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Chronic venous insufficiency as an independent risk factor for coronary artery disease: Evidence from coronary artery calcium score analysis

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Abstract

Background: Previous research has indicated a correlation between chronic venous insufficiency (CVI) and cardiovascular disease. However, whether CVI is an independent risk factor for coronary artery disease (CAD) remains underexplored. This study aimed to investigate this relationship by utilizing coronary artery calcium score (CACS) assessment during CVI screening and comparing it with CACS in patients undergoing cardiac ablation treatment.
Methods: and Subjects: A retrospective cohort study was conducted, approved by the ethical committee (IRB 2024012). From February to July 2023 Simultaneous non-contrast lower limb vein CT and CACS measurements were performed on CVI patients aged 50 and above and less than 90, excluding cases with history of heart failure, post-thrombotic syndrome, percutaneous coronary intervention (PCI), cardiac ablation, cardiac surgery, peripheral arterial disease, and renal failure. Parameters included coronary risk factors and CACS. Control group was composed of sex- and age-matched patients receiving cardiac ablation treatment from April 2020 to December 2023. A comparison between the two groups was made, and univariate and multivariate analyses were conducted. Statistical significance was set at $p < .05$.
Results: Comparison between CVI group ($n = 234$) and cardiac ablation group ($n = 234$) were as follows: mean age (71 ± 9: 71 ± 9, not significant (NS)), females (154:145, NS), body mass index (BMI) (23.6 ± 3.9:22.6 ± 3.5, $p = .004$), hypertension (103:121, NS), dyslipidemia (100:66, $p = .001$), diabetes (30:24, NS), Creatinine (0.76 ± 0.25:0.87 ± 0.64, $p = .02$), respectively. The total CACS was 214 ± 578 in the CVI group and 64.8 ± 233 in the cardiac ablation group ($p < .001$). The median CACS values were 14.8 (IQR: 0–178) and 0 (IQR: 0–16), respectively. CVI group included 35% with CACS >100 and the cardiac ablation group did 12%, respectively ($p < .001$). Univariate analysis identified age [beta 9.6 (95% CI 5.2 to 13.9), $p < .001$], hypertension [beta 142.4 (95% CI 62.5 to 222), diabetes [beta 179.1 (95% CI 53.5 to 305), $p = .005$], dyslipidemia [beta 164.5 (95% CI 81.2 to 248), $p < .001$],creatinine [beta 85.4 (95% CI 2.6 to 168), $p = .04$], and CVI [beta 149 (95% CI 69.4 to 229), $p < .001$], $p = .001$] as risk factors. Multivariate analysis revealed age [beta 7.1 (95% CI 2.7 to 11.5), $p = .002$], hypertension [beta 86.5 (95% CI 1.7 to 171), $p = .046$], dyslipidemia [beta87.5 (95% CI 1.4 to 174), $p = .047$], and CVI [beta 143.6 (95% CI 63.7 to 223), $p < .001$] as strong correlates of CACS.
Conclusions: Multivariate analysis indicated that CVI is an independent risk factor for coronary artery disease, even after adjusting for age, hypertension, and dyslipidemia as confounding factors.

Keywords

Coronary artery calcium score, chronic venous insufficiency, coronary risk factor

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Introduction

Chronic venous insufficiency (CVI) affects 30–50% of the population.[1,2] The Framingham Study, published in 1988, suggested an association between CVI and atherosclerotic cardiovascular disease.[3] Building on this, Prochaska et al. reported that CVI is a strong predictor of all-cause mortality and proposed that CVI should be considered a cardiovascular disease.[4–6] Despite the need for further research into their shared pathophysiology, it is crucial to treat CVI and atherosclerotic cardiovascular disease as interconnected conditions. However, CVI and coronary artery disease (CAD) have not yet been widely recognized as related, and CVI is often not considered a candidate for heart disease prevention and therapy in clinical practice.[1,2] Many clinicians lack a comprehensive approach to investigating both conditions.[5,]

Duplex sonography is the gold standard to evaluate haemodynamic parameters such as reflux. In addition to that we routinely use non-contrast three-dimensional computed tomography-venography (3DCTV) for CVI screening due to its several advantages.[7–9] This method provides an objective understanding of three-dimensional images of varices, allowing patients to quickly grasp the overall view of their varices. CT also provides important information, such as intra-abdominal malignancy and May-Thurner syndrome, which can cause leg edema. The usefulness of this modality has been reported in Japan.[7–9]

The coronary artery calcium score (CACS) measures calcium deposits in the coronary arteries using a coronary artery calcium scan, a type of CT scan.[10,11] The interpretation of CACS involves assessing the extent and severity of coronary artery calcification, with different score ranges used to categorize risk. CACS is a simple and effective tool for risk stratification in coronary artery disease.[12] A treatment strategy flowchart based on CACS rankings has also been developed.[13]

Since 2022, we have measured CACS at the time of 3DCTV screening to identify potential coronary artery sclerosis. This study aimed to investigate the relationship between CVI and coronary artery sclerosis by utilizing CACS assessment during CVI screening and comparing it with CACS in patients undergoing ablation treatment. The goal was to evaluate whether CVI is an independent risk factor for CAD.

