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A sex-oriented analysis concerning skeletal muscle quantity and quality and associations to quality of life in hospitalized patients with cirrhosis

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Abstract

Background There is a paucity of data regarding sex-oriented analyses of connection between muscle quantity and quality and health-related quality of life (HRQoL), taking into account the pathophysiological differences of sarcopenia/myosteatosis in males *versus* females. We sought to investigate the associations between skeletal muscle index (SMI)-defined sarcopenia and intramuscular adipose tissue content (IMAC)-defined myosteatosis and EuroQol-5D (EQ-5D)-defined HRQoL in patients with decompensated cirrhosis concerning sex disparities.

Methods Totally, 382 patients were enrolled. The relationship between SMI/IMAC and HRQoL was evaluated with restricted cubic spline and Pearson correlation analyses. Furthermore, association between SMI or sarcopenia and EQ-5D utility index was determined by multiple linear regression, adjusted for age, BMI and concurrent disease severity.

Results The study population comprised evenly distributed male and female patients (190: 192), mean age 61.9 years. The prevalence of sarcopenia (40.5 *versus* 9.9%, $P<0.001$) and SMI (48.8 *versus* 42.2 cm^2/m^2, $P<0.001$) were significantly higher in males relative to females, with comparable myosteatosis prevalence (15.3 *versus* 16.7%, $P=0.708$). Self-care, usual activities and pain within EQ-5D scale were more prevalent in the sarcopenia compared with non-sarcopenia groups across entire population and stratified by sex. The SMI values exhibited a significantly linear correlation with EQ-5D utility index in male but not female patients (P for non-linearity = 0.281). In multiple analysis, SMI or the presence of sarcopenia was both significantly associated with EQ-5D utility index. Subgroup analyses unveiled no discernible interactions between sarcopenia and EQ-5D utility index.

Conclusions Muscle quantity measured by SMI was associated with declined HRQoL in males rather than females, whereas no associations were found regarding muscle quality measured by IMAC in both sexes. It is tempting to manage sarcopenia by increasing SMI levels as high as possible in hopes of achieving better health consequence. Our findings represent the importance of connecting CT-demarcated body composition abnormalities to meaningful patient-centered outcomes. Future targeted studies with sizable multi-center populations are warranted to clarify this

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causality, and in consequence develop optimized intervention against sarcopenia/myosteatosis or key determinants concerning impaired HRQoL.

Keywords Skeletal muscle index, Intramuscular adipose tissue content, Sarcopenia, Myosteatosis, Health-related quality of life, EQ-5D

Background

The concept of sarcopenia has its roots in the field of geriatrics, manifested with a decrease in muscle mass (quantity) alongside muscle dysfunction (poor quality or functioning). Generally, the contributory factor and pathogenic cause can be predominantly attributed to ageing-related process and decrement accompanying pathological alterations. On the other hand, sarcopenia can also occur during the advent and progression of a wealth of acute and chronic diseases such as advanced liver diseases [1]. In this direction, the presence of sarcopenia has been linked to various detrimental health consequences including disability, frailty, morbidity and mortality [2, 3]. It is noticed that the reports of assessing tool, diagnostic criteria and pathogenesis of sarcopenia may be highly heterogeneous in the context of cirrhosis according to the existing literature. Computed tomograph (CT)-derived images demarcating skeletal muscle on specific cross-sectional levels, as a routine workup for disease monitor and surveillance, account for the "gold standard" to evaluate sarcopenia among patients with cirrhosis, given cumbersome fluid retention in this scenario and unavailability concerning muscle strength measurement in the majority of hepatology centers. It is anticipated that the presence of sarcopenia can negatively impact health-related quality of life (HRQoL) in both direct and indirect manners, considering its close connection with malnutrition, physical inactivity and metabolic derangement [4].

Referring to the recent publications, some pilot studies have focused on the association between sarcopenia and HRQoL impairment among patients with cirrhosis. Ando et al. found psoas muscle index-defined sarcopenia served as an independent risk factor for physical and role-social HRQoL in a small cohort of 88 patients with cirrhosis, however, emerging evidence indicates the muscle quantity determined by psoas muscle index correlate poor with the total body protein, leading to misclassification of mortality risk [5–7]. Another research recruiting 288 patients with cirrhosis utilized thigh muscle-based indices on ultrasound as alternatives to evaluate sarcopenia, whose validity can be curtailed due to peripheral edema and fluid overload [8]. Notably, to the best of our knowledge, no previous reports have elaborated on the influence of sex differences on connections between the SMI values, the presence of sarcopenia and declined HRQoL in the context of cirrhosis. Actually, it is a theory that sarcopenia is mainly driven by poor nutritional status in female and by hypoandrogenism in male patients with cirrhosis [9]. At last but not least, a non-linear relationship between muscle quantity and functional status has been uncovered in diverse settings of populations and pathological conditions [10–12]. Taken together, we hypothesize a non-linear dose–response relationship would exist between SMI, known as a sarcopenia metric, in addition to another muscle quality metric suggestive of myosteatosis determined by intramuscular adipose tissue content (IMAC) and HRQoL in patients with cirrhosis. Moreover, in-depth exploration pertinent to associations outlined should focus on sex disparities.

Methods

Patients and assessments

This is a cross-sectional study by enrolling consecutive adult patients with decompensated cirrhosis between 2018 and 2022, with indications for hospitalization as gastroesophageal variceal bleeding, ascites, hepatic encephalopathy and infection. The main exclusive criteria were as follows: 1) presence of acute-on-chronic liver failure; 2) concomitant hepatocellular carcinoma or other malignancies and 3) incomplete CT or questionnaire data. The study was carried out in terms of the Declaration of Helsinki and approved by the Ethnic Committee of Tianjin Medical University General Hospital (IRB2021-YX-136–01). Written informed consent was obtained from all patients participating in the present study.

Baseline data comprised demographics, a spectrum of body composition parameters incorporating weight, height, body mass index (BMI), laboratory results incorporating alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, creatinine, sodium, prothrombin time-international normalized ratio (PT-INR), etiologies of cirrhosis attributable to chronic HBV/HCV infection, alcohol, autoimmune/cholestatic liver disease, metabolic dysfunction-associated fatty liver disease and cryptogenic reasons. Three scoring systems specific to underlying liver disease severity were calculated: Child-Turcotte-Pugh (CTP) classification, Model for End-stage Liver Disease (MELD) score and MELD-Sodium (MELD-Na) score.

