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Relationship between sarcopenia/myosteatosis and frailty in hospitalized patients with cirrhosis: a sex-stratified analysis

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Abstract

Background: Previous studies have shown that sarcopenia appears to be a significant contributor to physical frailty among outpatients with cirrhosis. However, the evidence is scant regarding the relationship between sarcopenia and multi-dimensional frailty among inpatients. We aimed to investigate the potential contribution of sarcopenia to frailty in hospitalized patients with cirrhosis in a sex-dependent manner.

Methods: This cohort enrolled consecutive cirrhotics. Muscle quantity and quality were assessed using the computed tomography-based skeletal muscle index (SMI) and intramuscular adipose tissue content, respectively. Frailty phenotype was clarified by a self-reported Frailty Index. Multiple linear regression determined the association between sarcopenia and frailty phenotype.

Results: A total of 202 cirrhotic patients with 48.5% male were included. The median Frailty Index was 0.13, rendering 17.3% subjects as frail. Among the 16 frail men, 68.8% had sarcopenia and 62.5% exhibited myosteatosis. In contrast, among the 19 frail women, 26.3% had sarcopenia and 15.8% exhibited myosteatosis. Frail patients had a significantly lower median SMI (42.80 cm^2/m^2) compared with those with pre-frailty (48.23 cm^2/m^2) and with robust status (50.82 cm^2/m^2) in the male but not the female group. In male patients, multivariate linear regression implicated age ($\beta = 0.330$, $p < 0.001$), SMI ($\beta = -0.260$, $p < 0.001$), albumin ($\beta = -0.245$, $p = 0.005$), and sodium ($\beta = -0.179$, $p = 0.037$) as independent risk factors for frailty.

Conclusion: Sarcopenia is associated with multi-dimensional frailty in male patients with cirrhosis. It is tempting to incorporate sex-specific intervention with the purpose of mitigating frailty among inpatients.

Keywords: cirrhosis, frailty, myosteatosis, sarcopenia, sex difference

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Introduction

Frailty and sarcopenia are prevalent in patients with cirrhosis, and both have been proved to negatively impact morbidity and mortality.[1–4] Although accumulating evidence indicates that sarcopenia might serve as a component of frailty, frailty itself is more multi-faceted than sarcopenia alone.[5] Tapper *et al.*[6] found bedside measures of frailty (handgrip strength and number of chair stands), cognitive function, and computed tomography (CT)-based indices of sarcopenia exhibit sex-dependent correlations. Furthermore,

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in a cohort of 291 cirrhotic outpatients, sarcopenia was associated with approximately two-fold increased odds of being frail.[7] However, two-thirds of frail male cirrhotics had sarcopenia, whilst only 25% of frail female represented sarcopenia. It is not surprising that foregoing studies showed more overlap with sarcopenia since their modalities employed a physical frailty definition with low handgrip strength as part of diagnostic criteria.[8,9] As a matter of fact, the construct of frailty goes beyond physical dimensions and embraces psychological and social constituents as well, including cognitive function and social support.[10] Taken together, it is an unmet need to explore the relationship between sarcopenia and frailty phenotype determined by multiple metrics.

More recently, we have developed a self-reported Frailty Index for prognostication, which sounds more applicable, in comparison with physical tests, among severely frail cirrhotics with mobilizing difficulty.[11–13] The proposed scale allows us to converge on a relatively parsimonious number of tests relevant to physical frailty. Herein we aimed to investigate the association between sarcopenia and multi-dimensional frailty in hospitalized patients with cirrhosis. Additionally, in-depth sex-dependent disparities were illuminated.

Methods

Study cohort

A cohort of adult patients with cirrhosis was consecutively enrolled in the Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital (TJMUGH) between March 2017 and November 2019. Written informed consent was obtained from all participants. The diagnosis of liver cirrhosis was made in terms of medical history, clinical, laboratory, and imaging results, as well as transient elastography or biopsy. The exclusion criteria were as follows: (i) primary liver tumors or extrahepatic cancers; (ii) acute on chronic liver failure upon admission; (iii) presence of severe hepatic encephalopathy (as recognized by a time to complete a numbers connection test of more than 120 s); (iv) liver transplantation; (v) refusal of follow-up; (vi) more than 26 empty items in questionnaire. A total of 202 patients with cirrhosis were left for final analysis (Supplemental material Figure S1 online). The present study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of TJMUGH (2016-033).

