used to evaluate the relationship between the two variables. The normative reference data of the L3-SMD were calculated using the formula: 90% lower = mean − 1.28 × SD. The survival and complications between the various groups were compared with Cox proportional hazards models with a 2-sided test. The Kaplan–Meier method was used to estimate the overall survival and breakthrough episodes of complications in cirrhotic patients. Survival curves were compared using the log-rank test. For the determination of the prognostic model, variables with $p < 0.05$ according to the univariate analysis were selected for inclusion in the multivariate Cox proportional hazards model. The stepwise method was used to select the variables. The entry criterion was $p < 0.05$, and the exclusion criterion was $p > 0.1$. A nomogram was used to construct a prediction model based on the results of the multivariate Cox proportional hazards model using the rms package and the receiver-operating characteristic curves, the decision curve analysis (DCA) and forest plot were performed with the time ROC package, dcurves package and forestplot package in R software. A p value < 0.05 was considered statistically significant.

Role of the funding source

All authors had access to the study data and reviewed and approved the final manuscript. The corresponding authors made the final decision to submit the manuscript for publication.

Results

Determination of the cut-off of the L3-SMD for myosteatosis diagnosis and the impact factors of the L3-SMD

Our previous study has established the diagnostic criteria of sarcopenia based on L3-SMI < 44.77 cm^2/m^2 in males and < 32.50 cm^2/m^2 in females, and demonstrated that age, sex, height, weight, biceps circumference, and triceps skinfold thickness significantly impact on L3-SMI [21]. The same cohort including 911 healthy volunteers were used to determine the factors that affected the L3-SMD. The basic characteristics of the group were reported in the previous study [21]. According to the univariate analysis, several factors were associated with the value of the L3-SMD, including age, sex, height, weight, waist circumference, biceps circumference, triceps skinfold thickness, subscapular skinfold thickness, and abdominal skinfold thickness. In the multivariate analysis, only age, sex, weight, waist circumference, and biceps circumference had a remarkable influence on the L3-SMD (Supplementary Table 1). Among all of these factors, the impact of age on the L3-SMD is the most obvious. The average value of the L3-SMD gradually decreased with age. Considering the critical influence of age on muscle mass and quality, only the adults younger than 60 years in cohort 1 were enrolled to determine the cut-off of the L3-SMD for the diagnosis of myosteatosis. The imaging parameter data of the 665 individuals (365 male, 296 female) are listed in Table 1. Based on the mean − 1.28 × SD among the adults aged < 60 years, the cut-off of the L3-SMD for myosteatosis diagnosis was 38.93 Hu in males and 32.82 Hu in females. The prevalence of myosteatosis was 49.4% in individuals aged 60 to 69 years and up to 80.0% in patients older than 70 years (Supplementary Table 2).

Myosteatosis is associated with poor liver function and portal hypertension

The representative figures for sarcopenia and myosteatosis in cirrhotic patients were listed in Fig. 2. To determine the impact of myosteatosis on liver function, the data of 480 cirrhotic patients in Cohort 2 were subsequently analyzed. As shown in Table 2, based on the cut-off of 38.93 Hu in males and 32.82 Hu in females, 147 (30.63%) patients were diagnosed with myosteatosis. The prevalence of myosteatosis in male and female patients with liver cirrhosis was 30.41% and 30.98%, respectively. Compared with the nonmyosteatotic individuals, the patients with myosteatosis were much older and had

Table 1 Characteristics of the imaging parameters in healthy population younger than 60 years in Cohort 1

Group	Male ($n=365$)	Female ($n=296$)	p value
Area			
L3-SMA (cm^2)	158.87 ± 22.20	104.27 ± 12.76	< 0.001
L3-IMATA (cm^2)	9.20 ± 5.12	8.57 ± 5.61	0.135
L3-VATA (cm^2)	123.52 ± 70.17	63.89 ± 42.84	< 0.001
L3-SATA (cm^2)	127.57 ± 63.82	137.26 ± 54.73	0.039
Indexes			
L3-SMI (cm^2/m^2)	54.70 ± 7.76	39.62 ± 5.56	< 0.001
L3-IMATI (cm^2/m^2)	3.17 ± 1.76	3.25 ± 2.15	0.589
L3-VATI (cm^2/m^2)	42.54 ± 24.08	24.36 ± 16.65	< 0.001
L3-SATI (cm^2/m^2)	43.87 ± 21.58	52.19 ± 22.00	< 0.001
Density			
L3-SMD (Hu)	44.84 ± 4.62	39.72 ± 5.39	< 0.001
L3-IMATD (Hu)	− 64.82 ± 5.45	− 63.31 ± 4.52	< 0.001
L3-VATD (Hu)	− 96.8 ± 7.44	− 92.56 ± 7.31	< 0.001
L3-SATD (Hu)	− 101.21 ± 7.71	− 103.61 ± 5.09	< 0.001
Liver density (Hu)	58.45 ± 8.78	60.08 ± 8.34	0.015
Spleen density (Hu)	51.69 ± 5.21	49.70 ± 4.71	< 0.001
Ratio			
Liver density/Spleen density	1.14 ± 0.20	1.22 ± 0.20	< 0.001

SMA: skeletal muscle area; IMATA: intermuscular adipose tissue area; VATA: visceral adipose tissue area; SATA: subcutaneous adipose tissue area; SMI: skeletal muscle index; IMATI: intermuscular adipose tissue index; VATI: visceral adipose tissue index; SATI: subcutaneous adipose tissue index; SMD: skeletal muscle density; IMATD: intermuscular adipose tissue density; VATD: visceral adipose tissue density; SATD: subcutaneous adipose tissue density

