Decreased Subcutaneous Adipose Tissue Correlates With Higher Portal Hypertension and Poor Survival in Patients With Cirrhosis: A Retrospective Binary-Center Study

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INTRODUCTION: **The aim of this study was to investigate the impact of hepatic venous portal gradient (HVPG) on body composition (BC) values and the prognostic value of BC value in cirrhotic patients.**

METHODS: **A total of 173 cirrhotic patients with HVPG and computed tomography scan were screened retrospectively from a binary-center database. Seven BC values, including skeletal muscle index, subcutaneous adipose tissue index (SATI), deep SATI (dSATI), superficial SATI (sSATI), visceral adipose tissue index, and ratio of visceral adipose tissue index and SATI along with skeletal muscle radiodensity, were analyzed. The correlation analyses and multiple linear regression were used to assess the impact of HVPG on BC values. The cumulative survival rate was assessed, and risk factors of survival were identified by competing risk analysis using Fine-Gray model.**

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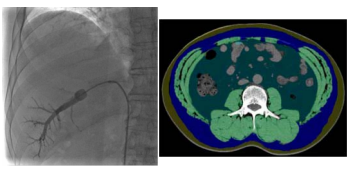
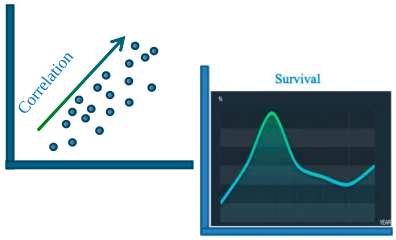
Body composition alternations are prevalently seen in cirrhosis, and their clinical and prognostic values were revealed



Limited data in the literature about whether and the extent to which portal hypertension affect BC values

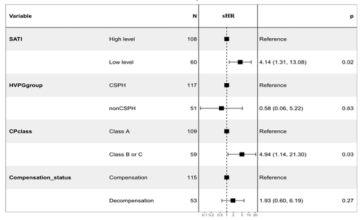
Retrospective reviewing epidemiology, correlation and survival in cirrhotic patients with hepatic venous pressure gradient and CT from 2 institutions



Results

#1 Decreased subcutaneous adipose tissue index(SATI) and its relevant indexes were more closely associated with increased HVPG

#2 A lower SATI and Child-Pugh B or C predicted mortality



This study explores the correlations between BC and HVPG quantitatively and the value of SATI in cirrhotic patients' prognoses. The findings highlight a need of comprehensive view of HVPG supervision beyond complication-centric view in the management of cirrhosis.

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RESULTS: **Among 173 patients with a mean age of 53.7 ± 10.5 years, there were 111 male patients (64.2%) and 62 female patients (35.8%). In male patients, SATI, dSATI, and sSATI inversely correlated with HVPG, respectively (SATI: rho = −0.227; dSATI: rho = −0.229; sSATI: rho = −0.219; all $P < 0.05$), especially in patients aged 60 years or younger or with compensated cirrhosis; male patients with clinically significant portal hypertension had a lower SATI, dSATI, sSATI, and skeletal muscle radiodensity than those without clinically significant portal hypertension. After adjusted multiple linear models, male sex, Child-Pugh class B or C, and elevated HVPG contributed to decreased SATI. Multiple competing survival analysis showed a lower SATI (male: <38 cm²/m²; female: <23 cm²/m²), and Child-Pugh B or C predict mortality.**

DISCUSSION: **Decreased SATI, dSATI, and sSATI were more closely associated with increased HVPG. A lower SATI and Child-Pugh B or C predicted mortality.**

KEYWORDS: portal hypertension; liver cirrhosis; body composition; correlation; prognosis

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B288, http://links.lww.com/CTG/B289

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LIVER

INTRODUCTION

Liver cirrhosis is an advanced stage of chronic liver disease, characterized by impaired liver function and distorted hepatic architecture (1). Cirrhosis and its consequences are major causes of morbidity and mortality globally, with an increasing incidence (2).

Extensive evidence has described the body composition (BC) alternations prevalently seen in cirrhosis and suggesting their clinical and prognostic values (3). Sarcopenia, a progressive and generalized skeletal muscle disorder (4), is considered a common complication of cirrhosis and an important prognostic determinant (5,6), Myosteatosis, defined as anomalous ectopic fatty infiltration within skeletal muscle, is used to reflect muscle quality (7). In addition, subcutaneous and visceral adipose tissue derangements are widely found in cirrhotic patients and are associated with a range of adverse outcomes (8,9). Deep subcutaneous adipose tissue (SAT), a newly investigated area within SAT, has been identified as a promising imaging marker (10).

Portal hypertension (PH) is a major consequence of cirrhosis, leading to severe complications. The hepatic venous pressure gradient (HVPG) is the gold-standard method to estimate severity of PH (11). Various pathophysiological changes of cirrhosis, including hyperdynamic circulation, bacterial translocation, and activation of systemic inflammation, are centered on PH (12). Some common mechanisms, such as inflammation activation, underlie BC alternations (13). BC alternations are subjected to natural course of cirrhosis and associated with poorer liver function and advanced liver cirrhosis (7,14). Therefore, it was hypothesized that the extent of muscle or adipose tissue alternation is associated with severity of PH.

However, there are currently limited data in the literature about whether and the extent to which PH affects BC values. A recent meta-analysis, which included relevant studies reporting the correlation coefficient between HVPG and BC value, indicated an ambiguous conclusion (15). However, it was not an individual patient data meta-analysis and thus lacked necessary data, resulting in a considerable heterogeneity across included studies. Another study by Zeng et al (16) suggested that myosteatosis, rather than sarcopenia, was closely correlated with PH. A major limitation lied in these studies was that the correlation between HVPG and BC values was analyzed within whole HVPG spectrum in the entire cohort, rather than different HVPG intervals after stratification by sex. Considering that BC differs by sex, correlation analysis without sex stratification would lead to inaccurate results. Furthermore, all current results were descriptive rather than quantitative.

In the latest Baveno workshop, consensus recommendations pointed out that other complications of cirrhosis besides variceal hemorrhage are critical unmet needs in the daily management of cirrhosis (11). Therefore, the aim of this study was to investigate the impact of HVPG on BC values by sex using a quantitative approach and to further explore prognostic role of BC values in cirrhotic patients.

METHODS

Study population

This study was performed by retrospective reviewing the clinical and imaging data of patients consecutively enrolled in a prospective study (17).

The institutional review board approved this retrospective stu dy (Ethical registration number is 2024-P2-092–01, and individual informed consent was waived due to its retrospective nature. Consecutive cirrhotic patients who underwent clinically indicated initial HVPG measurements, and computed tomography (CT) scans were collected retrospectively from Third People's Hospital of Taiyuan from 2021 to 2023 and from Beijing Friendship hospital from 2019 to 2020. The indications for HVPG measurement included a diagnosis of cirrhosis, based on histological, radiological, and biochemical criteria and clinical features. Specifically, this encompassed biopsy-proven cirrhosis, endoscopic evidence of esophagogastric varices, and imaging findings suggestive of cirrhosis and/or PH. In addition, for patients with cryptogenic liver disease requiring biopsy, HVPG measurement was performed during transjugular liver biopsy, after the acquisition of informed consent (18).