Methods

A retrospective cohort study was conducted, approved by the ethical committee of our hospital (IRB2024012). At the outpatient clinic in our hospital, consecutive 234 patients with CVI symptoms, aged 50 to under 90, were screened between February and July 2023. Based on Guideline,[14] the pre-test probability of asymptomatic ischemic heart disease in individuals under 50 years old is quite low at 3%, and it was difficult to match sex and age in the control group for individuals over 90 years old due to the small number of subjects. Exclusion criteria included a history of heart failure, post-thrombotic syndrome, percutaneous coronary intervention (PCI), cardiac ablation, cardiac surgery, peripheral arterial disease, and renal failure. Patients with C3 due to cardiac and renal failure (as indicated by chest X-ray, blood tests including proBNP > 400,[15] and eGFR < 30[16]) were also excluded. Additionally, intra-abdominal malignancies identified by CT scan were excluded.

Screening was performed using simultaneous lower limb vein CT and coronary artery calcium score (CACS) measurements via CT (SOMATOM definition AS+, Siemens Healthineers Japan, Tokyo, Japan). Patients with heart failure, post-thrombotic syndrome, or a history of PCI were excluded. The control group consisted of sex- and age-matched patients who had undergone cardiac ablation treatment between April 2020 and December 2023.

CVI was diagnosed based on symptoms such as edema, pain, cramping, skin pigmentation, ulcers, and varicose veins. CT imaging was used to identify and localize dilatation of the great and small saphenous veins and other varicosities. Vein valve insufficiency and deep vein thrombosis (DVT) were diagnosed using color Doppler echography for the whole length of the vein. Patients with dilatation and regurgitation of the great and small saphenous veins or other veins were classified as having varicose veins, while those without such findings were classified as having functional venous insufficiency (FVI).

Parameters assessed included age, gender, BMI (classified as overweight if > 25), coronary risk factors, causes of CVI (varicose veins vs FVI), CACS, CEAP classification, and revised venous clinical severity score (rVCSS). CACS categories were defined as >400, 101–400, 11–100, and 0–10 (Table 1).[11] Subgroups of FVI and varicose vein were compared.

A CACS >100 was defined as a calcified plaque, whereas a CACS <100 was classified as a non-calcified plaque. Subgroups with CACS >100 and CACS <100 were compared. Multivariate analysis was performed to identify factors correlated with CACS.

Statistical analyses were conducted using unpaired t-tests or Mann-Whitney U test for continuous variables and chi-square tests for ratios in intergroup comparisons. Both univariate and multivariate analyses were performed, with statistical significance set at $p < .05$.

Result

Patient background

All patients were asymptomatic regarding anginal pain and discomfort. Effective CT doses for the legs and heart were 0.75 mSv and 0.08 mSv, respectively. The control group

included 95 patients with chronic AF and 139 with paroxysmal AF.

A comparison between the CVI group (n = 234) and the cardiac ablation group (n = 234) is as follows (Table 2). There were no significant differences in mean age (71 ± 9 vs 71 ± 9, NS), the proportion of females (154 vs 145, NS), prevalence of hypertension (103 vs 121, NS), or diabetes (30 vs 24, NS).

Variables in the CVI group were significantly higher than those in the control group for BMI (23.6 ± 3.9 vs 22.6 ± 3.5), dyslipidemia (100 vs 66), total CACS (214 ± 578 vs 64.8 ± 233), The median CACS (14.8 (IQR, 0-178) vs 0 (IQR, 0-16)), CACS >100 (82 vs 28), and CVI incidence (234 vs 0), and the CVI group had a lower prevalence of CACS = 0 (95 vs 142). Creatinine levels in the CVI group were lower than those in the control group.

Table 1. Coronary artery calcium score (CACS).