Frailty Index assessment

As deciphered in our previous work, Frailty Index derives from a self-reported scale, Carolina Frailty Index (CFI).[11] CFI is a questionnaire consisting of 36 items regarding various components, such as instrumental activities of daily living, physical function, unintentional weight loss, exhaustion, depression, and social activities. Taking account of the pathophysiological nature of cirrhosis, we modulated the original CFI and obtained a new Frailty Index (Supplemental Table S1). A questionnaire which is fulfilled with 10 items or more will be regarded as valid. The Frailty Index is determined according to the score that patients retrieve from the total points of the questionnaire. For instance, a patient who gets 12 points after finishing all 36 items has a Frailty Index of 0.33 (12/36); a patient who gets six points after finishing 12 items of the questionnaire has a Frailty Index of 0.50 (6/12). In terms of quartile, we defined the Frailty Index thus: less than 0.07 as robust, 0.07–0.38 as pre-frail, and more than 0.38 as frail. Furthermore, we collected the Frailty Index questionnaire soon after (within 48 h) the first admission to our department.

Sarcopenia and myosteatosis evaluation

A spectral computed tomography (CT) scanner (Discovery 750 HD 64-row, General Electric Company, Boston, USA) was applied to obtain all CT imaging. Skeletal muscle and adipose tissue at the third lumbar vertebra (L3) level were measured by using non-commercial software based on Matlab version R2010a (Mathworks Inc., Natick, MA, USA).[14] Skeletal muscle area covered the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. Tissue-specific Hounsfield unit (HU) thresholds were adopted to discriminate tissue types. The CT thresholds were −29 to 150 HU for quantifying skeletal muscle and −190 to −30 HU for subcutaneous adipose tissue and visceral adipose tissue. The skeletal muscle index (SMI) was retrieved by dividing the muscle area at L3 by height in square meters (cm^2/m^2). Notably, sarcopenia was defined according to our previous publication as a SMI $< 46.96\ cm^2/m^2$ for male

and SMI $< 32.46\,cm^2/m^2$ for female.[2] A weaker correlation has been reported between sarcopenia and various adverse outcomes in female.[15,16] Thus we hypothesized that muscle quality would be more closely relevant to frailty phenotype.[17] Accordingly, the muscle quality was determined by intramuscular adipose tissue content (IMAC) at the L3 level, whose efficacy and feasibility has been validated by us and others.[2,18,19] IMAC was calculated by dividing the CT attenuation of the multifidus muscles (HU) by that of subcutaneous adipose tissue (HU). Higher IMAC reveals a greater amount of fat infiltration in muscle tissue and, therefore, a lower quality of muscle (myosteatosis). Moreover, the value of IMAC is normalized to the value of subcutaneous fat individually, and it is not influenced by the CT system or scanning conditions.[20] Collectively, we assume that this indicator could more sensitively reflect skeletal muscle quality.[21,22] The sex-specific cutoff values for defining myosteatosis were IMAC > -0.44 in male and > -0.37 in female, respectively.

Statistical analysis

Data were expressed as mean ± standard deviation, median [interquartile range (IQR)], simple frequency or proportion (%) as appropriate. Continuous data were compared using an independent Student's *t* test or the Mann–Whitney *U* test. Categorical variables were compared by χ^2 test or Fisher's exact test. Multiple comparisons were performed by using Kruskal–Wallis test with Dunn's *post hoc* test. Correlations were evaluated by the Spearman's correlation coefficient (r_s). The univariate analysis accounted for the correlation existing between demographic/clinical data, body composition parameters, and Frailty Index. Multivariate linear regression analysis was then used to identify the independent factors related to frailty phenotype. Of note, we selected to examine skeletal muscle metrics as continuums without dichotomization to better understand the association with frailty.[5] This approach enables a more thorough understanding of the relationship of skeletal muscle measures without making erroneous assumptions with respect to cutoff points. We set statistical significance at $p < 0.05$. All statistical analyses were carried out using SPSS 21.0 (IBM, New York, NY, USA) or Graphpad Prism 8.0.1 (La Jolla, CA, USA).

Results

Patients' characteristics

The baseline demographic and laboratory data are presented in Table 1. A total of 202 patients (male: $n = 98$, 48.5%) with a median age of 63 years (IQR, 55–68) were recruited to the study. The primary etiology of cirrhosis was hepatitis B virus/hepatitis C virus in 21.8%, alcoholism/non-alcoholic fatty liver disease in 25.2%, and autoimmune liver disease in 20.8%. The median model for end-stage liver disease (MELD) score upon admission was 10 points (IQR, 8–13). Seventy-seven patients were classified as Child–Turcotte–Pugh (CTP)-A, 108 as CTP-B and 17 as CTP-C.