Inclusion and exclusion criteria

The diagnosis of cirrhosis was based on the typical imaging characteristics and a clear etiology of liver disease, histological characteristics (if available), and/or presence of ascites and/or

varices at endoscopy. The inclusion and exclusion criteria were as follows:

Inclusion criteria: (i) determined sinusoidal PH, irrespective of etiology; (ii) underwent HVPG measurement and CT scan with an interval of less than 3 months; and (iii) aged 18–75 years. Exclusion criteria: (i) history of transjugular intrahepatic portosystemic shunts (TIPS), hepatectomy, splenectomy, or liver transplantation (LT); (ii) presence of a severe intrahepatic venous shunt, a hepatic arteriovenous shunt, or an intrahepatic arterial-portal fistula; (iii) failure of HVPG measurement; (iv) occlusive disease or thrombosis within the hepatic or portal veins; (v) confirmed or suspected malignancy; (vi) administration of nonselective beta-blockers; and (vii) incomplete information.

Data collection

All demographic, clinical, laboratory, radiological, and endoscopic data, as well as history of surgery and medicine administration, were collected at the time of HVPG measurement. Concomitant chronic diseases, such as hypertension and diabetes, were evaluated based on past diagnosis record and prescribed medications. The stage of cirrhosis, whether compensated or decompensated, was determined by the presence of history of variceal bleeding, ascites, jaundice, or encephalopathy (19).

CT protocols

All patients were examined using one of the following CT scanners: PHILIPS Incisive CT at institution A; GE Revolution CT, Lightspeed VCT scanner at institution B. All CT examinations were obtained using a fixed tube voltage of 120 kVp. Tube current (mA) was set within a certain range. Other parameters that do not affect body composition values, including slice thickness, scan pitch ratio, reconstruction diameter, and spacing between slice, were set according to established protocols of the respective institutions.

HVPG measurement

HVPG was conducted using a balloon catheter with a pressure transducer at the tip with a standard catheterization protocol. All procedures were performed by 3 broad-certified interventional radiologists (Jianan Yu with 10 years of interventional radiology experience; Long Jin and Linpeng Zhang, with more than 30 year of interventional radiology experience, respectively). With the patient under local anesthesia a 5.5-French balloon catheter (Fogarty 12TLW805F35, ,Edwards Lifesciences, CA, USA) was introduced through the right internal jugular vein to catheterize the right hepatic vein. The wedged hepatic venous pressure was obtained when the balloon could completely occlude the hepatic vein, and free hepatic venous pressure was obtained approximately at a distance of 2–3 cm from the hepatic vein to the opening of the inferior vena cava. The values were recorded when the tracings of pressure values reached stable.

Triplicate measurements were performed to get average value. HVPG was calculated as difference between wedged hepatic venous pressure and free hepatic venous pressure. Clinically significant portal hypertension (CSPH) was defined as HVPG $\geq$10 mm Hg (11). Severe PH was defined as HVPG $\geq$16 mm Hg (20).

Body composition values

Seven BC values, including skeletal muscle index (SMI), SAT index (SATI), deep SATI (dSATI), superficial SATI (sSATI), visceral adipose tissue index (VATI), ratio of VATI and SATI, and skeletal muscle radiodensity (SMRD) were analyzed. Visceral fat area was not measured because of the presence of ascites in the mesenteric fat space in patients with moderate-to-large amounts of ascites.

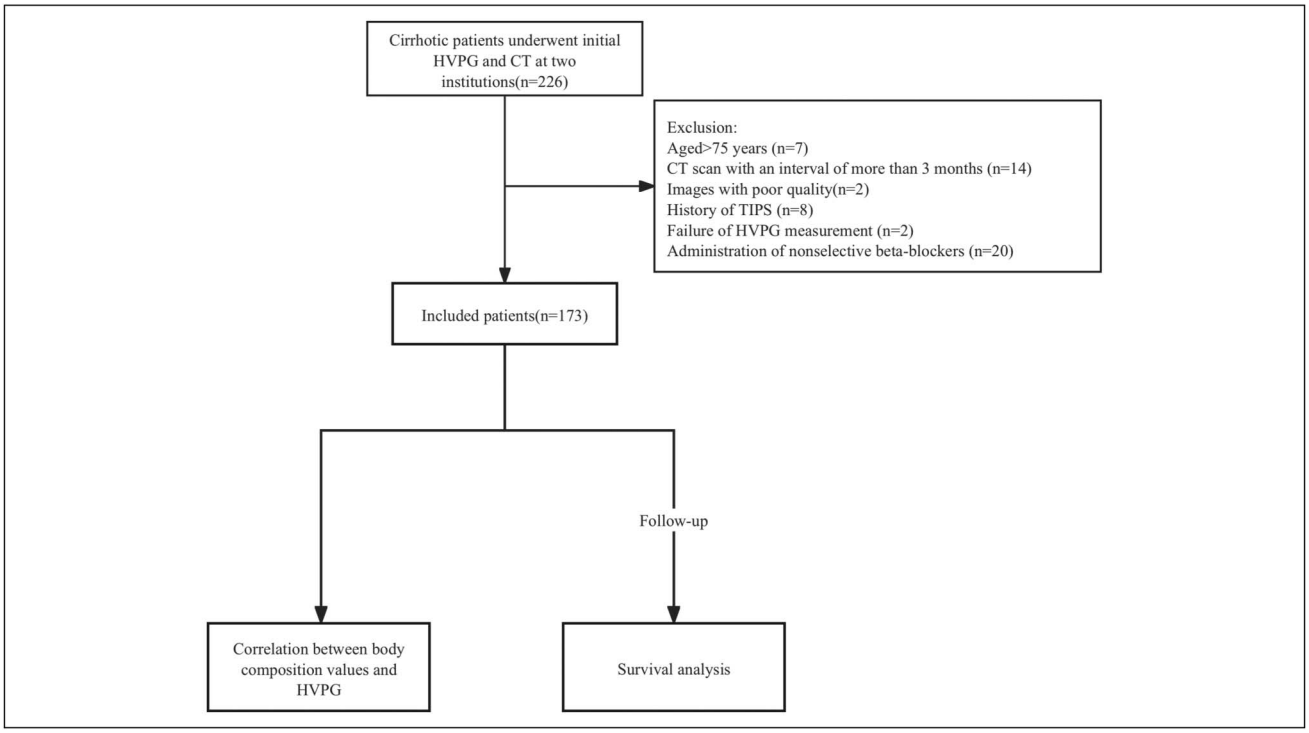

Figure 1. Flowchart of patient selection. CT, computed tomography; HVPG, hepatic venous pressure gradient; TIPS, transjugular intrahepatic portosystemic shunts.

