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ORIGINAL ARTICLE
Ischemic Heart Disease

Impact of Cardio-Ankle Vascular Index on Future Cancer in Patients With Coronary Artery Disease

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Background: Cardiovascular risk factors are associated with increased risk of future cancer. However, the relationship between quantitative parameters of atherosclerosis and future cancer risk is unclear.

Methods and Results: A total of 1,057 consecutive patients with coronary artery disease was divided into 2 groups according to the cutoff value of the cardio-ankle vascular index (CAVI) derived by receiver operating characteristic curve analysis: low CAVI group (CAVI <8.82; n=487), and high CAVI group (CAVI ≥8.82; n=570). Patients in the high CAVI group were older and had a higher prevalence of diabetes, chronic kidney disease, anemia and history of stroke compared with patients in the low CAVI group. There were 141 new cancers during the follow-up period. The cumulative incidence of new cancer was significantly higher in the high CAVI group than in the low CAVI group (P=0.001). In a multivariate Cox proportional hazard analysis, high CAVI was found to be an independent predictor of new cancer diagnosis (hazard ratio 1.62; 95% confidence interval 1.11–2.36; P=0.012). In the analysis of individual cancer types, high CAVI was associated with lung cancer (hazard ratio 2.85; 95% confidence interval 1.01–8.07; P=0.049).

Conclusions: High CAVI was associated with the risk of future cancer in patients with coronary artery disease.

Key Words: Atherosclerosis; Cancer; Cardio-ankle vascular index; Coronary artery disease

Cardiovascular disease (CVD) and cancer are the leading causes of death worldwide.[1] There is growing evidence supporting a potential link between the 2 diseases.[2] An increasing number of cancer patients are developing cancer treatment-related cardiotoxicity, which interferes with optimal cancer treatment and impacts the clinical outcomes of cancer patients and cancer survivors.[3] The importance of cooperation between cardiologists and oncologists has led to the development of the scientific field of cardio-oncology.

In recent years, attention has focused not only on the increased risk of cardiovascular adverse events during cancer treatment, but also on the increased risk of cancer development among patients with CVD. In particular, several studies including the present study, have reported an increased risk of cancer in heart failure patients.[4–6] Another study reported an association between CVD risk, as indicated by the 10-year atherosclerosis risk score, and the risk of future cancer.[7] This was partly due to several shared risk factors including age, smoking, obesity and diabetes. Furthermore, recent evidence suggests that CVD and cancer share common underlying pathophysiologic mechanisms, such as inflammation, platelet function and clonal hematopoiesis of indeterminate potential.[8] Several studies have reported that cancer patients have more severe atherosclerosis, and that patients with a current or past history of malignancy are associated with increased coronary artery calcification and impaired atherosclerotic markers such as ankle-brachial index and pulse wave velocity (PWV).[9,10] However, there have been few studies on the prediction of future cancer development by quantitative indicators of atherosclerosis. Here, we investigated the association between the cardio-ankle vascular index (CAVI), an indicator of arterial stiffness, and future cancer in patients with coronary artery disease (CAD).

Methods

Patient Population and Study Protocol

This was a prospective observational study that enrolled 1,430 consecutive patients with CAD who were hospitalized at Fukushima Medical University Hospital and underwent

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percutaneous coronary intervention and CAVI measurement between January 2010 and March 2022. Exclusion criteria included history of atrial fibrillation, ongoing maintenance dialysis, ankle-brachial index <0.9, and untreated or undertreated cancer. There were 373 patients excluded according to the criteria, which left a total of 1,057 patients for analysis. Receiver operating characteristic (ROC) curve analysis revealed that the accurate cutoff value of CAVI in predicting new cancer diagnosis was 8.82 (**Figure 1**). The patients were divided into 2 groups based on this cutoff value: low CAVI group (CAVI <8.82; n=487; 46.1%), and high CAVI group (CAVI ≥8.82; n=570; 53.9%). All patients were followed up until February 2023. Patient characteristics and incidence of new cancer diagnosis were compared between the 2 groups. All patients provided written informed consent. The study protocol was approved by the Ethics Committee of Fukushima Medical University and was carried out in accordance with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), along with references to STROBE and the broader EQUATOR guidelines.[11]

