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Original Article

Appendicular Skeletal Muscle Mass to Visceral Fat Area Ratio Predicts Hepatic Morbidities

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Background/Aims: Reports on the association between sarcopenic visceral obesity and non-alcoholic fatty liver disease (NAFLD)-associated morbidities remain scarce. We investigated the association between sarcopenia and visceral obesity, and the influence of this association on hepatic and coronary comorbidities.

Methods: The appendicular skeletal muscle mass to visceral fat area ratio (SV ratio) was evaluated using bioelectric impedance analysis. NAFLD and significant liver fibrosis were assessed using transient elastography, and high atherosclerotic cardiovascular disease (ASCVD) risk was defined as a 10-year ASCVD risk score >10%. Sarcopenia was defined as appendicular skeletal muscle mass adjusted by body mass index (<0.789 for men and <0.512 for women).

Results: In total, 82.0% (n=1,205) of the entire study population had NAFLD, and 14.6% of these individuals (n=176) exhibited significant liver fibrosis. Individuals with the lowest SV ratio had a significantly increased risk of NAFLD, significant liver fibrosis, and high ASCVD risk (all p<0.05). Individuals with both the lowest SV ratio and sarcopenia had the highest risk of developing NAFLD (odds ratio [OR]=3.11), significant liver fibrosis (OR=2.03), and high ASCVD risk (OR=4.15), compared with those with a higher SV ratio and without sarcopenia (all p<0.05).

Conclusions: Low SV ratio combined with sarcopenia was significantly associated with an increased risk of NAFLD, significant liver fibrosis, and high ASCVD risk among individuals with a high risk of NAFLD. **(Gut Liver 2024;18:509-519)**

Key Words: Non-alcoholic fatty liver disease; Obesity; Sarcopenia; Morbidity

INTRODUCTION

Sarcopenia is a progressive chronic muscle disorder complicated by other chronic diseases.[1] The burden of sarcopenia is magnified due to its high morbidity and mortality and increased socioeconomic costs.[2] The prevalence of sarcopenia is expected to increase in the future as the rate of aging and metabolic diseases increases.[3,4] Although sarcopenia is more prevalent in the older population, the decline in muscle mass starts earlier after peak in young adulthood,[1] indicating that the adverse effects of sarcopenia can also occur in the young population. Along with the loss of muscle mass, increased adiposity or sarcopenic obesity frequently occurs.[5] As sarcopenia and obesity share common denominators,[5] mainly insulin resistance, sarcopenic obesity causes more aggravated metabolic dysfunction than either sarcopenia or obesity alone.[5,6]

With the increase in obesity prevalence, nonalcoholic fatty liver disease (NAFLD) is the most predominant phenotype of chronic liver diseases worldwide, and over a quarter of adults suffer from NAFLD.[7] NAFLD is significantly associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), hepatic morbidity, including cirrhosis and hepatocellular carcinoma (HCC), and complication-related mortality.[8,9] Among these complications, ASCVD is the leading cause of mortality in individuals with NAFLD.[8] The dense linkages between NAFLD and ASCVD likely arise from the evidence that the

liver plays a central role in glucose and lipid metabolism, independent of other cardiometabolic risk factors, such as diabetes, obesity, hypertension, and dyslipidemia.[9,10] The contribution of NAFLD to HCC or cirrhosis is parallel to obesity, suggesting the role of lipotoxicity and insulin resistance, which are reflected as visceral adiposity in the pathogenesis of NAFLD-related HCC.[11,12]

Recently, clinical unfavorable outcomes of sarcopenic obesity, especially high visceral adiposity, have been reported.[5,13-15] This evidence suggests that the assessment of adiposity and muscle mass measurement is required to identify high-risk populations. The ratio of appendicular skeletal muscle mass (ASM) to visceral fat area (VFA) is a single integrated assessment used to determine sarcopenic visceral obesity, considering both muscle mass and visceral fat.[13,15] Although a close association between sarcopenia and NAFLD has been clearly demonstrated in previous studies,[10,16,17] reports on the association between sarcopenic visceral obesity and NAFLD-associated morbidities are scarce.

Thus, we investigated whether sarcopenic visceral obesity, as an expression of ASM to VFA ratio (SV ratio), is significantly associated with the risk of NAFLD and its hepatic and coronary comorbidities.

MATERIALS AND METHODS

1. Study population

In this retrospective study, patients were identified by reviewing case notes using electronic medical records at Severance Hospital, a tertiary university hospital in Korea. In total, 2,055 patients (aged ≥20 years) referred from primary clinics to assess NAFLD and visited the Liver Center between January 2012 and December 2018 were included.

Individuals were excluded if they met any of the following criteria: (1) history of HCC or liver cirrhosis; (2) positive serologic markers for viral hepatitis, including hepatitis B surface antigen and hepatitis C antibody; (3) history of addiction to alcohol, heavy alcohol consumption (≥210 g/week for men or ≥140 g/week for women); (4) use of medications associated with NAFLD (e.g., amiodarone, methotrexate, tamoxifen, or valproate); (5) pregnant or nursing women; (6) unreliable transient liver elastography (TE) data; and (7) insufficient clinical or laboratory data.

Patient records were anonymized and de-identified prior to the analysis and informed consents were waived. The study protocol was approved by the Institutional Review Board of Yonsei University College of Medicine (IRB number: 2019-2169-002).

2. Assessment of hepatic steatosis and fibrosis

Abdominal ultrasonography was performed in all patients, and NAFLD was confirmed. TE (FibroScan®; Echosens, Paris, France) was used to assess hepatic steatosis burden and degree of fibrosis. The detecting power of TE is comparable to that of liver biopsy, which is superior to that of abdominal ultrasound.[18-21] Liver fat content was evaluated using the controlled attenuation parameter (CAP), and liver fibrotic burden was estimated via liver stiffness measurement (LSM). Both CAP and LSM measure ultrasonic attenuations at 3.5 MHz, using signals acquired by TE with an M probe. Individuals whose results were unmeasurable or invalid using M probe were excluded. A ratio of the interquartile range to the median of the LSM (interquartile range/median, LSM) ≤30% was considered a reliable measurement.[22] The NAFLD was determined using a previously reported CAP cutoff value (≥ 238 dB/m).[18] The hepatic fibrosis cutoff value was LSM ≥7.5 kPa for significant liver fibrosis (≥F2).[19,23] Among 215 individuals with NAFLD (87 men and 128 women), follow-up TE was performed for 6 to 24 months (median 11.0 months).

