

The Association Between Sarcopenia Index and Aortic Valve Sclerosis in Coronary Artery Disease Patients: Insights from a Retrospective Cross-Sectional Analysis and Animal Models

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Background: The Sarcopenia Index (SI) is a recognized predictor of cardiovascular risk in patients with coronary artery disease (CAD), yet its association with aortic valve sclerosis (AVSc) remains insufficiently studied. This study aimed to examine the relationship between SI and AVSc in CAD patients.

Methods: In this retrospective study, 1056 CAD patients at Shanghai Ruijin Hospital underwent SI assessment and Doppler echocardiography. SI was calculated as $[\text{serum creatinine (mg/dL)}/\text{cystatin C (mg/L)}] \times 100$. Logistic regression, subgroup analyses, and restricted cubic splines evaluated the SI-AVSc association. ROC curves determined SI's diagnostic value and its addition to traditional AVSc factors. In parallel with clinical observations, aortic valve changes were analyzed in mice via hematoxylin and eosin, AlizarinRed S, and Masson's trichrome to assess valve thickness, fibrosis and calcification.

Results: Patients with the lowest SI levels showed a higher prevalence of AVSc. Multivariate logistic regression revealed that SI was independently associated with AVSc ($P < 0.001$). The C-statistic for SI in identifying AVSc was 0.708 (95% CI: 0.671, 0.744), and it improved risk stratification when SI was added to traditional clinical models (C-statistic increased from 0.840 to 0.866). In the subgroup analysis, the discriminatory power of SI was enhanced among elderly patients. Findings from animal models supported these results, and Spearman correlation analyses revealed negative correlation between SI and peak systolic aortic valve flow velocity (Spearman's $\rho = -0.578$, $P = 0.006$). Histological analysis demonstrated that aortic valve leaflets in the low SI group were thicker and more fibrotic than those in the high SI group, and this complementary approach provided mechanistic insights into how sarcopenia may promote valve degeneration in elder mice.

Conclusion: Lower Sarcopenia Index is associated with the presence of AVSc in CAD patients. SI improves risk stratification and acts as a valuable associated marker for AVSc, emphasizing its potential clinical utility in enhancing patient management.

Keywords: sarcopenia index, aortic valve sclerosis, coronary artery disease

Introduction

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality among older adults.¹ Aortic valve sclerosis (AVSc), defined by thickening and/or calcification of the aortic valve without significant obstruction to blood flow, affects

approximately 30% of individuals over the age of 65.^{2,3} Epidemiological studies have shown that the prevalence of AVSc increases with age and that it serves as a valuable marker of systemic atherosclerotic burden.⁴ Early detection of AVSc has important clinical implications, potentially improving disease management strategies in practice.⁵ However, aside from echocardiography, there are few biomarkers available for identifying AVSc.

Sarcopenia, a progressive condition characterized by the gradual loss of skeletal muscle mass and function, progresses at a rate of 0.5% to 1% per year starting in middle age, with acceleration beyond 60 years.⁶ Notably, CAD has been found to accelerate the progression of sarcopenia even in relatively young patients.⁷ The Sarcopenia Index (SI), calculated as [serum creatinine (mg/dL)/cystatin C (mg/L)] \times 100, has been proposed as a novel marker for assessing sarcopenia.⁸ Recent studies have confirmed the prognostic value of SI in CAD patients undergoing invasive procedures.⁹ Given that AVSc and sarcopenia share key pathophysiological mechanisms driving their progression and increasing cardiovascular risk, the interplay between these conditions in the context of CAD represents a critical area of research.^{10,11} Understanding this interaction may provide promising opportunities for improving prognostic accuracy in CAD management.

Despite the recognized importance of AVSc and sarcopenia in CAD, most existing studies focus on their independent prognostic roles. However, there is a lack of research investigating the combined associated value of the SI for AVSc in CAD patients. This study aims to evaluate the prognostic significance of the SI in predicting the development of aortic valve sclerosis in patients with coronary artery disease. Specifically, it will assess the predictive value of SI for the presence of AVSc in CAD patients.

Methods

Study Design and Populations

In this retrospective study, 3053 patients diagnosed with CAD via coronary computed tomography angiography or conventional coronary angiography were recruited from the Department of Cardiovascular Medicine at Shanghai Ruijin Hospital between January 2020 and January 2021. Among these, 2852 patients underwent standard transthoracic echocardiography. The study excluded individuals based on the following criteria: absence of creatinine or cystatin C data (n=380), acute coronary syndrome (n=366), an estimated glomerular filtration rate (eGFR) below 30 mL/min per 1.73 m² (n=87), severe heart failure (New York Heart Association class III or IV, or left ventricular ejection fraction <30%) (n=281), rheumatic disease (n=96), valvular stenosis (n=59), congenital aortic valve malformation (n=52), prior aortic valve replacement (n=46), thyroid or parathyroid disorders (n=184), chronic immobilization (n=86), and cancer (n=124). Additionally, 35 patients declined participation. Consequently, 1056 patients were included in the final analysis (Figure 1). The study protocol was approved by