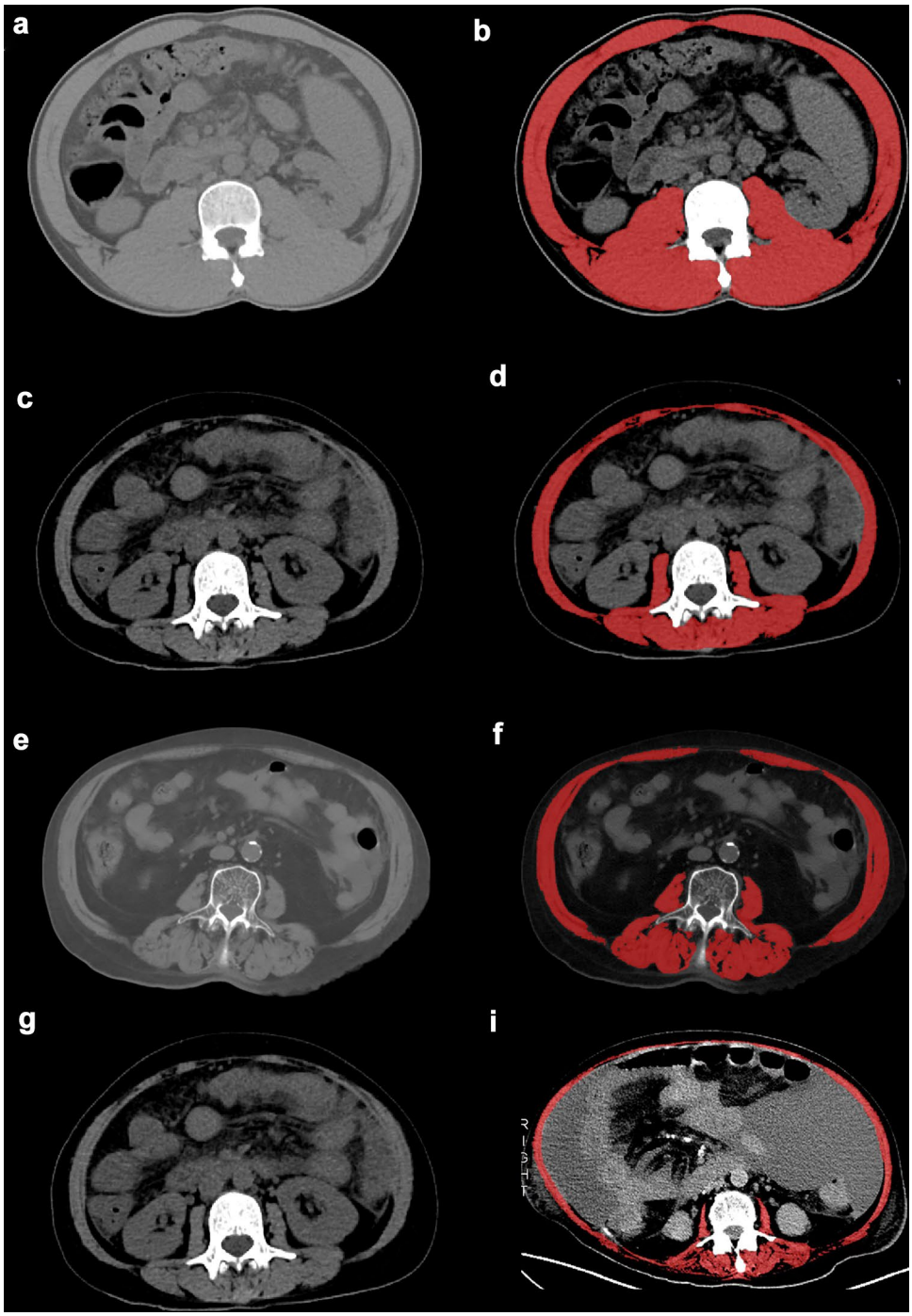

Fig. 2 The representative CT scan figures for sarcopenia and myosteatosis in cirrhotic patients. **a**, **b** The representative CT scan figures for patients without sarcopenia and myosteatosis. **c**, **d** The representative CT scan figures for patients with only sarcopenia. **e**, **f** The representative CT scan figures for patients with only myosteatosis. **h**, **i** The representative CT scan figures for patients with both sarcopenia and myosteatosis

higher BMI values (24.28 ± 3.90 vs. 23.14 ± 3.29 kg/m^2, $p = 0.003$), lower red blood cell (RBC) counts (3.36 ± 0.76 vs. 3.55 ± 0.77 × 10^{12}/L, $p = 0.004$), albumin levels (30.87 ± 6.00 vs. 33.40 ± 5.80 g/L, $p < 0.001$), longer PT (16.46 ± 3.67 vs. 15.60 ± 2.89 s, $p = 0.006$) and higher total bilirubin (TBil) (40.57 ± 47.36 vs. 31.80 ± 34.23 μmol/L, $p = 0.023$) and direct bilirubin (DBil) concentrations (21.65 ± 38.50 vs. 11.82 ± 21.01 μmol/L, $p < 0.001$) and INR (1.40 ± 0.33 vs. 1.31 ± 0.29, $p = 0.005$). Furthermore, Child–Pugh score (8.18 ± 2.27 vs. 7.18 ± 1.91, $p < 0.001$) and MELD score (12.29 ± 4.49 vs. 11.25 ± 3.75, $p = 0.009$) were worse and the prevalence of ascites, HE, spontaneous bacterial peritonitis (SBP), esophageal and gastric variceal bleeding (EGVB) and acute kidney injury (AKI) / hepatorenal syndrome (HRS), and portal vein thrombosis (PVT) were all higher in the myosteatosis group. In addition, there was an obvious difference in the etiology constitute distribution between the non-myosteatosis

