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Original Article

Dissecting the Contributing Role of Divergent Adipose Tissue to Multidimensional Frailty in Cirrhosis

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Abstract

Background and Aims: Emerging evidence has demonstrated that abnormal body composition may potentiate the development of frailty, whereas little work focuses on the role of divergent adipose tissue. Therefore, we aimed to determine the potential contribution of adipose tissue distribution to multidimensional frailty in decompensated cirrhosis. ***Methods:*** We conducted a retrospective cohort study. Divergent adipose tissues were assessed by computed tomography-derived subcutaneous adipose tissue index (SATI), visceral adipose tissue index (VATI) and total adipose tissue index (TATI), respectively. Frailty was identified by our validated self-reported Frailty Index. Multiple binary logistic models incorporating different covariates were established to assess the relationship between adipose tissue distribution and frailty. ***Results:*** The study cohort comprised 245 cirrhotic patients with 45.3% being male. The median Frailty Index, body mass index (BMI) and model for end-stage liver disease (MELD) score were 0.11, 24.3 kg/m^2 and 8.9 points, respectively. In both men and women, patients who were frail exhibited lower levels of SATI in comparison with nonfrail patients. SATI inversely correlated with Frailty Index in the entire cohort (r_s=−0.1361, p=0.0332). Furthermore, SATI or TATI was independently associated with frail phenotype in several multiple logistic regression models adjusting for age, BMI, presence of ascites, sodium, Child-Pugh class or MELD score in isolation. ***Conclusions:*** In the context of decompensated cirrhosis, low SATI and concomitant TATI were associated with higher risk of being frail. These findings highlight the importance to further apply tissue-specific tools of body composition in place of crude metric like BMI.

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Introduction

In the field of hepatology or liver transplantation, the conceptual frame of frailty mainly concentrates on physical frailty because it is measured in ambulatory and transplant settings.[1] For instance, Lai and colleagues developed a feasible and reliable liver frailty index metric based on performance, including handgrip strength, chair stands, and balance, and successfully linked it to various adverse outcomes.[2–4] However, a major limitation of these performance-based metrics is the need of active patient participation during the testing process, which is not applicable in acutely ill and severely decompensated cirrhotics who are hospitalized.[5] As a matter of fact, the original definition of frailty in the geriatrics indicates a distinct syndrome pertaining to decreased physiological reserve and increased vulnerability to health stressors.[6] Multidimensional frailty arises from multiple derangements of one or combined physiological systems including endocrine, musculoskeletal, neurological, cardiovascular, and immune systems. Recently, our research team has revised and obtained an Frailty Index that includes global frail components and we validated the clinical utility of this self-reported scale for prognostication in the context of cirrhosis.[7,8] Despite a consistent relationship between both physical and multidimensional frailty and adverse outcomes across populations, gaps remain in identifying risk factors for the development of frailty in advanced chronic liver diseases. It is pivotal to identify risk factors for frailty with the purpose of delineating its pathobiology as well as introducing novel preventive and therapeutic targets.

Unlike sarcopenia, the clinical relevance of adipose tissue has not been well recognized in patients with cirrhosis. Rodrigues *et al.* found that adipopenia, or a low total adipose tissue index (TATI), was associated with decompensation

Keywords: Frailty; Adipose tissue; Liver cirrhosis; Subcutaneous adipose tissue index.

Abbreviations: AILD, auto-immune liver disease; BMI, body mass index; CI, confidence interval; CT, computed tomography; HU, Hounsfield unit; INR, international normalized ratio; IQR, interquartile range; L3, third lumbar vertebra; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; TATI, total adipose tissue index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

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in patients with cirrhosis.[9] Furthermore, low subcutaneous adipose tissue index (SATI) was shown to be independently associated with increased mortality in female cirrhotic patients,[10] but no relationship was observed between visceral adipose tissue index (VATI) and waitlist mortality in subjects evaluated for liver transplantation.[11] Notably, subcutaneous and visceral adipose tissue, two divergent types of adipose tissue, vary remarkably in anatomical location, adipocyte size, lipolytic ability, insulin sensitivity, and adipokine secretion.[12] Intriguingly, Anderson *et al*. found a nonlinear relationship between VAT and frailty in adult lung transplant candidates.[13] On the other hand, computed tomography (CT)-based SAT at the third lumbar vertebra (L3) and body mass index (BMI) were significantly lower in frail men compared with prefrailty in elderly pelvic trauma patients.[14] However, the association between adipose tissue distribution and frailty in patients with cirrhosis is unclear. Taken together, we sought to determine the relationship between multidimensional frailty and a diverse panel of measures of body composition, including BMI, waist circumference, skeletal muscle index (SMI), SATI, VATI, TATI, and visceral to subcutaneous adipose tissue area ratio (VSR) in patients with decompensated cirrhosis.