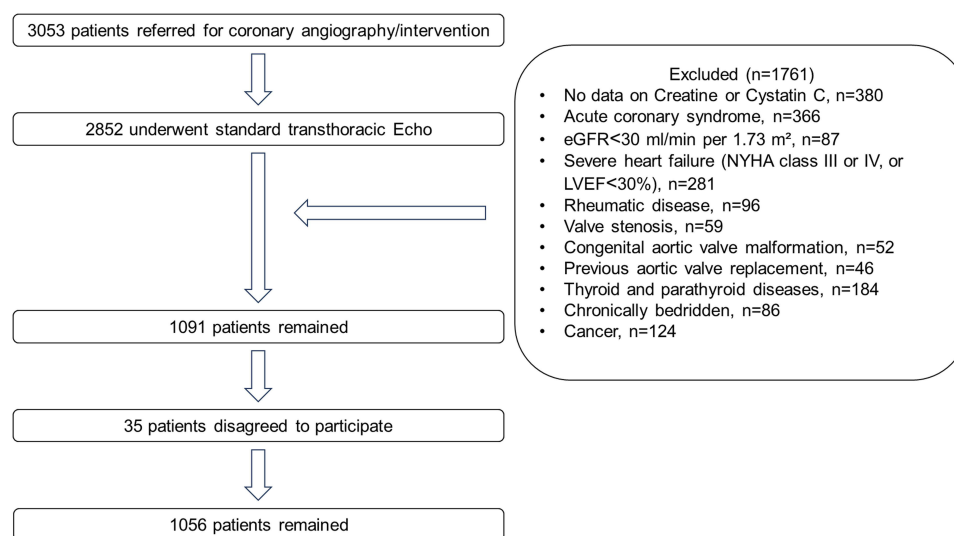


Figure 1 Flowchart of patient enrollment.

the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and all participants provided written informed consent. This study complies with the Declaration of Helsinki.

Definitions and Measurements

Function and morphology of aortic valve was measured by echocardiograph. Peak and mean velocity across the aortic valve were calculated using the modified Bernoulli equation, with continuous-wave Doppler.¹² AVSc was characterized by the presence of aortic valve leaflets that showed localized areas of slight thickness or enhanced echogenicity, without any associated limitation in mobility or a peak flow velocity surpassing 2.0 m/s across the aortic valve.^{13,14} As ESC recommends, hypertension is defined as systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg measured on at least three occasions in two separate places, or the use of any antihypertensive medication.¹⁵ Diabetes is characterized by a fasting blood glucose level equal to or greater than 7.0 mmol/L, or a post-load blood glucose level equal to or greater than 11.1 mmol/L, or the administration of antidiabetic medications.¹⁶ CAD was identified by the American College of Cardiology/American Heart Association lesion classification scheme, and involved a luminal diameter stenosis of at least 50% in one or more major epicardial coronary arteries.¹⁷ The calculation of the SI was performed utilizing the following formula: $[\text{Serum creatinine (mg/dL)}/\text{Cystatin C (mg/L)}] \times 100$.⁸

Animals and Experiments

The experimental and animal protocols adhered to the guidelines set forth by the Guide for the Care and Use of Laboratory Animals and received approval from the animal care and use committee at Shanghai Jiao Tong University, China. These protocols also complied with Directive 2010/63/EU from the European Parliament concerning the protection of animals used for scientific purposes.

Male SPF-grade C57BL/6 mice, aged six weeks, were procured from Beijing Vital River Laboratory Animal Products Co. Ltd., China. These mice were housed at a temperature of $25 \pm 1^\circ\text{C}$ with $65 \pm 5\%$ humidity, and under a 12-hour light/dark cycle in the animal facility of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. All studies observed the 3R principles of reduce, reuse, and recycle.

During the experiments, 20 male C57BL/6 mice were conventionally fed for 78 weeks to simulate natural aging. At the end of the protocol, the mice fasted overnight for echocardiography assessment. A Vevo 2100 (FujiFilm Visual Sonics) with an MS-400 imaging transducer was employed for two-dimensional echocardiography of cardiac and aortic valve function. Following the echocardiogram, the mice were subjected to anesthesia and subsequently euthanized by inhaling isoflurane followed by an intraperitoneal injection of pentobarbital sodium at a dosage of 30 mg/kg of body weight. Hearts were collected, and blood samples were extracted to measure fasting glucose levels, blood lipid profile, C-reactive protein, creatinine, and blood calcium and phosphorus levels. Cystatin C concentration was measured by a commercial ELISA kit (Cat# KE10066, Proteintech, USA).

Immunohistochemistry

The harvested hearts were immersed in a 4% paraformaldehyde solution for 12 hours to ensure proper fixation, then embedded in a medium suitable for optimal cutting at low temperatures. The tissues were sectioned into 6 μm -thick slices for frozen section histology. For comprehensive histological examination, these sections were stained with hematoxylin and eosin, AlizarinRed S, and Masson's trichrome. Images of the stained sections were captured using an Olympus BX61TRF microscope (Tokyo, Japan) and analyzed quantitatively with ImageJ software (National Institutes of Health, Bethesda, MD).