3. Assessment of muscle mass and visceral adiposity

A multi-frequency bioelectrical impedance analyzer (InBody 720; Biospace Co., Seoul, Korea) was used to measure body composition. ASM was measured as the sum of skeletal muscle mass in both legs and arms, and visceral adiposity was assessed by VFA (cm^2). Multi-frequency bioelectrical impedance analyzer has been validated for assessing body composition, showing an excellent correlation with dual-energy X-ray absorptiometry or abdominal computed tomography.[24] SV ratio was categorized into sex-specific tertiles (cutoff value of 0.211 and 0.282 for men; 0.116 and 0.153 for women). ASM was divided by body mass index (BMI), considering the presence of low muscle mass and sarcopenia, which was characterized by a cutoff value of <0.789 for men and <0.512 for women, according to the Foundation for the National Institutes of Health sarcopenia project.[25] Another sarcopenia definition, ASM adjusted by body weight, was applied (<31.5% for men and <22.1% for women).[26]

4. Evaluation of ASCVD risk and disease risk components

ASCVD risk was estimated using a 10-year ASCVD risk score from the 2013 American College of Cardiology/American Heart Association guidelines equation.[27] An American College of Cardiology/American Heart Association ASCVD risk score >10% was classified as a "high ASCVD risk."[27] Presence of diabetes mellitus, hypertension, or dyslipidemia was defined according to the International

Classification of Diseases 10th revision or if patients were using medications for managing each disease. Information on previous ASCVD history was collected by reviewing each patient's International Classification of Diseases 10th revision code. Lifestyle behaviors, including smoking and alcohol consumption, were described in the medical history.

5. Statistical analysis

Data are expressed as mean±standard deviation for continuous variables and as numbers (n) or percentages (%) for categorical variables. We analyzed participants' characteristics according to SV ratio tertiles using one-way analysis of variance to compare continuous variables and chi-square tests for categorical variables, followed by post hoc analyses using the Bonferroni method. To better reflect muscle mass and visceral adiposity with sarcopenia, we classified individuals according to the presence of sarcopenia and SV ratio. The highest and middle sex-specific SV ratio tertiles were categorized into higher SV ratio group, whereas the lowest SV ratio tertile group was classified into lowest SV ratio group. For individuals with follow-up TE data, the proportion of those with the lowest SV ratio was skewed (46.7%); therefore, we re-classified individuals with sex-specific median SV ratio cutoff of 0.232 for men and 0.131 for women, as low SV ratio group and high SV ratio group.

Multivariate logistic regression analysis was used to determine the independent association between SV ratio, NAFLD, significant liver fibrosis, and high ASCVD risk after adjusting for age and sex in model 1. Variables in model 1, cigarette smoking, alcohol consumption, BMI, homeostatic model assessment for insulin resistance, liver enzymes, lipid profile, diabetes, and hypertension were adjusted in model 2. The risk of significant liver fibrosis was estimated in individuals with NAFLD (ASCVD risk >10%). In a sensitivity analysis, the risk of high probability of ASCVD was calculated in a population free from previous ASCVD. As triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, insulin, homeostatic model assessment for insulin resistance, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, and platelet values were not normally distributed, analyses were performed using log-transformed data to achieve approximately symmetrical distributions. We tested differences in CAP and LSM using analysis of covariance models, with SV ratio and sarcopenia as fixed effects and age and sex as covariates. Statistical analyses were performed using IBM SPSS version 27.0 for Windows (IBM Corp., Armonk, NY, USA). $p<0.05$ was considered statistically significant.

RESULTS

1. Baseline characteristics

After excluding participants who met our exclusion criteria, 1,455 individuals (634 men and 821 women) were included in the final statistical analysis. The baseline characteristics of the study population are shown in Table 1. The mean age of the entire population was 57.4 years, and the mean BMI was 26.2 kg/m^2. The prevalence rates of hypertension, diabetes, and dyslipidemia were 42.7%, 62.6%, and 51.5%, respectively. Of the entire study population with a high risk of NAFLD based on referral for the evaluation of NAFLD, 82.0% (n=1,205) had NAFLD. Of these, 176 (14.6%) had significant liver fibrosis. Overall, 247 individuals (16.8%) have sarcopenia.

2. Comparison between SV tertile groups

Dividing by SV ratio, the proportion of men was statistically similar across the three tertile groups (p=0.978), and the mean age was lower in the highest SV ratio tertile group than in other groups (p=0.010). Individuals in the highest SV ratio tertile had a significantly lower BMI, waist circumference, blood pressure, fasting blood glucose, homeostatic model assessment for insulin resistance, triglyceride, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase than those in the lowest SV ratio tertile (all $p<0.05$), whereas high-density lipoprotein cholesterol level was significantly higher in individuals in the highest SV ratio tertile ($p<0.05$). Individuals in the highest SV ratio tertile had a significantly lower VFA ($p<0.001$) and statistically similar ASM (p=0.368), compared with those in the lowest SV ratio tertile. In addition, significantly low prevalence rates of hypertension and diabetes were observed in individuals with the highest SV ratio compared with those with the lowest SV ratio (all $p<0.05$). The proportion of individuals treated with oral hypoglycemic agents or insulin was 62.6% overall (patients classified as having diabetes were treated with oral hypoglycemic agents or insulin), and this proportion was the lowest in the highest SV ratio tertile (56.9%), compared with other groups.