Methods

Study cohort

This retrospective cohort study was approved by the ethnic committee of Tianjin Medical University General Hospital (TJMUGH, IRB2021-YX-136-01) and conducted following the ethical guidelines of the Declaration of Helsinki. We consecutively recruited adult patients diagnosed with cirrhosis by their medical records, biochemical data, radiological findings, or histological results in our department between 2017 and 2021. The following exclusion criteria were adopted: (1) primary hepatocellular carcinoma or extrahepatic malignancies; (2) acute-on-chronic liver failure during hospitalization; (3) severe hepatic encephalopathy precluding finishing Frailty Index questionnaire; (4) liver transplantation, and (5) denial of regular follow-up. A total of 245 patients with decompensated cirrhosis was included in the analysis (Fig. S1). The baseline patient characteristics such as demographics (age, sex), Child-Pugh class, model for end-stage liver disease (MELD) score, laboratory parameters, etiology, anthropometry (weight and height) were retrieved from our hospital's electronic database. BMI values were estimated on the basis of dry weight as has been previously described, taking into consideration the fluid retention that occurs in a large percentage of cirrhotics.[15,16]

CT evaluation of body composition

We collected imaging biomarkers of body composition including SMI and several adipose tissues (subcutaneous SAT and visceral VAT). The parameters were measured by analyzing CT images at the L3 level using a noncommercial software based on Matlab version R2010a (Mathworks Inc., Natick, MA, USA). The cross-sectional area of SAT/VAT and skeletal muscles was reported as square meters (m^2). Tissue-specific Hounsfield unit (HU) thresholds were applied to discriminate divergent tissue types. The CT thresholds were −190 to −30 for SAT, −150 to −50 for VAT and −29 to 150 HU for quantifying skeletal muscles.[9,17,18] All values were normalized to height in m^2 and used to calculated indexes such as SMI, SATI, VATI and TATI (cm^2/m^2). Visceral adiposity was assessed by VSR. All abdominal CT scans were performed within 3 months prior to hospitalization.

Frailty Index evaluation

We have previously described the use of our Frailty Index.[7] In brief, this self-reported scale derives from the Carolina Frailty Index with minor modification. The Frailty Index comprises 36 variables including unintentional weight loss, exhaustion, instrumental activities of daily living, physical function, and social activities, etc. A valid questionnaire contained at least 10 fulfilled issues. For instance, a patient would have a score of 0.33 after getting 12 points in the case of finishing all 36 issues (12/36). We regarded patients with an Frailty Index of >0.38 as frail phenotype. All Frailty Index questionnaires were collected within 48 h of the first admission to our department.

Statistical analysis

Continuous variables were reported as medians and interquartile range (IQR) and compared by the Mann–Whitney *U* test. For categorical variables, descriptive data were reported as frequency or proportion (%) and compared by χ^2 or Fisher's exact test. Correlations between body composition biomarkers and the Frailty Index were determined by the Spearman's rank correlation coefficient (r_s). Multivariate logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for each measure of body composition with distinct levels of frailty as the outcome (that is, frailty and nonfrailty). The covariates that we used in the multivariate analysis were chosen on the basis of statistically significant univariate association with frail status and previously established scientific knowledge. We examined all body composition metrics as continuums without dichotomization to better understand the association with frailty. To avoid overfitting and maximize statistical power, we made four multiple regression models incorporating Child-Pugh class or MELD score. A p-value < 0.05 was considered statistically significant. The statistical analysis was performed with SPSS 23.0 (IBM Corp., Armonk, New York, NY, USA) or Graphpad Prism 8.0.1 (La Jolla, CA, USA).

Results

Of the 245 patients with cirrhosis included in the study, 111 were men with an average age of 63 (IQR: 57, 69) years (Table 1). In the entire cohort, the median Frailty Index, BMI, and MELD score were 0.11 (IQR: 0.06, 0.24), 24.3 (IQR: 21.3, 27.3) kg/m^2 and 8.9 (IQR: 6.5, 11.7) points, respectively. Frail patients had lower levels of BMI and albumin, higher levels of total bilirubin and creatinine, and greater proportions of Child-Pugh class B and C and ascites. Regarding body composition, SATI, and TATI were lower in patients with cirrhosis and frailty, and no significant differences in VSR or VATI were observed.

