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U-shaped relationship between subcutaneous adipose tissue index and mortality in liver cirrhosis

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Abstract

Background Subcutaneous and visceral adipose tissues are important body components, but their effects on the mortality in patients with liver cirrhosis remain controversial based on the current evidence.

Methods We retrospectively identified 372 eligible patients in whom subcutaneous adipose tissue index (SATI) and visceral adipose tissue index (VATI) could be measured by computed tomography images at the third lumbar vertebra. The association of SATI and VATI with the risk of death was evaluated on a continuous scale with restricted cubic spline curves based on Cox proportional hazards models. Cumulative probability of mortality was estimated by Nelson–Aalen cumulative risk curve analyses. Independent predictors of death were evaluated by competing risk analyses after adjusting for age, sex, and model for end-stage liver disease score.

Results Majority of patients were male (69.4%) with a mean age of 55.40 ± 10.68 years. SATI had a U-shaped association with mortality (P for non-linearity <0.001). Cutoff values of SATI were 19.7 and 51.8 cm^2/m^2 at the points where hazard ratios were just <1.2. SATI was categorized as low (<19.7 cm^2/m^2), moderate (19.7–51.8 cm^2/m^2), and high (>51.8 cm^2/m^2) level. There was no significant difference in the cumulative probability of mortality between low versus moderate SATI groups (Gray's test, $P = 0.052$) and high versus moderate SATI groups (Gray's test, $P = 0.054$). Competing risk analyses demonstrated that low SATI could increase the mortality compared with moderate SATI (subdistribution hazard ratio [sHR] = 1.66, 95% confidence interval [CI]: 0.992–2.78, $P = 0.054$) and was an independent predictor of death (sHR = 1.86, 95% CI: 1.059–3.28, $P = 0.031$). Competing risk analyses also demonstrated that high SATI could significantly increase the mortality compared with moderate SATI (sHR = 1.6, 95% CI: 1–2.54, $P = 0.049$), and was an independent predictor of death (sHR = 2.007, 95% CI: 1.195–3.37, $P = 0.0085$). VATI had an irregularly shaped association with mortality (P for non-linearity <0.001). Cutoff values of VATI were 9.8 and 40.2 cm^2/m^2 at the points where hazard ratios were just <1.2. VATI was categorized as low (<9.8 cm^2/m^2), moderate (9.8–40.2 cm^2/m^2), and high (>40.2 cm^2/m^2) level. There was no significant difference in the cumulative probability of mortality between low versus moderate VATI groups (Gray's test, $P = 0.381$) and high versus moderate VATI groups (Gray's test, $P = 0.787$). Competing risk analyses demonstrated that neither low (sHR = 1.27, 95% CI: 0.599–2.7, $P = 0.53$) nor high VATI (sHR = 0.848, 95% CI: 0.539–1.34, $P = 0.48$) was an independent predictor of death compared with moderate VATI.

Conclusions Both excessive deficiency and accumulation of subcutaneous adipose tissues negatively influence the outcomes of cirrhotic patients.

Keywords Liver cirrhosis; Subcutaneous adipose tissue; Visceral adipose tissue; Prognosis

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Introduction

Liver cirrhosis, the end stage of various chronic liver diseases, is often accompanied by severe clinical complications, mainly including gastroesophageal variceal bleeding, ascites, hepatic encephalopathy, and renal and cardiac dysfunction, which negatively affect the quality of life and long-term outcomes.[1,2] Globally, the number of patients with liver cirrhosis increased from 71.1 million in 1990 to 122.6 million in 2017, and the proportion of liver cirrhosis-related deaths among all-cause deaths also increased from 1.9% in 1990 to 2.4% in 2017.[3] Assessing the risk of death in patients with liver cirrhosis is important for guiding the selection of appropriate interventions.

Visceral and subcutaneous adipose tissues provide energy by generating free fatty acids and regulate fat and glucose metabolism, appetite, inflammation, angiogenesis, and insulin sensitivity by secreting adipokines.[4] They can be quantified by visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI) on computed tomography (CT) scans[5] to represent the body's nutritional and metabolic status.[6] Recently, the association between adipose tissue and outcomes of patients with liver cirrhosis has been widely explored, but remains controversial. Some studies found a significant correlation between VATI and mortality,[7–9] whereas others did not demonstrate any association.[10] On the other hand, one study found that low SATI, defined as SATI <60 cm^2/m^2, would increase the risk of death in cirrhotic patients awaiting liver transplantation; by contrast, another study showed that subcutaneous adipose tissue accumulation, defined as total adipose tissue index >55 cm^2/m^2 and SATI $>$ VATI, could increase the mortality in patients with alcoholic cirrhosis.[11] Such contrasting findings among studies may be primarily attributed to the difference in grouping the study population. Prior studies mostly divided the patient population into two groups by only a single cutoff value of adipose tissue index. However, either excessive accumulation or deficiency of adipose tissue may be detrimental to the patients' survival. Indeed, the evidence suggested a U-shaped association of body mass index[12] and body fat percentage[13] with mortality in the general population. Therefore, it seems reasonable that such a U-shaped association can also be established between adipose tissue and mortality in liver cirrhosis.