The median Frailty Index was 0.13 (IQR, 0.06–0.30). Thirty-five (17.3%) subjects were classified as frail. The distribution of frailty was even between male and female patients (16.3% *versus* 18.3%, $p = 0.853$). The median SMI was $44.2\,cm^2/m^2$, and 30.2% of patients showed sarcopenia according to our proposed criteria. On the contrary, 69.8% (141/202) of patients were diagnosed as non-sarcopenia. The median IMAC was −0.50, and 18.8% of recruited patients (38/202) exhibited myosteatosis. In contrast, 81.2% (164/202) of subjects were categorized into the non-myosteatosis group.

Overlap between sarcopenia, myosteatosis, and frailty phenotype

Relationships between sarcopenia, myosteatosis, and frailty overall and separately for male and female are detailed in Figure 1 and Supplemental Figure S2. In the entire cohort, 16 (7.9%) met the criteria for both sarcopenia and frailty, and 13 (6.4%) met the criteria for both myosteatosis and frailty. In male patients, among the 16 patients who were frail, 68.8% also had sarcopenia and 62.5% had myosteatosis. In female patients, among the 19 patients who were frail, 26.3% also had sarcopenia and 15.8% had myosteatosis.

Cross-sectional association between sarcopenia and domains of the Frailty Index

Given that the depiction of frailty is multifaceted, we further performed secondary analyses about the association between sarcopenia and multiple components of the Frailty Index in the entire

Table 1. Baseline characteristics of the entire cohort, categorized by sex and multi-dimensional frailty phenotype.

	All *N* = 202	Male *n* = 98			Female *n* = 104		
		Frailty[$] *n* = 16	Not frailty *n* = 82	*p*	Frailty[$] *n* = 19	Not frailty *n* = 85	*p*
Age, years	63 (55, 68)	67 (62, 76)	58 (52, 66)	0.004	69 (63, 74)	63 (57, 68)	0.077
BMI[#], kg/m^2	23.7 (20.7, 26.5)	24.7 (18.8, 26.7)	24.5 (22.5, 27.7)	0.484	21.5 (19.7, 23.9)	22.9 (19.8, 25.4)	0.418
VATI, cm^2/m^2	46.0 (29.4, 67.0)	52.4 (52.5, 64.9)	49.7 (33.2, 71.4)	0.743	31.6 (25.6, 61.7)	41.8 (25.8, 64.6)	0.739
SMI, cm^2/m^2	44.2 (38.7, 50.8)	42.6 (30.8, 49.9)	48.4 (42.6, 55.8)	0.042	42.6 (36.7, 49.4)	40.1 (35.9, 45.6)	0.176
Sarcopenia[$] (%)							
Yes	61 (30.2)	11 (68.8)	29 (35.4)	0.024	5 (26.3)	16 (18.8)	0.529
No	141 (69.8)	5 (31.3)	53 (64.6)		14 (73.7)	69 (81.2)	
IMAC	−0.50 (−0.61, −0.42)	−0.42 (−0.57, −0.38)	−0.53 (−0.64, −0.45)	0.010	−0.48 (−0.61, −0.39)	−0.5 (−0.60, −0.40)	0.512
Myosteatosis[$] (%)							
Yes	38 (18.8)	10 (62.5)	13 (15.8)	0.001	3 (15.8)	12 (14.1)	0.546
No	164 (81.2)	6 (37.5)	69 (84.2)		16 (84.2)	73 (85.9)	
MELD score	10.0 (8.0, 13.0)	11.6 (8.0, 14.7)	9.1 (6.8, 12.0)	0.207	13.0 (10.0, 17.0)	10.0 (8.0, 12.0)	0.011
Albumin, g/l	28 (25, 33)	26 (22, 28)	29 (25, 34)	0.029	26 (20, 31)	29 (25, 33)	0.115
INR	1.26 (1.17, 1.44)	1.35 (1.30, 1.52)	1.29 (1.20, 1.43)	0.167	1.27 (1.13, 1.44)	1.21 (1.11, 1.39)	0.578
Total bilirubin, μmol/l	21.6 (14.6, 41.7)	32.2 (19.8, 52.3)	19.5 (13.8, 43.3)	0.059	30 (21.9, 57.7)	20.6 (13.8, 37.2)	0.041
Creatinine, μmol/l	59 (51, 77)	83 (61, 105)	66 (57, 80)	0.094	62 (52, 102)	52 (43, 59)	0.058
Sodium, mmol/l	140 (137, 142)	134 (129, 139)	140 (138, 142)	<0.001	139 (136, 142)	140 (137, 142.5)	0.903
ALT, U/l	24.0 (15.8, 37.0)	18 (13, 21)	26 (17, 44)	0.020	17 (13, 27)	25 (17.5, 37)	0.161
ALP, U/l	89.5 (67.8, 127.5)	87.5 (65.8, 109.7)	83 (65.6, 115.8)	0.659	105.7 (72, 158)	100 (68, 141)	0.755
Frailty Index	0.13 (0.06, 0.30)	0.46 (0.44, 0.51)	0.08 (0.04, 0.17)	<0.001	0.49 (0.42, 0.53)	0.11 (0.04, 0.20)	<0.001