Taking into consideration sex-differences in the distribution of divergent adipose tissue, women store higher levels of SATI and VATI is higher in men in the context of cirrhosis.[10] These characteristics are shown separately for men and women in Fig. 1. Intriguingly, frail men had lower levels of SATI (33.87 vs. 38.13 cm^2/m^2, p=0.0585) and lower TATI (81.28 vs. 96.19 cm^2/m^2, p=0.0538) that were of borderline statistical significance. In women, lower levels of SATI (35.14 vs. 59.74 cm^2/m^2, p=0.0329) and a trend favoring lower TATI (69.65 vs. 110.00 cm^2/m^2, p=0.0771) were observed in frail compared with nonfrail individuals.

Table 1. Baseline characteristics of the entire cohort, categorized by sex and multidimensional frail phenotype

Characteristic	All (n=245)	All (n=245)			Men (n=111)			Women (n=134)		
		Frailty (n=27)	Nonfrailty (n=218)	*p*	Frailty (n=14)	Nonfrailty (n=97)	*p*	Frailty (n=13)	Nonfrailty (n=121)	*p*
Age, year	63 [57,69]	65 [57,74]	63 [57,68]	0.0708	65 [57,68]	59 [50,67]	0.1541	71 [55,76]	65 [58,69]	0.0804
Height, m	1.65 [1.60,1.70]	1.65 [1.63,1.70]	1.65 [1.60,1.70]	0.2731	1.70 [1.66,1.73]	1.71 [1.65,1.76]	0.5061	1.64 [1.60,1.65]	1.60 [1.57,1.65]	0.0686
Weight, kg	65 [57,75]	60 [54,73]	67 [58,75]	0.0437	67 [55,80]	72 [65,82]	0.1954	58 [48,61]	64 [53,70]	0.0590
BMI, kg/m^2	24.3 [21.3,27.3]	22.3 [18.7,26.0]	24.6 [21.5,27.3]	0.0098	23.7 [19.0,27.4]	24.6 [22.5,27.8]	0.3559	21.3 [18.2,23.4]	24.4 [20.6,27.3]	0.0065
Waist circumference, cm	96.1 [86.8,104.5]	97.0 [89.9,109.5]	96.1 [86.0,104.3]	0.2843	98.4 [91.8, 109.8]	98.3 [89.6,107.4]	0.7167	95.1 [88.1,108.1]	93.7 [83.2,100.3]	0.3354
VSR	0.92 [0.68,1.28]	1.14 [0.71,1.36]	0.91 [0.67,1.28]	0.1586	1.20 [1.07,1.87]	1.13 [0.78,1.70]	0.4153	0.87 [0.69,1.14]	0.78 [0.59,1.00]	0.4206
SMI, cm^2/m^2	45.88 [39.03,52.09]	45.13 [37.17, 50.65]	45.93 [38.05,52.30]	0.5617	45.72 [40.26, 52.72]	49.73 [42.63,55.52]	0.2720	43.58 [36.09,48.56]	42.15 [36.78,48.71]	0.9817
SATI, cm^2/m^2	44.86 [31.79,72.52]	34.70 [26.54, 42.64]	48.69 [32.49,74.27]	0.0027	33.87 [15.57, 38.54]	38.13 [27.46,55.01]	0.0585	35.14 [28.49,66.85]	59.74 [37.41,82.18]	0.0329
VATI, cm^2/m^2	45.67 [29.75,67.04]	41.10 [25.59, 55.26]	47.45 [30.14,68.97]	0.1494	43.41 [30.29, 51.66]	49.84 [32.06,73.10]	0.2417	35.17 [25.05,64.48]	45.25 [29.75,64.63]	0.3626
TATI, cm^2/m^2	97.79 [66.22, 134.10]	77.85 [55.98, 95.81]	102.00 [67.78, 135.40]	0.0107	81.28 [42.01, 87.06]	96.19 [62.72, 125.80]	0.0538	69.65 [56.42, 125.10]	110.00 [69.99, 140.40]	0.0771
Frailty Index	0.11 [0.06,0.24]	0.49 [0.43,0.51]	0.09 [0.06,0.17]	<0.0001	0.49 [0.41,0.51]	0.08 [0.06,0.17]	<0.0001	0.50 [0.44,0.58]	0.10 [0.05,0.18]	<0.0001
MELD score	8.9 [6.5,11.7]	11.7 [9.6,13.2]	8.6 [6.2,11.2]	0.0012	11.7 [8.4,13.2]	8.4 [5.1,10.6]	0.0387	11.7 [10.0,13.7]	8.7 [6.9,11.4]	0.0079
INR	1.28 [1.16,1.45]	1.33 [1.26,1.50]	1.27 [1.15,1.44]	0.0711	1.39 [1.26,1.50]	1.34 [1.20,1.59]	0.7076	1.30 [1.25,1.45]	1.22 [1.12,1.38]	0.0598
Albumin, g/L	[28 25,32]	[25 22,28]	[28 25,32]	0.0016	[25 22,28]	[28 25,33]	0.0090	[25 20,31]	[29 25,32]	0.0554
Total bilirubin, μmol/L	21.5 [14.3,37.5]	33.2 [21.9,54.3]	19.8 [13.9,35.9]	0.0056	32.2 [21.5,55.9]	19.9 [13.3,37.9]	0.0284	31.4 [22.1,53.6]	19.8 [14.2,34.3]	0.0197
Creatinine, μmol/L	58 [47,70]	63 [57,81]	57 [46,69]	0.0178	64 [60,86]	64 [56,75]	0.6653	61 [49,79]	50 [42,59]	0.0267
Sodium, mmol/L	141 [138,142]	139 [136, 142]	141 [138,142]	0.0751	140 [135,142]	141 [138,142]	0.4383	139 [136, 141]	141 [139,142]	0.0885
Child-Pugh class (%)				0.0013			0.0495			0.0021
A	74 (30.2)	2 (7.4)	72 (33.0)		0 (0.0)	30 (30.9)		2 (15.4)	42 (34.7)	
B	131 (53.5)	15 (55.6)	116 (53.2)		10 (71.4)	50 (51.5)		5 (38.5)	66 (54.5)	
C	40 (16.3)	10 (37.0)	30 (13.8)		4 (28.6)	17 (17.5)		6 (46.2)	13 (10.7)	