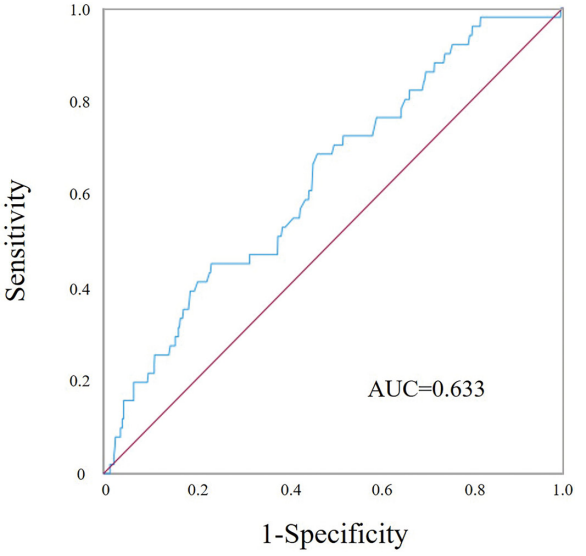

Figure 1. Receiver operating characteristic curve of the cardio-ankle vascular index (CAVI) for the prediction of new cancer diagnosis. AUC, area under the curve.

Comorbidities and Previous History

Comorbidities were assessed by several attending physicians. Smoking was defined as current smoking or cessation <6 months prior to hospitalization. Acute coronary syndrome included ST-elevation myocardial infarction and non-ST-elevation acute coronary syndrome, which was defined as new ST segment depression, horizontal or down sloping ≥0.05 mV in 2 consecutive leads, T-wave inversion >0.01 mV in 2 leads with prominent R wave or an increase in coronary markers of ischemia such as troponin I.[12] Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure of ≥140 mmHg, and/or diastolic blood pressure of ≥90 mmHg. Diabetes was defined as the recent use of insulin or antidiabetic drugs or fasting blood glucose value of ≥126 mg/dL and/or hemoglobin A1c value of ≥6.5%. Dyslipidemia was defined as the use of cholesterol-lowering drugs or a triglyceride value of ≥150 mg/dL, a low-density lipoprotein cholesterol value of ≥140 mg/dL and/or high-density lipoprotein cholesterol value of <40 mg/dL. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease formula.[13] Anemia was defined as a hemoglobin level of <12.0 g/dL in females and <13.0 g/dL in males, and hyperuricemia was defined as the use of uric acid-lowering drugs or a uric acid value of ≥7.0 mg/dL. Chronic heart failure was defined according to the Framingham criteria,[14] and was diagnosed by several cardiologists based on the guidelines.[15] Stroke was defined as an acute episode of focal dysfunction of the brain, retina, or spinal cord lasting ≥24 h or of any duration if computed tomography and/or magnetic resonance imaging showed focal brain infarction or hemorrhage relevant to the patient's symptoms.[16] Laboratory data were obtained when the patients were in a stable condition within 1 week prior to discharge.

Measurement of CAVI

CAVI was measured automatically using VaSera VS-1000 (Fukuda Denshi Co., Ltd, Tokyo, Japan) as described previously.[17] Cuffs were attached bilaterally to the upper arms and ankles with the patient in the supine position. Electrocardiogram electrodes and microphones were placed on both wrists and on the sternum, respectively. The examination was performed after 10 min of rest. CAVI was calculated using the following formula: $CAVI = a\{(2\rho/\Delta P)\times \ln(Ps/Pd)PWV^2\} + b$, where a and b are constants, ρ is blood density, ΔP is Ps-Pd, Ps is systolic blood pressure, and Pd is diastolic blood pressure. The average values of bilateral CAVI were used for analyses. CAVI was measured when patients were in a stable condition within 1 week prior to discharge.

Outcome

The primary endpoint was diagnosis of a new cancer after discharge. Recurrence of previously treated cancer was not included as an endpoint. The diagnosis of a new cancer was obtained from the patient's medical records or by contacting the attending physicians at the patient's referring hospital. The priority to confirm the diagnosis of cancer was a definitive pathological diagnosis obtained from pathology or cytology examinations. If a tissue sample was not available, the cancer diagnosis was confirmed based on strong clinical, radiological or laboratory-marker evidence.[18] The date of cancer diagnosis was defined as the date of pathologic diagnosis, or as the date of clinical diagnosis when the diagnosis by pathology or cytology was not available. Cancer types were classified by anatomic and systemic primary involvement. Colorectal cancer was defined as cancer involving the colon or rectum, and hematologic cancer was defined as hematologic malignant diseases including leukemia, lymphoma and myeloma. There were 209 patients who died during the follow-up period and they were handled as censored.