Methods

Ethics

This retrospective study was carried out following the rules of the 1975 Declaration of Helsinki and approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command with an approval number of Y (2022) 013.

Study population

Potentially eligible patients with liver cirrhosis and without malignancy were selected from our prospectively established database between December 2014 and June 2021.[14,15] Exclusion criteria were as follows: (1) patients did not undergo abdominal CT at the time of admission; (2) cross-sectional CT images at the level of the third lumbar (L3) vertebrae could not be obtained; and (3) height data were unavailable. Patients were regularly followed via telephone, through outpatient visits, and/or by reviewing medical records until death or liver transplantation. The last follow-up date was December 2021.

Data collection

Demographic, clinical, and laboratory data at admission were collected, including age, gender, height, co-morbidities (i.e., diabetes and hypertension), aetiologies of liver cirrhosis (i.e., hepatitis B virus, hepatitis C virus, and alcohol abuse), and decompensated events (i.e., acute gastrointestinal bleeding, hepatic encephalopathy, jaundice, and ascites). Model for end-stage liver disease (MELD) score[16] and Child–Pugh score[17] were calculated.

Measurement of SATI and VATI

Adipose tissue was assessed by analysing abdominal CT images at the level of the L3 vertebra.[5] Subcutaneous and visceral adipose tissues are defined as the areas outside and inside the abdominal muscular wall, respectively. These tissue regions were specially identified by using Slice-O-Matic V5.0 software (Tomovision, Montreal, Quebec, Canada) with standard thresholds of -190 to -30 Hounsfield Unit (HU) for subcutaneous adipose tissue[18] and -150 to -50 HU for visceral adipose tissue.[19] Adipose tissue areas were automatically calculated by summing tissue pixels and then multiplying by pixel surface area (*Figure* 1). These tissue areas were normalized by dividing by the square of the height in meters, and then described as SATI and VATI.[10]

Statistical analyses

Continuous variables were presented as mean ± standard deviation and median (range), and categorical variables were presented as frequency (percentage). Mann–Whitney *U* test and χ^2 test or Fisher's exact test were used to compare the differences. Pearson correlation tests were used to evaluate the correlation of SATI and VATI with MELD score. The association of SATI and VATI with mortality was evaluated on a continuous scale with restricted cubic spline (RCS) curves

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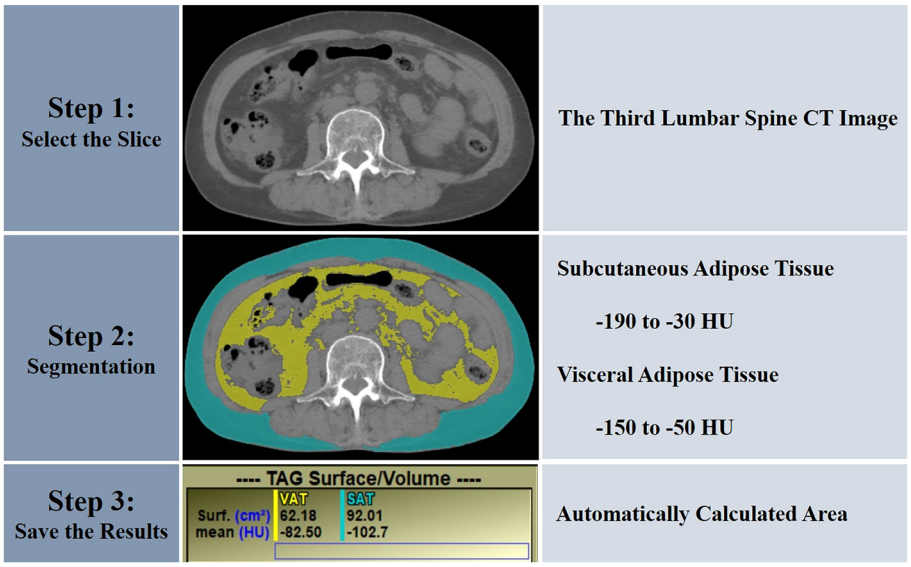