Table 2 Baseline characteristics is compared between myosteatosis group and non-myosteatosis group according to the Cohort 2

	Non-myosteatosis ($n=333$)	myosteatosis ($n=147$)	p value
Age, years (mean ± SD)	52.10 ± 11.51	62.44 ± 10.09	< 0.001
Gender (Male/Female)	206/127	90/57	0.895
Body mass index (kg/m^2)	23.14 ± 3.29	24.28 ± 3.90	0.003
Etiology			0.013
HBV (%)	165 (49.55)	43 (29.25)	
Alcohol (%)	37 (11.11)	24 (16.33)	
AIH (%)	9 (2.70)	10 (6.80)	
PBC (%)	12 (3.60)	8 (5.44)	
AIH-PBC overlap syndrome (%)	0 (0.00)	1 (0.68)	
HCV (%)	3 (0.90)	2 (1.36)	
Schistosomiasis (%)	3 (0.90)	9 (6.12)	
Others (%)	28 (8.41)	5 (3.40)	
Cryptogenic (%)	65 (19.52)	33 (22.45)	
Combined (%)	11 (3.30)	12 (8.16)	
Comorbidities			
Diabetes	52 (15.6)	44 (29.93)	< 0.001
Child–Pugh score	7.18 ± 1.91	8.18 ± 2.27	< 0.001
MELD	11.25 ± 3.75	12.29 ± 4.49	0.009
Serum index			
RBC (10^{12}/L)	3.55 ± 0.77	3.36 ± 0.76	0.011
WBC (10^9/L)	4.28 ± 3.32	4.58 ± 2.85	0.346
PLT (10^9/L)	120.24 ± 165.88	103.59 ± 76.15	0.245
HCT (%)	30.86 ± 7.63	30.40 ± 6.90	0.527
Hemoglobin (g/L)	102.28 ± 28.38	100.55 ± 25.48	0.526
TBil (μmol/L)	31.80 ± 34.23	40.57 ± 47.36	0.023
DBil (μmol/L)	11.82 ± 21.01	21.65 ± 38.50	< 0.001
Albumin (g/L)	33.40 ± 5.80	30.87 ± 6.00	< 0.001
Scr (mmol/L)	63.81 ± 41.01	75.10 ± 46.73	0.008
PT (s)	15.60 ± 2.89	16.46 ± 3.67	0.006
INR	1.31 ± 0.29	1.40 ± 0.33	0.005
Complications			
Ascites (%)	212/333(64.0)	110/147(74.8)	0.016
Grade			< 0.001
0	142	39	
1	115	42	
2	25	14	
3	51	52	
HE (%)	26/333 (7.8)	20/147 (13.6)	0.047
SBP (%)	9/333 (3)	12/147 (8.2)	0.007
UGIB (%)	208/333 (62.5)	63/147 (42.9)	< 0.001
HRS (%)	2/333 (0.6)	6/147 (17.7)	0.006
PVT (%)	107/333 (32.1)	25/147 (17.0)	0.001
L3 body composition parameters			
L3-SMI (cm^2/m^2)	46.84 ± 8.21	43.35 ± 9.11	< 0.001
L3-IMAT (cm^2/m^2)	2.45 ± 1.42	5.08 ± 3.90	< 0.001
L3-VAT (cm^2/m^2)	25.68 ± 17.78	39.28 ± 27.32	< 0.001
L3-SAT (cm^2/m^2)	35.36 ± 21.35	42.67 ± 27.58	0.002
Sarcopenia%	55/333 (16.5)	53/147 (36.0)	< 0.001

MELD: model for end-stage liver disease; RBC: red blood cell; WBC: white blood cell; PLT: blood platelet; HCT: hematocrit; TBil: total bilirubin; DBil: direct bilirubin; Scr: serum creatinine; PT: prothrombin time; INR: international normalized ratio; HE: hepatic encephalopathy; SBP: spontaneous bacterial peritonitis; UGIB: upper gastrointestinal bleeding; AKI: acute kidney injury; HRS: hepatorenal syndrome; PVT: portal venous thrombosis; SMI: skeletal muscle index; IMATI: intermuscular adipose tissue index; VATI: visceral adipose tissue index; SATI: subcutaneous adipose tissue index

and myosteatosis groups ($p = 0.013$, Table 2). However, there was no correlation between L3-SMD and the various etiology of cirrhosis (Supplementary Table 3). It has been documented that myosteatosis was associated with insulin resistance, diabetes, and NAFLD. Those individuals with myosteatosis had prevalent diabetes and NAFLD and a higher risk for incident diabetes. In this study, we compared the proportion of patients with diabetes and NAFLD in the two groups. Totally 29.93% of patients with myosteatosis and 15.6% of individuals without myosteatosis suffered from diabetes. Predictably, the patients with myosteatosis had a higher prevalence of diabetes ($p < 0.001$). There was no report of NAFLD-associated cirrhosis in Cohort 2, but 17 (5.11%) patients in the non-myosteatosis group and 22 (14.96%) patients in the myosteatosis group were diagnosed as NAFLD with the CT density ratio of liver/spleen < 1. The prevalence of NAFLD was much higher in the myosteatosis group than that in the non-myosteatosis group ($p = 0.001$). However, it seems to be no correlation between the CT density ratio of the liver and spleen and L3-SMD ($r = -0.095$, 95% CI −0.193–0.005, $p = 0.062$).