(continued)

Table 1. *(continued)*

Characteristic	All (n=245)	All (n=245)			Men (n=111)			Women (n=134)		
		Frailty (n=27)	Nonfrailty (n=218)	*p*	Frailty (n=14)	Nonfrailty (n=97)	*p*	Frailty (n=13)	Nonfrailty (n=121)	*p*
Etiology (%)				0.5673			0.7272			0.3686
HBV/HCV	67 (27.3)	4 (14.8)	63 (28.9)		3 (21.4)	26 (26.8)		1 (7.7)	37 (30.6)	
Alcohol	62 (25.3)	7 (25.9)	55 (25.2)		7 (50.0)	53 (54.6)		0 (0.0)	2 (1.7)	
AILD	66 (26.9)	9 (33.3)	57 (26.1)		2 (14.3)	15 (15.5)		7 (53.8)	42 (34.7)	
Biliary	31 (12.7)	2 (7.4)	29 (13.3)		0 (0.0)	2 (2.1)		2 (15.4)	27 (22.3)	
NAFLD/ Cryptogenic	49 (20.0)	6 (22.2)	43 (19.7)		2 (14.3)	16 (16.5)		4 (30.8)	27 (22.3)	
Ascites (%)				<0.0001			0.0078			0.0062
Yes	140 (57.1)	25 (92.6)	115 (52.8)		13 (92.9)	54 (55.7)		12 (92.3)	61 (50.4)	
No	105 (42.9)	2 (7.4)	103 (47.2)		1 (7.1)	43 (44.3)		1 (7.7)	60 (49.6)	

Data are medians (interquartile range) or frequency and proportion (%). *p*-values were derived from the Mann–Whitney U test or Fisher's exact test. AILD, auto-immune liver disease; BMI, body mass index; INR, international normalized ratio; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; TATI, total adipose tissue index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

Correlation between biomarkers of adipose tissue and Frailty Index

In the entire cohort, Frailty Index positively correlated with VSR (r_s=0.1710, p=0.0073) and negatively with SATI (r_s=−0.1361, p=0.0332). When stratified by sex, a correlation was also found regarding VSR both in men (r_s=0.1896, p=0.0463) and women (r_s=0.1777, p=0.0400). No significant correlations were observed between Frailty Index and VATI/TATI across the study cohort (Fig. 2).