The mean values of CAP, LSM, and ASCVD risk score were the lowest in the tertile group with the highest SV ratio, and the proportion of NAFLD, significant liver fibrosis, sarcopenia, prior ASCVD history, and high ASCVD risk were the lowest in individuals with the highest SV ratio. The proportion of current smokers was comparable among the groups (p=0.815).

Table 1. Baseline Characteristics of Study Population

Variable	Entire population (n=1,455)	Lowest SV ratio tertile (n=489)	Middle SV ratio tertile (n=481)	Highest SV ratio tertile (n=485)	p-value
Male sex	634 (43.2)	211 (43.0)	212 (43.4)	211 (43.1)	0.978
Age, yr	57.4±14.0	58.6±16.6	57.6±13.2	55.9±11.7¶	0.010
BMI, kg/m^2	26.2±4.1	29.0±4.3	26.1±3.0¶	23.5±2.7¶,#	<0.001
ASM, kg	19.1±4.9	19.2±4.6	19.2±4.6	19.1±4.9	0.386
Ratio of ASM to BMI	0.7±0.2	0.6±0.1	0.7±0.1¶	0.8±0.2¶,#	<0.001
VFA, cm^2	113.4±43.9	156.6±36.8	109.9±24.4¶	73.8±19.2¶,#	<0.001
Waist circumference, cm	90.6±10.5	97.1±10.5	90.5±7.7¶	83.1±7.4¶,#	<0.001
Systolic BP, mm Hg	126.3±15.6	129.0±15.9	126.9±14.9	122.9±15.5¶,#	<0.001
Diastolic BP, mm Hg	76.2±11.0	77.5±11.0	76.5±11.0	74.6±11.0¶	0.002
Fasting blood glucose, mg/dL	128.7±40.0	123.2±38.2	121.2±34.3	121.2±34.3¶	0.005
Insulin, μIU/mL*	12.4±13.7	15.8±17.2	12.1±11.6¶	9.3±10.6¶,#	<0.001
HOMA-IR*	3.9±5.1	5.1±6.4	3.7±3.8¶	2.9±4.6¶,#	<0.001
AST, IU/L*	30.5±27.1	34.7±31.4	29.8±25.4¶	27.1±23.3¶,#	<0.001
ALT, IU/L*	34.9±40.4	40.4±49.6	35.2±41.0	29.0±26.0¶,#	<0.001
Gamma-GT, IU/L*	40.4±53.3	47.1±58.4	40.8±47.8	33.3±52.4¶	0.007
Albumin, mg/dL	4.4±1.8	4.4±1.7	4.5±1.9	4.5±1.9	0.725
TC, mg/dL	177.1±43.2	176.3±44.1	177.1±44.0	177.8±41.6	0.853
HDL-C, mg/dL*	47.8±11.7	46.7±11.0	47.3±10.8	49.5±12.9¶	<0.001
Triglyceride, mg/dL*	142.0±86.3	165.5±109.6	153.2±82.9	142.0±86.3¶,#	<0.001
LDL-C, mg/dL*	101.0±49.6	99.6±38.0	103.1±54.3	102.4±54.6	0.360
Hemoglobin, g/dL	13.9±1.5	13.9±1.6	13.9±1.6	13.9±1.6	0.966
HbA1c, %	7.1±1.5	7.4±1.7	7.1±1.5	6.7±1.3¶	<0.001
Platelet, 10^9/L*	244.4±65.8	245.8±68.2	243.8±65.7	243.4±63.5	0.878
Uric acid, mg/dL	5.2±2.1	5.3±1.5	5.2±2.3	5.1±2.3	0.416
eGFR, mL/min/1.73 m^2	92.7±20.1	91.7±22.6	91.9±18.7	94.6±18.6	0.036
Hypertension	878 (42.7)	365 (53.5)	311 (45.3)¶	202 (29.4)¶,#	<0.001
Diabetes mellitus	920 (62.6)	340 (69.2)	301 (61.7)	279 (56.9)¶	<0.001
Dyslipidemia	757 (51.5)	265 (54.0)	253 (51.8)	239 (48.8)	0.104
CAP, dB/m	280.8±47.7	396.7±42.1	282.9±46.0¶	261.0±48.3¶,#	<0.001
LSM, kPa	6.1±4.1	7.2±5.6	5.8±3.4¶	5.2±2.2¶,#	<0.001
NAFLD†	1,205 (82.0)	463 (94.3)	416 (85.2)¶	326 (66.5)¶,#	<0.001
Liver fibrosis‡	176 (14.6)	94 (20.3)	51 (12.3)¶	31 (9.5)¶	<0.001
Sarcopenia§	247 (16.8)	202 (41.1)	40 (8.2)¶	5 (1.0)¶,#	<0.001
Previous ASCVD	215 (14.6)	94 (19.1)	68 (13.9)	53 (10.8)¶	<0.001
ASCVD risk score‖	14.8±15.9	19.8±18.8	14.3±14.9¶	9.8±11.3¶,#	<0.001
High ASCVD risk (>10%)	606 (46.2)	258 (58.6)	201 (46.9)¶	147 (33.1)¶,#	<0.001
Current cigarette smoker	110 (7.5)	36 (7.3)	40 (8.2)	34 (6.9)	0.815

Data are presented as number (%) or mean±SD.

SV, ASM to VFA ratio; ASM, appendicular skeletal muscle mass; VFA, visceral fat area; BMI, body mass index; BP, blood pressure; HOMA-IR, homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GT, glutamyl transpeptidase; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; ASCVD, atherosclerotic cardiovascular disease.

*Log transformed; †Fatty liver disease was defined as CAP ≥238 dB/m; ‡Liver fibrosis was defined as LSM ≥7.5 dB/m in patients with NAFLD; §Sarcopenia was defined as ratio of appendicular muscle mass to BMI with cutoff 0.789 for men and 0.512 for women; ‖ASCVD risk score calculated in 1,313 individuals; ¶p<0.05 by *post hoc* analyses when compared with the lowest SV ratio tertile; #p<0.05 by *post hoc* analyses when compared with the middle SV ratio tertile.