Among the 182 cirrhotic patients who underwent HVPG determination, 168 patients who met the enrolment criteria were included to evaluate the role of muscle alterations in portal hypertension (Supplementary Table 4). Based on our cut-off value, 19.05% (32/168) of the patients (26 males and 6 females) were diagnosed with sarcopenia, and 16.07% (27/168) of them were diagnosed with myosteatosis, including 16 males and 11 females. Among all of the investigated imaging-based nutritional indicators, L3-SMD was the only variable that was negatively related to the HVPG ($r = -0.266$, $p < 0.001$, Supplementary Table 5). No correlation between L3-SMI and HVPG was observed. The average HVPG in the patients with myosteatosis was 21.57 ± 8.20 mmHg, which was much higher than that in the nonmyosteatosis group (16.13 ± 6.89 mmHg, $p < 0.001$). Subsequently, we compared the CT-based nutritional indicators among the patients with different HVPGs (Supplementary Tables 6–7). Surprisingly, none of the patients with HVPG < 10 mmHg were diagnosed with myosteatosis, but 27 of the 138 patients with HVPG ≥ 10 mmHg had myosteatosis ($p < 0.001$). The mean L3-SMD was remarkedly decreased in patients with CSPH compared with those without CSPH (42.28 ± 7.47 Hu vs. 45.99 ± 5.97 Hu, $p = 0.012$). Similarly, the prevalence of myosteatosis (20.16% vs. 2.56%, $p = 0.006$) was much higher, and the average L3-SMD (42.09 ± 7.48 Hu vs. 45.74 ± 6.18 Hu, $p = 0.006$) was lower in patients with HVPG ≥ 12 mmHg than in those with HVPG < 12 mmHg (Supplementary Table 7). However, other CT-based nutritional indicators, including L3-SMI, seem to be irrelevant to the HVPG. Thus, we believe that myosteatosis, not sarcopenia has an obvious effect on portal hypertension.

Concurrence of sarcopenia and myosteatosis reflect severe cirrhosis and is an indicator of poor prognosis of cirrhosis

Among the 480 cirrhotic patients in cohort 2, 53 (11.04%) patients had both sarcopenia and myosteatosis, 55 (11.46%) had only sarcopenia, 94 (19.58%) had only myosteatosis, and 278 (57.92%) had neither sarcopenia nor myosteatosis. As shown in Table 3, compared with the individuals without any kind of muscle alterations or those who had only sarcopenia or myosteatosis, the patients with complex skeletal muscle alterations had lower RBC counts and albumin levels, longer PT, higher TBil and DBil concentration and INR. Moreover, the Child–Pugh score and MELD score, two important indicators of the extent of cirrhosis, were both worse in the complex skeletal muscle alterations group (Child–Pugh score, $p < 0.001$; MELD score, $p = 0.045$). Therefore, all the observations suggested that concurrence of sarcopenia and myosteatosis has a strong correlation with poorer liver function and more serious liver cirrhosis. Furthermore, the mortality within the 2-year follow-up period was 39.62% (21/53) in the patients with complex skeletal muscle alterations, significantly higher than that in those with only sarcopenia (14.54%, 8/55) or myosteatosis (18.09%, 17/94), and without any skeletal muscle alterations (8.99%, 25/278). A total of 10 patients received liver transplantations, including 3 in the complex skeletal muscle alterations group, 3 in patients with only myosteatosis, and 4 in patients without skeletal muscle alterations. As shown in Fig. 3a, patients with complex skeletal muscle alterations had significantly elevated mortality. The concurrence of sarcopenia and myosteatosis evidently reduced the overall and liver transplantation-free survival of the cirrhotic patients (Fig. 3b and Supplementary Fig. 1, both $p < 0.001$). Moreover, the episodes of the breakthrough of HE, SBP, EGVB, and AKI/HRS occurred in 22.6% (12/53), 13.2% (7/53), 67.9% (36/53), and 7.6% (4/53) of the patients with complex skeletal muscle alterations, respectively, which were all much higher than those in the other groups (HE, $p = 0.002$; SBP, $p = 0.004$; EGVB, $p = 0.002$; AKI/HRS, $p = 0.003$).

Establishment of a new prognostic prediction model for liver cirrhosis and performance of the prognostic nomograms

We incorporated sarcopenia, myosteatosis, and nine variables commonly used in previous non-invasive diagnostic models to select the major factors associated with the overall survival of liver cirrhosis, including sex, PLT, TBil, albumin, ALT, AST, INR, Scr, ascites grade, and so on.