Association between frailty and various measures of body composition

Univariate logistic regression demonstrated that age, BMI, SATI, TATI, albumin, sodium, MELD score, Child-Pugh class, and the presence of ascites were risk factors in relation to frailty (Table 2). To avoid redundancy and to maximize statistical power, we planned to establish four multiple logistic models incorporating MELD score or Child-Pugh class in isolation with distinct panels of measures pertaining to adipose tissue distribution. In model 1, adjusting for BMI and sodium, age (OR=1.059, 95% CI: 1.008–1.113; p=0.024), SATI (OR=0.972, 95% CI: 0.950–0.994; p=0.013), MELD score (OR=1.018, 95% CI: 1.014–1.211; p=0.023), and presence of ascites (OR=6.077, 95% CI: 1.340–27.560; p=0.019) were independent risk factors of frailty. In model 2, accounting for BMI and sodium, age (OR=1.066, 95% CI: 1.017–1.118; p=0.008), TATI (OR=0.987, 95% CI: 0.976–0.998; p=0.019) and Child-Pugh class C (OR=10.773, 95% CI: 2.149–53.997; p=0.004) were independent risk factors of frailty. In model 3, adjusting for BMI and sodium, age (OR=1.065, 95% CI: 1.016–1.117; p=0.009), SATI (OR=0.972, 95% CI: 0.952–0.993; p=0.008), and Child-Pugh class C (OR=10.747, 95% CI: 2.132–54.182; p=0.004) were independent risk factors of frailty. In model 4, accounting for BMI and sodium, age (OR=1.059, 95% CI: 1.008–1.113; p=0.023), TATI (OR=0.986, 95% CI: 0.975–0.997; p=0.016), MELD score (OR=1.106, 95% CI: 1.012–1.209; p=0.027), and presence of ascites (OR=6.525, 95% CI: 1.451–29.343; p=0.014) were independent risk factors of frailty.

Discussion

In this study of patients with decompensated cirrhosis, we found a strong relationship between SAT and frailty. Whilst the biomedical literature has mainly concentrated on the association between sarcopenia and frailty, our findings are in line with a smaller body of work reporting an association between abnormal adipose tissue distribution and frailty in a variety of pathological entities.[13,14,19] Of note, patients with either low SATI or concomitant TATI in particular are at increased risk of frailty after controlling for age, conventional predictive scores (Child-Pugh class/MELD score), BMI, and presence of ascites. Although the reasons for negative impact of low SATI are not well known, investigating the mechanisms driving this relationship may help develop strategies to prevent and even treat frailty.

Given the emerging role and clinical relevance of adipose tissue in frailty, the research focus has been identified across different populations. For instance, Hawkins *et al*. showed that older men with or without HIV infection, with higher VAT, higher waist circumference, sarcopenia, and osteoporosis were more likely to be frail.[19] Another study conducted in a cohort of adult lung transplant candidates revealed that both patients with extremely low or high VAT were at increased risk of frailty after adjusting for age, sex,