Figure 1 Measurement of adipose tissue area using Slice-O-Matic software.

based on Cox regression analyses with four knots at the 5th, 35th, 65th, and 95th percentiles.[20] The risk of death at various levels of SATI and VATI was described as hazard ratios (HRs) on the spline curve. Their optimal cutoff values for predicting the mortality were determined by HRs and the shape of the curves. Cumulative incidence function was used to estimate the cumulative probability of mortality. Univariate and multivariate competing risk analyses adjusted for age, sex, and MELD score were performed to identify whether SATI or VATI was an independent predictor of increased mortality, where liver transplantation was a competing event to the onset of death. Subdistribution hazard ratios (sHRs) and their 95% confidence intervals (CIs) were calculated. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed by using Statistical Package for Social Science (SPSS version 26.0, IBM Corp, Armonk, New York, USA) and R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) with packages rms, survival, and cmprsk.

Results

Patients

A total of 372 patients with liver cirrhosis were included in our study (*Figure* 2), and their baseline characteristics were

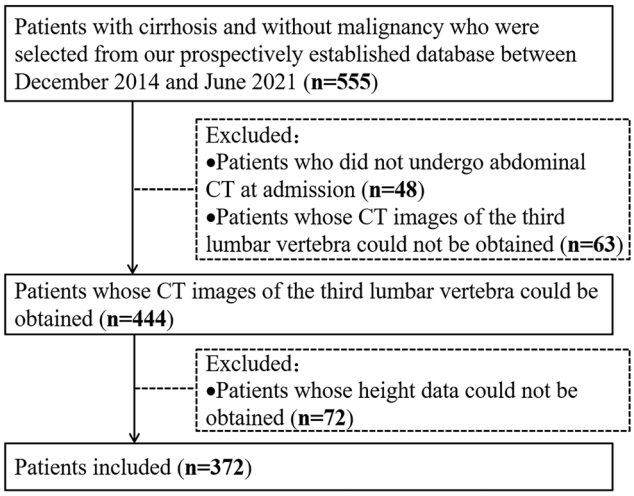

Figure 2 A flowchart of patient enrolment.

shown in *Table* 1. Majority were male (69.4%). The median age was 55.35 (range: 20.58–88.73 years), and the median MELD score was 10.26 (range: 6.43–30.03). The primary aetiologies of liver cirrhosis included alcohol use disorder (44.9%), chronic hepatitis B (36.3%) and hepatitis C virus infection (8.9%). The median SATI was 36.66 (range: 1.00–146.86 cm^2/m^2), and the median VATI was 28.81 (range: 0.09–125.78 cm^2/m^2).

During a median follow-up period of 2.99 (range: 0.03–6.85 years), 94 (25.3%) patients died and 5 (1.3%) underwent liver transplantation. Of the 94 patients who died, 65 (69.1%) died of liver diseases related events, 16 (17.0%) non-liver diseases related events, and 13 (13.8%) unknown causes.

Table 1 Baseline characteristics of patients with cirrhosis

Variables	No. pts	Percentage (%) Mean ± SD Median (range)
Demographics		
Age (years)	372	55.40 ± 10.68 55.35 (20.58–88.73)
Gender (male)	372	258 (69.4%)
Height (m)	372	1.68 ± 0.07 1.70 (1.50–1.90)
BMI (kg/m^2)	372	23.36 ± 3.35 23.21 (14.82–37.37)
Co-morbidities		
Diabetes	372	61 (16.4%)
Hypertension	372	63 (16.9%)
Aetiologies of liver cirrhosis		
Chronic HBV infection	372	135 (36.3%)
Chronic HCV infection	372	33 (8.9%)
Alcohol use disorder	372	167 (44.9%)
Decompensated events		
AGIB	372	116 (31.2%)
HE	372	8 (2.2%)
Jaundice	372	55 (14.8%)
Ascites	372	221 (59.4%)
Laboratory tests		
WBC ($10^9/L$)	372	4.25 ± 3.04 3.5 (0.7–23.1)
Hb (g/L)	372	95.51 ± 29.0 94.0 (28–178)
PLT ($10^9/L$)	372	98.83 ± 71.15 79.5 (18–646)
TBIL (μmol/L)	372	29.43 ± 29.05 20.45 (4.9–216.5)
ALB (g/L)	370	32.52 ± 6.55 32.40 (14.2–65.1)
ALT (U/L)	372	37.57 ± 82.94 23.98 (4.23–1465.5)
ALP (U/L)	372	112.57 ± 86.20 90.73 (28.83–983.93)
SCr (μmol/L)	368	65.96 ± 21.50 63.46 (14.80–267.63)
Na (mmol/L)	370	138.32 ± 3.37 138.0 (118.0–159.0)
INR	368	1.33 ± 0.27 1.26 (0.91–2.77)
Child–Pugh score	367	7.21 ± 1.84 7 (5–13)
MELD score	366	11.45 ± 4.13 10.26 (6.43–30.03)
Body composition variables		
VATI (cm^2/m^2)	372	32.59 ± 21.19 28.81 (0.09–125.78)
SATI (cm^2/m^2)	372	40.24 ± 24.71 36.66 (1.00–146.86)