Table 3 Comparison of baseline characteristics among the cirrhotic patients with different skeletal muscle alterations according Cohort 2

	Neither sarcopenia nor myosteatosis ($n=278$)	Only Sarcopenia ($n=55$)	Only myosteatosis ($n=94$)	Both sarcopenia and myosteatosis ($n=53$)	p value
Age, years (mean ± SD)[a]	50.99 ± 11.19	51.91 ± 12.68	62.40 ± 9.90	60.89 ± 9.54	< 0.001
Gender (Male/Female)	118/160	9/46	44/50	13/40	< 0.001
Body mass index (kg/m^2)[a]	23.74 ± 3.16	20.15 ± 2.12	25.30 ± 3.87	22.59 ± 3.36	< 0.001
Child–Pugh score[a]	7.13 ± 1.94	7.42 ± 1.82	7.88 ± 2.26	8.70 ± 2.21	< 0.001
MELD	11.50 ± 3.85	11.40 ± 3.65	11.90 ± 4.10	13.33 ± 5.06	0.043
Serum index					
RBC (10^{12}/L)[a]	3.59 ± 0.77	3.37 ± 0.76	3.43 ± 0.71	3.23 ± 0.82	0.006
WBC (10^9/L)[a]	4.15 ± 3.32	4.95 ± 3.29	5.50 ± 9.81	4.65 ± 2.80	0.006
PLT (10^9/L)	113.76 ± 133.15	152.96 ± 277.36	105.47 ± 68.44	100.26 ± 88.81	0.176
HCT (%)	31.18 ± 7.60	29.27 ± 7.67	30.92 ± 6.72	29.48 ± 7.18	0.195
Hemoglobin (g/L)	103.41 ± 28.07	96.60 ± 29.47	101.72 ± 25.64	98.47 ± 25.31	0.465
TBil (μmol/L)[a]	31.54 ± 32.65	33.16 ± 41.74	35.44 ± 27.67	49.67 ± 69.25	0.072
DBil (μmol/L)[a]	11.26 ± 18.34	14.67 ± 31.42	18.45 ± 29.29	27.44 ± 50.95	< 0.001
Albumin (g/L)	33.52 ± 5.77	32.77 ± 5.99	31.20 ± 6.19	30.28 ± 5.67	< 0.001
Scr (mmol/L)[a]	64.08 ± 44.27	62.51 ± 17.32	71.05 ± 45.17	82.21 ± 49.03	0.003
PT (s)[a]	15.56 ± 2.94	15.80 ± 2.64	16.15 ± 3.83	17.00 ± 3.34	0.008
INR[a]	1.31 ± 0.30	1.33 ± 0.25	1.37 ± 0.35	1.43 ± 0.30	0.005
Complications					
Ascites (%)	169/278 (60.8)	43/55 (78.2)	62/94 (66.0)	48/53(90.6)	< 0.001
Grade					< 0.001
0	126	16	34	5	
1	92	23	24	18	
2	21	4	9	5	
3	29	12	27	25	
HE (%)	25/278 (9.0)	1/55 (1.8)	8/94 (8.5)	12/53 (22.6)	0.002
SBP (%)	6/278 (2.2)	3/55 (5.5)	5/94(5.3)	7/53 (13.2)	0.004
EGVB (%)	122/278 (43.9)	23/55 (41.8)	42/94 (44.7)	36/53 (67.9)	0.002
AKI/HRS (%)	1/278 (0.36)	1/55 (1.8)	2/94 (2.1)	4/53 (7.6)	0.003
L3 body composition parameters					
L3-SMI (cm^2/m^2)[a]	48.48 ± 7.80	38.57 ± 4.35	46.95 ± 8.58	36.97 ± 6.01	< 0.001
L3-IMAT (cm^2/m^2)[a]	2.58 ± 1.44	1.79 ± 1.09	6.09 ± 4.27	3.31 ± 2.24	< 0.001
L3-VAT (cm^2/m^2)[a]	27.45 ± 18.09	16.76 ± 12.95	45.28 ± 28.14	28.63 ± 22.34	< 0.001
L3-SAT (cm^2/m^2)[a]	38.50 ± 21.33	19.46 ± 12.59	49.78 ± 27.73	30.06 ± 22.51	< 0.001

MELD: model for end-stage liver disease; RBC: red blood cell; WBC: white blood cell; PLT: blood platelet; HCT: hematocrit; TBil: total bilirubin; DBil: direct bilirubin; Scr: serum creatinine; PT: prothrombin time; INR: international normalized ratio; HE: hepatic encephalopathy; SBP: spontaneous bacterial peritonitis; UGIB: upper gastrointestinal bleeding; AKI: acute kidney injury; HRS: hepatorenal syndrome; SMI: skeletal muscle index; IMATI: intermuscular adipose tissue index; VATI: visceral adipose tissue index; SATI: subcutaneous adipose tissue index

[a]Compared with Meld Kruskal–Wallis test. The other continuous variables were determined by one-way analysis of variance (ANOVA). Categorical variables were analyzed with two-tailed χ^2 tests

Univariate analysis found that TBil, albumin, INR, history of HE, ascites-grade, sarcopenia, and myosteatosis had a remarkable effect on the outcomes of cirrhosis (Supplementary Table 8). Of these initial 7 variables, 6 predictors were integrated into the new model for the prognostic prediction of liver cirrhosis according to the stepwise Cox regression hazard model analysis, including TBil, albumin, history of HE, ascites-grade, sarcopenia, and myosteatosis (Fig. 4a). The model is presented as nomograms in Fig. 4b. Six-month survival, 1-year survival, and 2-year survival probability can be estimated with the nomograms. The calibration curve showed that the survival probabilities predicted by the nomogram agreed well with the actual survival probabilities (Fig. 4c–e). The area under the receiver operating characteristic curve (AUC) of the nomograms for predicting the prognosis in cirrhotic patients is 0.874 (95% CI 0.800–0.949) for 6-month survival, 0.831 (95% CI 0.764–0.898) for 1-year survival and 0.813 (95% CI 0.756–0.871) for 2-year survival