Statistical Analysis

Continuous variables are presented as means \pm standard deviations (SD) for normally distributed data or as medians with interquartile ranges (IQRs) for non-normally distributed data, while categorical variables are expressed as proportions and frequencies. Comparative analyses of continuous variables were performed using the one-way analysis or Kruskal–Wallis test, and χ^2 -tests were used for categorical variables. In the logistic regression models, the SI was analyzed both as a continuous variable in 10-unit increments and as an ordinal variable divided into tertiles, with the lowest tertile serving

as the reference category. A multivariable logistic regression analysis was conducted to evaluate the independent diagnostic significance of SI in identifying AVSc. Model 1 adjusted for demographic information including age and gender, model 2 adjusted for covariates that were significantly meaningful in the baseline table, model 3 adjusted for covariates, which may influence the process of AVSc in previous study.^{5,18,19} All variations were examined multicollinearity by calculating variance inflation factors (VIFs). Hosmer–Lemeshow test was used to test the goodness of fit metrics. Receiver operating characteristic (ROC) curves were generated to assess the effectiveness of SI in distinguishing AVSc across the study cohort, with the optimal SI cutoff determined by the highest Youden index (sensitivity + specificity – 1). C-statistics and their 95% confidence intervals (CIs) were reported. The incremental benefit of adding SI to the conventional diagnostic model was evaluated using C-statistics, net reclassification improvement (NRI) index, and integrated discrimination improvement (IDI) index. Additionally, restricted cubic splines were used to explore potential nonlinear associations between SI and AVSc, with knots placed at the 5th, 35th, 65th, and 95th percentiles of SI for a smoothly integrated graph. In animal studies, Spearman correlation analyses were conducted to examine the relationship between SI and peak systolic aortic valve flow velocity. All statistical analyses were performed using SPSS version 26.0 or R version 4.4.1, with statistical significance set at $P < 0.05$.

Results

Baseline Clinical Characteristics

This study involved 1056 stable CAD patients (Figure 1). The baseline characteristics of the participants are shown in Table 1. Patients with the lowest SI level tended to be older, included a smaller proportion of males, and had higher systolic blood pressure (all $P < 0.05$). Additionally, patients with the lowest SI level had a higher prevalence of AVSc (Figure 2).

Table 1 Baseline Characteristics of CAD Patients According to SI Levels

Variables	SI≤82.87 (n=352)	82.87<SI≤95.48 (n=352)	SI>95.48 (n=352)	P value
Age, years	69 (60, 76)	66 (59, 71)	65 (59, 71)	<0.001
BMI, kg/m ²	24.785 (22.729, 26.971)	24.858 (23.144, 26.774)	25.391 (23.384, 26.986)	0.170
Male, n (%)	188 (53.4%)	275 (78.1%)	307 (87.2%)	<0.001
Smoking, n (%)	152 (43.2%)	149 (42.3%)	142 (40.3%)	0.736
Alcohol use, n (%)	80 (22.7%)	64 (18.2%)	64 (18.2%)	0.216
Hypertension, n (%)	261 (74.1%)	251 (71.3%)	235 (66.8%)	0.094
Diabetes mellitus, n (%)	103 (29.3%)	101 (28.7%)	89 (25.3%)	0.444
Aortic valve sclerosis, n (%)	149 (42.3%)	72 (20.5%)	47 (13.4%)	<0.001
Systolic BP, mmHg	140 (128, 154)	136 (122, 149)	133 (121, 145)	<0.001
Diastolic BP, mmHg	77 (68, 84)	78 (69, 84)	77 (70, 84)	0.524
Fasting glucose, mmol/L	5.200 (4.690, 5.860)	5.170 (4.623, 5.943)	4.990 (4.613, 5.828)	0.146
HbA1c, %	6.000 (5.700, 6.600)	6.000 (5.700, 6.700)	5.900 (5.600, 6.500)	0.074
Triglyceride, mmol/L	1.370 (1.023, 1.990)	1.390 (0.980, 1.890)	1.425 (1.073, 1.928)	0.741
Total cholesterol, mmol/L	3.870 (3.193, 4.568)	3.690 (3.120, 4.455)	3.790 (3.150, 4.488)	0.366
Apolipoprotein A, g/L	1.300 (1.173, 1.410)	1.260 (1.120, 1.380)	1.270 (1.150, 1.390)	0.020
Apolipoprotein B, g/L	0.760 (0.610, 0.950)	0.760 (0.600, 0.930)	0.750 (0.600, 0.938)	0.926
Lp (a), mmol/L	0.135 (0.080, 0.348)	0.130 (0.070, 0.333)	0.140 (0.070, 0.308)	0.565
LDL-C, mmol/L	2.230 (1.625, 2.820)	2.100 (1.650, 2.730)	2.160 (1.673, 2.833)	0.577
HDL-C, mmol/L	1.030 (0.863, 1.230)	0.965 (0.830, 1.160)	0.990 (0.840, 1.150)	0.002
γ-GT, mmol/L	19 (13, 28)	20 (14, 29)	21 (15, 30)	0.238
Serum calcium, mmol/L	2.240 (2.160, 2.300)	2.220 (2.160, 2.280)	2.240 (2.180, 2.305)	0.023
Serum phosphorus, mmol/L	1.130 (1.020, 1.253)	1.091 (0.990, 1.220)	1.110 (1.000, 1.220)	0.028
CRP (mg/L)	0.760 (0.253, 2.135)	0.520 (0.190, 1.728)	0.440 (0.150, 1.208)	<0.001
eGFR (mL/min/1.73m ²)	78.85 (68.13, 90.90)	84.55 (72.73, 93.50)	80.65 (71.63, 91.30)	0.004

(Continued)

Table 1 (Continued).