(Continued)

Table 1. (Continued)

	All *N* = 202	Male *n* = 98			Female *n* = 104		
		Frailty[$] *n* = 16	Not frailty *n* = 82	*p*	Frailty[$] *n* = 19	Not frailty *n* = 85	*p*
CTP (%)							
A	77 (38.1)	4 (35.0)	35 (42.7)	0.329	4 (21.1)	34 (40.0)	0.004
B	108 (53.5)	9 (56.3)	39 (47.6)		11 (57.9)	49 (57.6)	
C	17 (8.4)	3 (18.8)	8 (9.8)		4 (21.1)	2 (2.4)	
Etiology (%)							
HBV/HCV	44 (21.8)	3 (18.8)	25 (30.5)	0.337	1 (5.3)	15 (17.6)	0.230
Alcohol	51 (25.2)	6 (37.5)	34 (41.5)		1 (10.5)	10 (11.8)	
AILD	42 (20.8)	3 (18.8)	5 (6.1)		9 (47.4)	25 (29.4)	
Biliary	10 (5.0)	0 (0)	0 (0)		0 (0)	10 (11.8)	
Other	55 (27.2)	4 (25.0)	18 (22.0)		8 (42.1)	25 (29.4)	
Ascites (%)							
Yes	110 (54.5)	14 (87.5)	39 (47.6)	0.005	16 (84.2)	41 (48.2)	0.005
No	92 (45.5)	2 (12.5)	43 (52.4)		3 (15.8)	44 (51.8)	

Data are expressed as median (interquartile range), simple frequency or proportion (%). *p* values are derived from the Mann–Whitney *U* test or Fisher's exact test.
[$]We defined the Frailty Index thus: less than 0.07 as robust, 0.07–0.38 as pre-frail, and more than 0.38 as frail. Sarcopenia was defined as a SMI $< 46.96\,cm^2/m^2$ for male and SMI $< 32.46\,cm^2/m^2$ for female. Myosteatosis was defined as an IMAC > -0.44 in male and > -0.37 in female.
#Dry weight was implemented for calculating BMI. The dry weight was determined by subtracting 5% for mild ascites, 10% for moderate ascites, and 15% for bulky ascites for patients with ascites and edema, and 5% of body weight was subtracted for patients with peripheral edema.
AILD, auto-immune liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; CTP, Child–Turcotte–Pugh class; HBV, hepatitis B virus; HCV, hepatitis C virus; IMAC, intramuscular adipose tissue content; INR, international normalized ratio; MELD, model for end-stage liver disease; SMI, skeletal muscle index; VATI, visceral adipose tissue index.

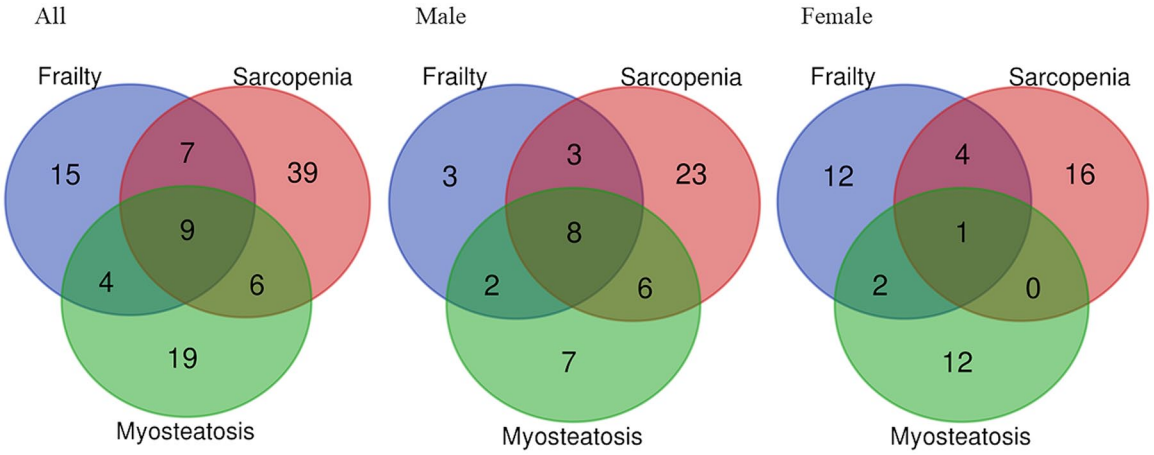

Figure 1. Venn diagram illustrating the overlap between sarcopenia, myosteatosis, and multi-dimensional frailty (absolute number of each subset).