The HRQoL assessment was performed in terms of EuroQol-5D (EQ-5D) questionnaire, a preference-based and generic scale, designating as a well-constructed quality-of-life metric. Specifically, this questionnaire consists of a descriptive setting entailing 5 distinct domains: self-care, mobility, usual activities, pain and anxiety/depression. In total, the practitioners/users are capable of generating 243 (3^5) probably disparate health states on the basis of three levels regarding each domain. The questionnaire is displayed on a scale ranging from 1 to 3: 1 refers to no problems, 2 some problems when 3 extreme problems. Furthermore, a single value complying with each disparate health state is calculated via trade-off method according to a country-specific value setting and regarded as EQ-5D utility index [13]. In this regard, an EQ-5D utility index of "1" equals the best health state, while negative value pertinent to utility index indicates worse health state relative to death.

A CT scan (Discovery 750 HD 64-row; GE Company, Boston, MA, USA) of the abdomen was performed during the period of hospitalization or within 3 months prior to initial evaluation. The collection of CT imaging data has been comprehensively demonstrated in our previous work [14]. Briefly, all radiological data were analyzed using a non-commercial open-source project by two independent members of our research team blinded to patients' information (CQL and WTY) [15]. Total cross-sectional areas covering adipose tissue and skeletal muscle tissue were extracted in terms of pre-constructed Hounsfield unit (HU) with the range of -190 ~ -30 HU for subcutaneous adipose tissue, -150 ~ -50 HU for visceral adipose tissue and -29 ~ + 150 HU for skeletal muscle tissue at the third lumbar vertebra (L3). To measure muscle quantity, the cross-sectional skeletal muscle area in total (cm^2) was normalized for squared stature (m^2), expressed as SMI (cm^2/m^2). To measure muscle quality, the CT attenuation (HU) of the multifidus muscles was dividing by that of subcutaneous adipose tissue, expressed as IMAC. Furthermore, two indexes regarding adipose tissue depots were calculated and normalized to squared stature as subcutaneous adipose tissue index and visceral adipose tissue index. Of note, it is pivotal to correct the sex-associated differences in muscular volume and radiodensity to generate sex-oriented (male–female) cutoffs. Referring to recommendations by authoritative institution and experts in the field of hepatology [16, 17], we have selected the optimal reference values closely linked to patient mortality as previously determined in our research [2]. The SMI cutoffs were < 46.96 and < 32.46 cm^2/m^2 for male and female patients, respectively, to predict long-term mortality in a sizable cohort enrolling hundreds of patients with decompensated cirrhosis. The presence of myosteatosis was defined in terms of sex-specific cutoffs (male: IMAC > − 0.44, female: IMAC > − 0.37). This radiodensity-oriented metric has been broadly utilized and validated across plenty of Japan researches, advantageous in discriminating the variation between individual CT scan and subjects, bringing about clinically significant changes alongside meaningful outcomes [18, 19]. High IMAC value corresponds to severe magnitude of fatty infiltrating the muscle indicative of low muscle quality.

Sample size estimation

As there was no existing research on comparing EQ-5D utility index between distinct groups according to sarcopenic phenotype, we refer to retaining data in the present study for estimation. Accordingly, at least 194 patients were required to reach a power of 80% (α: 0.05, β: 0.80, κ: 0.70 and σ: 0.27).

Statistical analyses

Considering the descriptive context, all continuous data are reported as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. In addition, the categorical data are expressed as absolute frequency (proportion). Independent Student *t* test or Mann–Whitney *U* test were used to detect differences between groups pertaining to continuous data in terms of distribution characteristics (Normal *versus* Non-normal). On the other hand, Pearson's chi-square test or Fisher's exact test was applied for comparisons between groups concerning categorical data.

Considering sex disparities in muscle quantity as well as quality, their associations to EQ-5D-defined HRQoL decline was analyzed separately for males and females. As for muscle quantity, SMI was defined as the explanatory variable as well as IMAC for muscle quality. We used the restricted cubic splines (RCS) to investigate the dose–response trend regarding the associations of SMI or IMAC with EQ-5D utility index. The values of EQ-5D utility index were expressed in *y*-axis alongside the levels of SMI/IMAC on *x*-axis. Pearson correlation was employed in the further step. Multiple linear regression analyses were deployed to estimate the relationship between the presence of sarcopenia as a categorical variable or SMI as a continuous exposure and HRQoL presented by values of EQ-5D utility index among male patients with decompensated cirrhosis. We established four models: Model 1, adjusted for age, SMI, BMI and CTP classification; Model 2, adjusted for age, sarcopenia, BMI and CTP classification; Model 3, adjusted for age, SMI, BMI and MELD-Na score; Model 4, adjusted for age, sarcopenia, BMI and MELD-Na score. The resulting standardized β coefficient alongside 95% confidence interval (CI) were shown. Subgroup analyses, stratified

by age (< 60 *versus* ≥ 60 years), BMI (< 25 *versus* ≥ 25 kg/m^2) as well as liver disease severity (CTP: A *versus* B + C or MELD: < 9 *versus* ≥ 9), were performed using linear regression analysis. Furthermore, we established forest plots describing β coefficient and 95% CI to foster visualization regarding the relationship between sarcopenia and EQ-5D utility index. *P* for interaction was used to examine any possible interaction. All *P* values were 2-sided with a statistical significance indicative of < 0.05. The analytical processes were carried out by using the Graphpad Prism (version 8.0.1, La Jolla, CA) and software packages R (version 3.3.2, http://www.R-project.org).

Results

Study population and baseline characteristics

We initially recruited 621 patients while 57 subjects were excluded due to acute-on-chronic liver failure, 60 due to various types of malignancies and 122 due to incomplete CT/questionnaire data, leaving a total of 382 patients with decompensated cirrhosis for final analyses (Fig. 1). Moreover, the final sample of the current study was composed of even distribution concerning 190 male (49.7%) and 192 female (50.3%) (Table 1). The mean age was 61.9 (SD: 10.3) years and main etiologies of cirrhosis were attributed to chronic HBV/HCV infection (27.4%) and metabolic dysfunction-associated fatty liver disease/cryptogenic (25.4%). The cirrhosis-associated complications comprised gastroesophageal variceal bleeding and ascites in 279 (73.0%) and 239 (62.6%) subjects, respectively. Regarding liver disease severity, 127 (33.2%), 200 (52.4%) and 55 (14.4%) patients were categorized into CTP classification A, B and C, respectively. The median MELD score and MELD-Na score were 9.2 (IQR: 7.3, 11.6) and 9.5 (IQR: 7.5, 12.1) points, respectively. Additionally, female patients were older, and had significantly lower levels of sodium, creatinine and PT-INR when compared with male patients.