Statistical Analysis

Continuous variables are presented as mean±SD (for normal distribution of data) or median with an interquartile range (for non-normal distribution of data), and the student's t-test or the Mann-Whitney U test was used for

Table 1. Baseline Clinical Characteristics of the Study Population

	Low CAVI group (n=487)	High CAVI group (n=570)	P value
Age (years)	63.1±11.5	71.9±8.9	<0.001
Male gender	391 (80.3)	457 (80.2)	0.964
Body mass index (kg/cm^2)	25.5±4.0	23.8±3.3	<0.001
Smoking	336 (69.0)	377 (66.1)	0.324
Acute coronary syndrome	236 (48.5)	249 (43.7)	0.120
Comorbidities			
Hypertension	388 (79.7)	478 (83.9)	0.078
Diabetes	210 (43.1)	297 (52.1)	0.004
Dyslipidemia	452 (92.8)	521 (91.4)	0.398
Chronic kidney disease	151 (31.0)	262 (46.0)	<0.001
Anemia	143 (29.4)	255 (44.7)	<0.001
Hyperuricemia	171 (35.1)	232 (40.7)	0.062
Chronic heart failure	148 (30.4)	162 (28.4)	0.483
History of stroke	64 (13.1)	105 (18.4)	0.020
History of cancer	48 (9.9)	75 (13.2)	0.095
Laboratory data			
White blood cell (×10^3/μL)	7.9±3.9	7.4±3.1	0.046
Hemoglobin (g/dL)	13.8±1.8	13.1±1.9	<0.001
Platelet count (×10^3/μL)	217.0±64.2	207.5±58.8	0.017
eGFR (mL/min/1.73 m^2)	70.7±21.0	63.5±20.0	<0.001
LDL-cholesterol (mg/dL)	107.1±37.4	100.8±33.5	0.020
HDL-cholesterol (mg/dL)	50.7±19.0	48.9±15.4	0.156
Hemoglobin A1c (%)	6.1±1.0	6.3±1.2	0.019
Albumin (g/dL)	4.1±0.4	3.9±0.5	<0.001
BNP (pg/mL)	28.8 [11.9–100.1]	43.3 [19.4–137.6]	0.001
C-reactive protein (mg/dL)	0.09 [0.04–0.29]	0.10 [0.05–0.31]	0.330
D-dimer (μg/mL)	0.7 [0.5–1.1]	0.9 [0.6–1.6]	<0.001
Physiological data			
CAVI	7.7±1.0	10.0±1.1	<0.001
Left ventricular ejection fraction (%)	55.8±11.7	55.1±12.3	0.466
Left atrial diameter (mm)	37.2±6.2	37.0±6.1	0.635
Medications			
β-blockers	297 (61.0)	341 (59.8)	0.700
RAS inhibitors	366 (75.2)	419 (73.5)	0.542
Calcium channel blockers	252 (51.7)	327 (57.4)	0.067
Statins	425 (87.3)	463 (81.2)	0.008
Antiplatelet agents	472 (96.9)	557 (97.7)	0.420

Unless indicated otherwise, data are presented as n (%), mean±SD, or median [interquartile range]. BNP, B-type natriuretic peptide; CAVI, cardio-ankle vascular index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin-aldosterone system.

comparisons. The categorical variables were expressed as numbers and percentages, and the chi-square test was used for comparisons. Kaplan-Meier cumulative event curves were constructed for new cancer diagnoses, and compared with the log-rank test. We assessed CAVI as a predictor for new cancer diagnosis using the Cox proportional hazard analysis. To adjust for clinical confounding factors, we performed both the multivariate Cox proportional hazard analysis and the subgroup analysis. In the univariate Cox proportional hazard analysis, the subjects were divided into subgroups based on the presence or absence of categorical factors and the median of continuous variables. Interaction P values were obtained using a multivariate model including CAVI, subgroup factors, and interactions between CAVI and subgroup factors. The Cox proportional hazard analysis with CAVI as a continuous variable was performed, and the hazard ratio (HR) of new cancer diagnosis according to CAVI level was drawn using a cubic spline curve. A value of $P<0.05$ was considered statistically significant for all comparisons. These analyses were performed using a statistical software package (SPSS version 25.0; IBM, Armonk, NY, USA), except for cubic spline analysis. The cubic spline analysis was performed using EZR (version 1.51; Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