3. Associations among SV ratio, sarcopenia, NAFLD, and significant liver fibrosis

As there was a statistically significant difference between SV ratio stratified by tertiles and NAFLD (Fig. 1A), we further divided individuals by the presence of sarcopenia. The prevalence of NAFLD gradually decreased from the lowest to the highest SV ratio tertile group without sarcopenia (p for trend <0.001) (Fig. 1B). A decreasing NAFLD prevalence trend in the middle and highest SV ratio group was found in the population with sarcopenia; however, the result was not statistically significant (p>0.05) (Fig. 1C).

Among individuals with NAFLD, the prevalence of significant liver fibrosis also decreased from the lowest to highest SV ratio tertile group (Fig. 1D). After being strati-

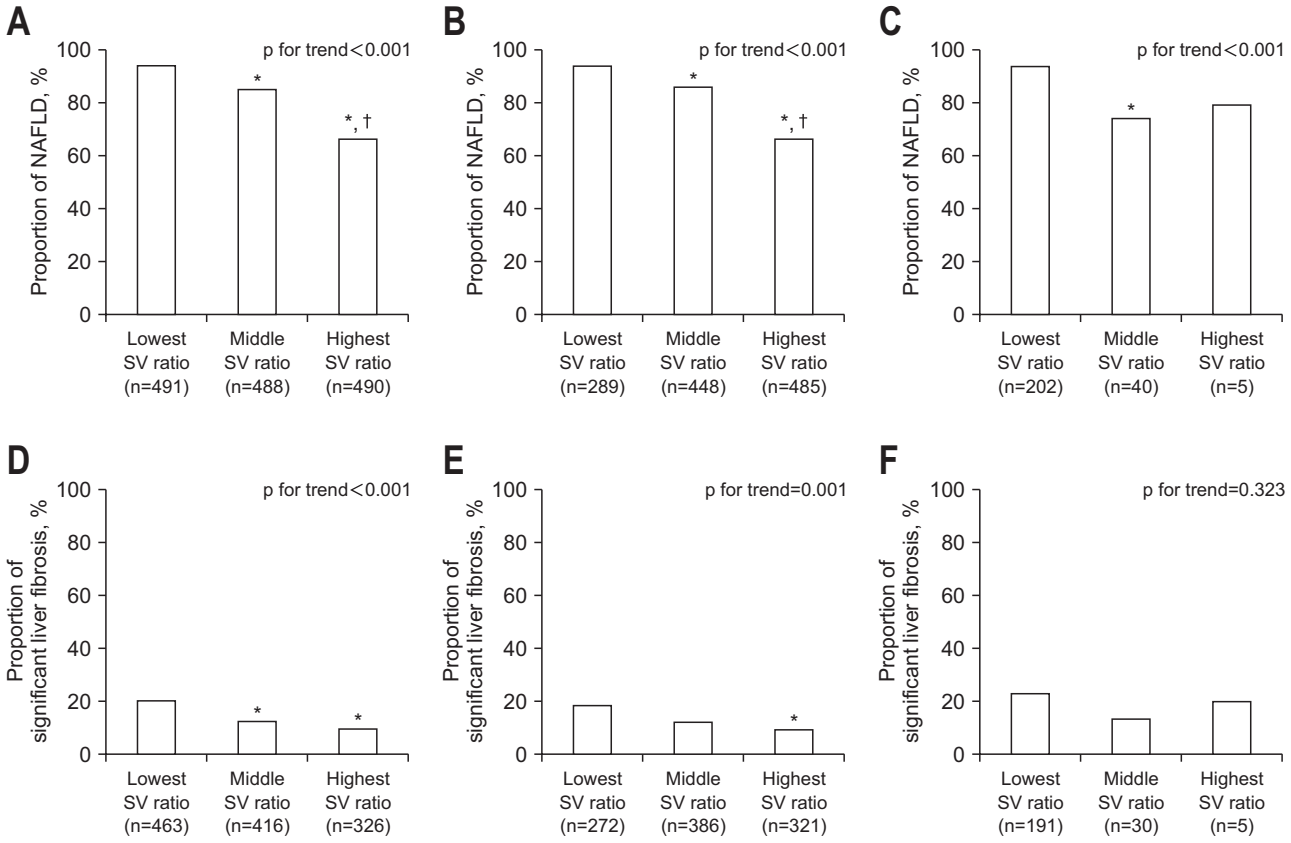

Fig. 1. Associations among SV ratio, NAFLD, and significant liver fibrosis. The proportion of NAFLD in the entire population (A), individuals without sarcopenia (B), and individuals with sarcopenia (C). The proportion of significant liver fibrosis in individuals with NAFLD (D), individuals with NAFLD but without sarcopenia (E), and individuals with NAFLD and sarcopenia (F). SV ratio, appendicular skeletal muscle mass to visceral fat area ratio; NAFLD, nonalcoholic fatty liver disease. *p<0.05 by post hoc analyses when compared with the lowest SV ratio tertile; †p<0.05 by post hoc analyses when compared with the middle SV ratio tertile.

fied according to the presence of sarcopenia, similar results were observed in individuals without sarcopenia (p for trend <0.001) (Fig. 1E), whereas a decreasing trend in the highest SV ratio group was found in the population with sarcopenia; however, the result was not statistically significant (p>0.05) (Fig. 1F).

4. SV ratio rather than sarcopenia is associated with NAFLD and significant liver fibrosis

To further assess the association between sarcopenia, SV ratio (higher [highest plus middle] vs lowest), and hepatic morbidities, we categorized the individuals according to sarcopenia and SV ratio. The prevalence of NAFLD gradually increased in individuals without sarcopenia and higher SV ratio to individuals with sarcopenia and the lowest SV ratio (75.8% vs 94.1% vs 77.8% vs 94.6%; all p<0.001) (Fig. 2A). Individuals without sarcopenia and with the lowest SV ratio had a significantly increased proportion of NAFLD compared to those with sarcopenia and a higher SV ratio (p<0.05) (Fig. 2A).