Body composition

The mean BMI of both sexes was comparable and almost within the normal range. The muscle quantity metrics differed largely. The median SMI was 48.8 (IQR: 41.4, 55.1) cm^2/m^2 in males and 42.2 (IQR: 36.4, 48.7) cm^2/m^2 in females ($P < 0.001$). Accordingly, the presence of SMI-defined sarcopenia was significantly higher in male patients with cirrhosis (40.5% *versus* 9.9%, $P < 0.001$). Regarding muscle quantity measures, the median IMAC (-0.58 *versus* -0.52, $P < 0.001$) was significantly higher in female in comparison with male patients, whereas the presence of IMAC-defined myosteatosis was comparable (15.3% *versus* 16.7%, $P = 0.708$). Intriguingly, we also found the subcutaneous adipose tissue index was significantly higher in female than in male counterparts, but out of the scope of present investigation.

Health-related quality of life and associations to muscle quantity and quality

A detailed description of patients' HRQoL determined by EQ-5D and stratified by sex as well as the presence of sarcopenia is presented in Table 2 and Fig. 2. Regarding

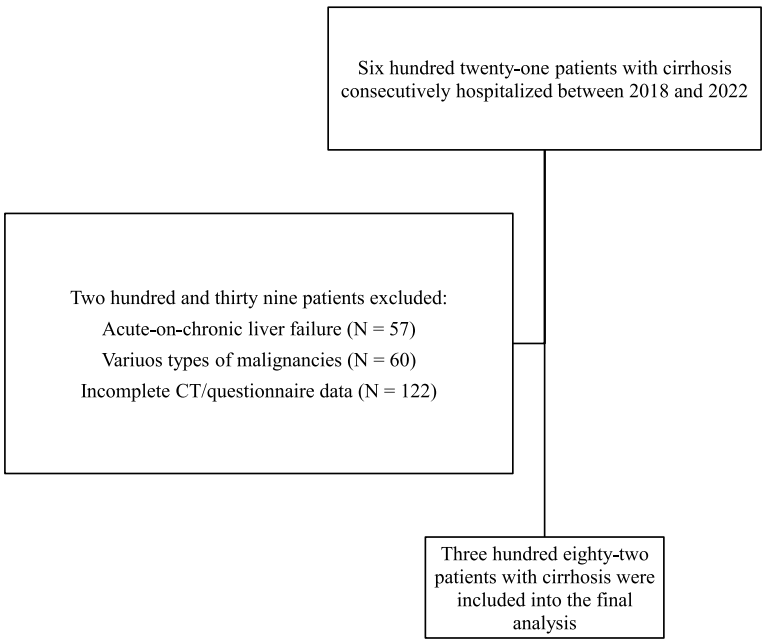

Fig. 1 A flow chart concerning the study population. CT, computed tomography

Table 1 Baseline patient characteristics

	Patients			*P*
	All *n* = 382 (100%)	**Male *n* = 190 (49.7%)**	**Female *n* = 192 (50.3%)**	
Age (years)	61.9 (10.30)	59.9 (10.53)	63.9 (9.69)	< 0.001
Body composition parameters				
BMI, kg/m^2	24.7 (4.90)	25.1 (4.87)	24.3 (4.90)	0.098
VATI, cm^2/m^2	40.2 (26.2, 60.6)	43.2 (28.4, 63.5)	37.5 (24.6, 58.6)	0.167
SATI, cm^2/m^2	44.1 (30.6, 68.5)	38.1 (25.3, 54.8)	53.6 (33.3, 79.9)	< 0.001
SMI, cm^2/m^2	45.5 (38.4, 52.3)	48.8 (41.4, 55.1)	42.2 (36.4, 48.7)	< 0.001
Sarcopenia, *n* (%)	96 (25.1)	77 (40.5)	19 (9.9)	< 0.001
IMAC	-0.54 (-0.71, -0.44)	-0.58 (-0.78, -0.47)	-0.52 (-0.66, -0.42)	< 0.001
Myosteatosis, *n* (%)	61 (16.0)	29 (15.3)	32 (16.7)	0.708
CTP classification, *n* (%)				0.318
A	127 (33.2)	57 (30.0)	70 (36.5)	
B	200 (52.4)	102 (53.7)	98 (51.0)	
C	55 (14.4)	31 (16.3)	24 (12.5)	
Etiology, *n* (%)				< 0.001
HBV/HCV	105 (27.4)	56 (26.8)	49 (22.9)	
Alcohol	84 (22.0)	82 (43.2)	2 (1.0)	
Autoimmune/Cholestasis	96 (27.7)	28 (6.8)	68 (48.4)	
MAFLD/Cryptogenic	97 (25.4)	24 (23.2)	73 (27.6)	
MELD score	9.2 (7.3, 11.6)	9.1 (5.4, 11.8)	9.3 (8.1, 11.5)	0.082
MELD-Na score	9.5 (7.50 12.1)	9.5 (6.1, 12.6)	9.4 (8.1, 11.7)	0.541
AST (U/L)	32.0 (22.0, 47.8)	32.0 (21.0, 47.8)	32.0 (22.0, 49.0)	0.649
ALT (U/L)	23.0 (16.0, 36.3)	23.0 (16.0, 36.3)	23.0 (15.0, 36.3)	0.880
Total bilirubin (μmol/L)	21.6 (14.0, 33.2)	21.6 (13.7, 33.3)	21.6 (14.2, 33.4)	0.750
Albumin (g/L)	29.0 (25.0, 33.0)	28.0 (26.0, 33.0)	29.0 (25.0, 33.0)	0.873
Sodium (mmol/L)	140.0 (137.0, 142.0)	140.0 (137.0, 142.0)	140.0 (138.0, 142.0)	0.029
Creatinine (μmol/L)	58.0 (47.0, 71.3)	65.0 (54.0, 75.5)	52.0 (43.0, 63.8)	< 0.001
PT-INR	1.3 (1.1, 1.4)	1.3 (1.2, 1.5)	1.2 (1.1, 1.4)	0.001
Complications, *n* (%)				0.084
Ascites	239 (62.6)	124 (65.3)	115 (59.9)	
Hepatic encephalopathy	23 (6.0)	17 (8.9)	6 (3.1)	
GEVB	279 (73.0)	131 (68.9)	148 (77.1)	
Infection	43 (11.3)	21 (11.1)	22 (11.5)	