ROC Curve Analysis

ROC curves were constructed for the prediction of new

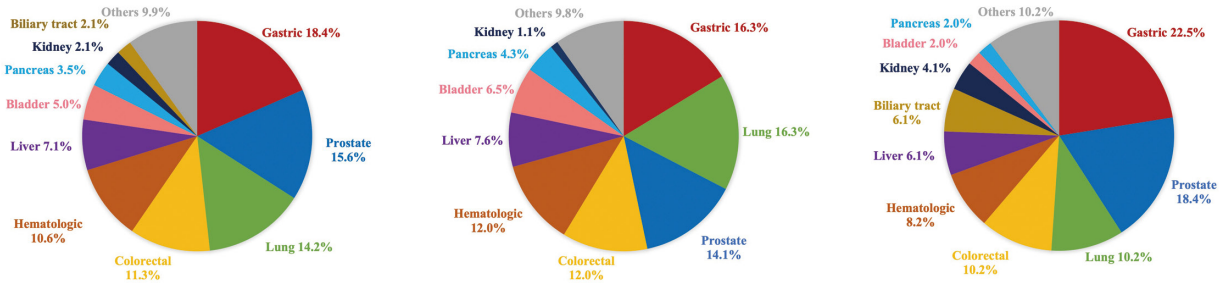

Figure 2. Percentage of each cancer type among all cancers (**A**), cancers in patients with high cardio-ankle vascular index (CAVI; **B**), and cancers in patients with low CAVI (**C**).

cancer diagnosis. ROC analysis demonstrated that CAVI was associated with new cancer diagnosis (area under the curve 0.633; 95% confidence interval (CI) 0.557–0.708; P=0.001; **Figure 1**). The cutoff value was 8.82 with a sensitivity 68.6% and specificity 53.5%.

Clinical Characteristics

Comparisons of clinical characteristics between the high and low CAVI groups are shown in **Table 1**. Patients in the high CAVI group were older (71.9 vs. 63.1 years; P<0.001) and had a higher prevalence of diabetes (52.1% vs. 43.1%; P=0.004), chronic kidney disease (46.0% vs. 31.0%; P<0.001), anemia (44.7% vs. 29.4%; P<0.001), and history of stroke (18.4% vs. 13.1%; P=0.020). The prevalence of smoking history and history of cancer did not differ between the 2 groups.

Outcomes

During the follow-up period (mean 2,223 days), there were 141 new cancer diagnoses. Gastric cancer was the most common primary cancer (n=26; 18.4%), followed by prostate cancer (n=22; 15.6%), lung cancer (n=20; 14.2%), colorectal cancer (n=16; 11.3%), hematologic cancer (n=15; 10.6%), liver cancer (n=10; 7.1%), bladder cancer (n=7; 5.0%), pancreatic cancer (n=5; 3.5%), renal cancer (n=3; 2.1%), biliary tract cancer (n=3; 2.1%), and cancers of other origins (n=14; 9.9%; **Figure 2A**). The proportions of each cancer type in the high and low CAVI groups are presented in **Figure 2B**,**C**. There was no statistically significant difference in cancer type between the 2 groups. In the Kaplan-Meier analysis, as shown in **Figure 3**, the cumulative incidence of new cancer diagnoses was significantly higher in the high CAVI group than in the low CAVI group (P=0.001). In the multivariate Cox proportional hazard analysis, the predictive value of high CAVI (as a categorical variable) was adjusted for 3 models: age and gender (Model 1); Model 1 plus variables considered risk factors for cancer including smoking history, diabetes, heart failure and history of cancer (Model 2); and Model 2 plus body mass index, acute coronary syndrome, hypertension, dyslipidemia, chronic kidney disease, anemia, hyperuricemia and history of stroke (Model 3). After adjusting