Table 1. Patient characteristics

Characteristic	Overall patients (N = 173)
Age	53.7 ± 10.5
Sex	
Female	62 (35.84%)
Male	111 (64.16%)
Hypertension	62 (35.84%)
Diabetes mellitus	23 (13.29%)
ACLF	1 (0.58%)
HRS	1 (0.58%)
CVD	31 (17.92%)
Etiology	
HBV	106 (61.27%)
HCV	21 (12.14%)
HBV + HCV	2 (1.16%)
ALD	14 (8.09%)
NASH	5 (2.90%)
PBC	5 (2.89%)
AIH	4 (2.31%)
Cryptogenic	16 (9.25%)
Decompensation	55 (31.79%)
Decompensation reason	
Ascites	14 (8.09%)
Bleeding	29 (16.76%)
Jaundice	12 (6.94%)
BMI	24.56 ± 4.42
MELD score	9.00 (7.00–12.00)
Child-Pugh score	6.00 (5.00–8.00)
Child-Pugh class	
A	110 (63.58%)
B	48 (27.75%)
C	15 (8.67%)
HVPG	13.00 (8.00–18.00)
CSPH	121 (69.94%)
Varicose_classification[a] (109)	
Mild	57 (32.95%)
Moderate	25 (14.45%)
Severe	27 (15.61%)
WBC	3.80 (2.83–5.00)
HGB	130.00 (108.00–143.00)
PLT	79.00 (55.00–126.00)
INR	1.18 (1.08–1.33)
TBIL	22.85 (15.62–34.45)
AST	32.00 (26.00–52.00)
ALT	27.00 (19.00–38.00)
ALB	36.60 (32.00–42.40)
Ammonia	25.00 (20.00–39.00)
Creatinine	60.00 (53.00–69.00)
Na	139.30 (137.60–141.00)
SMRD	
Male (N = 111)	46.21 ± 5.02
Female (N = 62)	45.16 ± 6.45
SMI	
Male (N = 111)	48.43 ± 8.30
Female (N = 62)	36.30 ± 6.08
SATI	
Male (N = 111)	41.64 ± 21.39
Female (N = 62)	58.37 ± 24.27
dSATI	
Male (N = 111)	19.21 ± 12.08
Female (N = 62)	24.17 ± 12.41
sSATI	
Male (N = 111)	22.43 ± 10.51
Female (N = 62)	34.20 ± 14.06
VATI[a] (161)	
Male (N = 111)	38.93 ± 22.71
Female (N = 62)	31.46 ± 16.25
VSR[a] (161)	
Male (N = 111)	0.93 ± 0.49
Female (N = 62)	0.57 ± 0.26
Myosteatosis (lowest 10%)	20 (11.56%)
Sarcopenia (lowest 10%)	11 (6.36%)
Sarcopenia	56 (32.37%)

Results for continuous data are expressed as means ± SDs and for categorical data as N (%).
ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALB, albumin; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CSPH, clinical significant portal hypertension; CVD, cardiovascular disease; dSATI, deep subcutaneous adipose tissue index; HBV, hepatitis B virus; HCV, hepatitis C virus; HGB, hemoglobin; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PLT, platelet count; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; SMRD, skeletal muscle radiodensity; sSATI, superficial subcutaneous adipose tissue index; TBIL, total bilirubin; VATI, visceral adipose tissue index; WBC, white blood cell count.
[a](actual number): indicates presence of missing data.

All BC values were obtained at plain CT scans with a 5 mm slice thickness using a fixed tube voltage individually using SliceOmatic Version 4.2 software (Tomovision, Montreal, Quebec, Canada) and analyzed by 2 trained radiologists blinded to patient information. These tissues were delineated according to tissue-specific Hounsfield units (SMI: −29 to +150; SATI: −190 to −30; VATI: −150 to −50) (21). All analyzed BC data were average values of 2 trained radiologists' results, and the consistence between results of 2

radiologists was provided in Supplementary Digital Content (see Supplemental Table 1, http://links.lww.com/CTG/B289).

SMI was defined as the total muscle area at the level of L3 (cm^2) normalized for height in meters squared (m^2); SATI was defined as the adipose area between the skin line and the outer abdominal wall, normalized for height in meters squared. Superficial and deep SAT are separated by the fascia that divides the 2 adipose tissue depots (10). VATI was defined as the area of adipose tissue within the abdominal wall, normalized for height in meters squared. SMRD was defined as the average radiodensity of the total skeletal muscle at the L3 level. The representative image is provided in Supplementary Digital Content (see Supplementary Figure S1, http://links.lww.com/CTG/B288).

Sarcopenia was determined as the lowest 10%, approximately equal to the mean $-1.28 \times$ SD of SMI, stratified by sex, assuming a normal distribution. Another sex-specific and ethnic cutoff, namely <44.77 cm^2/m^2 for male patients and <32.50 cm^2/m^2 for female patients, was used for supplemental analysis (16). Similarly, myosteatosis was determined based on the cutoff of the mean $-1.28 \times$ SD of entire cohort.

Statistical analysis

Descriptive statistics were presented as the mean ± SD or median (interquartile range) for continuous variable and frequency (percentage) for categorical variable. The Shapiro-Wilk test was used to assess the normal distribution of continuous variables. A 2-sample *t* test or Mann-Whitney *U* test was used to investigate differences in BC values between groups. Intervariable correlation was assessed using Pearson or Spearman correlation analyses depending on the normality of data. The consistence between BC values as continuous scale was assessed by intervariable correlation analysis.

The sex-specific cutoffs of BC were determined based on the Youden index. The cumulative survival rate was assessed, and risk factors of survival were identified using competing risk analysis with the Fine-Gray proportional subdistribution hazard model, with LT as a competing event. Survival time was defined as the interval between HVPG measurement and the date of the last follow-up (May 31, 2024), LT, or death.

Multiple linear regression or polynomial regression was applied to assess the impact of HVPG on BC value, depending on the distributions of BC values across the HVPG scope. A bidirectional elimination mode of variable selection was used, and the effects of interaction term were also considered. For each model, an adjusted coefficient of determination (R^2) was calculated, and model performance was assessed using the Akaike information criterion. Multicollinearity was tested using the variance inflation factor (VIF). Intervariable correlation analysis was performed