BMI body mass index, *VATI* visceral adipose tissue index, *SATI* subcutaneous adipose tissue index, *SMI* skeletal muscle index, *CTP* Child-Turcotte-Pugh, *MAFLD* metabolic dysfunction-associated fatty liver disease, *MELD* Model for End-stage Liver Disease, *MELD-Na* MELD-Sodium, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PT-INR* prothrombin time-international normalized ratio, *GEVB* gastroesophageal variceal bleeding

the whole study population, the proportions of subjects complained of some and extreme problems, respectively, were 21.7% and 12.1% in mobility, 17.0% and 8.1% in self-care, 21.7% and 8.4% in usual activities, 27.0% and 2.1% in pain, and 21.5% and 10.2% in anxiety/depression. In terms of sarcopenic phenotype, our findings implicated that self-care, usual activities and pain within EQ-5D scale (i.e., some + extreme problems) were more prevalent in sarcopenia compared with non-sarcopenia groups across the entire population and stratified by sex (Figure S1). In contrast, mobility was more prevalent in sarcopenic compared with non-sarcopenic male patients, whereas no significant difference was found among female patients. The EQ-5D utility index was also significantly higher in the non-sarcopenia group relative to sarcopenia group across the entire population (0.78 *versus* 0.68, $P = 0.001$) as well as both sexes (male: 0.81 *versus* 0.70, $P = 0.006$; female: 0.76 *versus* 0.59, $P = 0.002$).

Next, we asked and explored the dose–response relationship between EQ-5D utility index and SMI/IMAC, which were displayed in Fig. 3. For male patients, a significant association between SMI and EQ-5D utility index was observed ($P = 0.013$) in contrast to female patients ($P = 0.346$). In addition, aforesaid dose–response

Table 2 Comparisons of the EQ-5D profile and utility index between patients with sarcopenia and non-sarcopenia

	Total $n=382$			P	Male $n=190$			P	Female $n=192$			P
		Sarcopenia ($n=96$)	Non-Sarcopenia ($n=286$)			Sarcopenia ($n=77$)	Non-sarcopenia ($n=113$)			Sarcopenia ($n=19$)	Non-sarcopenia ($n=173$)	
Mobility, *n* (%)				0.001				0.008				0.098
No	253 (66.2)	50 (52.1)	203 (71.0)		120 (63.2)	40 (51.9)	80 (70.8)		133 (69.3)	10 (52.6)	123 (71.1)	
Some + Extreme	129 (33.8)	46 (47.9)	83 (29.0)		70 (36.8)	37 (48.1)	33 (29.2)		59 (30.7)	9 (47.7)	50 (28.9)	
Self-care, *n* (%)				0.007				0.028				0.026
No	286 (74.9)	62 (64.6)	224 (78.3)		144 (75.8)	52 (67.5)	92 (81.4)		142 (74.0)	10 (52.6)	132 (76.3)	
Some + Extreme	96 (25.1)	34 (35.1)	62 (21.7)		46 (24.2)	25 (32.5)	21 (18.6)		50 (26.0)	9 (47.7)	41 (23.7)	
Usual activities, *n* (%)				0.000				0.005				0.002
No	267 (69.9)	53 (55.2)	214 (74.8)		135 (71.1)	46 (59.7)	89 (78.8)		132 (68.8)	7 (36.8)	125 (72.3)	
Some + Extreme	115 (30.1)	43 (44.8)	72 (25.2)		55 (28.9)	31 (40.3)	24 (21.2)		60 (31.3)	12 (63.2)	48 (27.7)	
Pain, *n* (%)				0.004				0.002				0.005
No	271 (70.9)	57 (59.4)	214 (74.8)		145 (76.3)	50 (64.9)	95 (84.1)		126 (65.6)	7 (36.8)	119 (68.8)	
Some + Extreme	111 (29.1)	39 (40.6)	72 (25.1)		45 (23.7)	27 (35.1)	18 (15.9)		66 (34.4)	12 (63.2)	54 (31.2)	
Anxiety/depression, *n* (%)				0.721				0.715				0.749
No	261 (68.3)	67 (69.8)	194 (67.8)		136 (71.6)	54 (70.1)	82 (72.6)		125 (65.1)	13 (68.4)	112 (64.7)	
Some + Extreme	121 (31.7)	29 (30.2)	92 (32.2)		54 (28.4)	23 (29.9)	31 (27.4)		67 (34.9)	6 (31.6)	61 (35.3)	
EQ-5D utility index				0.001				0.006				0.002
Mean ± SD	0.75 ± 0.27	0.68 ± 0.30	0.78 ± 0.25		0.77 ± 0.27	0.70 ± 0.31	0.81 ± 0.23		0.74 ± 0.26	0.59 ± 0.26	0.76 ± 0.26	
Median (IQR)	0.77 (0.65, 1)	0.70 (0.53, 1)	0.79 (0.68, 1)		0.79 (0.61, 1)	0.73 (0.53, 1)	0.80 (0.71, 1)		0.76 (0.66, 1)	0.65 (0.48, 0.74)	0.77 (0.66, 1)	

EQ-5D EuroQol-5D, *SD* standard deviation, *IQR* interquartile range

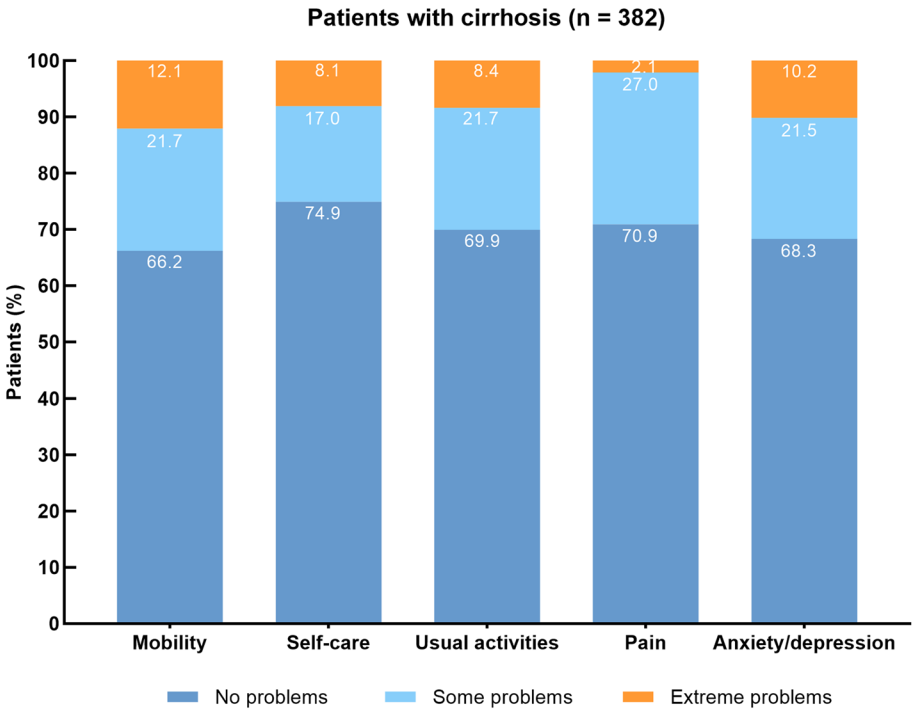

Fig. 2 Distribution of the EQ-5D profiles in the entire population with decompensated cirrhosis ($n=382$). EQ-5D, EuroQol-5D

relationship was not significantly non-linear (P for non-linearity = 0.281), which implied that higher muscle quantity may correspond to better quality of life. For muscle quality determined by IMAC, no significant association or non-linear dose–response relationship was seen in both sexes, to some degree denying our hypothesis pertaining to a connection between muscle quality and HRQoL.