Among individuals with NAFLD, the proportion of significant liver fibrosis showed similar results; individuals with the lowest SV ratio regardless of the presence of sarcopenia had a significantly higher prevalence of significant liver fibrosis than individuals without sarcopenia and a higher SV ratio (p<0.05) (Fig. 2B).

5. Multiple logistic regression analysis for NAFLD and significant liver fibrosis

We analyzed the risk of NAFLD according to sarcopenia and the SV ratio after adjusting for multiple confounders (Table 2). In univariate analysis, individuals with sarcopenia and the lowest SV ratio had a significantly higher risk of NAFLD (odds ratio [OR]=5.55; p<0.001), followed by individuals with the lowest SV ratio but without sarcopenia (OR=5.12; p<0.001), compared with individuals with a higher SV ratio but without sarcopenia. In model 1, adjusted for sex and age, individuals with sarcopenia and the lowest SV ratio had a significantly higher risk of NAFLD (OR=6.76; p<0.001), followed by individuals with the lowest SV ratio but without sarcopenia (OR=5.38; p<0.001), compared with individuals with a higher SV ratio but

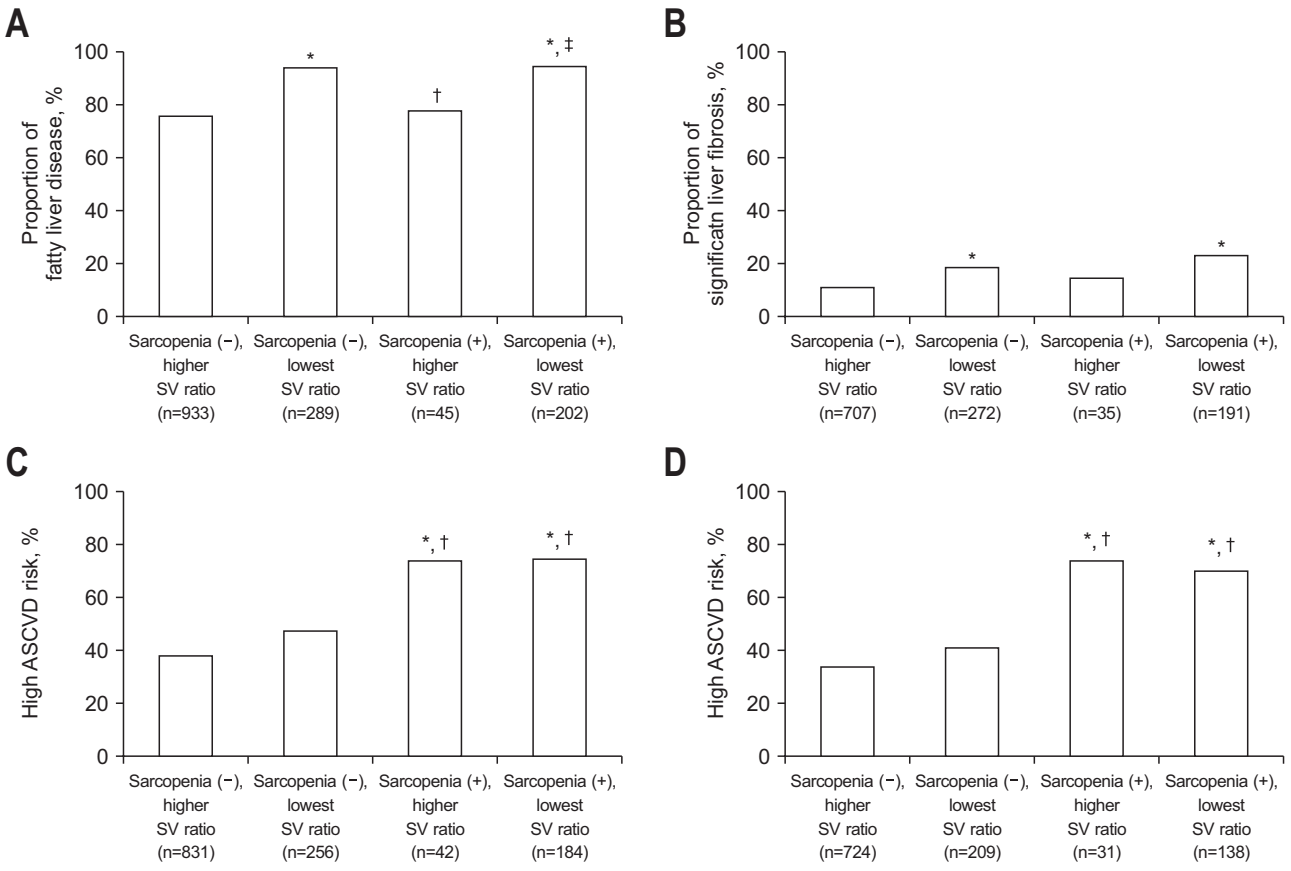

Fig. 2. Associations among sarcopenia, SV ratio, NAFLD, significant liver fibrosis, and high ASCVD risk. The proportion of fatty liver disease (A), significant liver fibrosis (B), high ASCVD risk (C), and high ASCVD risk in individuals without a history of ASCVD (D). SV ratio, skeletal muscle mass to visceral fat area ratio; NAFLD, nonalcoholic fatty liver disease; ASCVD, atherosclerotic cardiovascular disease. *p<0.05 by post hoc analyses when compared with sarcopenia (–) and a higher SV ratio; †p<0.05 by post hoc analyses when compared with sarcopenia (–) and the lowest SV ratio; ‡p<0.05 by post hoc analyses when compared with sarcopenia (+) and a higher SV ratio.