Variables	SI≤82.87 (n=352)	82.87<SI≤95.48 (n=352)	SI>95.48 (n=352)	P value
LVEF (%)	66 (62, 70)	66 (61, 69)	66 (63, 69)	0.244
Serum creatine (mg/dL)	0.871 (0.769, 0.981)	0.928 (0.837, 1.018)	0.990 (0.882, 1.075)	<0.001
Cystatin C (mg/L)	1.190 (1.048, 1.353)	1.035 (0.930, 1.130)	0.920 (0.820, 1.030)	<0.001
Medications				
Aspirin, n (%)	298 (84.7%)	301 (85.5%)	303 (86.1%)	0.866
ACEI/ARB, n (%)	217 (61.6%)	223 (61.4%)	207 (58.8%)	0.223
Beta-blocker, n (%)	278 (79.0%)	266 (75.6%)	285 (81.0%)	0.211
Statin, n (%)	312 (88.6%)	311 (88.4%)	299 (84.9%)	0.261

Abbreviations: BMI, body mass index; HbA1c, hemoglobinA1c; Lp(a), lipoprotein a; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; γ -GT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVDd, left ventricular end diastolic dimension; LVDs, left ventricular end systolic dimension; IVS, interventricular septum; ACEI, angiotensin-converting enzyme Inhibitors, angiotensin receptor blocker receptor blocker.

Association Between SI and AVSc

In logistic regression analysis, each 10-unit increase in SI was significantly associated with a reduced incidence of AVSc [OR = 0.598 (95% CI: 0.539, 0.664), $P < 0.001$, [Table 2](#)]. This inverse relationship remained consistent after adjusting for demographic, clinical, and laboratory confounders in Model 3 [OR = 0.580 (95% CI: 0.500, 0.673), $P < 0.001$, [Table 2](#)]. Moreover, when SI was divided into tertiles, patients in the second and third tertiles exhibited a lower incidence of AVSc compared to those in the first tertile after adjusting for the same confounders [Tertile 2: OR = 0.390 (95% CI: 0.253, 0.603), $P < 0.001$; Tertile 3: OR = 0.228 (95% CI: 0.139, 0.374), $P < 0.001$, [Table 2](#)]. Besides, all variations were examined multicollinearity by calculating variance inflation factors (VIFs), which were both less than 5 ([Table S1](#)), and the goodness of fit of logistic regression model was evaluated by Hosmer–Lemeshow test to ensure the accuracy of the estimated probabilities ($p = 0.644$). To fully explored the potential residual impact of confounding factors, the role of SI in discriminating AVSc among different subgroups was performed ([Figure 3](#)). Notably, this association was particularly significant in individuals aged ≥ 65 years ($p < 0.001$, p for interaction = 0.002).

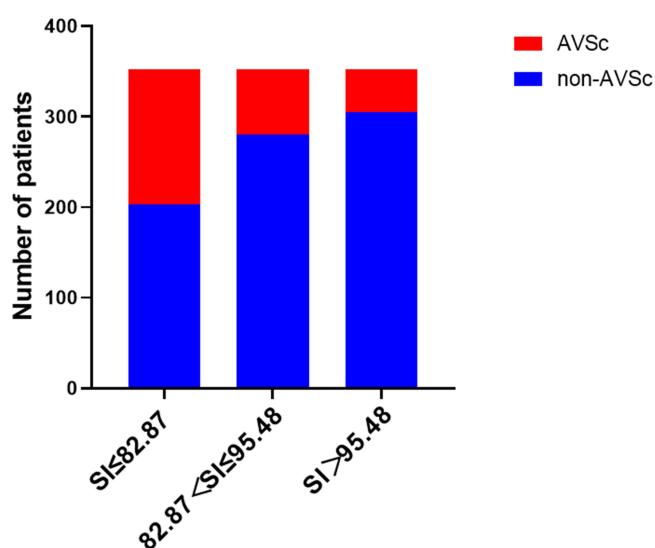


Figure 2 The proportion of AVSc among CAD patients divided by tertile of SI level.

Table 2 Association Between SI Level and AVSc

	Crude Model OR (95% CI)	P value	Model 1 OR (95% CI)	P Value	Model 2 OR (95% CI)	P Value	Model 3 OR (95% CI)	P Value
SI Per 10-unit increment	0.598 (0.539, 0.664)	<0.001	0.601 (0.529, 0.684)	<0.001	0.565 (0.491, 0.650)	<0.001	0.580 (0.500, 0.673)	<0.001
Median								
SI 1 st tertile	I (ref)		I (ref)		I (ref)		I (ref)	
SI 2 nd tertile	0.350 (0.251, 0.489)	<0.001	0.416 (0.280, 0.619)	<0.001	0.380 (0.251, 0.575)	<0.001	0.390 (0.253, 0.603)	<0.001
SI 3 rd tertile	0.210 (0.145, 0.305)	<0.001	0.223 (0.143, 0.348)	<0.001	0.206 (0.129, 0.330)	<0.001	0.228 (0.139, 0.374)	<0.001

Notes: Crude model: unadjusted model. Model 1: adjusted for age and gender. Model 2: model 1 in addition to systolic blood pressure, Apolipoprotein A, HDL, Ca, P, CRP, eGFR. Model 3: model 2 in addition to smoking, alcohol use, fasting glucose, HbA1c%, lipid profiles, γ -GT, LVEF, history of diabetes and hypertension, and drug usage.