EBCT calcium score	Plaque burden	Probability of significant CAD	Implications for CVrisk	Recommendation
0	No identifiable plaque	Very low, generally <5%	Very low	Reassure patient while discussing general public health guidelines for primary prevention of CV diseases
1-10	Minimal identifiable plaque burden	Very unlikely, <10%	Low	Discuss general public health guide lines for primary prevention of CV diseases
11-100	Definite, at least mild atherosclerotic plaque burden	Mild or minimal coronary stenoses likely	Moderate	Counsel about risk factor modification, strict adherence with NCEP ATP II primary prevention cholesterol guidelines, daily ASA
101-400	Definite, at least moderate atherosclerotic plaque burden	Nonobstructive CAD highly likely, although obstructive disease possible	Moderately high	Institute risk factor modification and secondary prevention NCEP ATP II guidelines. Consider exercise testing for further risk stratification
>400	Extensive atherosclerotic plaque burden	High likelihood (~90%) of at least 1 "significant" coronary stenosis	High	Institute very aggressive risk factor modification. Consider exercise or pharmacologic stress imaging to evaluate for inducible ischemia

As table 1 indicated, CACS>100 indicated possible coronary artery disease and the guideline recommended optimal medical therapy (OMT).[13].

Table 2. Patients characteristics.

Variables	Overall	CVI	Control	p Value
n	468	234	234	
Gender, female (%)	299 (64)	154 (66)	145 (62)	0.441
Age (y.o), mean ± SD	71.3 ± 9.1	71.4 ± 9.1	71.2 ± 9.1	0.847
Height (cm), mean ± SD	159.6 ± 9.2	158.5 ± 9.4	160.7 ± 8.9	0.010
Weight (kg), mean ± SD	59.0 ± 12.1	59.4 ± 13.0	58.5 ± 11.1	0.397
BMI(kg/m2), mean ± SD	23.1 ± 3.7	23.6 ± 3.9	22.6 ± 3.5	0.004
Hypertension, (%)	224 (47.9)	103 (44.0)	121 (51.7)	0.116
Diabetes, (%)	54 (11.5)	30 (12.8)	24 (10.3)	0.469
Dyslipidemia, (%)	166 (35.5)	100 (42.7)	66 (28.2)	0.001
Creatinine (mg/ml), mean ± SD	0.81 ± 0.49	0.76 ± 0.25	0.87 ± 0.64	0.023
eGFR (ml/min/1.732), mean ± SD	64.9 ± 15.2	67.3 ± 15.7	62.4 ± 14.3	<0.001
CVI (%)	234 (50.0)	234 (100.0)	0 (0.0)	<0.001
CACS, mean ± SD	139.4 ± 446.2	214.0 ± 577.5	64.8 ± 233.1	<0.001
CACS, median (IQR)	0 (IQR: 0-85)	14.8 (IQR: 0–178)	0 (IQR: 0–16)	<0.001
CACS>100 (%)	110 (23.5)	82 (35.0)	28 (12.0)	<0.001
CACS = 0 (%)	237 (51)	95 (39)	142 (58)	<0.001

BMI: body mass index, eGFR: estimated glomerular filtration rate, CVI: chronic venous insufficiency, CACS: coronary artery calcium score.

In the CVI group, 68% had varicose veins, and 32% had functional venous insufficiency. The rVCSS was 5.3 ± 2.8. CEAP classification was distributed as follows: CEAP 0 (1), CEAP 1 (1), CEAP 2 (0), CEAP 3 (203), CEAP 4 (26), CEAP 5 (0), and CEAP 6 (3). When the CVI group was subdivided into two groups based on CACS >100 and CACS <100, the rVCSS scores were 5.2 ± 2.9 and 5.3 ± 2.7, (NS).

Figure 1 illustrates the age distribution of the CVI group, showing that the most frequent age group was the 70s (97 patients, 41%), followed by the 60s (60 patients, 26%), the 80s (49 patients, 21%), and the 50s (28 patients, 12%) Control is almost identical because of age-matched group.

There is huge difference in CACS distribution between two groups. (Figure 2) The CACS distribution in the CVI group showed scores of >400 in 12%, 101-400 in 24%, 11-100 in 19%, and 0-10 in 46%. The CVI group included 82 patients (35%) with CACS >100 (calcified plaque), while the cardiac ablation group included 29 patients (13%) ($p < .001$). The CVI group also included 95 patients (39%) with CACS = 0 compared to 142 patients (58%) in the cardiac ablation group ($p < .001$). Figure 3: The mean CACS in the CVI group (214) was significantly higher than that in the control group ($p < .001$).

FVI demonstrated higher CACS than varicose veins and was characterized by advanced age, higher rates of hypertension and, lower values of eGFR, albumin, and rVCSS. (Table.3). CEAP classification was distributed as follows: C 0 (1), C 3 (72), and C 4 (2) in FVI and C 1 (1), C 3 (131), and C 4 (24), C6 (3) in varicose vein. (Table 4)

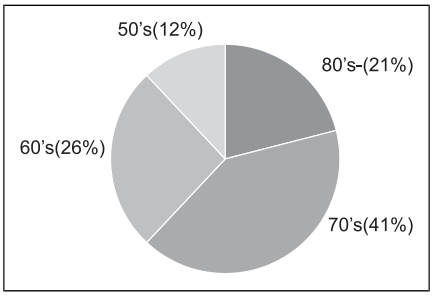

Figure 1. Distribution of age.