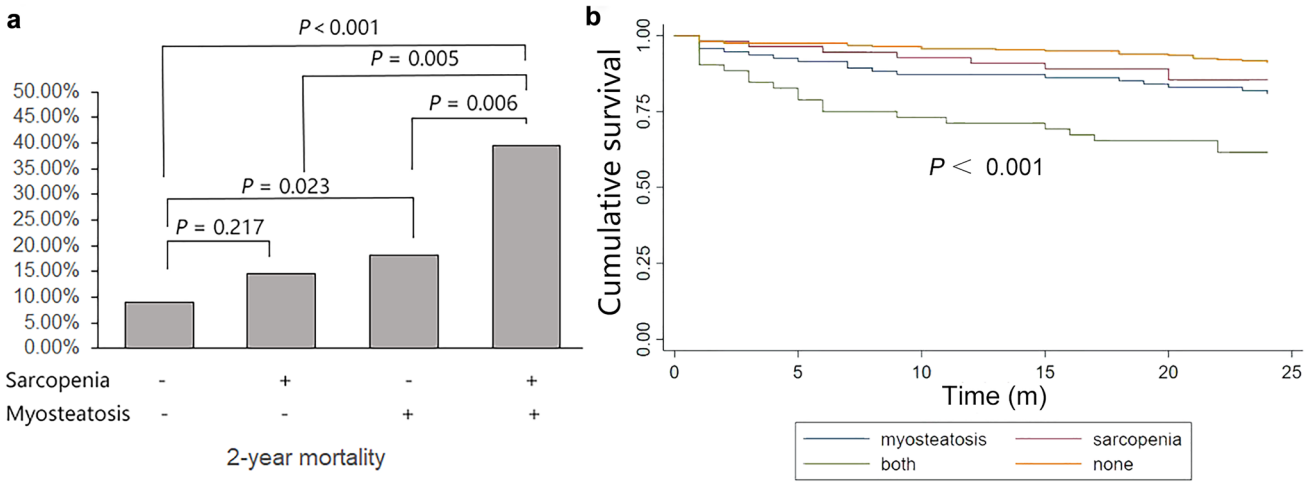

Fig. 3 Skeletal muscle alterations are important indicators for poor prognosis of liver cirrhosis according to cohort 2 including 480 cirrhotic patients. **a** Comparison of the mortality within the 2-year follow-up period among different groups according to cohort 2. **b** Kaplan–Meier estimates of the overall survival among different groups according to cohort 2