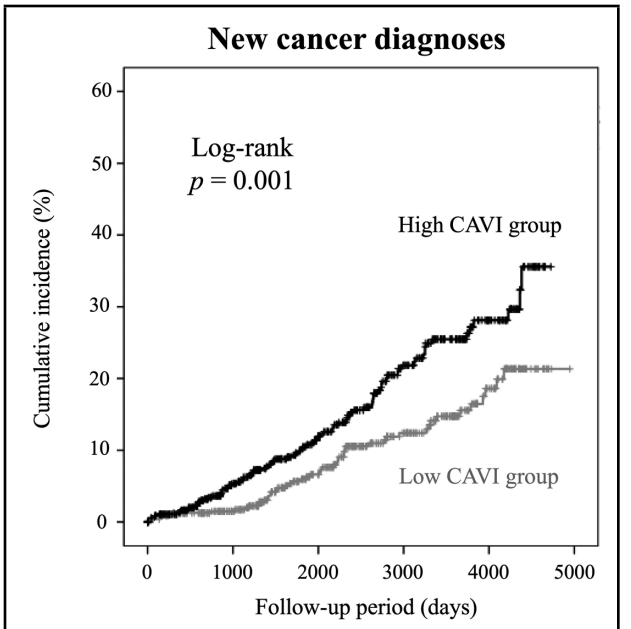

Figure 3. Cumulative incidence of new cancer diagnoses in the high and low cardio-ankle vascular index (CAVI) groups using Kaplan-Meier curve analysis.

for the above confounding factors, high CAVI was an independent predictor of new cancer diagnosis (Model 1: HR 1.67; 95% CI 1.16–2.40; P=0.006; Model 2: HR 1.73; 95% CI 1.20–2.50; P=0.003; and Model 3: HR 1.62; 95% CI 1.11–2.36; P=0.012; **Table 2**). A multivariate Cox proportional hazard analysis was also performed with CAVI as a continuous variable, which revealed that CAVI (per 1 increase) was independently associated with new cancer diagnosis (Model 1: HR 1.19; 95% CI 1.06–1.33; P=0.002; Model 2: HR 1.19; 95% CI 1.07–1.33; P=0.002; and Model 3: HR 1.16; 95% CI 1.03–1.30; P=0.013; **Table 2**). In the cubic spline curve analysis with CAVI as a continuous variable, patients with higher CAVI had a higher risk of

Table 2. Multivariate Cox Proportional Hazard Analysis for New Cancer Diagnosis

	HR	95% CI	P value
CAVI as a categorical variable			
High CAVI (vs. low CAVI), unadjusted	1.79	1.27–2.54	0.001
High CAVI (vs. low CAVI), adjusted model 1	1.67	1.16–2.40	0.006
High CAVI (vs. low CAVI), adjusted model 2	1.73	1.20–2.50	0.003
High CAVI (vs. low CAVI), adjusted model 3	1.62	1.11–2.36	0.012
CAVI as a continuous variable			
Per CAVI 1 increase, unadjusted	1.22	1.10–1.35	<0.001
Per CAVI 1 increase, adjusted model 1	1.19	1.06–1.33	0.002
Per CAVI 1 increase, adjusted model 2	1.19	1.07–1.33	0.002
Per CAVI 1 increase, adjusted model 3	1.16	1.03–1.30	0.013

Model 1: adjusted for age and gender. Model 2: adjusted for age, gender, smoking history, diabetes, heart failure and history of cancer. Model 3: adjusted for age, gender, body mass index, smoking history, acute coronary syndrome, hypertension, diabetes, dyslipidemia, chronic kidney disease, anemia, hyperuricemia, heart failure, history of stroke and history of cancer. CAVI, cardio-ankle vascular index; CI, confidence interval; HR, hazard ratio.