Table 2. Multiple Logistic Regression Analysis for the Risk of NAFLD in the Entire Population and Significant Liver Fibrosis among the Population with NAFLD

Population	Crude OR (95% CI)	p-value	Model 1*		Model 2*	
			OR (95% CI)	p-value	OR (95% CI)	p-value
NAFLD risk in total population						
Sarcopenia (–), higher SV ratio	Reference		Reference		Reference	
Sarcopenia (–), lowest SV ratio	5.12 (3.06–8.54)	<0.001	5.38 (3.21–9.02)	<0.001	2.44 (1.36–4.38)	0.003
Sarcopenia (+), higher SV ratio	1.12 (0.55–2.30)	0.759	1.30 (0.62–2.72)	0.490	1.49 (0.64–3.47)	0.360
Sarcopenia (+), lowest SV ratio	5.55 (2.97–10.38)	<0.001	6.76 (3.57–12.81)	<0.001	3.11 (1.55–6.23)	0.001
Significant liver fibrosis in NAFLD population						
Sarcopenia (–), higher SV ratio	Reference		Reference		Reference	
Sarcopenia (–), lowest SV ratio	1.84 (1.25–2.72)	0.002	1.82 (1.23–2.70)	0.003	1.17 (0.74–1.86)	0.505
Sarcopenia (+), higher SV ratio	1.36 (0.51–3.62)	0.533	1.60 (0.59–4.35)	0.355	1.68 (0.60–4.75)	0.324
Sarcopenia (+), lowest SV ratio	2.45 (1.62–3.70)	<0.001	2.79 (1.82–4.28)	<0.001	2.03 (1.23–3.35)	0.005

NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; CI, confidence interval; SV ratio, appendicular skeletal muscle mass to visceral fat area ratio; HOMA-IR, homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol.
*Model 1: adjusted for age and sex; Model 2: model 1 + body mass index, HOMA-IR, AST, ALT, diabetes mellitus, hypertension, eGFR, triglycerides, HDL-C, and cigarette smoking.

Table 3. Multiple Logistic Regression Analysis for Risk of High ASCVD Risk

Population	Crude OR (95% CI)	p-value	Model 1*		Model 2*	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Entire population						
Sarcopenia (–), higher SV ratio	Reference		Reference		Reference	
Sarcopenia (–), lowest SV ratio	1.45 (1.10–1.93)	0.009	2.15 (1.34–3.45)	0.001	1.46 (0.79–2.72)	0.230
Sarcopenia (+), higher SV ratio	4.57 (2.27–9.22)	<0.001	1.17 (0.44–3.15)	0.753	1.02 (0.32–3.26)	0.976
Sarcopenia (+), lowest SV ratio	4.73 (3.30–6.77)	<0.001	3.39 (1.75–6.56)	<0.001	2.66 (1.13–6.25)	0.025
Without previous ASCVD						
Sarcopenia (–), higher SV ratio	Reference		Reference		Reference	
Sarcopenia (–), lowest SV ratio	1.35 (0.99–1.85)	0.062	2.11 (1.28–3.49)	0.004	1.60 (0.81–3.13)	0.173
Sarcopenia (+), higher SV ratio	5.55 (2.25–12.59)	<0.001	1.48 (0.48–4.60)	0.496	1.07 (0.30–3.76)	0.920
Sarcopenia (+), lowest SV ratio	4.57 (3.08–6.79)	<0.001	4.47 (2.20–9.09)	<0.001	4.15 (1.65–10.45)	0.003

ASCVD, atherosclerotic cardiovascular disease; OR, odds ratio; CI, confidence interval; SV ratio, appendicular skeletal muscle mass to visceral fat area ratio; HOMA-IR, homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

*Model 1: adjusted for age and sex; Model 2: model 1 + body mass index, HOMA-IR, AST, ALT, diabetes mellitus, hypertension, eGFR, triglyceride, HDL-C, and cigarette smoking.

without sarcopenia. Individuals with sarcopenia and a higher SV ratio did not have an increased risk (OR=1.30; p=0.490). In further adjusted model 2, individuals with the lowest SV ratio and sarcopenia and those with the lowest SV ratio but without sarcopenia showed 3.11- and 2.44-fold increased risks of NAFLD (all p<0.05), respectively.

Among individuals with NAFLD (Table 2), the risk of significant liver fibrosis was analyzed using multivariable logistic regression models. In model 1, adjusted for sex and age, individuals with sarcopenia and the lowest SV ratio had a significantly higher risk of significant liver fibrosis (OR=2.79; p<0.001). In a fully adjusted model (model 2), individuals with sarcopenia and the lowest SV ratio had a significantly higher risk of significant liver fibrosis (OR=2.03; p=0.005), whereas individuals with sarcopenia and a higher SV ratio or individuals without sarcopenia and the lowest SV ratio had an inconsequential risk of significant liver fibrosis (OR=1.17; p=0.505 for the lowest SV ratio without sarcopenia, OR=1.68; p=0.324 for the higher SV ratio with sarcopenia). When sarcopenia was defined as ASM adjusted by body weight, similar results were observed (Supplementary Table 1).

6. Associations among high ASCVD risk, sarcopenia, and SV ratio

As sarcopenia can increase ASCVD risk, we evaluated whether SV ratio affected the association between high ASCVD risk and sarcopenia. Individuals with sarcopenia were more likely to be categorized as having a high ASCVD risk, regardless of the SV ratio (p<0.05) (Fig. 2C). No statistical difference in high ASCVD risk was observed according to SV ratio among individuals with sarcopenia (p=0.998). Similar results were observed in individuals without a history of ASCVD (Fig. 2D).