Factors associated with EQ-5D utility index

Because of the relatively small size of participants in terms of sex stratification, multiple linear regression models were generated adjusted for a limited number of variables in males (Table 3). In model 1 adjusted for age, BMI, CTP classification, SMI was independently associated with EQ-5D utility index [standardized β coefficient (95% CI): 0.234 (0.229, 0.239), $P=0.017$). In model 2 adjusted for age, BMI, CTP classification, the presence of sarcopenia was independently associated with EQ-5D utility index [standardized β coefficient (95% CI): -0.210 (-0.304, -0.117), $P=0.015$]. Similarly, SMI [standardized β coefficient (95% CI): 0.229 (0.224, 0.234), $P=0.018$] and the presence of sarcopenia [standardized β coefficient (95% CI): -0.194 (-0.288, -0.101), $P=0.024$] were both independently associated with EQ-5D utility index, respectively, in model 3 and model 4 adjusted for age, BMI and MELD-Na score.

Subgroup and interaction analyses

As depicted in Fig. 4, it was noted that sarcopenia exhibited a negative correlation with EQ-5D utility index among males in the age ≥ 60 years [β coefficient (95% CI): -0.16 (-0.27, -0.05), $P=0.004$], BMI ≥ 25 kg/m^2 [β coefficient (95% CI): -0.20 (-0.35, -0.05), $P=0.010$], CTP classification B + C [β coefficient (95% CI): -0.14 (-0.23, -0.04), $P=0.006$] and MELD-Na ≥ 9 [β coefficient (95% CI): -0.13 (-0.24, -0.03), $P=0.015$]. However, no statistically significant interaction between the presence of sarcopenia and EQ-5D utility index was observed in these subgroups (all P for interaction > 0.05). This implicated that the association remained consistent across different demographic, anthropometric and disease magnitude-related variables, incorporating age, BMI, CTP classification and MELD-Na score.

Correlation analysis between values of SMI and EQ-5D utility index

Finally, we analyzed the correlation between SMI values and EQ-5D utility index. As expected, SMI values just positively correlated with EQ-5D utility index in male patients with cirrhosis ($r=0.207$, $P=0.004$) but not IMAC values or in female patients (Fig. 5).

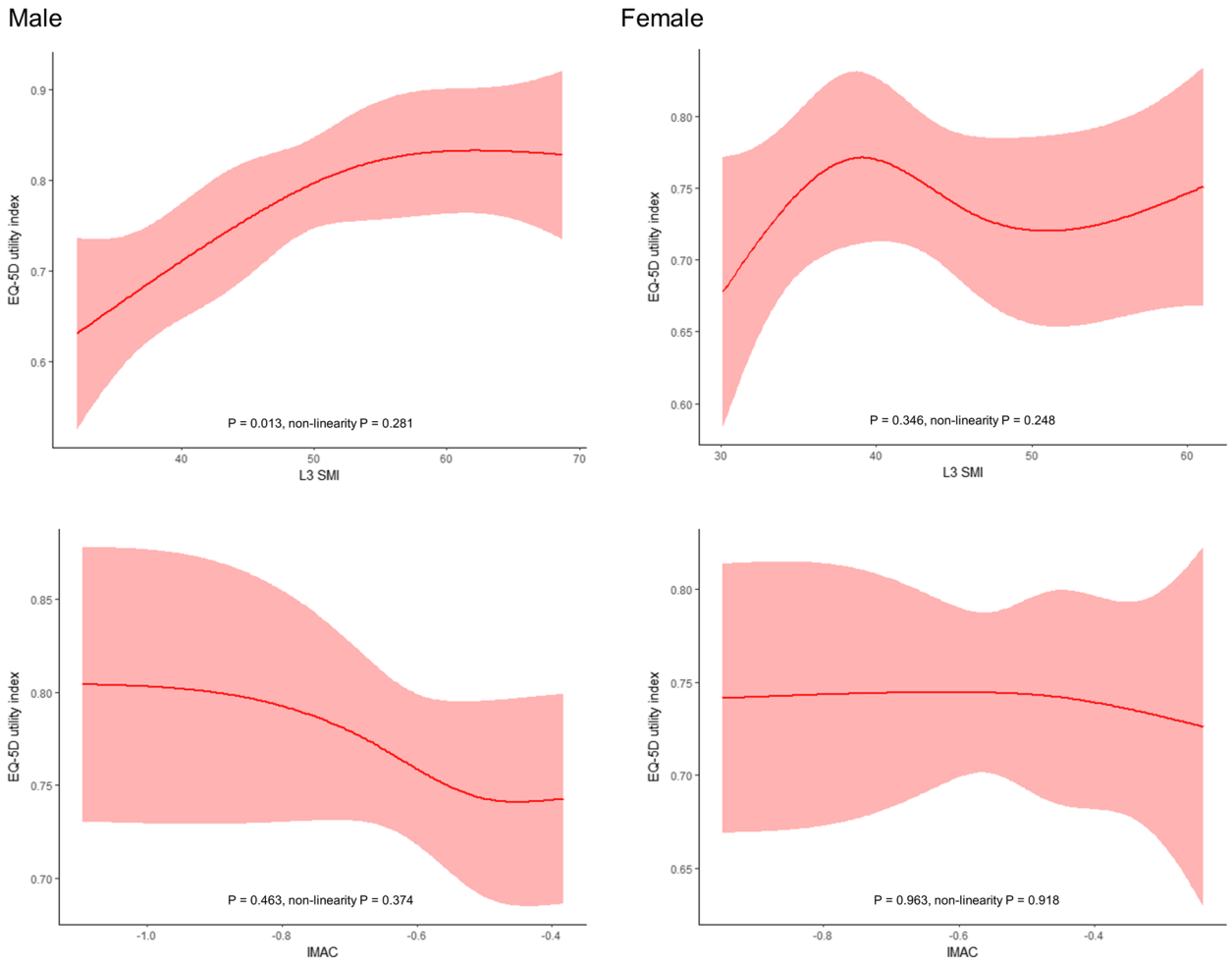

Fig. 3 The dose–response relationship between EQ-5D utility index and SMI/IMAC at L3. EQ-5D, EuroQol-5D; L3, the third lumbar vertebral; SMI, skeletal muscle index; IMAC, intramuscular adipose tissue index

Discussion

This study provides novel insights pertaining to the relationship between decreased muscle quantity and HRQoL decline taking sex disparities into account among hospitalized patients with cirrhosis. We found no significant association between neither SMI-defined sarcopenia or IMAC-defined myosteatosis and EQ-5D-defined HRQoL in females. On contrary, in the male cohort, muscle quantity measured by SMI exhibited a statistically significant linear relationship with EQ-5D utility index. Moreover, both the presence of sarcopenia and low levels of SMI served as independent risk factors for HRQoL decline, manifested as a decrement in EQ-5D utility index among male patients with cirrhosis.