Abbreviations: OR, odds ratio; SI, sarcopenia index; AVSc, aortic valve sclerosis.

Performance of SI for Discrimination of AVSc

Restricted cubic spline analysis with a multivariate logistic regression model revealed an inverse relationship between the SI and the incidence of AVSc ($P < 0.001$ for overall association; $P = 0.046$ for nonlinear; [Figure 4](#)). To assess the discriminative ability of SI levels for AVSc, ROC analysis was conducted, yielding a C-statistic of 0.708 (95% CI: 0.671, 0.744) with an optimal cutoff value of 85.26 ([Figure S1](#)) (sensitivity: 0.697, specificity: 0.642, [Table S2](#)) across the total cohort. Moreover, incorporating SI into the clinical traditional model significantly improved AVSc discrimination, increasing the C-statistic from 0.840 (95% CI: 0.814, 0.866) to 0.866 (95% CI: 0.841, 0.892). This enhancement was further supported by a category-free net reclassification improvement (NRI) of 0.597 (95% CI: 0.466, 0.728, $P < 0.001$) and an integrated discrimination improvement (IDI) of 0.064 (95% CI: 0.048, 0.081, $P < 0.001$, [Table 3](#)). Subgroup analysis by age indicated that SI exhibited a discriminative power for AVSc in elder patients compared to younger ones, with C-statistics of 0.742 (95% CI: 0.700, 0.784) versus 0.583 (95% CI: 0.494, 0.672), respectively ([Figure 5](#)), and with high sensitivity of 0.724, specificity of 0.675 in elder group ([Table S2](#)).

Decreased SI Level Promoted Pathological Change of Aortic Valve Sclerosis in Mice

To investigate the role of SI in regulating aortic valve sclerosis, aged mouse model was developed. SI was measured in these mice, which were then categorized into high ($n=10$) and low ($n=10$) SI groups, with baseline information provided in [Table S3](#). The study revealed a significant inverse relationship between SI levels and aortic valve sclerosis. Mice in the low SI group exhibited markedly higher peak systolic aortic valve flow velocity compared to the high SI group ([Figure 6A and B](#)). This relationship was further explored by a negative correlation between SI levels and peak systolic

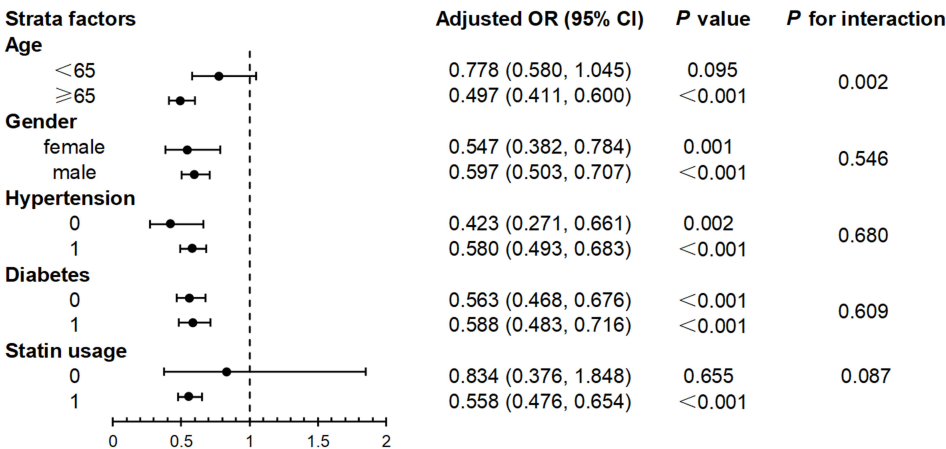


Figure 3 Forest plot for association between SI and AVSc in different subgroups. SI was analyzed as a per 10-unit continuous variable, the logistic model was adjusted for age, gender, systolic blood pressure, Apolipoprotein A, smoking, alcohol use, eGFR, lipid profiles, fasting glucose, HbA1c%, CRP, serum calcium, serum phosphorus, LVEF history of diabetes and hypertension and drug usage.

Abbreviations: OR, odds ratio; AVSc, aortic valve sclerosis; SI, sarcopenia index.