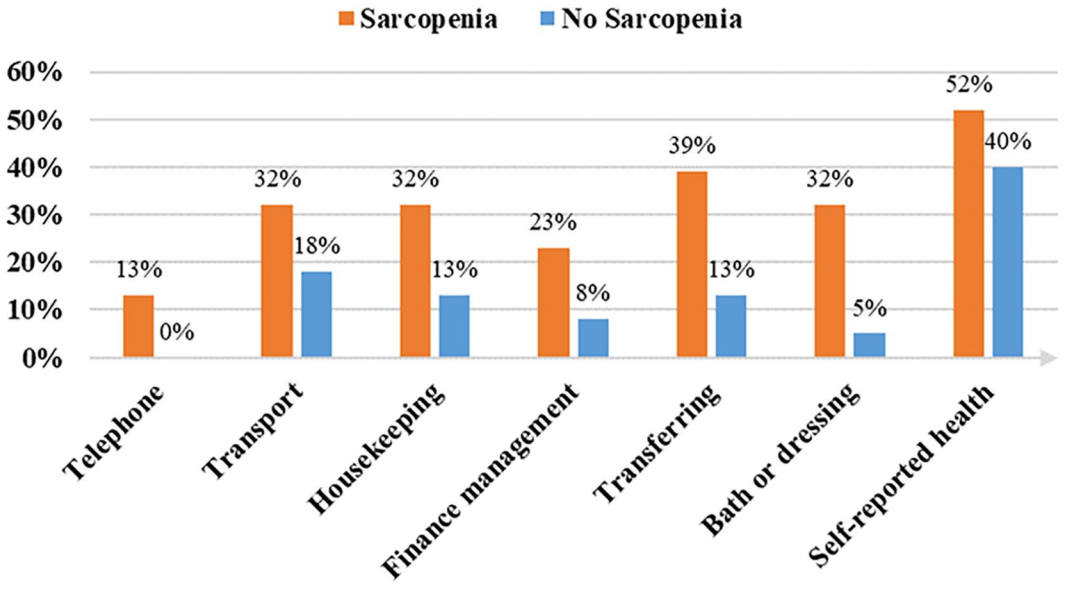

Figure 2. Comparisons of cirrhotic patients with some domains of the Frailty Index by the presence of sarcopenia ($p < 0.05$).
χ^2 test or Fisher's exact test were performed as appropriate.

cohort. Our results indicated that the proportions of sarcopenic patients are significantly higher ($p < 0.05$) across several components of the Frailty Index such as telephone, transport, housekeeping, finance management, and self-reported health (Figure 2 and Supplemental Figure S3).

Pairwise correlations between SMI, IMAC, and the Frailty Index

In the entire population, we observed no correlation between SMI and Frailty Index with a borderline significance ($r_s = -0.136$, $p = 0.053$) [Figure 3(a) to (c)]. When stratified by sex, a slightly inverse correlation was present between decreased SMI and high Frailty Index in male patients ($r_s = -0.280$, $p = 0.005$) but not female ($r_s = 0.042$, $p = 0.675$). Similarly, no significant correlation was found between IMAC and Frailty Index in all patients ($r_s = 0.183$, $p = 0.009$) [Figure 3(d) to (f)]. In contrast, a positive correlation was present between increased IMAC and high Frailty Index in male patients ($r_s = 0.238$, $p = 0.018$) but not female ($r_s = 0.123$, $p = 0.213$).