Stratification by presence of calcified plaque: CACS>100

Calcified plaque accounted for 23.5% of total cases. (Table. 5) The parameters for calcified plaque were significantly higher ($p < .001$) than for non-calcified plaque (CACS <100) in various aspects:

Age: 77 versus 70 years, CACS: 561 ± 785 versus 9.7 ± 21, Hypertension: 64% versus 43%, Diabetes: 24% versus 8%, Dyslipidemia: 56% versus 29%, Creatinine: 1.0 ± 0.9 versus 0.8 ± 0.1 mg/mL, and CVI prevalence: 74% versus 43% (Table 3). The calcified plaque group had more coronary risk factors such as age, hypertension, diabetes, and dyslipidemia, and a higher prevalence of CVI.

Factors associated with coronary calcification

Univariate analysis identified the following risk factors for coronary calcification: Age: [Beta 9.6 (95% CI: 5.2 to 13.9), $p < .001$], Hypertension: [Beta 142.4 (95% CI: 62.5 to 222), $p = .001$], Diabetes: [Beta 179.1 (95% CI: 53.5 to 305), $p = .005$], Dyslipidemia: [Beta 164.5 (95% CI: 81.2 to 248), $p < .001$], Creatinine: [Beta 85.4 (95% CI: 2.6 to 168), $p = .04$], and CVI: [Beta 149 (95% CI: 69.4 to 229), $p < .001$]. (Table 6).

Multivariate analysis revealed strong correlates of CACS: Age: [Beta 7.1 (95% CI: 2.7 to 11.5), $p = .002$], Hypertension: [Beta 86.5 (95% CI: 1.7 to 171), $p = .046$], Dyslipidemia: [Beta 87.5 (95% CI: 1.4 to 174), $p = .047$], and CVI: [Beta 143.6 (95% CI: 63.7 to 223), $p < .001$].

Concomitant coronary artery disease in patients with CVI

Out of 82 patients with CACS >100, 56 (68%) declined coronary CT or were lost to follow-up and 26 (32%) underwent coronary CT scans, revealing severe stenosis in

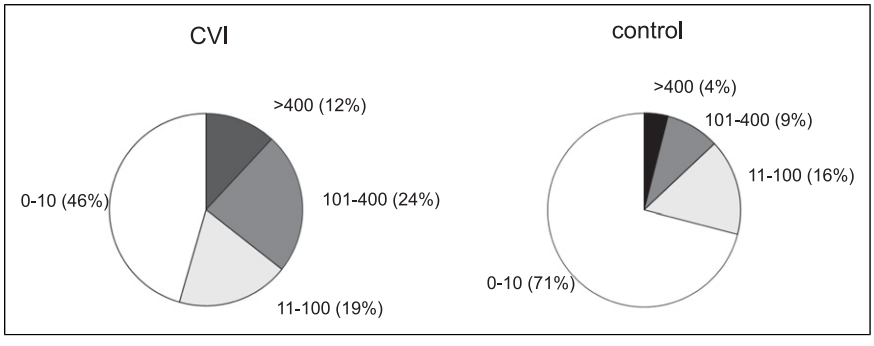

Figure 2. Distribution of CACS in CVI and control group.

12 patients, moderate stenosis in 3, and mild stenosis in 11 (Figure 4). 13 out of 26 (50%) patients underwent scintigraphy or coronary angiography (CAG), and 3 out of 13 (23%) patients were treated with PCI. If no critical ischemia was found but significant coronary calcium plaque was present, we recommended optimal medical therapy (OMT), including maintaining LDL-C <70 mg/dL.

Discussion

This study proposed two key insights:1) A strategy for diagnosing coronary artery disease (CAD) from chronic venous insufficiency (CVI) in a real-world clinical setting. (2) Concrete evidence supporting CVI as an independent risk factor for CAD, as identified through coronary artery calcium scoring (CACS).

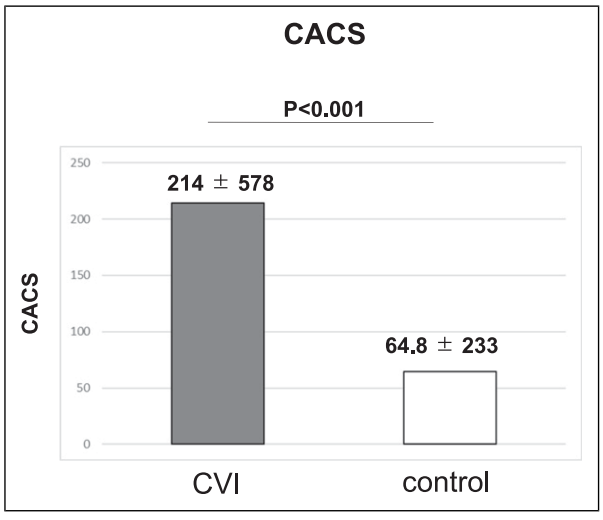

Figure 3. CACS of CVI and control group.