Unlike other dismal outcomes associated with the deterioration of decompensated cirrhosis such as unplanned hospitalization and mortality, HRQoL decline remains an underestimated aspect regarding patient care among this vulnerable population [4]. HRQoL, as a broad terminology, indicates subjects' perception on disease itself and treatment affecting their physical, emotional, functional as well as social conditions [20]. HRQoL can be evaluated in terms of both subjective and objective modalities, playing a pivotal role even beyond conventional clinical endpoints such as incurring complications or mortality [21]. The practical importance and clinical relevance are getting increasing attention, because of remarkable improvements with respect to long-term survival on account of disease management advances. For instance, the US Food and Drug Administration has released a guidance tool addressing a more structured and frequent usage of patient-reported outcome, such as HRQoL, in the clinical trials [22]. This policy and strategy considerably reinforce the significance by regarding HRQoL as an efficient endpoint independent of other medical effectiveness. In other words, it is crucial to substantially assess each patient's HRQoL in hopes of

Table 3 A multiple linear regression to analyze relationship between the following variables and the EQ-5D utility index in male patients with cirrhosis

Variables	Model 1			Model 2			Model 3			Model 4		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
Age (years)	-0.097	(-0.101, -0.093)	0.191	-0.113	(-0.117, -0.109)	0.123	-0.108	(-0.112, -0.105)	0.135	-0.124	(-0.127, -0.120)	0.084
SMI (cm^2/m^2)	0.234	(0.229, 0.239)	**0.017**				0.229	(0.224, 0.234)	**0.018**			
Sarcopenia												
No					Reference						Reference	
Yes				-0.210	(-0.304, -0.117)	**0.015**				-0.194	(-0.288, -0.101)	**0.024**
BMI (kg/m^2)	-0.076	(-0.086, -0.065)	0.427	-0.036	(-0.046, -0.027)	0.670	-0.082	(-0.092, -0.071)	0.386	-0.037	(-0.046, -0.028)	0.660
CTP classification				-0.127	(-0.184, -0.069)	0.077						
A		Reference			Reference							
B	-0.088	(-0.177, 0.001)	0.287	-0.078	(-0.167, 0.011)	0.343						
C	-0.145	(-0.263, -0.027)	0.074	-0.145	(-0.263, -0.027)	0.075						
MELD-Na							-0.164	(-0.167, -0.162)	**0.021**	-0.153	(-0.156, -0.151)	**0.032**

EQ-5D EuroQol-5D, *SMI* skeletal muscle index, *BMI* body mass index, *CTP* Child-Turcotte-Pugh, *MELD-Na* Model for End-stage Liver Disease-Sodium, *CI* confidence interval

Model 1 adjusted for age, SMI, BMI and CTP classification

Model 2 adjusted for age, sarcopenia, BMI and CTP classification

Model 3 adjusted for age, SMI, BMI and MELD-Na score

Model 4 adjusted for age, sarcopenia, BMI and MELD-Na score

Bold indicates statistical significance

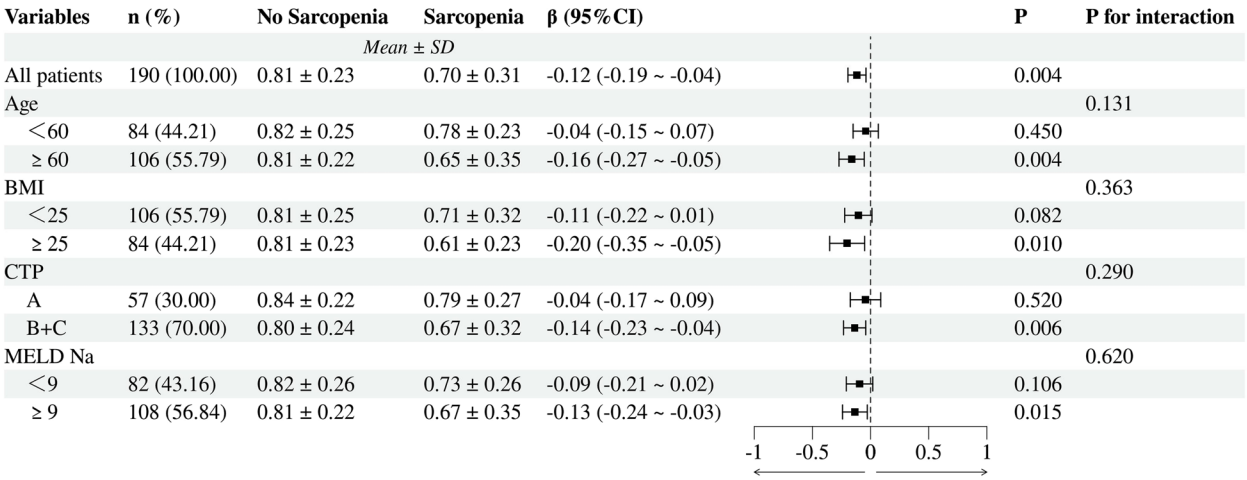

Fig. 4 Association between the presence of sarcopenia and EQ-5D utility index in distinct subgroups. BMI, body mass index; CTP, Child-Turcotte-Pugh; MELD-Na, Model for End-stage Liver Disease-Sodium

fostering medical practitioner and patient to decide the best therapeutic course.