7. Multiple logistic regression analysis for high ASCVD risk

The association between high ASCVD risk, sarcopenia, and SV ratio after multistep adjustments is shown in Table 3. In the crude model, the risk for high ASCVD risk was the highest in individuals with sarcopenia and the lowest SV ratio (OR=4.73; p<0.001), followed by individuals with sarcopenia and a higher SV ratio (OR=4.57; p<0.001), and individuals with the lowest SV ratio, but without sarcopenia (OR=1.45; p=0.009). Model 1 showed that the increased risk of high ASCVD was similarly maintained in individuals with both sarcopenia and the lowest SV ratio (OR=3.39; p<0.001), and in those without sarcopenia and the lowest SV ratio (OR=2.15; p=0.001). In model 2, individuals with sarcopenia and the lowest SV ratio had a significantly higher risk of high ASCVD risk (OR=2.66; p=0.025), whereas the other groups did not achieve statistical significance (all p>0.05). When individuals without a history of ASCVD were selected, the main findings were similar.

8. Higher improvement in hepatic steatosis in individuals with higher SV ratio

After a median of 11 months, 214 individuals with NAFLD were followed up for TE (Supplementary Table 2). Although the baseline CAP value was comparable between lowest and higher SV ratio groups (p=0.380), individuals with high SV showed a higher improvement in CAP values during follow-up (mean 312.4 dB/m at baseline to 305.6

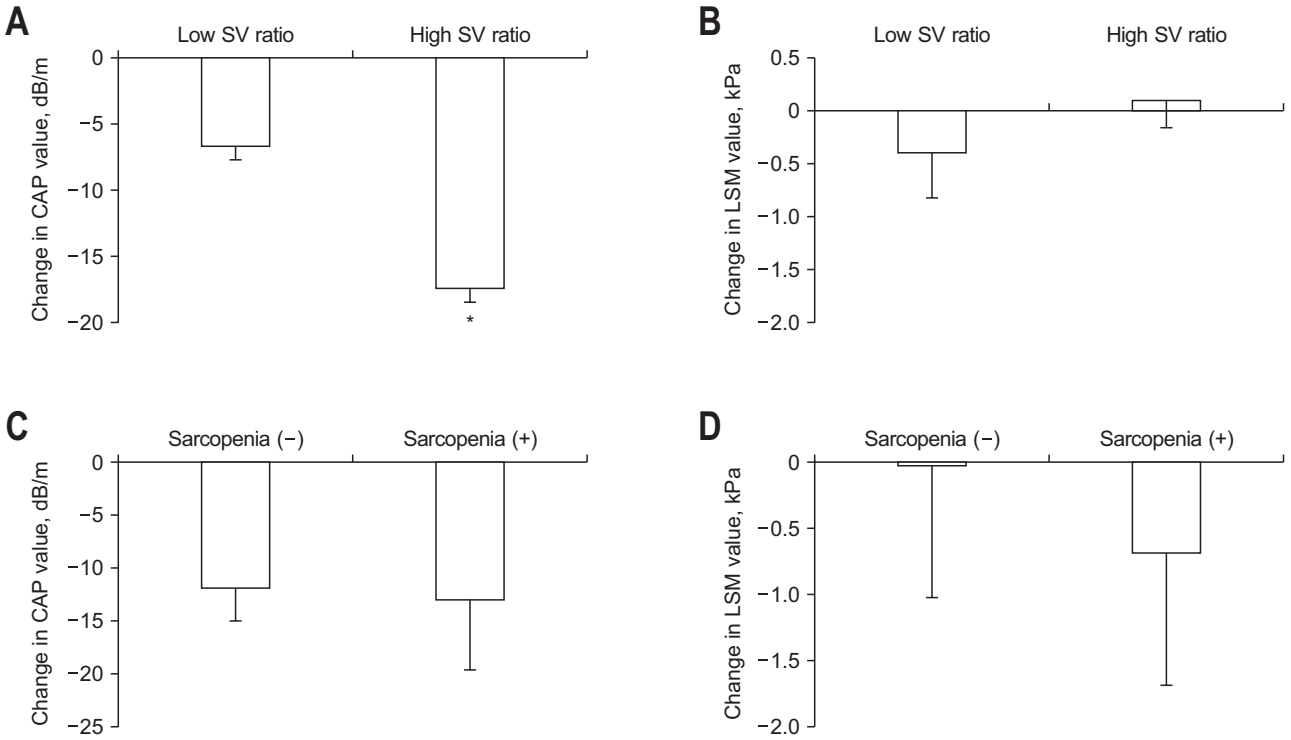

Fig. 3. Changes in CAP and LSM values in individuals with NAFLD. Changes in the CAP and LSM value according to the SV ratio (A, B) and sarcopenia (C, D) among individuals with NAFLD. Data are presented as the mean±SD. Between-group differences (change from baseline) were tested for significance using analysis of covariance.
CAP, controlled attenuation parameter; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; SV ratio, skeletal muscle mass to visceral fat area ratio. *p=0.049 for the mean change from baseline.

dB/m at follow-up; mean change –6.8 dB/m in low SV ratio group, p=0.081; mean 308.0 dB/m at baseline to 290.6 dB/m at follow-up; mean change –17.5 dB/m in high SV ratio group, p<0.001), whereas there was no change in improvement of hepatic fibrosis, assessed by LSM (p>0.05). The analysis of covariance showed that individuals with high SV ratio tended to have a decreased CAP value, whereas the LSM value remained (Fig. 3). When the population stratified by sarcopenia presence, no significant changes in CAP or LSM values were observed between the groups (Fig. 3).

DISCUSSION

In the current study, we observed that individuals with the lowest SV ratio had unfavorable clinical and laboratory characteristics, compared with those with a higher SV ratio, whereas ASM was statistically similar across the three tertile groups. Additionally, we observed that SV ratio, rather than sarcopenia, was more closely associated with hepatic comorbidities, including NAFLD, significant liver fibrosis, and high ASCVD risk in the entire population with a high risk of NAFLD, independent of other confounders. Individuals with coexisting sarcopenia and the lowest SV ratio had a 3.1-fold increased risk of NAFLD in the entire population and a 2.0-fold increased risk of significant liver fibrosis among those with NAFLD. Moreover, individuals with coexisting sarcopenia and the lowest SV ratio had a 2.6-fold and 4.1-fold increased risk of high ASCVD risk in the entire population and in the subgroup without previous ASCVD history, respectively. Finally, individuals with a higher SV ratio were more likely to experience an improvement in hepatic steatosis than those with the lowest SV ratio.