Although the concomitant use of duplex scanning is necessary for a comprehensive assessment, non-contrast 3DCTV give us additive important information, including: (1) The correlation between venodilation findings observed via non-contrast 3DCTV and venous function. (2) a tool to objectively explain to patients how their veins are diseased and where treatment is needed. and (3) additional information to aid in the diagnosis of leg edema includes intraabdominal malignancy, May-Thurner syndrome, and other associated benefits. and other benefits.[7–9]

We routinely use 3DCT for chronic venous insufficiency (CVI) screening and lower limb vein CT. Starting in 2022, we also initiated simultaneous coronary artery calcium scoring (CACS) measurement, building on numerous benefits reported in previous studies.[10–13] These measurements require only a few additional minutes and minimal radiation exposure. The effective dose for a CT leg scan is 0.75 mSv, and for a cardiac scan, it is 0.08 mSv, compared to the annual natural radiation exposure of 2.4 mSv.

In Japan, the cost-sharing system for medical expenses (CT scans) is designed so that even if multiple body parts are scanned, only the cost for one area (8400 yen) can be charged. For individuals aged 69 and under, the patient bears 30% of the cost (2520 yen). From age 70 to 74, the standard cost-sharing rate is 20% (1680 yen). For those aged 75 and older, the standard rate is 10% (840 yen).

Table 3. Characteristics of FVI and varicose vein.

Variables	FVI	Varicose vein	*p* value
n	75	159	
Gender, female (%)	51 (68)	103 (65)	0.63
Age, mean ± SD	74 ± 9	70 ± 8	0.007
BMI, mean ± SD	24 ± 4	23 ± 4	0.61
Hypertension (%)	40 (53)	63 (40)	0.048
Diabetes (%)	12 (16)	18 (11)	0.31
Dyslipidemia (%)	35 (47)	65 (41)	0.4
Creatinine (mg/ml), mean ± SD	0.8 ± 0.3	0.7 ± 0.2	0.025
eGFR (ml/min/1.73^2), mean ± SD	64 ± 18	69 ± 14	<0.001
Albumin (g/ml), mean ± SD	4.2 ± 0.3	4.3 ± 0.3	0.002
HDL (mg/dl), mean ± SD	65 ± 18	70 ± 18	0.06
rVCSS, mean ± SD	4.3 ± 2.4	5.7 ± 2.9	<0.001
CACS, mean ± SD	388 ± 895	132 ± 300	0.001
CACS>100 (%)	34 (45)	48 (30)	0.02
75th percentile for age and sex (%)	20 (27)	16 (10)	0.001

BMI: body mass index, eGFR: estimated Glomerular Filtration Rate, HDL: High Density Lipoprotein cholesterol, rVCSS: revised venous clinical severity score, CACS: coronary artery calcium score.

CACS and CAD risk

CACS (coronary artery calcium scoring) values of 101–400 are consistent with at least moderate non-obstructive coronary disease.[10,11] Patients with CACS greater than 100 (or scores lower than 100 but exceeding the 75th percentile for age and gender) are at moderately high risk and are candidates for aggressive risk factor modification.[11,12] This includes daily aspirin use and pharmacological treatment for mild to moderate hypercholesterolemia, among other interventions. These patients are at a significantly higher-than-anticipated moderate-term risk (19–72 months) for developing symptomatic coronary disease.

Patients with CACS >400 have advanced plaque disease, with a 90% specificity for at least one obstructive coronary lesion, and are at high risk for symptomatic ischemic disease. The Japanese Cardiology Society's (JCS) 2022 guidelines on diagnosing and treating stable coronary artery disease emphasize a pre-test probability-guided strategy for CAD diagnosis.[14] When the pre-test probability and clinical likelihood are less than 5%, selective use of CACS for risk assessment is deemed appropriate.

Table 4. CEAP stage of FVI and varicose vein.