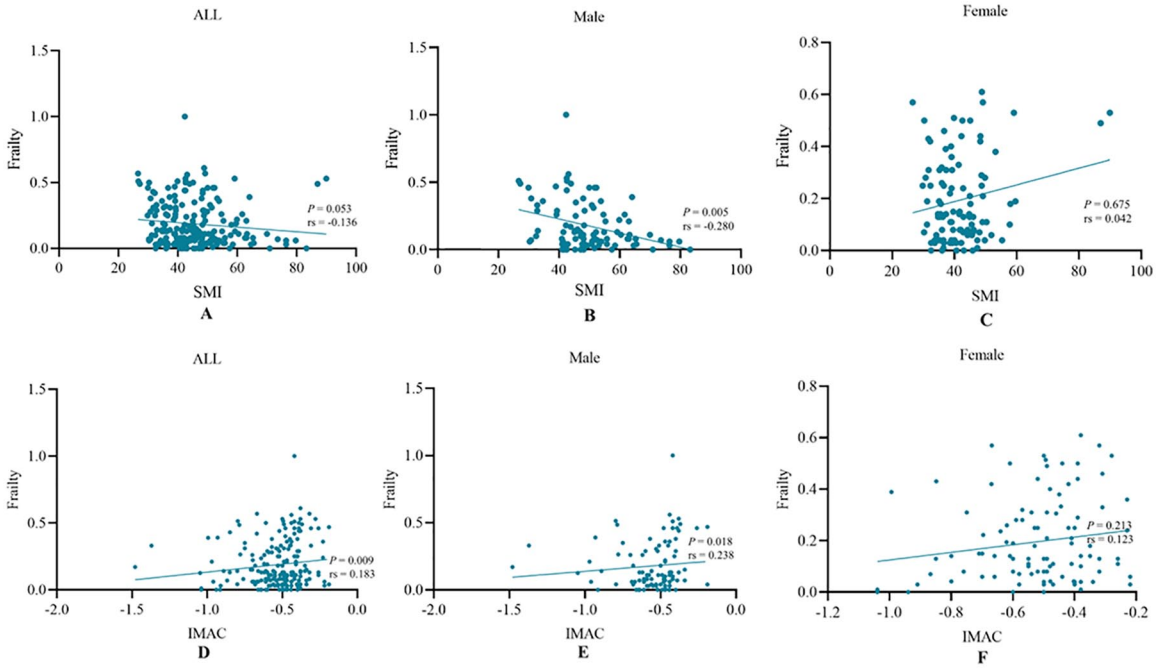

Figure 3. Correlation between the Frailty Index, SMI, and IMAC in the entire cohort [(a) and (d)], male patients with cirrhosis [(b) and (e)] and female patients with cirrhosis [(c) and (f)]. Spearman's rank correlation coefficients were indicated (r_s).
SMI, skeletal muscle index; IMAC, intramuscular adipose tissue content.

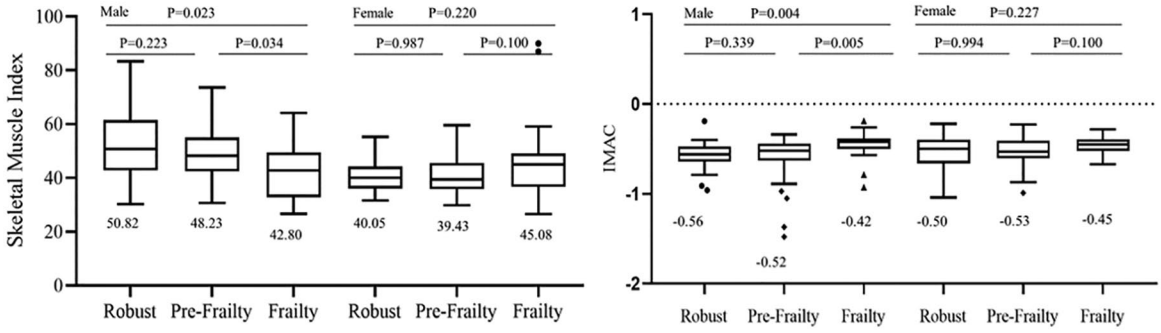

Figure 4. Comparison of the skeletal muscle index and IMAC by frailty status and sex.
Multiple comparisons were performed by using Kruskal–Wallis test with Dunn's *post hoc* test.
IMAC, intramuscular adipose tissue content.

Comparison of SMI/IMAC between robust, pre-frailty, and frailty patients

In male patients, subjects with frailty had a significantly lower median SMI [42.80 cm^2/m^2 (IQR, 32.8–49.5)] compared with those with pre-frailty [48.23 cm^2/m^2 (IQR, 42.4–55.1)] and with robust phenotype [50.82 cm^2/m^2 (IQR, 42.8, 61.6); $p = 0.023$] (Figure 4). Furthermore, male cirrhotics with frailty also represented a significantly higher median IMAC [−0.42 (IQR, −0.50, −0.38)] in comparison with those with pre-frailty [−0.52 (IQR, −0.63, −0.44)] and with robust phenotype [−0.56 (IQR, −0.64, −0.48); $p = 0.004$]. However, no difference regarding SMI or IMAC was found in female patients with cirrhosis.

Sex-stratified comparison of sarcopenia, myosteatosis, and biochemical tests between frail and non-frail patients

In male patients, frail subjects were more likely to be older (67 *vs.* 58 years, $p = 0.004$) in comparison with non-frail counterparts. Frail patients had

Table 2. Univariate and multivariate linear regression for Frailty Index in male patients with cirrhosis.