In the context of cirrhosis, particularly at more advanced stage (i.e., decompensated cirrhosis), a large proportion of patients has proved to experience HRQoL decline. Peng et al. conducted a meta-analysis and argued that the progression of cirrhosis resulted in significant worsening of physical and mental components within the 36-Item Short Form Survey-defined HRQoL (another generic tool) [23]. Intriguingly, results from the present study corroborate with aforesaid paper, unravelling that 60.4% of the population had abnormalities in at least one EQ-5D domain alongside corresponding mean utility index to be only 0.75 (SD: 0.27). Moreover, the majority of EQ-5D questionnaire aspects including mobility, self-care, usual activities and pain was profoundly prevalent in patients with sarcopenia compared to non-sarcopenia. These close relationships were further verified in terms

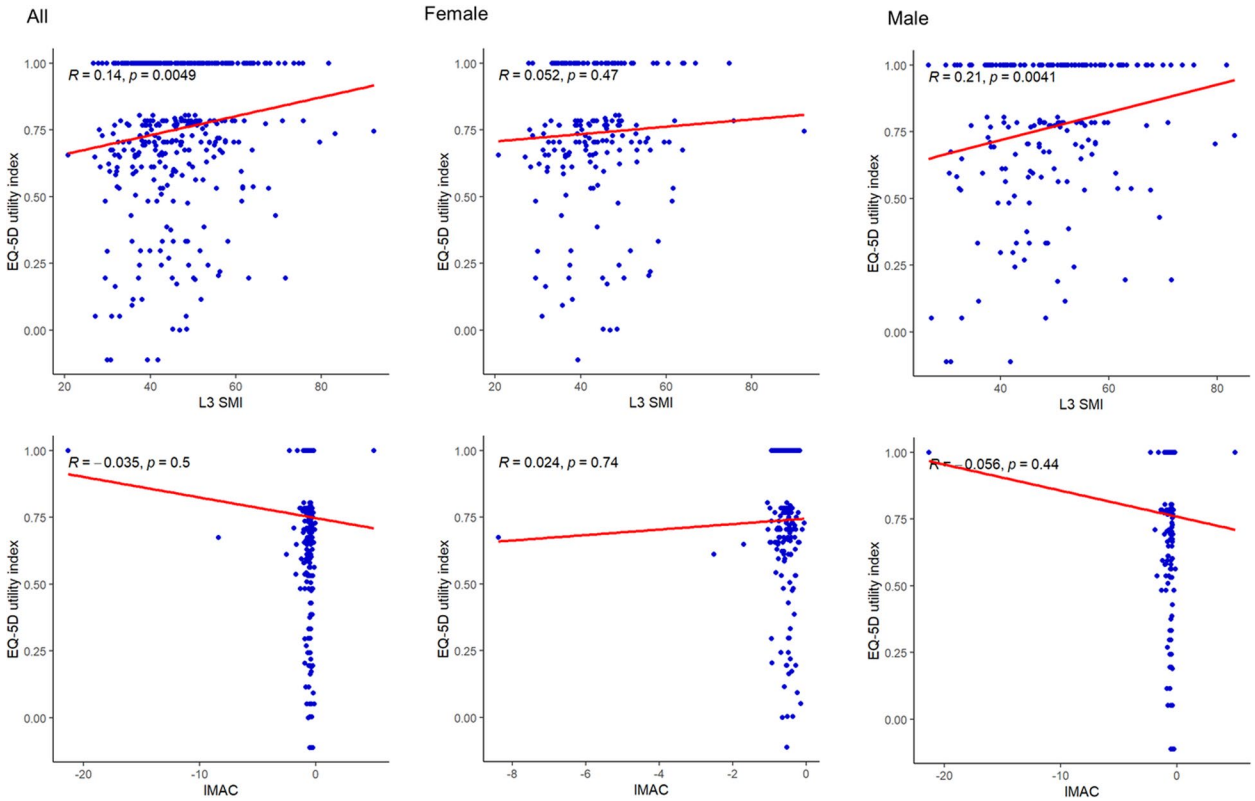

Fig. 5 Correlation analysis between values of SMI (A)/IMAC (B) and EQ-5D utility index. SMI, skeletal muscle index; IMAC, intramuscular adipose tissue content; EQ-5D, EuroQol-5D

of multiple regression analyses; high MELD-Na score, the presence of sarcopenia as well as low SMI levels were independently associated with a decrement in EQ-5D utility index pinpointing to HRQoL decline among male patients with decompensated cirrhosis.

The negative impact of sarcopenia on HRQoL has been explored and elucidated in a few studies, consulting skeletal muscle abnormalities as potential target for management. Ando et al. found that sarcopenia independently caused physical and role-social defect in a setting of 88 inpatients [24]. Shanavas et al. implicated that sarcopenia was negatively correlated with Chronic Liver Disease Questionnaire regarding activity and systemic symptoms [8]. Another study based on 77 patients with cirrhosis demonstrated a SarQoL® questionnaire can simultaneously assess quality of life and identify participants with altered HRQoL and sarcopenia [25]. However, those studies outlined appear to embrace several flaws: 1) the study population is not sizable enough; 2) no prior studies have shed light on influencing effect of sex differences in the muscle mass; 3) the gold standard to measure muscle quantity in the context of cirrhosis is not generally employed and 4) a non-linear relationship between muscle quantity and HRQoL metrics should be taken into account. Taken together, we herein utilized plenty of analytical methods in hopes of attaining in-depth insights concerning connection between muscle wasting and HRQoL decline.

Actually, it is anticipated and unsurprising that the presence of sarcopenia and low SMI levels can independently predict deterioration in several health consequences. Sarcopenia disrupts mobility and worsens functional ability which lead to dramatically physical decline [26, 27]. In this regard, Bye et al. demonstrated that low muscle mass leveraged negative impacts on self-reported physical function, role function in addition to global quality of life in patients with advanced non-small cell lung cancer [10]. Another study implicated that sarcopenia was in relation to greater depression symptoms and worse HRQoL in the context of advanced cancer [28]. Notably, preserved skeletal muscle mass has been linked to prominent and clinically relevant improvements regarding a spectrum of function and symptom scales and global health status in patients with metastatic colorectal cancer [29]. Consulting a meta-analysis involving 2776 adults experiencing various malignancies, it is noted that low SMI was connected to worse global and

physical function HRQoL domain scores, indicative of a multifaceted and bidirectional link between skeletal muscle abnormalities and wellbeing [30]. Specifically, reduced muscle mass may contribute to physical strength decline, wherein a link is evident between strength and HRQoL [31, 32]. Conversely, declined HRQoL due to side effects arising from malignancy treatment, emotional burden of experiencing life-threatening status as well as recovery from major operation may negatively impact an individual's engagement in daily routine and lead to physical inactivity, designated as a core contributor to muscle wasting [33]. Another paper combining 43 observational studies also highlighted a considerable decrement in HRQoL in sarcopenic when compared with non-sarcopenic older adults [34]. Moreover, the authors argued that it is imperative to initiate earlier prevention and prompt treatment in the circumstance of earlier detecting sarcopenia, aiming at effective elimination of negative impact that sarcopenia leveraging on HRQoL.