Abbreviations: No. pts, numbers of patients; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AGIB, acute gastrointestinal bleeding; HE, hepatic encephalopathy; WBC, white blood cell; Hb, haemoglobin; PLT, platelet; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; SCr, serum creatinine; Na, sodium; INR, international normalized ratio; MELD, model for end-stage liver disease; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index.

SATI and mortality

Pearson correlation tests suggested a significant correlation between SATI and MELD score, but the correlation was weak ($P = 0.012$, $R = -0.132$) (*Figure* 3A). A strong U-shaped association between SATI and the risk of death was identified after adjusting for age, sex, and MELD score (P for non-linearity <0.001) (*Figure* 4A). Accordingly, we selected two cutoff values of 19.7 and 51.8 cm^2/m^2 at the points where HRs were just <1.2. Thus, these patients with cirrhosis were divided into low (SATI $<$ 19.7 cm^2/m^2), moderate (19.7 $\leq$ SATI $\leq$ 51.8 cm^2/m^2), and high (SATI $>$ 51.8 cm^2/m^2) SATI groups, with the mortality of 31.5% (23/73), 21.7% (43/198), and 27.7% (28/101), respectively.

Nelson–Aalen cumulative risk curve analysis demonstrated that the cumulative probability of mortality was higher in low SATI group than in moderate SATI group, but the difference between them was not statistically significant (Gray's test, $P = 0.052$) (*Figure* 5A). Univariate competing risk analysis demonstrated that low SATI was associated with increased mortality compared with moderate SATI (sHR = 1.66, 95% CI: 0.992–2.78, $P = 0.054$), but their association was not statistically significant. Notably, multivariate competing risk analysis adjusted for age, sex, and MELD score demonstrated that low SATI was an independent predictor of increased mortality (sHR = 1.86, 95% CI: 1.059–3.28, $P = 0.031$) (*Table* 2).

Nelson–Aalen cumulative risk curve analysis demonstrated that the cumulative probability of mortality was higher in high SATI group than in moderate SATI group, but the difference between them was not statistically significant (Gray's test, $P = 0.054$) (*Figure* 5B). Univariate competing risk analysis demonstrated that high SATI was significantly associated with increased mortality compared with moderate SATI (sHR = 1.6, 95% CI: 1–2.54, $P = 0.049$), and multivariate competing risk analysis adjusted for age, sex, and MELD score demonstrated that high SATI was an independent predictor of increased mortality (sHR = 2.007, 95% CI: 1.195–3.37, $P = 0.0085$) (*Table* 2).

VATI and mortality

Pearson correlation tests did not demonstrate any significant correlation between VATI and MELD score (P = 0.09,