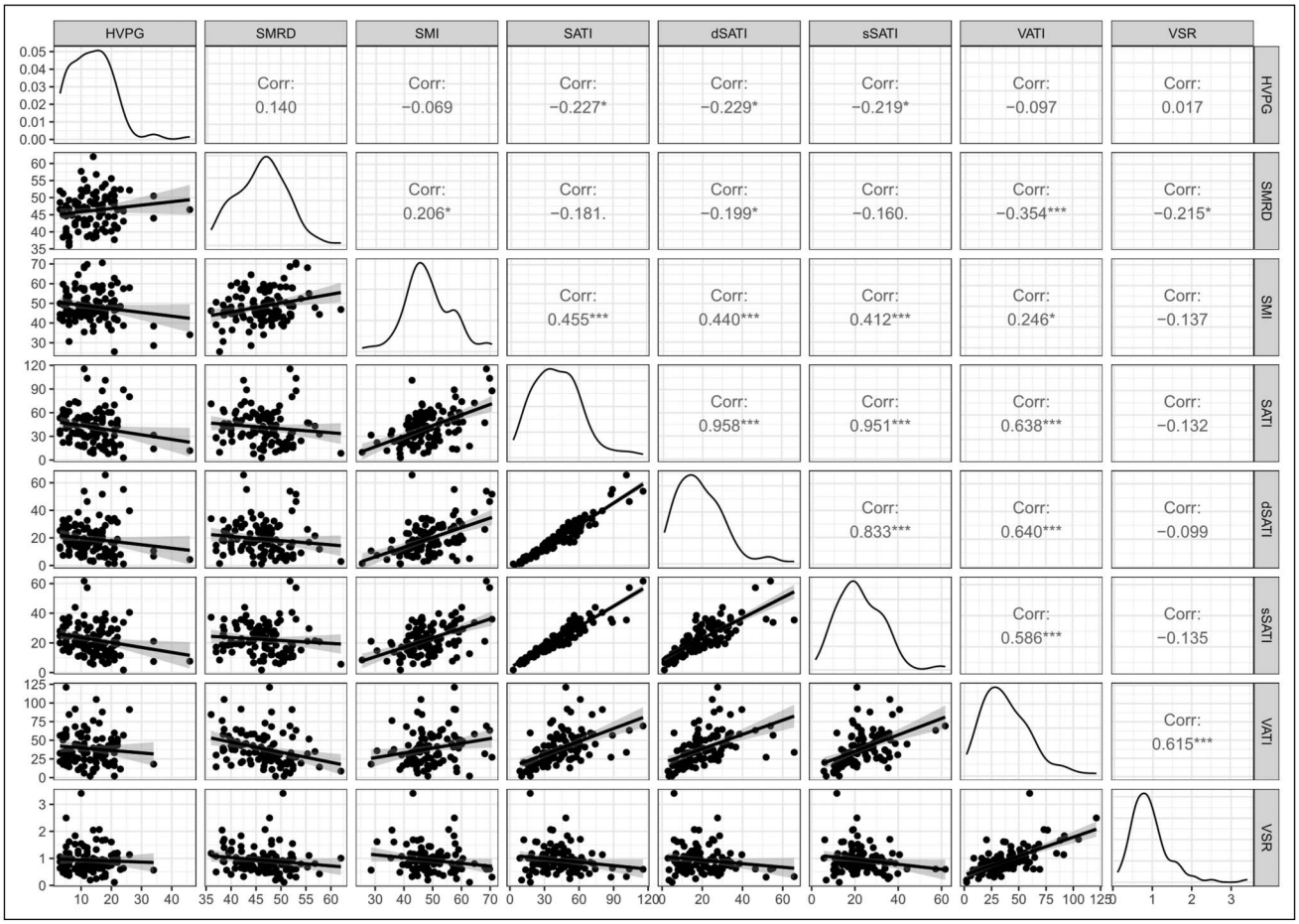

Figure 2. Correlations between BC values and HVPG in male patients. BC, body composition; dSATI, deep SATI; HVPG, hepatic venous pressure gradient; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; SMRD, skeletal muscle radiodensity; sSATI, superficial SATI; VATI, visceral adipose tissue index; VSR, ratio of VATI and SATI.

between independent variables with VIF greater than 10, and variables with larger VIF would be removed from the model.

For regression model, assumptions of linearity, normality of residuals, heteroscedasticity, and multicollinearity were checked using packages in R. All statistical analyses were performed using R (Version 4.3.3). A 2-sided P of < 0.05 was indicative of a significant difference.

RESULTS

Patient characteristics

A total of 226 patients were eligible, and 173 patients (111 [64.2%] were male; the mean age was 53.7 ± 10.5 years; 110 from Third People's Hospital of Taiyuan and 63 from Beijing Friendship hospital) were included in this study. The patient flowchart is shown in Figure 1.

VATI was missing in 12 patients because of the presence of ascites; other BC values were available for all patients. In the entire cohort, the median HVPG was 13 (8–18) mm Hg. Of these, 121 patients (69.9%) were classified into the CSPH group with a mean HVPG of 17 (13–20) mm Hg, and the remaining 52 patients were classified into the non-CSPH group with a mean HVPG of 6 (5–8) mm Hg. The mean Model for End-Stage Liver Disease score was 9.00 (7.00–12.00), and Child-Pugh score was 6.00 (5.00–8.00). There were 55 decompensated patients (31.8%). The most common etiology of cirrhosis was hepatitis B virus (HBV), followed by hepatitis C virus, alcoholic, and nonalcoholic steatohepatitis. The baseline characteristics of the included patients are provided in Table 1.

Correlations between BC values and HVPG

Given that BC values differ considerably between male patients and female patients, the correlation analyses were performed separately by sex. Figures 2 and 3 illustrate the correlations between BC values and HVPG in male and female subgroups, respectively. In male patients, SATI, dSATI, and sSATI were inversely correlated with HVPG value, respectively (SATI: rho = −0.227, P = 0.017; dSATI: rho = −0.229; P = 0.016; sSATI: rho = −0.219; P = 0.021). It was qualitatively observed that values of SATI, dSATI, and sSATI decrease with increasing HVPG (see Supplementary S2, http://links.lww.com/CTG/B288).

In sensitivity analyses, HVPG had significant inverse correlations with SATI, dSATI, and sSATI (rho = −0.244; rho = −0.253; rho = −234; $P < 0.05$) in male patients with compensated cirrhosis, whereas no correlation was found in male patients with decompensated cirrhosis. There were significant correlations between SATI, dSATI, and sSATI and HVPG in male patients aged 60 years or younger (rho = −0.231; rho = −0.231;

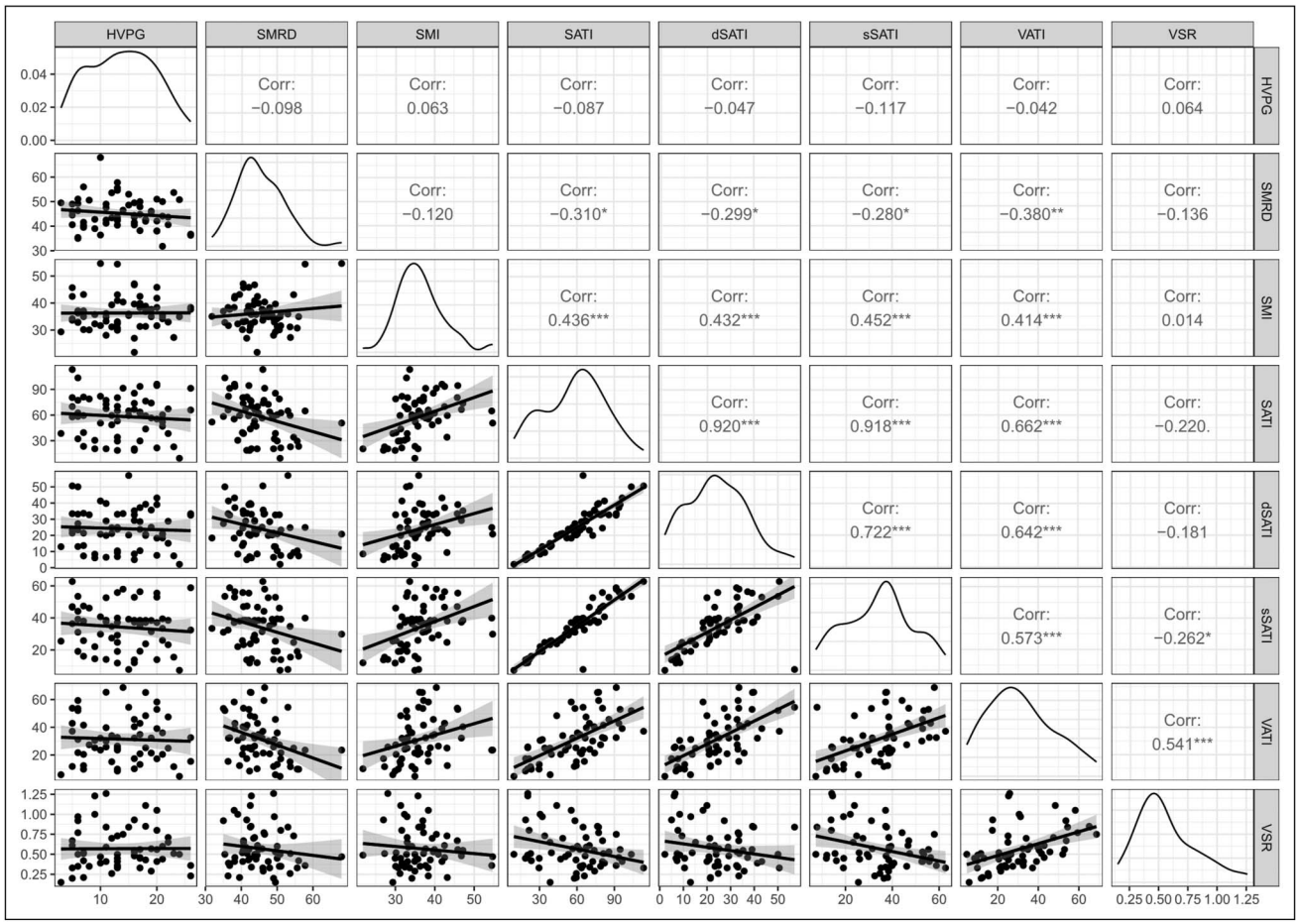

Figure 3. Correlations between BC values and HVPG in female patients. BC, body composition; dSATI, deep SATI; HVPG, hepatic venous pressure gradient; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; SMRD, skeletal muscle radiodensity; sSATI, superficial SATI; VATI, visceral adipose tissue index; VSR, ratio of VATI and SATI.