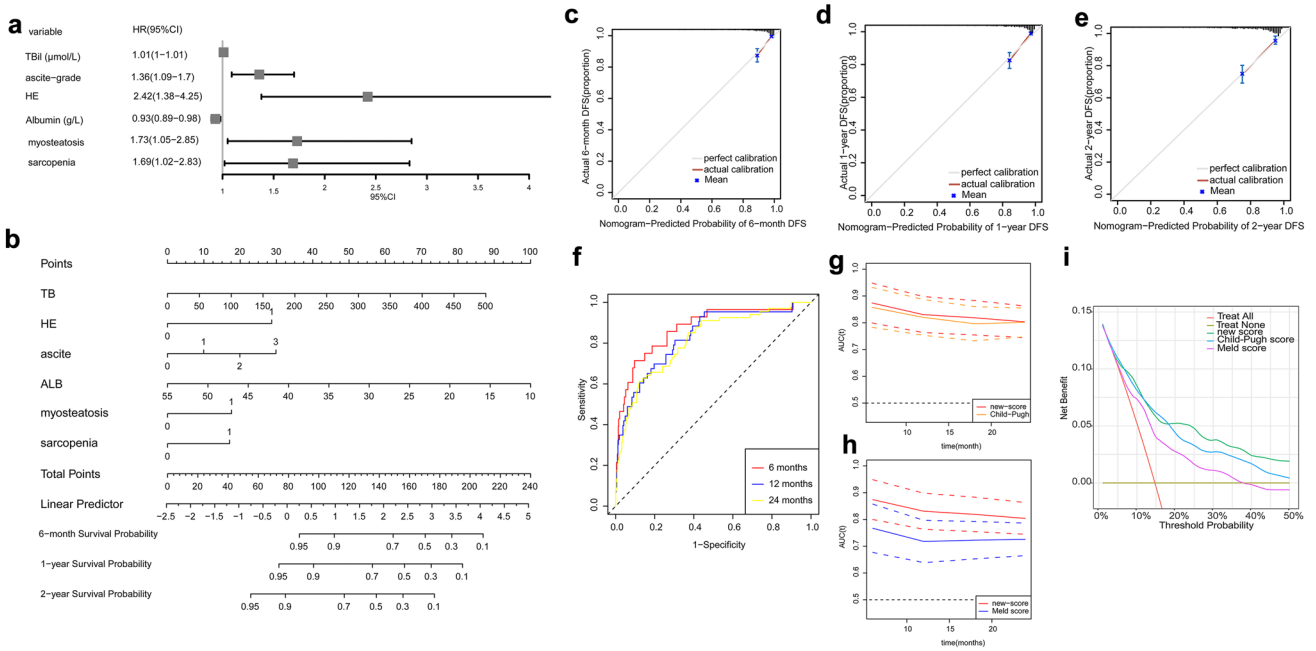

Fig. 4 Establishment and validation of the prognostic nomograms for liver cirrhosis. **a** Forest plots for the 6 predictors integrated into the new model for the prognostic prediction of liver cirrhosis according to the stepwise Cox regression hazard model analysis. **b** Nomograms for the new prognostic prediction model for liver cirrhosis. To calculate a patient's survival probability at different time point, points for each parameter are assigned by corresponding values from the "points" axis, and sum of the points is plotted on "total points" axis. The patient's 6-month, 1-year and 2-year survival probabilities are the value at a vertical line from corresponding total points. **c**–**e**. The calibration curve for the prognostic nomograms at different time point. The *x*-axis represents the nomogram-predicted probability and y-axis represents the actual probability of survival. Perfect prediction would correspond to the 45° grey line. The brown line represents the entire cohort bias-corrected by bootstrapping (B = 1000 repetitions), indicating observed nomogram performance. **f** The AUC of the nomograms for predicting the prognosis in cirrhotic patients at different time points. **g** The time-ROC analysis compared the AUC for prognostic prediction in cirrhotic patients between new model and Child–Pugh score. **h** The time-ROC analysis compared the AUC for prognostic prediction in cirrhotic patients between new model and MELD score. **i** The DCA analysis compared the accuracy for predicting prognosis of liver cirrhosis among Child–Pugh score, MELD score and the new nomograms

(Fig. 4f). The AUC of Child–Pugh and MELD score for prognostic prediction were 0.857 (95% CI 0.783–0.932), 0.767 (95% CI 0.677–0.857) for 6-month survival, 0.820 (95% CI 0.754–0.887), 0.718 (95% CI 0.639–0.797) for 1-year survival, 0.802 (95% CI 0.748–0.855), 0.726 (95% CI 0.665–0.786) for 2-year survival. The time-ROC analysis and DCA determination both revealed that the accuracy of the new nomograms for predicting the prognosis of liver cirrhosis was superior to Child–Pugh and MELD scores (Fig. 4g–i).

Discussion

Accumulating evidence indicates that liver cirrhosis and malnutrition might interact and mutually influence these processes, leading to disease exacerbation and a poor prognosis. Among malnutrition consequences, skeletal muscle disorders, including sarcopenia and myosteatosis, have attracted great attention in recent years [8–12]. Our previous study established the diagnostic criteria of sarcopenia in Chinese based on L3-SMI and documented that sarcopenia had a dominant influence on the development of complications and survival in cirrhosis patients [21]. However, limited studies have focused on the correlation between myosteatosis and cirrhosis. Due to the significant heterogeneity of the muscle quantity and quality, it is necessary to establish the diagnostic criteria of myosteatosis based on a local population and investigate the impact of skeletal muscle alterations on the episodes of cirrhosis-related complications, portal hypertension and overall survival in cirrhotic patients [27].

It is usually believed that when the lipid volume exceeds the disposal capacity of adipose tissues, excessive fatty acids will infiltrate into skeletal muscle [27]. These ectopic fatty depositions are described as myosteatosis and can result in alterations in muscle quality. L3-SMD is commonly used to represent myosteatosis. As noted, it is important to standardize the L3-SMD based on the local population norms. In this study, we established the cut-off value of the L3-SMD and defined myosteatosis as an L3-SMD < 38.93 Hu in males and < 32.82 Hu in females. This is the first established diagnostic criterion of L3-SMD in the Chinese population, and these results might provide a basis for subsequent studies of other diseases.

Previous studies documented that L3-SMD is affected by age, sex, and disease. Our results showed that age, sex, weight, waist circumference, and biceps circumference were the major factors interfering with the L3-SMD. Among these factors, age had the most principal influence on the L3-SMD. The mean L3-SMD diminished with increasing age, and the prevalence of myosteatosis was obviously increased in individuals aged ≥ 60 years, and the incidence was even up to 80% in those aged ≥ 70 years. The age-dependent variation in the L3-SMD was consistent with the L3-SMI and was in concordance with previous studies, suggesting that musculoskeletal disorders might be a pivotal impact factor for the quality of life of elderly individuals [28].

The association between malnutrition and liver diseases has become an attractive research area in recent years. It has been well-documented that sarcopenia is related to the severity of liver disease and is a strong predictor of mortality in cirrhotic patients [21]. In addition, sarcopenia promotes episodes of several cirrhosis-related complications, including HE, ascites, SBP, and HRS [8–14, 21]. Recent guidelines highlight that muscle quality is as important as muscle quantity [15]. As a promising indicator of poor muscle quality, myosteatosis has been identified as a new paradigm beyond sarcopenia. According to limited studies, myosteatosis was associated with a decreased overall survival and a higher prevalence of HE, and preoperative myosteatosis was an independent risk factor for short- and long-term mortality after liver transplantation [10, 15, 16, 29]. However, the effect of muscle alterations on portal hypertension is ambiguous, and the knowledge of the role of the concurrence of sarcopenia and myosteatosis on the episode of cirrhosis-related complications and overall outcomes is still limited.