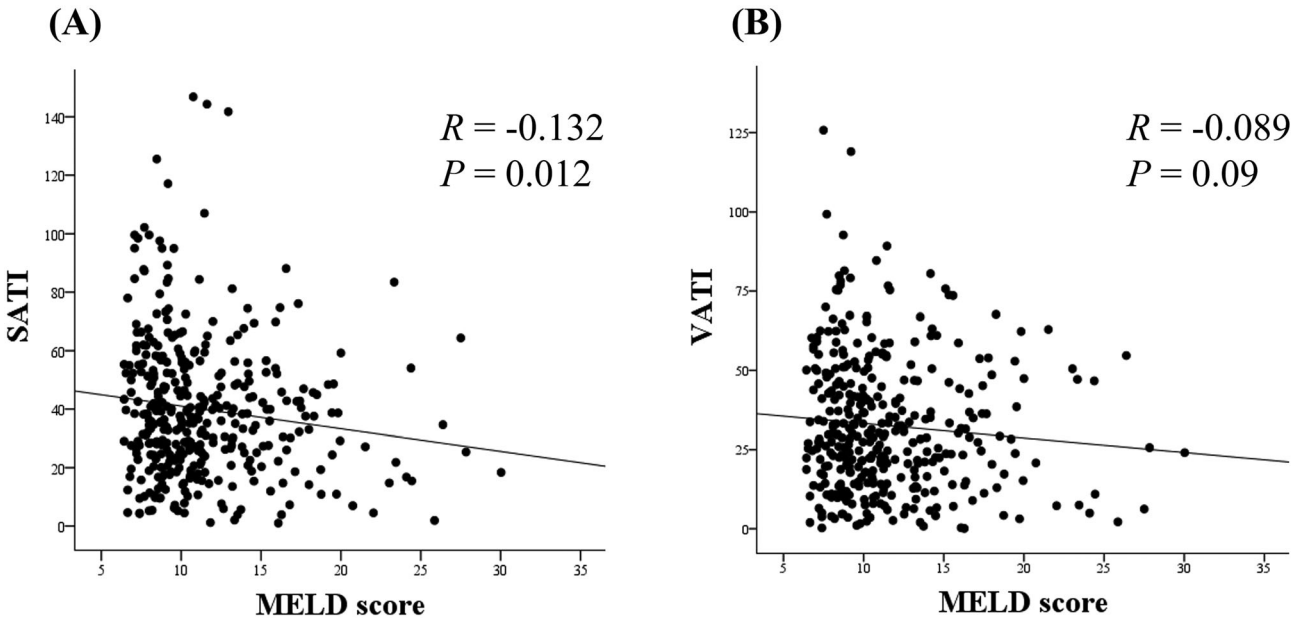

Figure 3 Correlation analyses of SATI and VATI with MELD score.

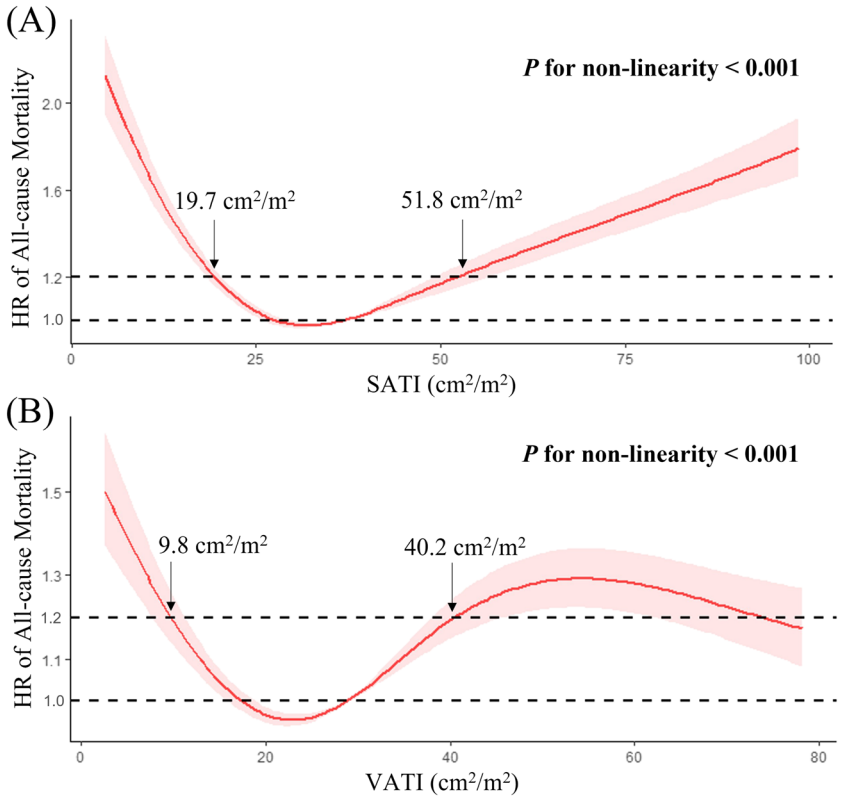

Figure 4 Analyses of restricted cubic spline curves based on Cox proportional hazards models. (A) A U-shaped association between SATI and the risk of death (*P* for non-linearity <0.001). (B) An irregularly shaped association between VATI and the risk of death (*P* for non-linearity <0.001).