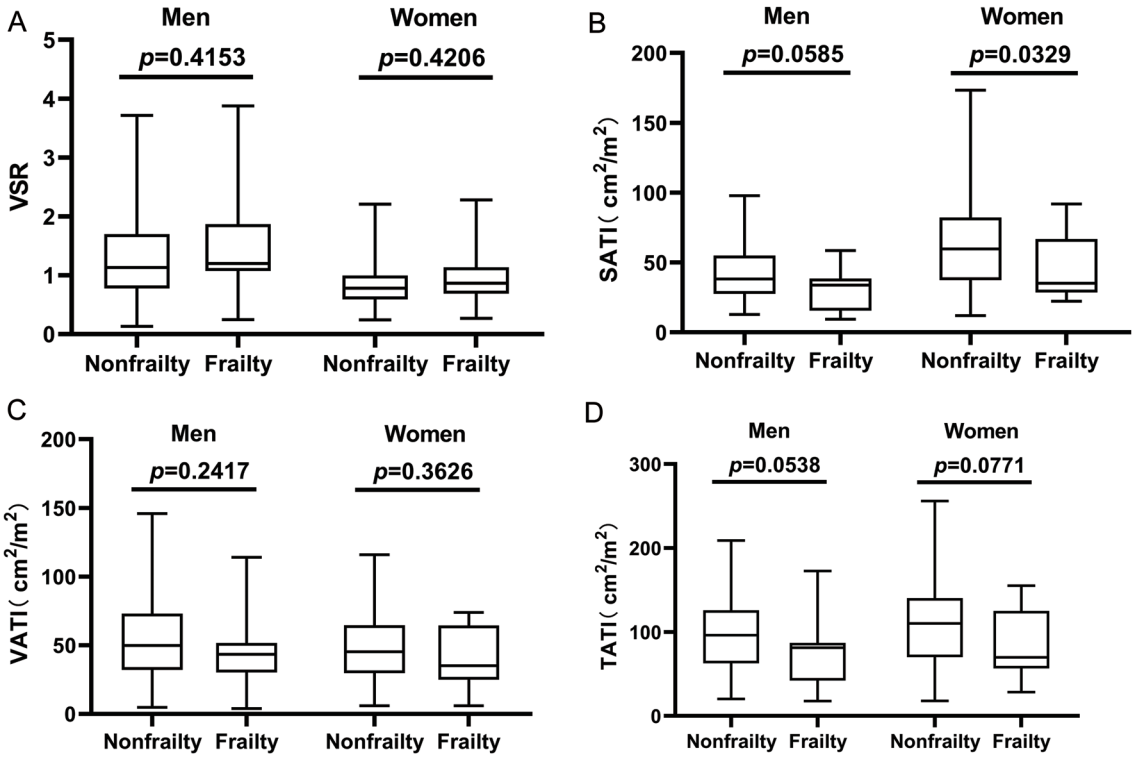

Fig. 1. Comparison of the VSR (A), SATI (B), VATI (C) and TATI (D) by frailty and sex. SATI, subcutaneous adipose tissue index; TATI, total adipose tissue index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

forced vital capacity, BMI, and skeletal muscle mass.[13] Furthermore, Laur and colleagues used CT-derived abdominal body composition at the L3 level to determine their association with a diagnosis of frailty in their institution's pelvic trauma registry.[14] They found that SAT was significantly lower in the frail men compared with prefrail men, which is consistent with our findings.

We and others corroborate that frailty is independent of traditional scoring systems and cirrhosis-associated complications like ascites and hepatic encephalopathy in the prediction of mortality.[7,20] More recently, Wang *et al*. found that frailty serves as an independent predictor of disease progression among patients with compensated and decompensated cirrhosis, all of which implicates that frailty may occur at an earlier stage of cirrhosis.[5] On the other hand, Rodrigues and colleagues addressed that lower TATI (adipopenia) is associated with 12-month decompensation; fat loss may precede sarcopenia development.[9] In addition, the severity of portal hypertension (indicative of hepatic venous pressure gradient) showed significantly inverse correlation with SATI (r=−0.282, p=0.01) and TATI (r=−0.220, p=0.045) but not VATI or SMI. Contextually, our study now adds a small but accumulating body of literature that SAT depletion may instigate the progression of frail phenotype prior to evident muscle depletion in early-decompensated cirrhosis (median MELD score of 8.9 points in our cohort).

Our finding of no relationship between VATI and frailty was unexpected. Actually, VAT is primarily involved in obesity-associated metabolic disturbance.[21] Free fatty acids and adipokines released from VAT are delivered directly to the liver via portal vein, where they lead to inflammation and abnormal lipids deposition.[12,22] As a consequence, high amount of VAT can exacerbate an existing dysregulated metabolic state in patients with cirrhosis, and thus foster frailty. However, in most patients, SAT represents the metabolically more favorable adipose compartment and is the most abundant of total fat tissue.[23] It has been suggested that failure to expand SAT is a major factor potentiating visceral fat accumulation and insulin resistance.[24,25] Moreover, preclinical data suggests that removing subcutaneous fat gives rise to visceral fat accumulation, insulin resistance, and expression of TNF-α.[26] Taken together, further dedicated studies in this field are warranted to validate our findings, that is, low SATI acts as a sign of abnormal adipose tissue distribution.

Our current understanding of the development of frailty is in its infancy and under extensive investigation. As the relationship between low SATI/TATI and frailty appears to be a novel finding in the context of cirrhosis, we are obligated to address several potential mechanisms. First, SAT serves to provide energy in a catabolic state and is responsible for uptake and storage of triglycerides and free fatty acids.[27] Low SATI and concomitant TATI may reflect a state of protein-energy malnutrition and the absence of energy reserves, while malnutrition and frailty have proved to be inter-related in cirrhosis.[28] Second, SAT can result in production of adipokines that regulate lipid metabolism and immune responses.[29] Both adipose tissue dysfunction and chronic systemic inflammation are pathobiological factors described in the frailty literature.[30] Third, Gioia *et al*. found that SAT contributed to handle and reduce ammonia levels, raising its role for ammonia and conversion of glutamate to glutamine by glutamine synthase.[31] Hyperammonemia results in decreased protein synthesis and increased autophagic proteolysis, and consequent sarcopenia is associated with the development of frailty.[32,33] Fourth, the adipose tissue depot is a major organ with microRNA (miRNA), and adipose miRNA profiles corresponding to body composition and functional status and predict adverse clinical outcomes. Chan *et al*. demonstrated that miRNA-130b