CEAP	FVI	Varicose vein	
0	1	0	1
1	0	1	1
2	0	0	0
3	72	131	203
4	2	24	26
5	0	0	0
6	0	3	3
Total	75	159	234

In our cohort, 35% of patients with chronic venous insufficiency (CVI) who visited the hospital without chest symptoms had a CACS of 100 or higher, indicating a high prevalence of non-obstructive coronary artery disease. An important marker is CACS = 0, which significantly lowers the likelihood of CAD after assessing pre-test probability.[17] Notably, the CVI group demonstrated fewer instances of CACS = 0 compared to the control group. This finding suggests that the CVI group is particularly suitable for CAD risk assessment.

These conditions are often unrecognized by patients and their primary care physicians. In our study, approximately 80% of patients with significant coronary calcium plaque had not been previously diagnosed with CAD. Alarmingly, 50% of these patients did not receive optimal medical therapy (OMT), such as statins. Both the American Society for Preventive Cardiology[13] and the 2022 JCS guidelines[14] recommend OMT, including low-dose aspirin and statins, for patients with high CACS scores. However, observational data indicate that OMT is often underutilized in clinical practice.[18]

For patients with comorbid conditions contributing to a 5%–85% pre-test probability of CAD—such as hypertension, dyslipidemia, diabetes mellitus, or chronic kidney disease—coronary CT angiography (CCTA) is recommended.[14] If ischemia is ruled out, OMT is advised. However, if left main coronary artery disease or an equivalent lesion is suspected, coronary angiography is warranted.

Recent advancements in artificial intelligence have improved the accuracy of evaluating CACS from non-ECG-gated chest CT imaging, with further developments anticipated.[19]

CACS offers straightforward visualization of ongoing coronary artery disease, helping guide preventive efforts. A

Table 5. Stratification by presence of calcified plaque.

Variables	Overall	Calcified plaque CACS>100	Non-calcified plaque CACS<100	p.Value
n	468	110	358	
Gender, female (%)	299 (64)	62 (56)	237 (66)	0.078
Age (y.o), mean ± SD	71.3 ± 9.1	76.8 ± 7.1	69.6 ± 9.0	<0.001
CACS, mean ± SD	139.4 ± 446.2	561.4 ± 785.2	9.7 ± 21.1	<0.001
Height (cm), mean ± SD	159.6± 9.2	158.8 ± 10.3	159.9 ± 8.9	0.265
Weight (kg), mean ± SD	59.0 ± 12.1	59.1 ± 13.0	58.9 ± 11.8	0.901
BMI(kg/m2), mean ± SD	23.1± 3.7	23.3 ± 3.9	23.0 ± 3.6	0.371
Hypertension, yes (%)	224 (47.9)	70 (63.6)	154 (43.0)	<0.001
Diabetes , yes (%)	54 (11.5)	26 (23.6)	28 (7.8)	<0.001
Dyslipidemia, yes (%)	166 (35.5)	61 (55.5)	105 (29.3)	<0.001
Creatinine (mg/ml), mean ± SD	0.81 ± 0.49	0.98 ± 0.94	0.76 ± 0.18	<0.001
eGFR (ml/min/1.732), mean ± SD	64.9 ± 15.2	60.7 ± 19.1	66.1 ± 13.5	0.001
CVI (%)	234 (50.0)	81 (73.6)	153 (42.7)	<0.001

CACS: coronary artery calcium score, BMI: body mass index, Cr: creatinine, eGFR: estimated glomerular filtration rate, CVI: chronic venous insufficiency.

Table 6. Association with calcified plaque.

	Univariable		Multivariable	
Variable	Beta [CI95]	*p* value	Beta [CI95]	*p* value
Gender, female	83.14 (−0.77 to 167.05)	0.053		
Age	9.55 (5.19 to 13.91)	<0.001	7.08 (2.67 to 11.49)	0.002
Height	−0.67 (−5.06 to 3.72)	0.765		
Weight	1.96 (−1.39 to 5.31)	0.252		
BMI	10.08 (−0.8 to 20.97)	0.07	2.47 (−8.56 to 13.51)	0.661
Hypertension	142.44 (62.47 to 222.41)	0.001	86.47 (1.7 to 171.23)	0.046
Diabetes	179.07 (53.45 to 304.68)	0.005	110.32 (−12.51 to 233.15)	0.079
Dyslipidemia	164.47 (81.21 to 247.73)	<0.001	87.49 (1.41 to 173.56)	0.047
Creatinine	85.42 (2.63 to 168.2)	0.044	65.6 (−15.55 to 146.75)	0.114
eGFR	−2.08 (−4.75 to 0.59)	0.127		
CVI	149.15 (69.36 to 228.95)	<0.001	143.6 (63.73 to 223.48)	<0.001

BMI: body mass index, eGFR: estimated glomerular filtration rate, CVI: chronic venous insufficiency.