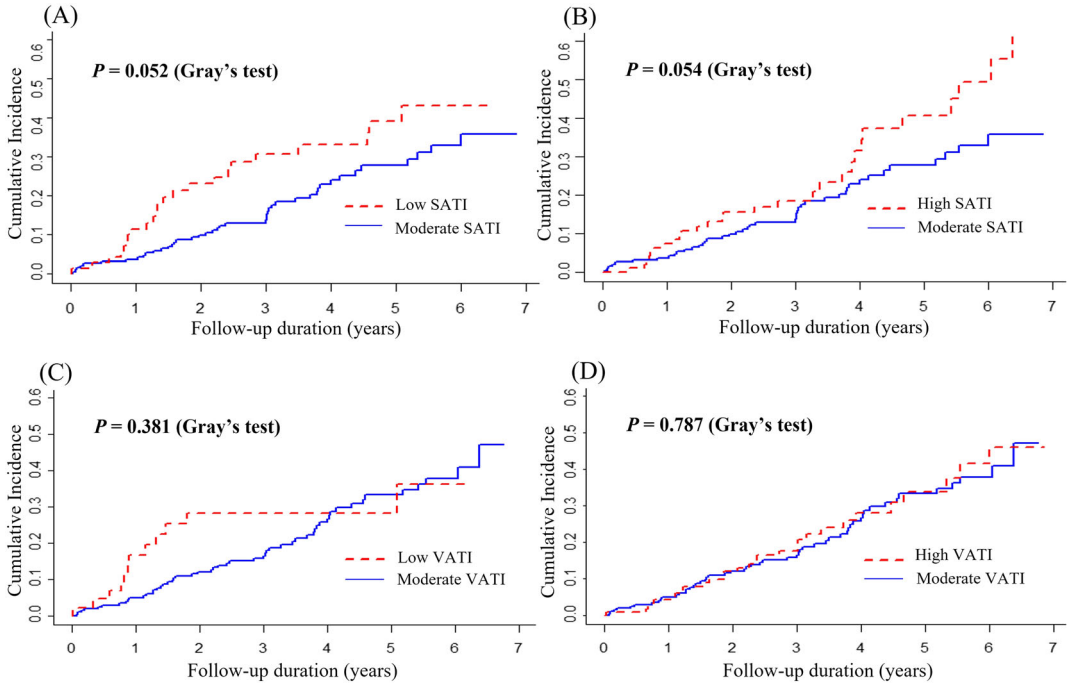

Figure 5 Nelson–Aalen cumulative risk curve analyses showing the effects of SATI and VATI on the long-term mortality of patients with cirrhosis. There was no significant difference in the cumulative probability of mortality between (A) low versus moderate SATI groups (Gray's test, $P = 0.052$), (B) high versus moderate SATI groups (Gray's test, $P = 0.054$), (C) low versus moderate VATI groups (Gray's test, $P = 0.381$), and (D) high versus moderate VATI groups (Gray's test, $P = 0.787$).

Table 2 Competing risk analyses regarding effects of SATI and VATI on long-term mortality in patients with cirrhosis

		Univariate analyses			Multivariate analyses[a]		
Variables (cm^2/m^2)	Mortality	sHR	95% CI	*P* value	sHR	95% CI	*P* value
SATI level							
SATI $<$ 19.7 vs. 19.7 $\leq$ SATI $\leq$ 51.8	31.5% (23/73) vs. 21.7% (43/198)	1.66	0.992–2.78	0.054	1.86	1.059–3.28	**0.031**
SATI $>$ 51.8 vs. 19.7 $\leq$ SATI $\leq$ 51.8	27.7% (28/101) vs. 21.7% (43/198)	1.6	1–2.54	**0.049**	2.007	1.195–3.37	**0.0085**
VATI level							
VATI $<$ 9.8 vs. 9.8 $\leq$ VATI $\leq$ 40.2	27.3% (12/44) vs. 25.6% (53/207)	1.33	0.679–2.58	0.41	1.27	0.599–2.7	0.530
VATI $>$ 40.2 vs. 9.8 $\leq$ VATI $\leq$ 40.2	24.0% (29/121) vs. 25.6% (53/207)	1.06	0.677–1.67	0.79	0.848	0.539–1.34	0.480

Abbreviations: sHR, subdistribution hazard ratio; CI, confidence interval; SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index.
[a]Multivariate analyses by adjusting for age, sex, and MELD score.