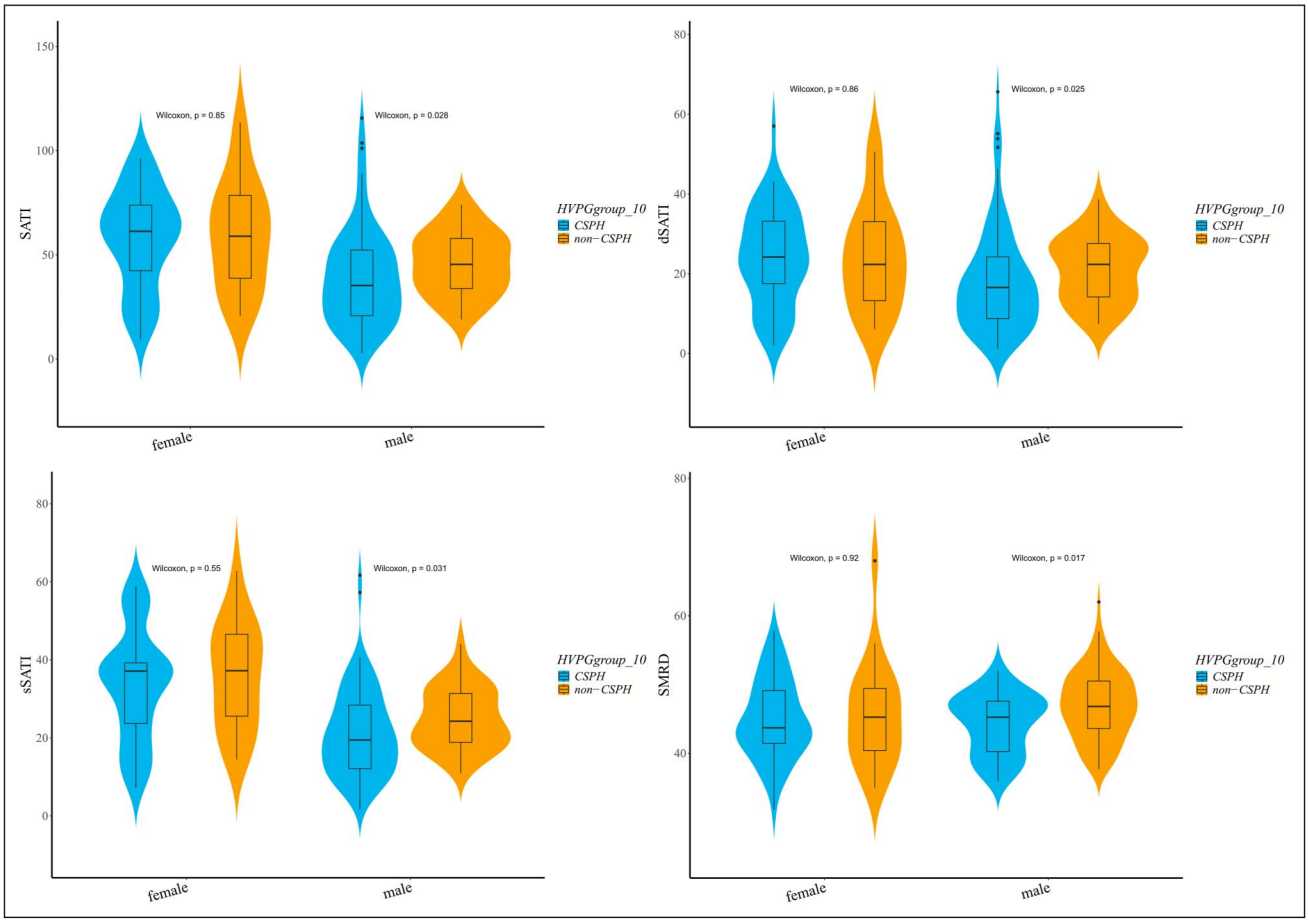

Figure 4. Violin plots showing significant differences of subcutaneous adipose tissue index (SATI), deep SATI, superficial SATI, and skeletal muscle radiodensity between the clinically significant portal hypertension (CSPH) and non-CSPH groups in male patients. dSATI, deep SATI; SATI, subcutaneous adipose tissue index; SMRD, skeletal muscle radiodensity; sSATI, superficial SATI; VATI, visceral adipose tissue index.

rho = −232; $P < 0.05$), but no similar results were observed in counterparts aged older than 60 years. In addition, in male HBV patients, inverse correlation was also observed between SATI, dSATI, and sSATI and HVPG (rho = −0.250; rho = −0.243; rho = −280; $P < 0.05$).

There was no evidence of significant correlations between BC values and HVPG in female patients.

Distributions of BC values in different HVPG intervals

Male patients with CSPH had lower SATI, dSATI, sSATI, and SMRD values than those without CSPH (Figure 4). There were no significant differences in other BC values between the high and low HVPG groups dichotomized by cutoffs of 10, 16, or 20 mm Hg.

Conversely, there were no significant difference in HVPG between patients with or without sarcopenia using the predefined cutoff (<44.77 cm^2/m^2 in male and <32.50 cm^2/m^2 in female). When individuals with the lowest 10% SMI were classified as having sarcopenia, the HVPG value in patients with sarcopenia was lower than that without (13.12 ± 6.25 mm Hg vs 21.71 ± 13.94 mm Hg; $P = 0.046$).

BC values by sex in different subgroups were tabulated in Table 2, including Child-Pugh class, sex, age, cirrhosis stage, HVPG intervals, and cirrhosis etiology. Regardless of sex, patients with Child-Pugh B or C had lower SATI and dSATI than those with Child-Pugh A. Male patients with Child-Pugh B or C had lower sSATI and VATI than those with Child-Pugh A. Compared with female patients, male patients had higher SMI and lower SATI, dSATI, sSATI, and ratio of VATI and SATI. Furthermore, SMRD was lower in patients aged older than 60 years than in those aged 60 years or younger, in both male and female patients.

The impact of HVPG on SATI alternation

To address heteroscedasticity and reduce the influence of the absolute value of independent variable on the fitting, SATI was log-transformed based on 10.

In model 1, age, sex, liver function, HVPG value, and cirrhosis stage were selected as independent variables. In model 2 and model 3, the effects of interaction terms, HVPG × cirrhosis stage, and HVPG × liver function were added based on model 1, respectively. Child-Pugh score or class and Model for End-Stage Liver Disease score were candidates of liver function to be included into models. Except for the continuous HVPG value, 2 binary variables were obtained by dichotomizing HVPG value based on 2 cutoff value, 10 and 16 mm Hg.