In contrast to our hypothesis, we failed to detect a non-linear relationship between SMI and EQ-5D utility index. It has been documented that muscle wasting over 30% relative to young adults may give rise to obviously observed decrease in functional abnormalities in elderly [31, 35]. Consistently, one report also implied that it was a prerequisite of muscle quantity falling below certain values ahead of remarkable impact on several HRQoL issues to be detected [10]. The discrepancies between our findings and background information may be attributable to multifaceted and complex pathogenesis of sarcopenia in distinct populations and entities, including age-related process, nutritional status, dysgeusia, dysregulated absorption, inadequate dietary intake and inappetence. As a matter of fact, we herein provide supporting evidence by reversing sarcopenic phenotype via increasing SMI levels as high as possible to achieve better HRQoL. Intriguingly, Bai et al. also unveiled a linear dose–response association between SMI and incidence of cirrhosis especially in male patients with acute-on-chronic liver failure [36]. Collectively, we suppose it is tempting to provide tailored interventions against sarcopenia and monitor longitudinal SMI changes to improve outcomes.

Another topic of concern raised by the present study indicates that no association was found between SMI-dictated muscle quantity or IMAC-dictated muscle quality in the female cohort. The possible interpretations can be found as follows: 1) The prevalence of sarcopenia and myosteatosis were lower in female patients when compared with male counterparts, therefore curtailing statistical significance; 2) Regarding muscle quantity, L3-SMI exhibits a weaker reflection in females [37]. Excessive fat infiltration in female muscular tissue occurs at the early stage of sarcopenia, responsible for discordance between L3-SMI and relevant muscle loss [38]; 3) Regarding muscle quality, there are two mainstays for measurement. Apart from IMAC adopted by us, skeletal muscle attenuation represents other components of muscle fat infiltration corresponding to distinct metabolic and muscle heath features [39]. Therefore, a more comprehensive picture of myosteatosis warrants joint use of IMAC and skeletal muscle attenuation [40].

The sex differences in muscle wasting in combination with our preliminary findings highlight the distinct mechanisms and potential treatment options tailored to male and female patients with cirrhosis. Besides common contributors to sarcopenia like altered metabolism, hyperammonemia and endotoxemia, hypogonadism due to reduced IGF-I and increased aromatase activity accounts for negative impact of relevant anabolic hormone on muscular homeostasis, ultimately giving rise to muscle wasting in around 50–80% of males with advanced liver disease [41, 42]. Intriguingly, total testosterone is reported to be lower when compared with healthy counterparts [43]. Conversely, estrogen exhibits a protective effect on the hepatic function as well as skeletal muscle, that is, a mechanism pertaining to decreased incidence of sarcopenia in females and whose deficiency may contribute to the develop of versatile liver diseases [44, 45]. Accordingly, it was reported that 1 year of testosterone supplementation to male patients with liver diseases significantly increased CT-demarcated appendicular and total muscle quantity in comparison with placebo [46]. However, it is still elusive whether testosterone replacement exhibited similarly therapeutic potentials in females, while estrogens are not a good candidate against muscle wasting on account of cardiovascular and malignancy risks [47]. On the other hand, interventions combining caloric supplementation and late-evening snack have proved to improve muscle mass in both sexes with cirrhosis [48].

Several limitations of the present study should be clarified. First, we used EQ-5D questionnaire to assess HRQoL. This belongs to a general health tool measuring the individual's global heath which is not developed to identify disease-specific symptoms sufficiently. However, EQ-5D has been broadly utilized and reliable, advantageous in.

enabling comparisons pertinent to scores between patients with other diseases or healthy population. Moreover, others and us have verified the predictive utility of EQ-5D in relation to various inferior outcomes [49–51]. Second, we carried out a single academic center study with relatively limited ethnic and racial diversity, hampering the generalizability of our findings to more heterogeneous populations. Third, we did not retrieve information concerning physical activities, nutritional status and underlying

metabolic derangement which may influence patients' capability to maintain muscle quantity. Fourth, we did not compare other body composition abnormalities such as low subcutaneous adiposity between patients with or without decreased HRQoL. Finally, the cross-sectional study design made us unable to determine directionality between muscle wasting and HRQoL, requiring for prospective, longitudinal studies examining the interplay of these outcomes. Actually, there exist certain barriers, that is, high heterogeneity pertinent to CT scan intervals (time over which change is measured), applied treatment and nutritional status. In other words, the lacking of standardization to assess and report of muscle change hinder our intention examining concurrent progression in relation to both muscle abnormalities and quality of life in the context of cirrhosis. Moreover, unlike most patients with solid tumors among whom more than one routine CT scan is taken over the cancer trajectory, proportional patients with cirrhosis did not undergo scheduled imaginal surveillance. Taken together, future targeted studies with sizable multicenter populations are warranted to clarify this causality, and in consequence develop optimized intervention against sarcopenia/myosteatosis or key determinants concerning impaired HRQoL.

Conclusions

In summary, low muscle quantity measured by SMI in patients with decompensated cirrhosis appeared to affect HRQoL negatively. Our data implicates it is tempting to manage sarcopenia by increasing SMI levels as high as possible in hopes of achieving better health consequence. Our findings represent the importance of connecting CT-demarcated body composition abnormalities to meaningful patient-centered outcomes.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CT	Computed tomography
CTP	Child-Turcotte-Pugh
EQ-5D	EuroQol-5D
HRQoL	Health-related quality of life
HU	Hounsfield unit
IMAC	Intramuscular adipose tissue content
IQR	Interquartile range
L3	The third lumbar vertebral
MELD	Model for End-stage Liver Disease
PT-INR	Prothrombin time-international normalized ratio
RCS	Restricted cubic splines
SD	Standard deviation
SMI	Skeletal muscle index

Supplementary Information

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Supplementary Material 1.

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None.

Authors' contributions

JY: Conceptualization; Investigation; formal analysis; GYG: Conceptualization; formal analysis; FY: Conceptualization; formal analysis; CQL: methodology; HW: methodology; WTY: Investigation; ZYY: Investigation; Qing L: formal analysis; Qian L: formal analysis; CS: Conceptualization; formal analysis; writing – original draft; writing – review and editing. All authors read and approved the final manuscript.

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Availability of data and materials

Dataset generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was carried out in terms of the Declaration of Helsinki and approved by the Ethnic Committee of Tianjin Medical University General Hospital (IRB2021-YX-136–01). Written informed consent was obtained from all patients participating in the present study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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