$R = -0.089$) (*Figure* 3B). An irregularly shaped association between VATI and the risk of death was identified after adjusting for age, sex, and MELD score (*P* for non-linearity <0.001) (*Figure* 4B). Accordingly, we selected two cutoff values of 9.8 and 40.2 cm^2/m^2 at the points where HRs were just <1.2. Thus, these cirrhotic patients were divided into low (VATI $<$ 9.8 cm^2/m^2), moderate (9.8 $\leq$ VATI $\leq$ 40.2 cm^2/m^2), and high (VATI $>$ 40.2 cm^2/m^2) VATI groups, with the mortality of 27.3% (12/44), 25.6% (53/207), and 24.0% (29/121), respectively.

Nelson–Aalen cumulative risk curve analysis demonstrated no significant difference in the cumulative probability of mortality between low and moderate VATI groups (Gray's test, $P = 0.381$) (*Figure* 5C). Univariate competing risk analysis also demonstrated that low VATI was not significantly associated with increased mortality compared with moderate VATI (sHR = 1.33, 95% CI: 0.679–2.58, $P = 0.41$), and multivariate competing risk analysis adjusted for age, sex, and MELD score further confirmed that low VATI was not a significant predictor of increased mortality (sHR = 1.27, 95% CI: 0.599–2.7, $P = 0.53$) (*Table* 2).

Nelson–Aalen cumulative risk curve analysis demonstrated no significant difference in the cumulative probability of mortality between high and moderate VATI groups (Gray's test, $P = 0.787$) (*Figure* 5D). Univariate competing risk analysis also demonstrated that high VATI was not significantly associated with increased mortality compared with moderate VATI (sHR = 1.06, 95% CI: 0.677–1.67, $P = 0.79$), and multivariate

competing risk analysis adjusted for age, sex, and MELD score further confirmed that high VATI was not a significant predictor of increased mortality (sHR = 0.848, 95% CI: 0.539–1.34, P = 0.48) (*Table* 2).

Discussion

Our study identified a nonlinear U-shaped association between SATI and mortality in patients with liver cirrhosis. Briefly, compared with the moderate SATI group ($19.7 \leq \text{SATI} \leq 51.8$ cm^2/m^2), the low (SATI < 19.7 cm^2/m^2) and high SATI groups (SATI > 51.8 cm^2/m^2) had a higher risk of death.

Dietary intake is often insufficient in patients with cirrhosis, which may be attributed to their loss of appetite caused by leptin[21] and tumour necrosis factor alpha[22] upregulation, limited gastric distensibility secondary to ascites,[23] and dietary restriction related to hepatic encephalopathy.[24] In addition, the absorption of nutrients is impaired in cirrhosis, which is attributed to their bile acid deficiency and small intestinal mucosal and villous atrophy secondary to bacterial overgrowth.[25] Therefore, energy supply from exogenous substrates cannot meet energy demands in some patients with liver cirrhosis.[26] In this case, it has to be partly dependent on adipose tissue stored in the body. Among those with cirrhosis and low SATI, subcutaneous adipose tissue is deficient, thereby compromising energy supply and patients' outcomes.

It was reported that the SATI was significantly lower in patients with hepatic venous pressure gradient (HVPG) >16 mmHg than those with HVPG <10 mmHg (65 ± 33 vs. 91 ± 47 cm^2/m^2, P = 0.028).[27] As known, an increase in HVPG can lead to the occurrence of ascites, variceal bleeding, and hepatic encephalopathy, and increase the risk of death.[28] Therefore, we may infer that low SATI should be associated with high risk of portal hypertension related complications, thereby deteriorating the patients' outcomes.

Excessive accumulation of subcutaneous adipose tissue can lead to chronic inflammation and fibrosis[29–34] (*Figure* 6). Chronic inflammation contributes to insulin resistance and metabolic disorders in the body.[35] Fibrosis restricts the expansion of adipocytes and promotes the deposition of excessive adipose tissue in other organs, including the liver, resulting in lipotoxicity.[36] These changes promote hepatic steatosis, which further activates Kupffer cells in the liver and induces the infiltration of other inflammatory cells, such as T lymphocytes and neutrophils. Subsequently, these inflammatory cells further activate hepatic stellate cells that are involved in the development of liver fibrosis and cirrhosis.[37] Accordingly, in cirrhosis with high SATI, subcutaneous obesity further exacerbates the severity of liver disease and worsens the clinical outcomes. However, it is worth mentioning that the causal association between subcutaneous adipose tissue accumulation and mortality is only an inference based on previous literature. Certainly, we should also consider that subcutaneous adipose tissue accumulation may be only a secondary phenotype as well as poor outcome in liver cirrhosis. It is known that women have more subcutaneous fat than men,[38] and the disturbances of sex hormones and feminization are observed in patients with advanced liver cirrhosis.[39] Furthermore, low testosterone levels are independently associated with a higher risk of death.[40] Regardless, prospective studies are needed to confirm the potential mechanisms.