Table 2. Comparisons of BC values between groups

Subgroup	Child-Pugh class			Sex		Age		Cirrhosis stage	
	A	B	C	Male	Female	≤60	>60	Compensated cirrhosis	Decompensated cirrhosis
SMI									
Male	49.97 ± 7.89*	46.36 ± 8.72*	44.14 ± 7.46*	48.43 ± 8.3	36.30 ± 6.08*	49.09 ± 9.07	46.25 ± 4.47	48.90 ± 6.60	47.61 ± 10.65
Female	36.22 ± 5.35	36.00 ± 7.15	37.62 ± 8.76			37.38 ± 6.33	33.87 ± 4.77	36.19 ± 5.11	36.68 ± 8.89
SATI									
Male	46.42 ± 21.39*	34.11 ± 19.37*	32.56 ± 19.49*	41.64 ± 21.39	58.37 ± 24.27*	41.77 ± 23.33	41.20 ± 13.63	41.90 ± 17.70	41.18 ± 26.80
Female	62.78 ± 24.24*	46.90 ± 23.80*	56.88 ± 18.60			61.21 ± 23.88	51.93 ± 24.57	60.64 ± 24.59	50.59 ± 22.23
dSATI									
Male	21.89 ± 12.25*	14.84 ± 10.70*	14.70 ± 10.44*	19.21 ± 12.08	24.17 ± 12.41*	19.00 ± 13.17	19.88 ± 7.67	19.56 ± 10.43	18.60 ± 14.60
Female	26.49 ± 12.75*	17.96 ± 10.7*	23.78 ± 9.75			25.02 ± 11.44	22.23 ± 14.51	25.79 ± 12.94	18.60 ± 8.61*
sSATI									
Male	24.53 ± 10.55*	19.26 ± 9.75*	17.86 ± 9.52*	22.43 ± 10.51	34.20 ± 14.06*	22.76 ± 11.34	21.33 ± 7.26	22.34 ± 8.60	22.58 ± 13.28
Female	36.28 ± 14.34	28.95 ± 13.79	33.11 ± 10.63			36.19 ± 13.50	29.70 ± 14.60*	34.85 ± 14.19	31.98 ± 13.89
VATI									
Male	43.14 ± 23.18*	31.31 ± 20.06*	29.73 ± 19.95	38.93 ± 22.71	31.46 ± 16.25	39.18 ± 23.73	38.16 ± 19.68	39.70 ± 24.28	37.48 ± 19.65
Female	34.56 ± 16.48	25.54 ± 14.31	22.64 ± 13.95			32.10 ± 17.11	29.85 ± 14.19	32.78 ± 16.14	26.20 ± 16.30
VSR									
Male	0.95 ± 0.54	0.93 ± 0.42	0.79 ± 0.27	0.57 ± 0.26	0.93 ± 0.49*	0.94 ± 0.54	0.92 ± 0.35	0.92 ± 0.46	0.96 ± 056
Female	0.57 ± 0.25	0.61 ± 0.30	0.41 ± 0.17			0.54 ± 0.25	0.64 ± 0.26	0.58 ± 0.27	0.52 ± 0.20
SMRD									
Male	45.88 ± 4.80	47.02 ± 5.50	45.81 ± 5.06	46.21 ± 5.02	45.16 ± 6.45	47.03 ± 4.82	43.53 ± 4.80*	45.39 ± 4.59	47.61 ± 5.46
Female	45.69 ± 6.48	44.84 ± 7.07	42.35 ± 4.41			46.24 ± 6.62	42.72 ± 5.44*	44.27 ± 5.12	48.21 ± 9.36

Subgroup	HVPG			Presence of CSPH		Cirrhosis etiology	
	0–9 mm Hg	10–19 mm Hg	≥20 mm Hg	Non-CSPH	CSPH	Non-hepatitis	Hepatitis
SMI							
Male	48.06 ± 6.96	49.42 ± 8.13	46.38 ± 10.48	48.06 ± 6.96	48.59 ± 8.87	44.98 ± 10.52	49.64 ± 7.04*
Female	35.58 ± 4.64	36.85 ± 7.25	35.90 ± 4.69	35.58 ± 4.64	36.58 ± 6.57	35.61 ± 6.75	36.75 ± 5.67
SATI							
Male	46.14 ± 15.07*	41.19 ± 23.28	35.53 ± 24.04*	46.14 ± 15.07	39.65 ± 23.47*	40.24 ± 26.59	42.13 ± 19.40
Female	60.44 ± 27.14	58.42 ± 21.65	55.53 ± 28.06	60.44 ± 27.14	57.59 ± 23.38	50.47 ± 23.52	63.36 ± 23.70*

Table 2. (*continued*)

Subgroup	HVPG			Presence of CSPH		Cirrhosis etiology	
	0–9 mm Hg	10–19 mm Hg	≥20 mm Hg	Non-CSPH	CSPH	Non-hepatitis	Hepatitis
dSATI							
Male	21.21 ± 8.30	19.10 ± 13.00	16.26 ± 14.41	21.21 ± 8.30	18.33 ± 13.37*	18.31 ± 14.14	19.53 ± 11.34
Female	24.24 ± 13.56	24.95 ± 11.99	22.14 ± 12.64	24.24 ± 13.56	24.14 ± 12.10	20.76 ± 13.57	26.32 ± 11.27
sSATI							
Male	24.93 ± 7.86*	22.09 ± 11.65	19.27 ± 10.55*	24.93 ± 7.86	21.32 ± 11.36*	21.93 ± 13.53	22.60 ± 9.31
Female	36.19 ± 14.03	33.47 ± 13.54	33.40 ± 16.15	36.19 ± 14.03	33.45 ± 14.15	29.71 ± 14.09	37.04 ± 13.45*
VATI							
Male	42.51 ± 24.13	36.71 ± 22.11	38.29 ± 21.92	42.51 ± 24.13	37.11 ± 21.91	43.03 ± 26.83	37.65 ± 21.30
Female	31.59 ± 16.95	31.93 ± 16.06	30.07 ± 17.11	31.59 ± 16.95	31.41 ± 16.17	28.04 ± 15.32	33.44 ± 16.64
SMRD							
Male	44.32 ± 4.39	47.14 ± 5.21	46.81 ± 4.83	44.32 ± 4.39	47.05 ± 5.08*	46.33 ± 5.98	46.17 ± 4.67
Female	44.49 ± 5.90	46.45 ± 6.46	42.84 ± 6.80	44.49 ± 5.90	45.41 ± 6.69	46.28 ± 6.84	44.45 ± 6.18
VSR							
Male	0.93 ± 0.46	0.94 ± 0.57	0.92 ± 0.33	0.93 ± 0.46	0.94 ± 0.51	1.10 ± 0.56	0.88 ± 0.46*
Female	0.57 ± 0.31	0.57 ± 0.24	0.57 ± 0.22	0.57 ± 0.31	0.57 ± 0.23	0.59 ± 0.23	0.56 ± 0.27

*Indicates $P < 0.05$.
dSATI, deep subcutaneous adipose tissue index; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; SMRD, skeletal muscle radiodensity; sSATI, superficial subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VSR, ratio of VATI and SATI.