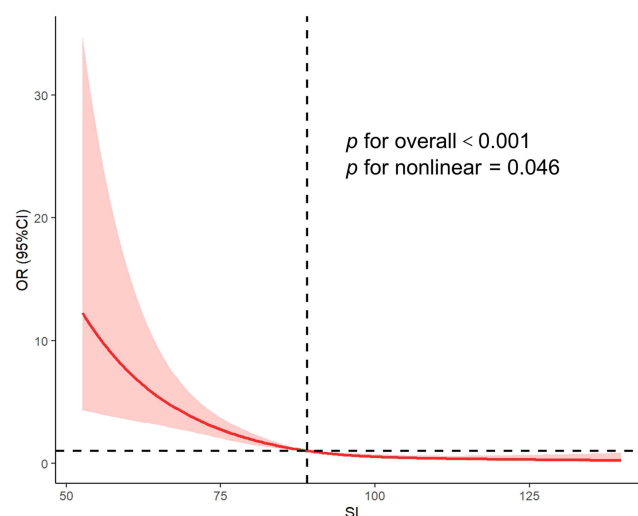


Figure 4 Restricted cubic splines for the association of SI and AVSc in CAD patients. Odd ratio was adjusted for age, gender, systolic blood pressure, Apolipoprotein A, smoking, alcohol use, eGFR, lipid profiles, fasting glucose, HbA1c%, CRP, serum calcium, serum phosphorus, LVEF history of diabetes and hypertension and drug usage. Knots were set at the 5%, 35%, 65%, and 95% percentiles. The median SI level (89.26) was used as the reference.

Abbreviations: OR, odd ratio; SI, sarcopenia index; CAD, coronary artery disease.

aortic valve flow velocity (Spearman's $\rho = -0.578$, $P = 0.006$, Figure 6C). Histological analysis demonstrated that aortic valve leaflets in the low SI group were thicker and more fibrotic than those in the high SI group (Figure 6D and F). Moreover, calcification foci were observed exclusively in the low SI group (3 cases) and were absent in the high SI group (Figure 6G). These findings suggest that change of SI may influence the progression of aortic valve sclerosis and calcification in aged mice, potentially offering new insights into the pathogenesis and prevention of this condition.

Discussion

In this study, we examined the relationship between the SI and AVSc in patients with CAD. Our results indicated that a lower SI was associated with a higher prevalence of AVSc, independent of traditional risk factors. The SI exhibited discriminatory power for AVSc, and its addition in clinical traditional models improved risk prediction. Supporting these clinical findings, an aged mouse model demonstrated that a lower SI was associated with increased aortic valve thickness, fibrosis, and calcification. Thus, the sarcopenia index may serve as a valuable marker for predicting AVSc in patients with CAD.

The present study highlights that patients with lowest SI level had a higher prevalence of AVSc in patients with CAD. Additionally, patients with lowest SI level tended to be older, less proportion of male, and had a higher systolic blood pressure. The findings are consistent with previous research that has identified age and hypertension as common risk factors for both AVSc and sarcopenia,^{11,20} suggesting that AVSc and sarcopenia may exhibit overlapping pathways. This study shows a significant association between a 10-unit increment in the SI and a reduced incidence of AVSc, as shown by an adjusted odds ratio of 0.580 ($P < 0.001$). Restricted cubic spline analysis with a multivariate logistic regression model revealed an inverse relationship between the SI and the incidence of AVSc, the observed nonlinear relationship need for further validation in larger, prospective cohorts to confirm. In this study, SI held a C-statistic of 0.708, given that the lack of gold standard biomarker, though it suggests moderate discriminative power, it is higher than the biomarker that had developed (eg t-PA

Table 3 Performance of SI in Improving Diagnosis of AVSc

	C-Statistics (95% CI)	Category-Free NRI (95% CI)	P-Value	IDI (95% CI)	P-Value
Clinical model	0.840 (0.814, 0.866)	Reference model		Reference model	
Clinical model + SI	0.866 (0.841, 0.892)	0.597 (0.466, 0.728)	<0.001	0.064 (0.048, 0.081)	<0.001

Notes: Traditional factors included age, gender, systolic blood pressure, history of hypertension and diabetes, lipid profiles, fasting glucose, HbA1c%, Ca, P, eGFR, and CRP. NRI indicates net reclassification improvement; IDI, integrated discrimination improvement; SI, sarcopenia index; AVSc, aortic valve sclerosis.