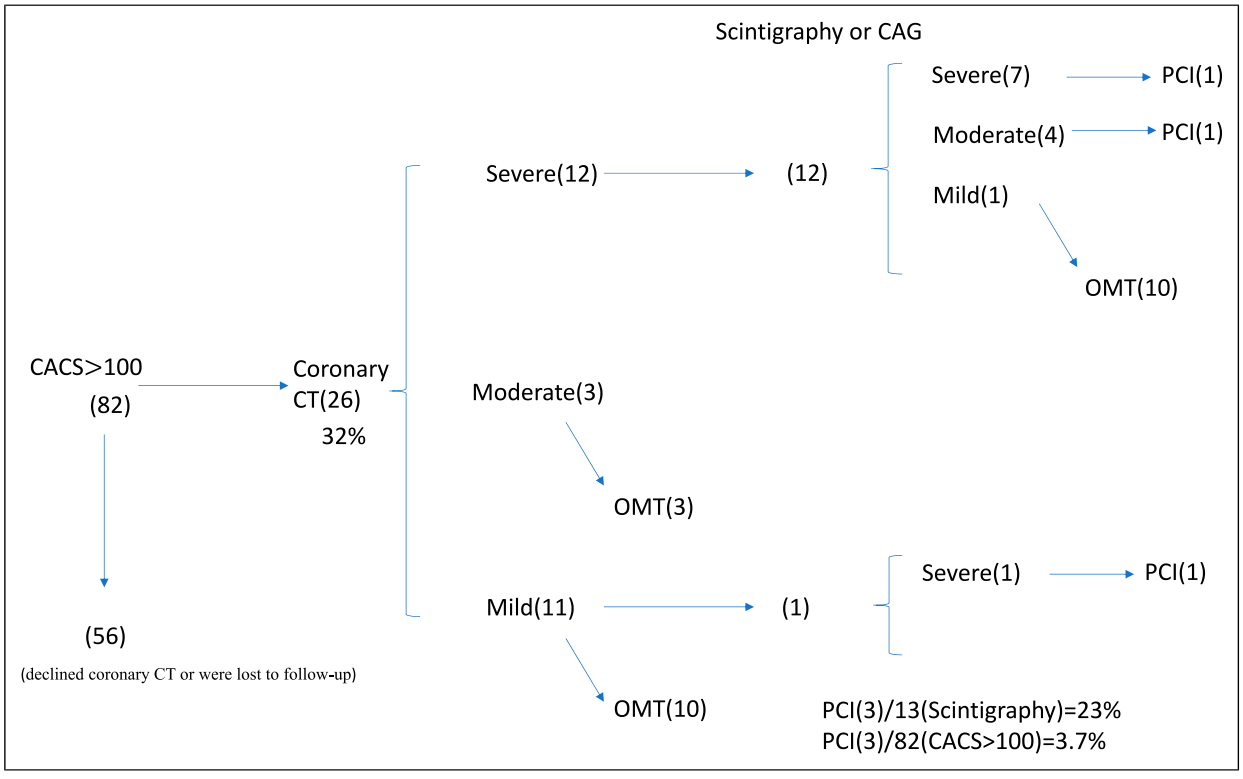

Figure 4. Concomitant coronary artery disease in patients with CVI. Note. OMT: optical medical therapy, PCI: percutaneous coronary intervention.

recent randomized controlled trial (RCT) reported that CAC scanning resulted in favorable changes in blood pressure, LDL cholesterol levels, and waist circumference, attributed to behavioral changes in patients and physicians.[20]

Our findings suggest that including CACS in CVI screening in outpatient clinics can help identify patients at risk for CAD, facilitating timely intervention. Sharing CAC scores with patients and their family doctors is essential to enable personalized guidance and raise awareness of the link between CVI and cardiovascular disease.

Selecting patients with possible heart disease from the large number of CVI patients remains a challenge in

outpatient settings, especially since many clinics lack clear guidelines for investigating both conditions. Understanding the typical demographics of these patients can aid in risk stratification when CT scans are unavailable.

Despite large population studies, there has been limited real-world implementation of these findings in clinical practice. We propose integrating CVI screening with CACS measurement to improve CAD diagnosis and prevention, thereby bridging this gap and addressing unmet needs in patient care.

CVI and CACS

Prochaska et al. demonstrated that chronic venous insufficiency (CVI) is highly prevalent in the population and is associated with the presence of cardiovascular risk factors and disease.[4] Individuals with CVI experience an elevated risk of death, independent of age, sex, cardiovascular risk factors, and comorbidities. They also proposed the potential for cross-talk between the arterial and venous vascular beds. Cardiovascular comorbidities include conditions such as congestive heart failure, coronary artery disease, peripheral artery disease, stroke, and others.