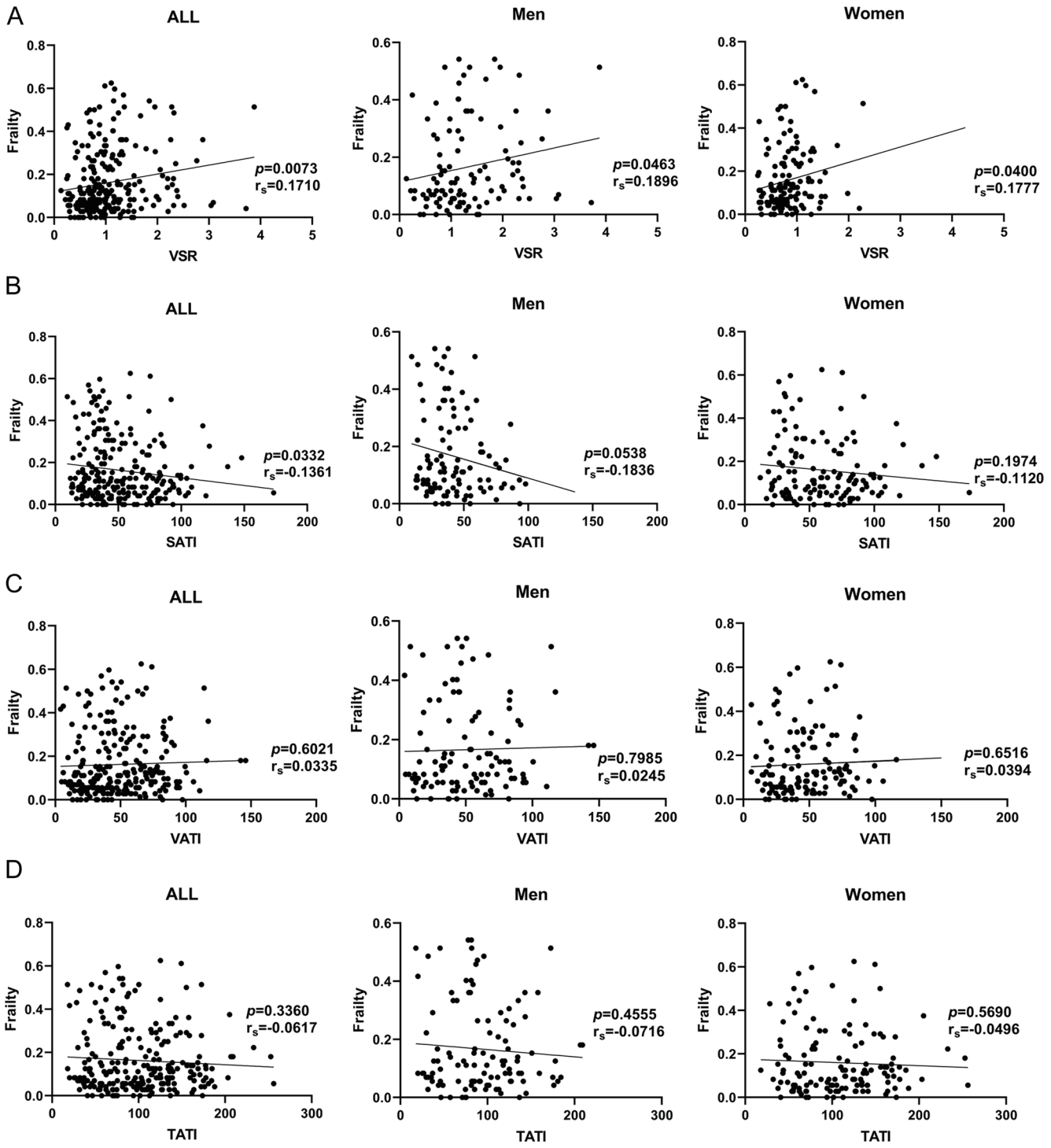

Fig. 2. Correlation between the Frailty Index, VSR (A), SATI (B), VATI (C) and TATI (D) in the entire cohort and subsettings by sex. r_s, Spearman's rank correlation coefficient; SATI, subcutaneous adipose tissue index; TATI, total adipose tissue index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

expression in adipose tissue decreased from nonfrail to severe frailty (1.01-fold vs. 0.32-fold, p=0.031) and predicted frailty independent of age and serum albumin level in patients with advanced chronic kidney disease.[34] It is tempting to conduct in-depth investigations of miRNA perturbation, adipose tissue distribution, and frail phenotype in the context of cirrhosis.