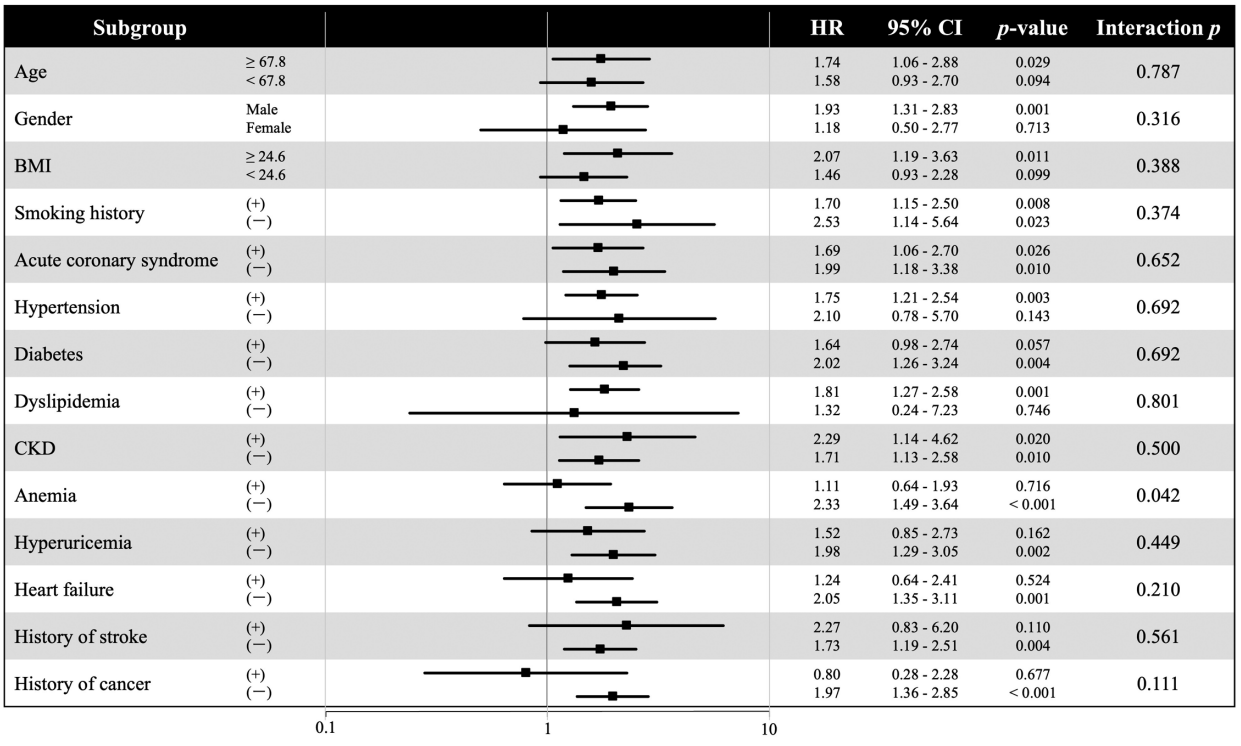

Figure 4. Forest plots of subgroup analysis depicting the hazard ratio as the center of the box and 95% confidence interval (CI) as a horizontal line. BMI, body mass index; CKD, chronic kidney disease.

new cancer diagnosis (**Supplementary Figure**).

The forest plot in **Figure 4** illustrates the association between high CAVI and new cancer diagnosis in subgroups after adjustment for interactions between high CAVI and prespecified clinically important variables. There were no interactions with important variables including age, smoking history, diabetes and heart failure, except for a significant interaction with anemia (P=0.042): HR 1.11 (95% CI 0.64–1.93; P=0.716) with anemia, and HR 2.33 (95% CI 1.49–3.64; P<0.001) without anemia.

Analysis With Different Cutoff Values

To improve external validity, a Cox proportional hazards analysis was performed using a cutoff value of 8 and 9, which is commonly used as the cutoff value for CAVI. After adjusting for confounding factors including age, gender, smoking history, diabetes, heart failure and history of cancer, CAVI ≥8 and ≥9 were independent predictors of new cancer diagnosis (HR 1.73; 95% CI 1.10–2.74; P=0.019; and HR 1.45; 95% CI 1.01–2.08; P=0.042; **Table 3**).

Table 3. Cox Proportional Hazard Analysis for New Cancer Diagnosis for Each Cutoff Value of CAVI

	HR	95% CI	P value
CAVI ≥8 (vs. CAVI <8)			
Unadjusted	1.83	1.19–2.82	0.006
Adjusted*	1.73	1.10–2.74	0.019
CAVI ≥8.82 (vs. CAVI <8.82)			
Unadjusted	1.79	1.27–2.54	0.001
Adjusted*	1.73	1.20–2.50	0.003
CAVI ≥9 (vs. CAVI <9)			
Unadjusted	1.56	1.12–2.18	0.009
Adjusted*	1.45	1.01–2.08	0.042

*Adjusted for age, gender, smoking history, diabetes, heart failure and history of cancer. Abbreviations as in Table 2.