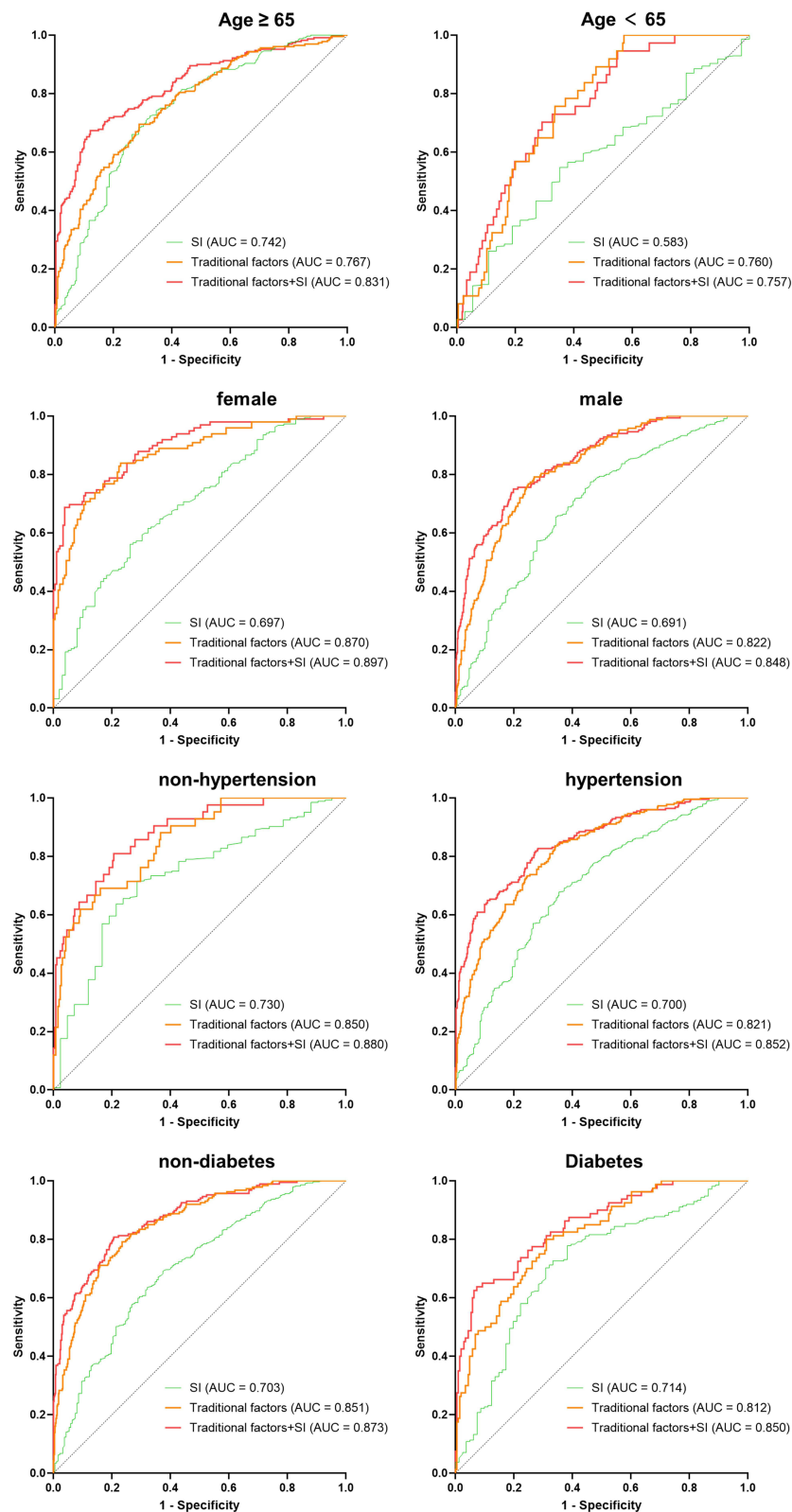


Figure 5 Diagnostic value of SI for AVSc in different subgroups.
Abbreviations: SI, sarcopenia index; AVSc, aortic valve sclerosis.

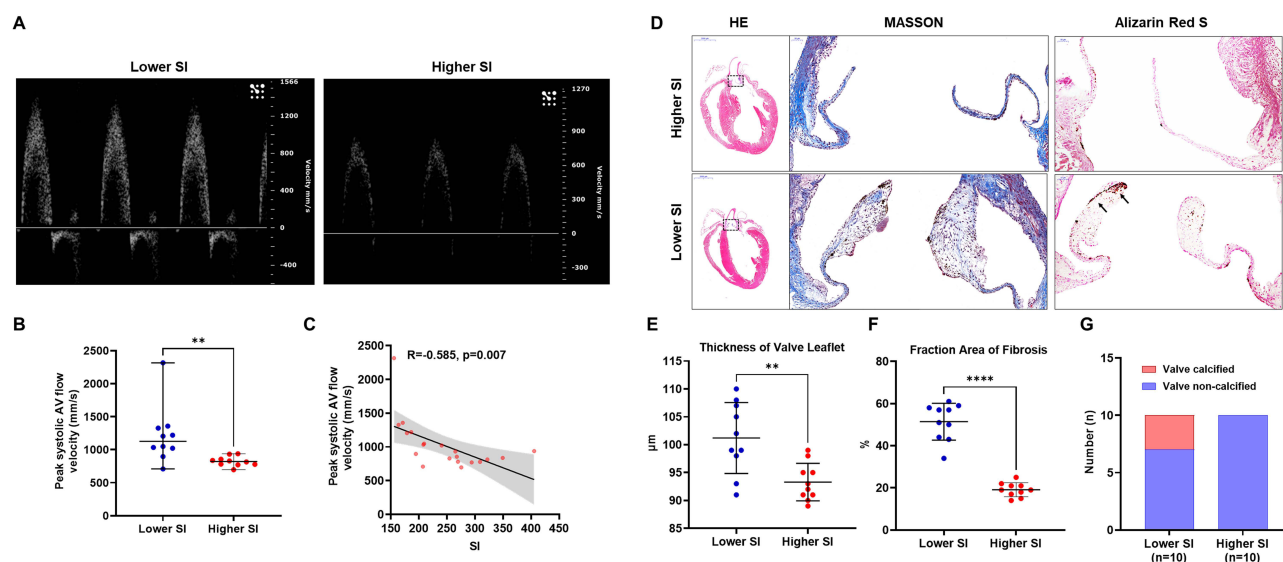


Figure 6 Comparison of aortic valve sclerosis between lower SI and higher SI mouse. (**A** and **B**), Peak systolic AV flow based on echocardiography, ** $P < 0.01$ (**C**), Spearman correlation analysis revealed a negative correlation trend between SI and peak systolic AV flow velocity. (**D**), the aortic valve leaflets were stained by HE, Masson and Alizarin Red S. Black arrows indicated positive staining with Alizarin Red S. (**E** and **F**), Quantification of the extent of thickness of valve leaflet based on HE, fibrosis based on Masson staining, ** $P < 0.01$, **** $P < 0.0001$. (**G**), Number of cases of aortic valve calcification in the lower SI and higher group.