There are several study limitations that should be acknowledged. The first is the study's observational nature, which does not allow determining whether abnormal adi-

Table 2. Univariate and multivariate logistic regression of frailty in patients with cirrhosis

Variable	Univariate analysis		Multivariate analysis							
			Model 1#		Model 2#		Model 3#		Model 4#	
	OR (95%CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex	1.343 [0.630,2.992]	0.470								
Age, years	1.056 [1.008,1.107]	0.022	1.059 [1.008,1.113]	0.024	1.066 [1.017,1.118]	0.008	1.065 [1.016,1.117]	0.009	1.059 [1.008,1.113]	0.023
BMI, kg/m^2	0.879 [0.793,0.973]	0.013								
VSR	1.520 [0.856,2.696]	0.153								
SMI, cm^2/m^2	0.991 [0.955,1.029]	0.649								
SATI, cm^2/m^2	0.971 [0.952,0.991]	0.005	0.972 [0.950,0.994]	0.013			0.972 [0.952,0.993]	0.008		
VATI, cm^2/m^2	0.987 [0.971,1.004]	0.134								
TATI, cm^2/m^2	0.987 [0.977,0.997]	0.012			0.987 [0.976,0.998]	0.019			0.986 [0.975,0.997]	0.016
INR	1.913 [0.477,7.672]	0.360								
Albumin, g/L	0.857 [0.783,0.937]	0.001								
Total bilirubin, μmol/L	1.004 [0.999,1.009]	0.095								
Creatinine, μmol/L	1.007 [0.995,1.019]	0.278								
Sodium, mmol/L	0.886 [0.808,0.971]	0.010								
MELD score	1.102 [1.020,1.189]	0.014	1.018 [1.014,1.211]	0.023					1.106 [1.012,1.209]	0.027
Child-Pugh Class										
A	Ref				Ref		Ref			
B	4.655 [1.034,20.956]	0.045			3.594 [0.780,16.563]	0.101	3.581 [0.776,16.532]	0.102		
C	12.000 [2.480,58.073]	0.002			10.773 [2.149,53.997]	0.004	10.747 [2.132,54.182]	0.004		
Ascites	11.196 [2.588,48.431]	0.001	6.077 [1.340,27.560]	0.019					6.525 [1.451,29.343]	0.014

#Model 1 adjusted for: Age, BMI, SATI, MELD score, ascites, and sodium. #Model 2 adjusted for: Age, BMI, TATI, Child-Pugh class, and sodium. #Model 3 adjusted for: Age, BMI, SATI, Child-Pugh class, and sodium. #Model 4 adjusted for: Age, BMI, TATI, MELD score, ascites, and sodium. BMI, body mass index; INR, international normalized ratio; MELD, model for end-stage liver disease; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; TATI, total adipose tissue index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

pose tissue distribution acts as a cause, a predisposing factor, or a consequence of frailty. Second, the investigation of the Frailty Index was based on single-center data, and is without external validation. It is possible that the relationship between low SATI and frail phenotype may differ from other metrics to evaluate frailty. However, our results are pivotal for instigating additional multicenter studies linking abnormal adipose tissue distribution to the development of frailty. Third, we arbitrarily dichotomized the study population into frailty and nonfrailty in terms of an established cutoff and performed binary logistic regression to identify independent risk factors. While an option determined by clinical availability rather than a limitation, this can partly explain why SMI values as a continuum lost its predictive value for frailty in contrast to sarcopenia. Fourth, ordinary stepwise regression with the purpose of noncausal prediction may incur overstated significance and relatively narrow confidence intervals. Other approaches, such as change-in-estimate strategies with selection of covariates by how much their control changes estimates of exposure effect can be considered.[35] Last, we did not examine nutritional, inflammatory, and metabolic indicators such as leptin, triglycerides, or cholesterol, which are intuitively relevant to abnormal adipose tissue deposition.

In summary, this study is the first to describe a complex and nuanced relationship between divergent adipose tissue and frailty in the context of decompensated cirrhosis, and to suggest that low SATI and concomitant TATI are associated with an increased risk of frailty. The findings highlight the importance of tissue-specific body composition in place of crude metrics like BMI. The novel association between SAT and frailty may assist in delineating the pathobiology of frailty and introducing preventive as well as therapeutic avenue.

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Conflict of interest

CS has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2020. The other authors have no conflict of interests related to this publication.

Author contributions

Involved in the conception or design of the work (LM, CL, XW, CS), literature screen and review (MS, YL, ZY), data acquisition and statistical analysis (BC), analysis and interpretation of data (GG, WY, YH, XF), drafted the article (CS). All authors critically revised the article and approved the version to be published.

Data sharing statement

No additional data are available.

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