Table 3. Multiple linear regression analyses

Independent variables	Model 1				Model 2				Model 3			
	Estimate	Standard error	*t* value	*P*	Estimate	Standard error	*t* value	*P*	Estimate	Standard error	*t* value	*P*
Intercept	1.867	0.058	32.417	<0.001	1.870	0.055	33.886	<0.001	1.870	0.055	33.886	<0.001
Sex (male)	−0.184	0.047	−3.881	<0.001	−0.178	0.045	−3.923	<0.001	−0.178	0.045	−3.923	<0.001
Child-Pugh class (B/C)	−0.126	0.052	−2.421	0.017	−0.121	0.050	−2.422	0.017	−0.121	0.050	−2.422	0.017
HVPG	−0.01	0.005	−1.805	0.048	−0.008	0.003	−1.774	0.050	−0.008	0.003	−1.774	0.050
HVPG × cirrhosis stage	NA				NS				NA			
Child-Pugh class × HVPG	NA				NA				NS			

HVPG, hepatic venous pressure gradient; NA, not available; NS, not significant.

In Table 3, following the adjusted multiple linear regression, sex, Child-Pugh class, and HVPG value showed a significant positive association with SATI; yet, no statistically significant interaction terms were observed. For regression coefficients (β value) ± standard error, SATI decreases by approximately 1 cm^2/m^2 with HVPG per 1 mm Hg, by approximately 18.4 cm^2/m^2 in male patients, and by approximately 12.6 cm^2/m^2 with Child-Pugh B or C class.

Factors associated with mortality

There were 19 death events in the 168 patients with available survival data. The follow-up period lasted for a median of 23.98 (19.75–28.58) months. The accumulative survival rate was 92.7% at 12 months. As shown in Figure 5, The cumulative incidence function curve showed a significant separation between patients with high SATI and those with low SATI after excluding competing events of LT (25.16 ± 15.96 months vs 29.58 ± 18.23

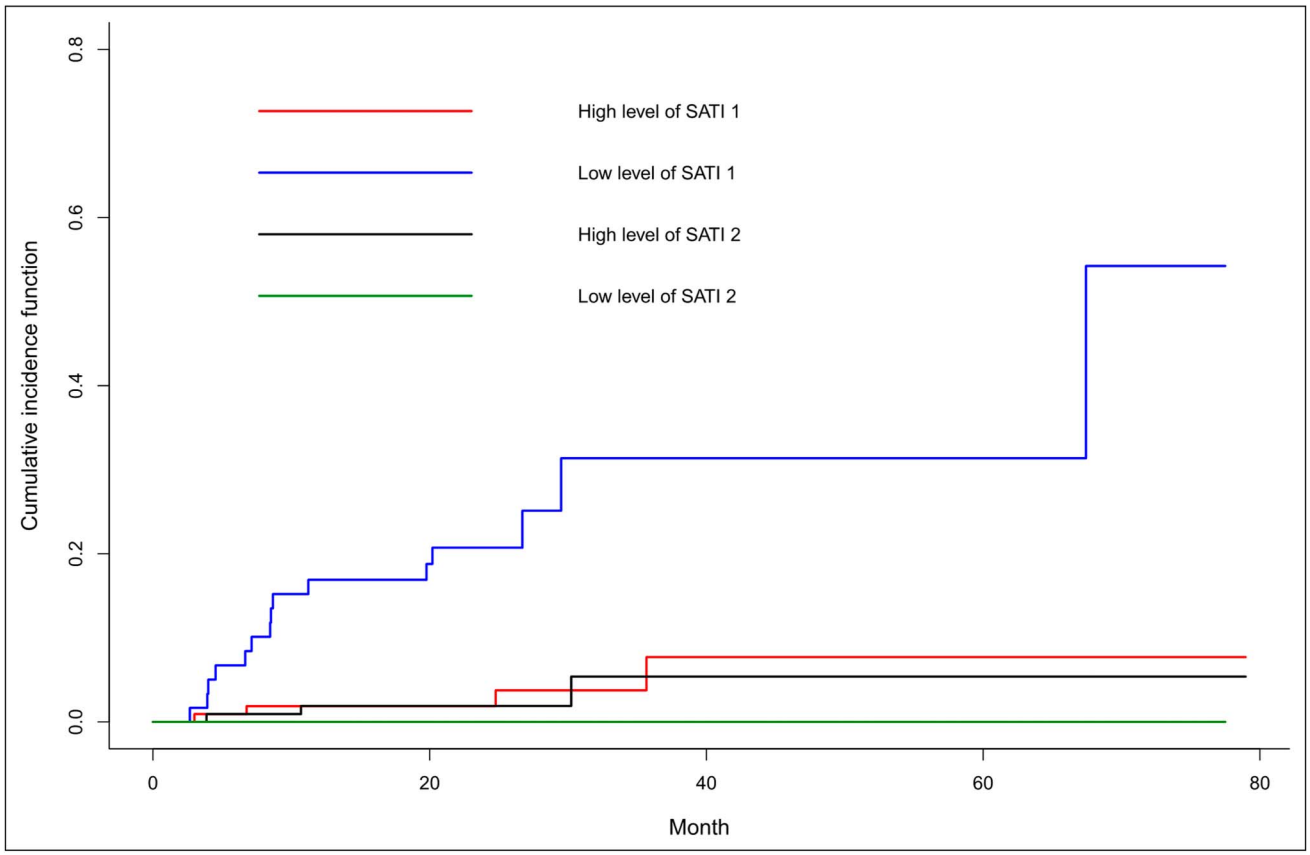

Figure 5. Cumulative incidence curves of survival with liver transplantation as a competing risk. A significant difference was detected between patients with high SATI and with low SATI (25.16 ± 15.96 months vs 29.58 ± 18.23 months; $P < 0.001$). Number 1 denoting noncompeting end points; number 2 denoting competing end points. SATI, subcutaneous adipose tissue index.