This study had some clinical implications. First, we showed that SV ratio, as a measure of sarcopenic visceral obesity, can be used to identify metabolically unhealthy individuals with NAFLD. Although sarcopenia is closely associated with the risk of hepatic morbidities, such as NAFLD, and the degree of liver fibrosis, indicating the clinical importance of ASM assessment,[10,22,28] the issue of how risk stratification should be assessed in patients with the same ASM with different visceral adiposity remains. We noticed a negative correlation between ASM and VFA (Pearson correlation coefficient=–0.206, p<0.001) after adjusting for age, sex, and BMI in entire population. Moreover, in those with NAFLD, LSM and VFA showed a positive association after adjusting for age and sex (Pearson

correlation coefficient=0.304, p<0.001). Indeed, a recent longitudinal study showed that low SV ratio, instead of ASM, independently predicted NAFLD development.[15] Similarly, our study demonstrated that individuals with low SV ratio had a greater risk of NAFLD and fibrotic burden, whereas the absolute value of ASM or mean age can significantly affect the risk of hepatic dysfunction. Additionally, individuals with a higher SV ratio at baseline were more likely to experience an improvement in hepatic steatosis than those with the lowest SV ratio. In our study, among the population with sarcopenia, the risk of NAFLD increased mildly in individuals with a higher SV ratio (OR=1.49) without statistical significance, whereas it increased abruptly in those with a low SV ratio (OR=3.11), which might indicate that SV ratio is closely associated with NAFLD in the clinical setting for sarcopenia treatment. Additionally, the risk for NAFLD increased even in individuals with a lower SV ratio and in those without sarcopenia (OR=2.44). However, no significant change was observed in the CAP or LSM values in individuals without sarcopenia. Although further validation studies are required, this finding suggests that visceral adiposity rather than body weight better reflects actual body fat associated with steatotic burden on the liver. Therefore, our findings implies that SV ratio can provide more detailed information on risk stratification.

Second, we showed that the SV ratio combined with sarcopenic index could be used to assess the risk of ASCVD. The potential link between sarcopenic visceral adiposity and ASCVD have been explained by several previous studies. A previous study by Kim *et al.*[13] showed a correlation between SV ratio and arterial stiffness using brachial-ankle pulse wave velocity in healthy adults. In another Japanese study, brachial-ankle pulse wave velocity increased stepwise from sarcopenia alone and visceral obesity alone to sarcopenic visceral obesity in men.[29] In a cardiovascular surgery cohort study, patients with sarcopenic visceral obesity had a 3-fold increase in all-cause mortality, compared with those without visceral obesity or sarcopenia.[30] Additionally, sarcopenic visceral obesity, measured by dual-energy X-ray absorptiometry, showed a 2.5-fold increase in incident cardiovascular disease risk in patients with type 2 diabetes.[31] Neither sarcopenia nor visceral obesity alone increased the risk of mortality or incident cardiovascular disease, suggesting that the impact of sarcopenia and visceral obesity on ASCVD plays an additional role. This is consistent with our findings that ASCVD risk was higher in individuals with low SV ratio and sarcopenia than in those with sarcopenia or low SV ratio in the population without prior ASCVD.

Despite the strengths of our study, several issues remained unresolved. First, although TE is a well-validated tool for detecting hepatic steatosis and fibrosis, histological information based on liver biopsy was not available. Second, although we showed the prognostic value of high SV ratio in the improvement of hepatic steatosis during follow-up, as our study was mainly cross-sectional, we could not assess the longitudinal dynamic associations among changes in SV ratio, hepatic steatosis, fibrosis, and ASCVD risk. Third, medical interventions that might affect CAP or LSM during the follow-up period were insufficient. Additionally, due to the lack of information on physical activity, which can affect changes in steatosis or follow-up bioelectrical impedance analyzer data, we could not consider changes in ASM or SV ratio in dynamic transition in NAFLD. Fourth, we applied a pooled cohort risk equation to assess ASCVD risk but could not examine the risk of incident ASCVD events; 10-year ASCVD risk with primary prevention was estimated using the American College of Cardiology/American Heart Association blood cholesterol guidelines. However, because there are some cautions regarding overestimation of ASCVD risk in Asian populations,[32] the current study findings should be interpreted carefully. Finally, as we enrolled individuals with a high risk of NAFLD referred from a local medical center, the prevalence rates of NAFLD (82.0%) and liver fibrosis (14.6%) were higher in this study population than those in the general population.[7]

In conclusion, low SV ratio combined with sarcopenia was significantly associated with an increased risk of NAFLD, significant liver fibrosis, and high ASCVD risk in this study population with a high risk of NAFLD. Further prospective investigations are required to establish the optimized cutoff values of SV ratio to identify individuals with a high risk of hepatic and coronary comorbidities.

CONFLICTS OF INTEREST

S.U.K. has served as an advisory committee member Gilead Sciences, Bayer, Eisai, and Novo Nordisk. He is a speaker for Gilead Sciences, GSK, Bayer, Eisai, AbbVie, Echosens, MSD, Eisai, Otsuka, and Bristol-Myers Squibb. He has also received a research grant from AbbVie and Bristol-Myers Squibb. S.H.A. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Study concept and design: E.H., Y.H.L., B.W.L., S.U.K. Development of methodology: E.H., B.W.L., S.U.K. Data analysis and interpretation: E.H., B.W.L., S.U.K. Drafting of the manuscript: E.H., Y.H.L., S.H.A., B.W.L., B.S.C., S.U.K. Critical revision of the manuscript for important intellectual content: E.H., Y.H.L., S.H.A., B.W.L., B.S.C., S.U.K. Administrative, technical, or material support: E.H., B.W.L., S.U.K. Study supervision: B.W.L., S.U.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl230238.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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