Abbreviations: HE, Hematoxylin-eosin; AV, aortic valve; SI, sarcopenia index.

0.698).⁵ Incorporating SI into predictive models significantly enhances their accuracy in detecting AVSc among patients with CAD. This is evidenced by an increase in the C-statistic from 0.840 to 0.866 with NRI of 0.597 and an IDI of 0.064 ($P < 0.001$). Additionally, SI proves to be a reliable predictor of sarcopenia, which in turn shows predictive capacity for AVSc. This study provides the inaugural evidence that a reduced SI correlates with the incidence of AVSc in individuals suffering from CAD, independent of demographic, clinical, and laboratory variables. The findings suggest that sarcopenia may play a crucial role in AVSc development, highlighting sarcopenia, a widespread skeletal muscle disorder, as a key factor. Skeletal muscle is integral to glucose metabolism and actin secretion,²¹ both of which decline with age, affecting muscle, bone, and fat tissue composition and reducing basal metabolic rate.²² The resultant muscle loss increases adiposity and insulin resistance, altering lipid metabolism and precipitating dyslipidemia.¹¹ These metabolic disturbances are implicated in AVSc progression. Additionally, skeletal muscle functions as a secretory organ,²³ releasing myokines such as irisin²⁴ and follistatin-like protein 1 (FSTL1),²⁵ both of which have been inversely associated with aortic valve calcification and stenosis. Previous research has also shed light on the common underlying mechanisms linking AVSc and sarcopenia, specifically chronic inflammation throughout the body and increased oxidative stress.²⁶ Chronic systemic inflammation emerges as a pivotal link, where inflammatory cytokines such as TNF- α and IL-6 drive muscle catabolism in sarcopenia and promote valve calcification progression in AVSc, thereby connecting these conditions.^{27,28} In sarcopenia, persistent inflammatory responses lead to muscle protein degradation and impede regenerative processes, resulting in muscle wasting and weakness.²⁹ Conversely, in AVSc, endothelial damage facilitates lipid infiltration and the recruitment of inflammatory cells, which contribute to the calcification of valve leaflets.³⁰ Additionally, metabolic disturbances commonly observed in AVSc patients, including dyslipidemia and insulin resistance, increase oxidative stress and inflammatory responses, adversely affecting muscle health.^{20,31,32} Elevated serum calcium levels, as noted by Tao et al,³³ further increase the risk of AVSc and disrupt muscle metabolism. The convergence of pathological factors in sarcopenia and AVSc indicates previously unrecognized clinical relationships between these conditions. However, the pathological and clinical relevance between declined SI and progression of SI still needs to be further investigated in a prospective, multi-center study.

Subgroup analysis further reveals that elevated SI levels are consistently associated with a lower risk of AVSc across diverse demographics, especially among elder adults, likewise, SI demonstrates stronger discriminative power for AVSc in elder age groups, with a C-statistic of 0.724 compared to 0.547 in younger cohorts, with high sensitivity. These findings underscore the potential of SI as a valuable detection indicator for enhancing AVSc risk prediction and

stratification in varied CAD patient populations, with particular applicability to older adults, who represent the highest risk group for AVSc, sarcopenia, and CAD. Our study using an aged murine model confirmed these findings. Mice in the lower SI group showed significantly higher peak systolic aortic valve flow velocities, inversely correlated with SI (Spearman's $\rho = -0.578$, $P = 0.006$). Additionally, the aortic valve leaflets in the lower SI group mice exhibited notable increases in thickness, fibrosis, and calcification ratios. These observations highlight the negative effects of reduced SI on aortic valve structure and function.

Limitations

This is a single-center retrospective study, the causal relationship between SI and AVSc cannot be established, and ROC analysis still needs to be further validated in a large, multi-center, prospective study. Besides, the population of this study is predominantly Chinese, which limits the applicability of this study to other ethnic and geographic groups. The molecular links between sarcopenia and AVSc are poorly understood, necessitating advanced research to uncover therapeutic targets. The study's reliance on the SI and its predominantly high-risk CAD patient population limit generalizability, highlighting the need for diverse cohorts and comprehensive sarcopenia assessments in future research.

Conclusion

This study elucidates the association between the SI and AVSc in patients with CAD. The findings reveal that lower SI levels are linked to a higher prevalence of AVSc. Furthermore, SI demonstrates moderate discriminatory capability for AVSc and enhances risk prediction when incorporated into clinical traditional models. Supporting these clinical observations, animal studies indicate that lower SI may correlate with increased aortic valve thickness, fibrosis, and calcification. Overall, the study highlights that sarcopenia index can be a valuable biomarker for predicting AVSc in CAD patients, which still need be further investigated by following up.

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Disclosure

The authors report no conflicts of interest in this work.

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