Variables	Univariate analysis			Multivariate analysis		
	β	95% CI	*p*	β	95% CI	*p*
Age, years	0.436	(0.254, 0.619)	<0.001	0.330	(0.159, 0.500)	<0.001
SMI, cm^2/m^2	−0.335	(−0.526, −0.144)	0.001	−0.260	(−0.428, −0.092)	0.003
IMAC	0.120	(−0.081, 0.321)	0.239			
Albumin, g/l	−0.319	(−0.511, −0.127)	0.001	−0.245	(−0.413, −0.077)	0.005
ALT, U/l	−0.229	(−0.426, −0.032)	0.023			
Creatinine, μmol/l	0.167	(−0.032, 0.367)	0.099			
Sodium, mmol/l	−0.282	(−0.476, −0.088)	0.005	−0.179	(−0.347, −0.011)	0.037
Ascites, yes or no	0.258	(0.062, 0.454)	0.010			

β indicates standardized coefficient of univariate and multivariate linear regression.
ALT, alanine aminotransferase; CI, confidence interval; IMAC, intramuscular adipose tissue content; SMI, skeletal muscle index.

lower albumin (26 *vs.* 29 g/l, $p = 0.029$) and lower serum sodium (134 *vs.*140 mmol/l, $p < 0.001$). Frail patients had higher incidence of sarcopenia (68.8 *vs.* 35.4%, $p = 0.024$) and myosteatosis (62.5 *vs.* 15.8%, $p = 0.001$). Correspondingly, frail patients exhibited lower SMI (42.6 *vs.* 48.4 cm^2/m^2, $p = 0.042$) and higher IMAC value (−0.42 *vs.* −0.53, $p = 0.010$). However, there was no significant difference in body mass index (BMI), MELD, CTP, and etiology.

In female patients, frail subjects had higher median MELD (13 *vs.* 10, $p = 0.011$) and were more likely categorized as CTP-B and C ($p = 0.004$). However, patients with frailty and without frailty had similar age, BMI, and etiology. Of note, there was no significant difference with respect to SMI/IMAC values or incidence of sarcopenia/myosteatosis.

Relationship between sarcopenia, myosteatosis, and the Frailty Index in male

In male patients, our univariate linear regression analysis implicated that age (β coefficient = 0.436, $p < 0.001$), SMI (β = −0.335, $p = 0.001$), albumin (β = −0.319, $p = 0.001$), alanine aminotransferase (β = −0.229, $p = 0.023$), and sodium (β = −0.282, $p = 0.005$) were factors associated with the Frailty Index (Table 2). Further multivariate linear regression showed that age (β = 0.330, $p < 0.001$), SMI (β = −0.260, $p = 0.003$), albumin (β = −0.245, $p = 0.005$) and sodium (β = −0.179, $p = 0.037$) were independent risk factors for frailty phenotype as determined by the Frailty Index.

Discussion

In this cohort of 202 cirrhotic patients, we showed an estimated prevalence of frailty in 17.3% subjects, which is comparable to previous reports citing rates of 17–19%.[7,23,24] Intriguingly, we found that significant relationships between SMI (indicator of sarcopenia)/IMAC (indicator of myosteatosis) and frailty phenotype were exclusively expressed in male patients with cirrhosis. Subsequent multiple regression analysis implicated a strong association between sarcopenia and frailty among males. Approximately 70% of frail male subjects exhibited concomitant muscle wasting, whilst this proportion was only 26.3% in female. These findings substantially unravel varying impacts of sarcopenia on multi-dimensional frailty in the context of sex difference, raising awareness of sex-specific therapeutic intervention in the clinical practice.

Mounting evidence has addressed that both sarcopenia and frailty are associated with a gamut of adverse outcomes in hepatic and extra-hepatic diseases.[25–28] Studies also intended to delineate the relationship between sarcopenia and frailty in various pathological conditions and, if possible,

causative effect. Souza *et al.*[29] found that frailty was associated with myosteatosis in a setting of 184 obese patients with colorectal cancer. In patients with hepatocellular carcinoma, frailty/pre-frailty was an independent predictor for muscle atrophy and Liver Frailty Index was inversely correlated with SMI.[30] Although sarcopenia is linked with frailty, Bhanji *et al.*[31] demonstrated that these entities occur with differing prevalence as well as distinct impacts on outcomes in wait-listed patients. Notably, a pioneer work conducted by Fozoun *et al.*[7] intended to quantify the contribution of sarcopenia to the frail phenotype, and highlight the importance of sex-stratified analysis. Moreover, the authors demonstrated that it is imperative to verify their observations in hospitalized cirrhotics and to take consideration of perspectives of frailty other than physical construct. Therefore, these concerns arouse scientific endeavor for performing in-depth analyses in our study cohort. Intriguingly, our results indicated that sarcopenic patients are more prevalent across several components of the Frailty Index, including instrumental activities of daily living, physical function, and self-reported health. We believe this finding is reasonable and informative, since mounting data have confirmed that sarcopenia is closely associated with disability, functional decline, and poor physical performance in geriatrics and hepatology medical fields.[32–34]