The current evidence did not reveal the direct relationship between sarcopenia and portal hypertension [30, 31]. A study from Korea showed that the proportion of patients with non-CSPH, CSPH, and severe portal hypertension was similar between the sarcopenia and non-sarcopenia cohorts, and there was no correlation between sarcopenia and HVPG ($r = 0.01$, $p = 0.832$) [30]. Another study from Austria compared the impact of sarcopenia on survival in the presence of different hepatic venous pressure gradient (HVPG) levels. In that study, the median HVPG in patients with or without sarcopenia had no difference, and sarcopenia doubled the risk for mortality regardless of the severity of HVPG elevation [31]. Thus, most researchers believe that sarcopenia was not dispensable for portal hypertension. The reason why sarcopenia does not affect HVPG is not elucidated. It was speculated that sarcopenia had no direct impact on intrahepatic vascular resistance and portal venous blood flow. Similarly, no correlation between sarcopenia and HVPG was found in our current study. This observation supported the contention that sarcopenia was a prognostic factor of cirrhosis independent of portal hypertension. On the other side, our observations proved that the L3-SMD was not only associated with poor liver function and serious liver cirrhosis but also negatively related to the HVPG. Patients with CSPH or HVPG ≥ 12 mmHg have a higher prevalence of myosteatosis and a lower L3-SMD. Surprisingly, myosteatosis was not found in any patients without CSPH. To our knowledge, this is the first study to demonstrate the association of myosteatosis with portal hypertension, and all of the findings in this

study encouraged us to determine myosteatosis as an indicator of the poor prognosis of liver cirrhosis.

The role of myosteatosis on portal hypertension was underappreciated. It has been estimated that lipid-induced systemic inflammation, increased reactive oxygen species (ROS) generation, and pro-inflammatory cytokine release induced by extramyocellular lipids storage in muscles could exacerbate the burden of liver metabolism, aggravate the injury of hepatocytes and vascular endothelial cells, leading to activation of hepatic stellate cells and impairment of portal vein blood flow, and ultimately resulting in the deterioration of portal hypertension [32, 33].

Recent research has revealed the straightforward clinical impact of myosteatosis and sarcopenia on the episodes of hepatic encephalopathy [4, 10, 28]. A study by Montano-Loza et al found that sarcopenic and myosteatosis are independently associated with higher long-term mortality in cirrhosis [15]. However, whether the concurrence of sarcopenia and myosteatosis results in the deterioration of outcomes is still essentially indefinite. In this study, patients with complex skeletal muscle abnormalities were not only associated with poor liver function and serious liver cirrhosis but also related to the remarkedly increased episodes of HE, SBP, EGVB, and AKI/HRS. Moreover, the patients with complex skeletal muscle alterations had an obvious reduction in overall survival and liver transplantation-free survival compared with those without muscle abnormalities and only with sarcopenia or myosteatosis. Therefore, our findings elucidated that the concurrence of sarcopenia and myosteatosis leads to a worse prognosis.

Nowadays, Child–Pugh score, MELD score, FIB4, and APRI are the most frequently used models for the severity categorization and prognosis evaluation of liver cirrhosis in clinical practice. However, the accuracy of the above methods in predicting prognosis is still not satisfactory. Hence, many studies have been concerned with establishing novel noninvasive models for the prognostic prediction of cirrhosis. Given the strong influence of musculoskeletal disorders on the prognosis and breakthrough of cirrhosis-related complications, some studies have struggled to construct a prognostic model by including sarcopenia in the widely used prognostic methods of liver cirrhosis (e.g., MELD or Child–Pugh scores) [34]. In this study, we attempted to conduct a new prognostic strategy on the basis of sarcopenia, muscular steatosis, and commonly used clinical indicators. Firstly, we enrolled the 9 principal variables in the commonly used models (Child–Pugh score, MELD score, FIB4, and APRI) and sarcopenia and myosteatosis to screen the major risk factors influencing the outcomes of cirrhosis, including sex, PLT, TBil, albumin, ALT, AST, INR, Scr, and ascites grade. Then we established a new model based on TBil, Albumin, history of HE, ascites-grade, sarcopenia, and myosteatosis by the stepwise Cox regression hazard model analysis and conducted the nomograms for easily calculating the 6-month, 1-year, and 2-year survival probability. The subsequent calibration curve, time-ROC, and DCA analysis verified that the new nomograms were superior to MELD and Child–Pugh scores in predicting cirrhosis-related prognosis. Therefore, our finding demonstrated that the combination of muscular disorders (e.g., sarcopenia and myosteatosis) with the commonly used indicators could give better predictive power for the prognosis of liver cirrhosis.

In conclusion, we determined the diagnostic criteria of myosteatosis in the Chinese population as L3-SMD < 38.93 Hu in males and < 32.82 Hu in females, and found that myosteatosis rather than sarcopenia has a close correlation with portal hypertension. Our findings demonstrated that the concurrence of sarcopenia and myosteatosis lead to poor liver function and serious liver cirrhosis and had an evident negative impact on survival. Ultimately, we established nomograms incorporating 6 parameters, TBil, albumin, history of HE, ascites-grade, sarcopenia, and myosteatosis. The AUC for the nomograms for predicting the 6-month, 1-year, and 2-year survival probability of cirrhotic patients was superior to the MELD and Child–Pugh scores. Taken together, our current study determined the basis for subsequent studies of other diseases in Chinese patients and provided valid and convenient nomograms for the prognostic prediction of liver cirrhosis. All these results encouraged the provision of interventions to address skeletal muscle alterations to improve cirrhosis-related outcomes.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Xin Zeng, Zhi-Wen Shi, Jia-Jun Yu, Li-Fen Wang, Chun-Yan Sun, Yuan-Yuan Luo, Pei-Mei Shi, Yong Lin, Yue-Xiang Chen, Jia Guo, Chun-Qing Zhang, Wei-Fen Xie have not disclosed any competing interests.

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