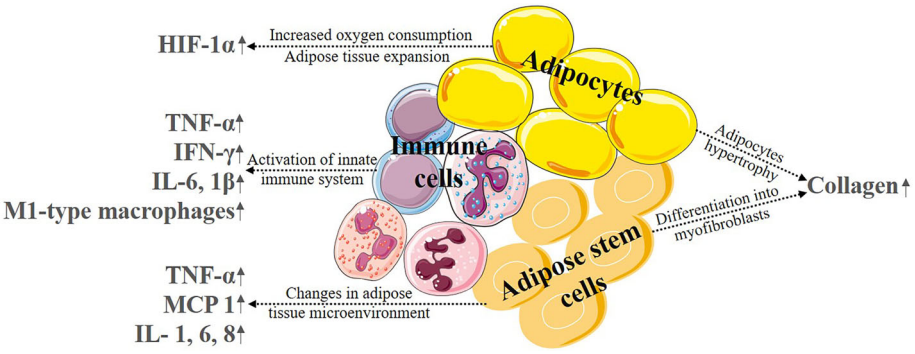

Figure 6 Potential mechanisms of chronic inflammation and fibrosis caused by excessive accumulation of subcutaneous adipose tissue. Adipocytes upregulate inflammatory gene hypoxia-inducible factor-1alpha (HIF-1α) due to the expansion of adipose tissue and the increase of secondary oxygen consumption, and secrete a large amount of collagen due to the adipocytes hypertrophy. Immune cells highly secrete inflammatory factors, including tumour necrosis factor-alpha (TNF-α), interleukin 6(IL-6), 1beta (1β), and interferon-gamma (IFN-γ), with a large number of M1-type macrophages infiltration due to activation of innate immune system. Adipose stem cells highly secrete inflammatory factors, including TNF-α, IL-1, 6, 8, and monocyte chemoattractant protein 1 (MCP-1) due to changes in adipose tissue microenvironment, and differentiate into myofibroblasts which secreting a large amount of collagen.

Abbreviations: TNF-α, tumour necrosis factor-alpha; MCP-1, monocyte chemoattractant protein 1; HIF-1α, hypoxia-inducible factor-1alpha; IL, interleukin; IFN-γ, interferon-gamma.

Unlike SATI, VATI was not associated with long-term prognosis in patients with liver cirrhosis. This might be related to the difference in terms of their contents and functions. Subcutaneous adipose tissue dominates the total adipose tissue.[27] Similarly, in our patients, the median SATI was higher than the median VATI (36.66 cm^2/m^2 vs. 28.81 cm^2/m^2). Subcutaneous adipose tissue can secrete leptin and systematically regulate insulin sensitivity and glucose and lipid metabolism,[41] whereas visceral adipose tissue is metabolically inferior to subcutaneous adipose tissue.[42] Additionally, in mouse models, the transplantation of the donor's subcutaneous adipose tissue into the recipient's visceral region significantly improved the recipient's metabolic performance, whereas the transplantation of the donor's visceral adipose tissue into the recipient's visceral region had little effect.[43]

A major advantage in our study design is that RCS curves based on Cox proportional hazards models were used to establish a U-shaped association between SATI and mortality. In addition, competing risk analyses were employed, in which liver transplantation was considered as a competing risk event, and the risk of death could be evaluated more appropriately as compared with traditional survival analyses.

Our study had some limitations. First, nutritional interventions during follow up were not recorded, which might be beneficial for survival. Second, CT images of the L3 vertebrae and height data were missing in some patients, probably producing a selection bias. Third, considering the difference in the quantity of adipose tissue among regions and ethnicities, the cutoff values of SATI derived from our study cannot be extrapolated and need to be further standardized. Fourth, we were unable to separately analyse the effects of superficial and deep subcutaneous adipose tissues on the mortality of patients with subcutaneous obesity. The former preferentially expresses metabolic genes and shows marked adipocyte hypertrophy, whereas the latter overexpresses inflammatory genes and displays obvious inflammatory infiltration.[44]

In conclusion, a modest amount of subcutaneous adipose tissue may be beneficial for long-term survival in cirrhotic patients, whereas its excessive deficiency or accumulation may be harmful. Early identification and timely intervention of these harms may improve long-term outcomes in patients with cirrhosis.

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Conflict of interest

None declared.

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