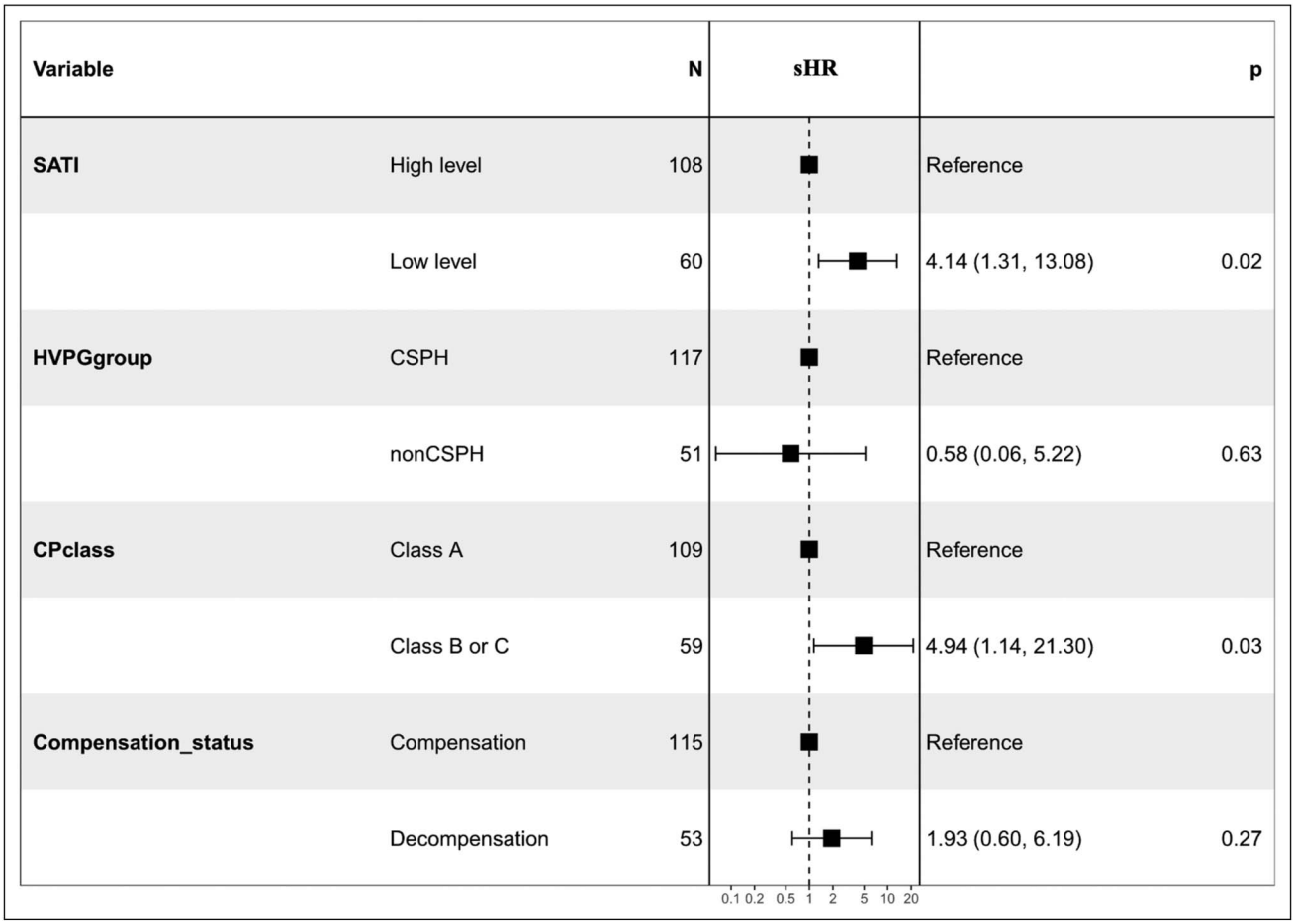

Figure 6. Forest plot showing risk factors of mortality after multiple competing survival analysis. A lower level of SATI (male: <38 cm^2/m^2; female: <23 cm^2/m^2) and Child-Pugh B or C were predictors of reduced survival. CSPH, clinically significant portal hypertension; SATI, subcutaneous adipose tissue index.

months; $P < 0.001$). This survival difference was also observed in both male or female subgroups (see Supplementary Figure S3-S4, http://links.lww.com/CTG/B288). As shown in forest plot, a lower level of SATI (male: <38 cm^2/m^2; female:<23 cm^2/m^2; sub-distribution hazard ratio: 4.14 [1.31–13.08]; $P = 0.02$) and Child-Pugh B or C (sub-distribution hazard ratio: 4.94 [1.14–21.30]; $P = 0.03$) were predictors of reduced survival (Figure 6). However, due to the limited number of end point events, multiple competing survival analyses were not performed in sex subgroups.

DISCUSSION

BC alternations are prevalent and secondary to PH. HVPG was performed to measure the severity of PH in cirrhosis management. The result of this study revealed that HVPG is roughly parallel to SATI in cirrhotic patients, particularly in male patients, compensated patients, and those with hepatitis-related cirrhosis. Child-Pugh B or C, male sex, and higher HVPG were predictive of decreased SATI. Furthermore, lower level of SATI and Child-Pugh B or C were associated with poorer survival.

Still date, few studies have been dedicated to analyzing the correlations between BC values and PH severity In 2019, Rodrigues et al (9) found that SATI negatively correlates with HVPG in 84 cirrhotic patients, but positive results were observed in female patients and decompensated cirrhosis. The differences could be likely explained by the following points. First, unlike our study where viral cirrhosis accounts for nearly 75%, alcohol-related or steatosis-related cirrhosis is the main disease etiology in Susana G. Rodrigues's study. It is well established that the agreement between HVPG and severity of PH was higher in viral and alcohol cirrhosis compared with cirrhosis caused by other liver diseases (11). In this study, the sensitivity analysis result for the HBV subgroup further corroborated the main findings, showing that PH primarily affects SATI indexes. Second, even with the same severity of PH, male patients commonly have higher muscle mass and lower SATI than female patients. Obviously, it is not appropriate to correlate BC values and HVPG without stratification of sex, as analyzed in previous studies (7,22–24). In Susana G. Rodrigues's study, correlation analysis in subgroups as per compensation, presence of sarcopenia, and disease etiology were not performed separately by sex.

This study quantitatively evaluated the impact of HVPG on SATI using linear regression. The results revealed that worse liver function, as assessed by Child-Pugh class, is associated with SATI

depletion, which is consistent with findings related to muscle mass (25,26). This might be the first study to assess the impact of liver function on SATI. In addition, it is established that muscle mass, quality, and adipose tissue gradually decrease with age. However, age was not predictive of SATI in this regression model, likely due to the young age and concentrated age distribution of the included patients. Only 22 (12.7%) and 9 patients (5.2%) were aged older than 65 and 70 years, respectively. In fact, to estimate the effect of PH on BC values, the pathophysiological factors of cirrhosis should be emphasized by minimizing the effects of natural aging.

In this study, lower SATI was identified as a risk factor of survival, a finding also reported previously (27,28). Different cutoffs of SATI across studies largely depended on baseline body mass index of the included patients. SAT is considered a metabolic depot to store energy, and its mechanism affecting the survival of cirrhotic patients has been suggested in some experimental and preclinical studies (29,30). Compared with other BC value, SAT alternation is probably more easily subject to appetite loss caused by ascites, decompensation events, bacterial translocation, and infection. A meta-analysis concluded that the TIPS primarily shifts SAT rather than visceral adipose tissue (VAT) or muscle (31). Besides, an inverse correlation between SATI increase and ammonia reduction was observed in cirrhotic patients undergoing TIPS (32).

Although VAT has been extensively proved to be linked to systemic inflammation and the histological severity of steatosis-related liver disease (33). It is undeniable that measurement of VAT on cross-sectional image might be susceptible to certain conditions, such as ascites, splenomegaly, and mesenteric panniculitis, potentially leading to underestimation of VATI.

The limitations of this study should be acknowledged. First, due to a lack of consensus regarding the definition of sarcopenia, thorough analyses on sarcopenia or myosteatosis were not performed. Second, although this was a binary-center study, the limited sample size could hinder extension of some conclusion in subgroup analyses. Finally, considering the heterogeneity of the target population, our results need further validation in a separate population.

In conclusion, this study concluded that the decreased SATI, dSATI, and sSATI were more closely associated with increased HVPG and a lower level of SATI was predictive of poor survival. These findings extended scope of HVPG supervision beyond complication-centric view, highlighting a need of comprehensive view in the management of cirrhotic patients.

CONFLICTS OF INTEREST

Guarantor of the article: Long Jin, MD.

Specific author contributions: S.Y.: conceptualization and methodology. S.Y., X.R., X.G., L.N., Y.N.: data curation and formal analysis. S.Y., J.Y.: writing–original draft. L.J., L.Z.: writing–review and editing. L.J., L.Z.: supervision.

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Study Highlights

WHAT IS KNOWN

- ✓ Sarcopenia is a prevalent complication in patients with cirrhosis.
- ✓ Portal hypertension is a key driver of pathophysiology of cirrhosis.

WHAT IS NEW HERE

- ✓ This study explores the correlations between body composition and HVPG by sex quantitatively.
- ✓ This study identifies the prognostic role of SATI in cirrhotic patients.
- ✓ These findings highlight a need of comprehensive view of HVPG supervision beyond complication-centric view in the management of cirrhotic patients.
- ✓ Decreased SATI, dSATI, and sSATI were more closely associated with increased HVPG. A lower SATI and Child-Pugh B or C predicted mortality.

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