Congruent with prior work, our results implicated a sex disparity with respect to relationship between sarcopenia and frailty.[7] An open question remains of why the observed alterations were more profound in male. Actually, frailty patients are always having endocrine changes, such as reduced concentrations of testosterone.[12] It has been suggested that testosterone significantly decreases in the cirrhotic male.[35] On the other hand, accumulating data have indicated sex-specific differences in muscle homeostasis. Correspondingly, androgens might represent dominant sex steroids regulating muscle homeostasis in male.[36] Low testosterone levels are evidenced to elicit a decrease in muscle mass and strength in male.[37,38] Collectively, hormonal difference between sexes might partially explain the predisposition of sarcopenic male with cirrhosis to frailty phenotype.

How might sarcopenia result in a self-reported frailty phenotype in terms of the Frailty Index, which embraces cognitive, social, as well as emotional aspects? We offer a probable mechanism underlying this pathway. A hospitalized patient with cirrhosis is always prone to chronic inflammation and malnutrition status.[39] Inflammation is proved as a potential contributor to frailty directly by affecting muscle protein synthesis and degradation, and indirectly by influencing important metabolic pathways.[40,41] As a matter of fact, the original report using CFI (where our Frailty Index comes from) showed a significant positive correlation between CFI and neutrophil-to-lymphocyte ratio (NLR) ($r_s = 0.22$, $p = 0.025$).[42] In particular, our group clarified that high NLR was positively correlated with the expression of IL-6 ($r_s = 0.39$, $p < 0.001$) and IL-8 ($r_s = 0.35$, $p < 0.001$) in cirrhotics.[43] Notably, malnutrition is another common complication of cirrhosis characterized by reduced muscle/adipose quantity, increased pro-inflammatory cytokines, and anorexia.[35] This entity could be reversed with nutrition supplementation, slowing its progression towards sarcopenia.[44] The overlap between frailty and malnutrition comprises reduced physical and cognitive function, and association with impaired clinical outcomes.[45] Taken together, the common mechanism underpinning the occurrence and development of two linked entities known as sarcopenia and frailty might partially be responsible for our discoveries.

We acknowledge the following limitations to our study. First, due to the nature of an observational study, we just demonstrate an association between sarcopenia and frailty phenotype in male cirrhotics. In other words, it is undetermined whether alterations in muscle compartment are a cause, an aggravating factor, a consequence of the ongoing pathology, or an epiphenomenon reflecting the general poor condition of patients with cirrhosis.[46] Second, we were unable to screen/assess nutrition status, sex steroid, and cytokines in the enrolled cohort, thus the potential role of these factors remains speculative. Third, we were lacking internal validation with respect to the proposed Frailty Index for generalizability in other populations. Further multi-center investigations are warranted to validate our findings. However, this single-center index appears to be a pivotal step to conceptual construct and clinical implication of multi-dimensional frailty in daily practice. Last, we excluded patients with severe hepatic encephalopathy, which might give rise to selection bias. However, taking account of limited applicability of physical metrics among inpatients and cognitive frailty likely prognosticating the prognosis in

cirrhosis,[47,48] it is suitable for us to employ a broadened conceptual frailty phenotype.

Despite these limitations, this study is the first to highlight the close relationship between sarcopenia and multi-dimensional frailty in hospitalized cirrhosis. Our estimation of frailty phenotype derives from a well-validated self-reported Frailty Index for predicting all-cause mortality. Furthermore, the sex distribution is even in the cohort, which facilitates fully sex-stratified analyses. In conclusion, our findings implicate that sarcopenia is strongly associated with multi-dimensional frailty among male cirrhotic inpatients. It is tempting to incorporate sex-specific treatment with the purpose of mitigating frailty.

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Author contributions

H.-J.F., X.-Y.W., L.-H.M. and C.S. designed the study, analyzed the data, and prepared the original draft. Z.-H.Y., B.-X.C. and L.L. conducted the study and edited the manuscript. Y.-Y.H., X.-L.Z., X.X. and X.-F.F. analyzed the data and reviewed the manuscript. B.-M.W. collected the data and conducted statistical analysis. Q.-X.Y., K.J. and C.S. designed and monitored the study and made critical revisions of the manuscript. All authors have approved the final draft submitted.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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