In this study, we specifically investigated CACS (coronary artery calcium scoring) as it relates directly to coronary artery disease. We objectively demonstrated that patients with CVI had a higher CACS, indicating a greater risk of coronary artery disease compared to the control group. Statistically significant differences were noted in coronary risk factors: the CVI group was older, had higher BMI, and more prevalent dyslipidemia. In contrast, the control group had higher creatinine levels, with no differences in the prevalence of hypertension or diabetes between the two groups. These findings may be attributed to the control group being composed of patients undergoing ablation rather than a normal population.

Functional chronic venous insufficiency (FVI) is an underestimated syndrome prevalent in the general population.[21] FVI is often considered a common phenomenon among inactive patients. Compared to those with lower limb varicose veins, patients with FVI tend to be older, have higher rates of hypertension, and have lower eGFR, albumin, and rVCSS.

When dividing the participants into subgroups with calcified plaque (CACS >100) and non-calcified plaque (CACS <100), it was observed that the calcified plaque subgroup had significantly more coronary risk factors. Notably, 73.6% of patients exhibiting calcified plaque had CVI.

This raises the question of why the CVI group has more calcified coronary arteries. Is this merely due to shared coronary risk factors? Large population studies have identified CVI as an important condition related to cardiovascular disease.[3,4,6] Previous reports have highlighted shared risk factors, such as obesity, aging, and diabetes, confirmed through multivariate analysis.[22,23] However, Prochaska et al. did not establish a causal role of CVI in the development of atherosclerosis or arterial cardiovascular disease.[4]

Another significant finding of our study is that CVI itself is an independent coronary risk factor. Multivariate analysis demonstrated that, even after adjusting for confounding factors such as age, hypertension, and dyslipidemia, CVI remained an independent risk factor for coronary artery disease. Routine scoring systems, such as QRISK3 may have their merits in the venous population to predict estimate future risk of cardiovascular disease.

Our findings raise the hypothesis of a direct interaction between CVI and arterial cardiovascular disease. CVI may increase arterial stiffness[24,25] and decrease right heart diastolic function.[26] CAVI (cardio-ankle vascular index), a measure of arterial stiffness and atherosclerosis, may be elevated due to capillary changes caused by venous hypertension associated with CVI. In the CVI group, the CAVI was 8.8 ± 1.2, falling within the marginal range of 8.0–9.0. CVI could affect heart function by increasing both afterload and preload.

Recent findings also suggest that varicose veins associated with CVI may induce edema, not only in the legs but systemically.[27,28] However, further studies and accumulated data are needed to fully understand these mechanisms.

In Prochaska's study, the distribution of CEAP classifications was C0 (906), C1 (3756), C2 (1399), C3 (3361), and C4–6 (1242). Their research was based on a large normal population, whereas our study involved a diseased population with the following distribution: C0 (1), C1 (1), C2 (0), C4 (26), C5 (0), and C6 (3), with C3 accounting for 203 cases (84%). This predominance of C3 may explain the lack of a relationship between CEAP, VCSS (Venous Clinical Severity Score), and CACS in our study.

Our study has several limitations, including a small sample size, single-center design, and is a retrospective nature of the study. The use of a cardiac ablation group as a control instead of a normal population. The control group also exhibited cardiovascular risk factors, such as hypertension, diabetes, and renal dysfunction. Additionally, other risk factors, such as physical inactivity, were not analyzed.

Future research should assess long-term outcomes, including cardiac events and mortality, to further elucidate the relationship between CVI and systemic cardiovascular health. Multicenter validation studies and randomized controlled trials are essential to provide robust evidence. Collaboration among specialists in cardiology, vascular surgery, phlebology, radiology, and rehabilitation is vital to advance our understanding of CVI and its systemic implications. Comprehensive patient management and increased awareness in both clinical and public settings are crucial for improving outcomes for patients with CVI.

Conclusion

Multivariate analysis indicated that CVI is an independent risk factor for coronary artery disease, even after adjusting for confounding factors such as age, hypertension, and dyslipidemia. Enhanced awareness and integration of CACS into CVI screening could improve early detection and management of cardiovascular risk, ultimately benefiting patient outcomes.

Author note

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Author contributions

Shinji Tomita researched literature and conceived the study and involved in protocol development, gaining ethical approval, and wrote the first draft of the manuscript. Takuya Mizukami performed data analysis. Shunsuke Imai and Taiji Miyake involved in patient recruitment and Hitoshi Matsuo involved in data analysis. YK, MI, SO, and YO involved in patient recruitment and TM performed data analysis. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used [chat GPT / open AI] in order to improve readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Ethical statement

Ethical approval

The Institutional Review Board (IRB) of Gifu Heart Center approved this study (IRB 2024012) on March 4, 2024.

Informed consent

The patients gave informed consent.

Guarantor

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