Table 4. HR for Development of Individual Cancer Types

Cancer type	High CAVI (vs. low CAVI)		
	HR	95% CI	P value
Gastric (n=26)			
Unadjusted	1.31	0.60–2.85	0.500
Adjusted*	1.32	0.59–2.97	0.502
Prostate (n=22)			
Unadjusted	1.31	0.55–3.10	0.547
Adjusted*	1.13	0.45–2.83	0.793
Lung (n=20)			
Unadjusted	2.88	1.05–7.92	0.041
Adjusted*	2.85	1.01–8.07	0.049
Colorectal (n=16)			
Unadjusted	2.15	0.75–6.18	0.157
Adjusted*	2.12	0.71–6.34	0.178
Hematologic (n=15)			
Unadjusted	2.67	0.85–8.37	0.093
Adjusted*	2.80	0.86–9.07	0.086

*Adjusted for age and gender. Abbreviations as in Table 2.

Individual Cancer-Specific HRs

HRs for development of individual cancer type are shown in **Table 4**. Among the top 5 cancer types, including gastric, prostate, lung, colorectal and hematologic cancer, the risk of lung cancer remained significantly increased for high CAVI after adjusting for age and gender (HR 2.85; 95% CI 1.01–8.07; P=0.049).

Discussion

The main findings of the present study are as follows. First, patients with high CAVI (i.e., CAVI ≥8.82) were older, had a lower body mass index, and had a higher prevalence of comorbidities such as diabetes, chronic kidney disease, anemia and history of stroke compared with patients with low CAVI (i.e., CAVI <8.82). Second, high CAVI was an independent predictor of new cancer diagnosis in patients with CAD. Last, the predictive value of CAVI was observed for lung cancer in individual cancer-specific analysis. To the best of our knowledge, the present study was the first to show the predictive value of CAVI, the measurable indicator of systemic atherosclerosis, for the risk of future cancer.

Cancer and CAD are closely associated with shared risk factors. Diabetes is associated with an increased risk of cancer of the colon, lung, pancreas, esophagus, liver, thyroid, breast, and uterus.[19] Proposed mechanisms to link diabetes and cancer include cell proliferation via enhanced insulin signaling due to hyperinsulinemia,[20] provision of nutrient sources to tumor cells with a Warburg effect,[21] and DNA damage via increased oxidative stress.[22] Previous reports have shown that diabetes was associated with 1.25–1.41 times higher cancer mortality.[23,24] Smoking is a well recognized risk factor for cancer, with a particularly high risk of cancer in the lung, larynx and pharynx. The risk of developing cancer is also increased in organs not directly exposed to mainstream smoke, such as the digestive tract, urinary tract, prostate, bone marrow and other organs. The relative risk of death from all cancers due to smoking is 1.97 times higher in men and 1.57 times higher in women.[25] Excessive salt intake, a main risk factor for hypertension, is associated with an increased risk of developing gastric and esophageal cancer.[26,27] It has also been reported that higher blood pressure in men increases the risk of developing colorectal cancer.[28] Moreover, there is growing evidence that CVD and cancer share not only common risk factors but also underlying pathophysiologic mechanisms such as inflammation, platelet dysfunction,

and clonal hematopoiesis of indeterminate potential.[8] A randomized controlled trial demonstrated that anti-inflammatory therapy, inhibition of IL-1β by canakinumab, reduced both cardiovascular events and cancer risk in patients with a history of myocardial infarction and increased C-reactive protein levels.[29,30]

From a CAD standpoint, patients with CAD had 1.06–1.46 times higher risk of developing all types of cancer than those without.[31–33] Suzuki et al. reported an association between polyvascular disease and cancer incidence, indicating that the increased severity of atherosclerosis plays an important role in cancer development.[34] In contrast, patients with cancer have more advanced atherosclerosis, leading to an increased risk of cardiovascular events.[10,35] Cancer patients have a higher mortality rate from CVD than from other causes.[36] Therefore, both cancer in CVD patients and CVD in cancer patients are emerging issues, but there is a lack of guidelines for their prediction and treatment. Coronary artery calcification is a measurable indicator of atherosclerosis, which has been reported to have a predictive ability for the risk of colon and lung cancer depending on its severity.[37] In the present study, we demonstrated the predictive value of CAVI, which is an easily measurable indicator of systemic arterial stiffness, for identifying future cancer in patients with CAD.

PWV has been the gold standard of measuring arterial stiffness; however, PWV is essentially affected by blood pressure at the time of measurement. CAVI has the advantage of being independent of blood pressure.[17] Several factors including aging,[38] hypertension,[39] diabetes,[40] smoking,[41] renal dysfunction,[42] metabolic syndrome[43] and sleep-disordered breathing[44] have been reported to increase CAVI. The predictive ability of CAVI for cancer risk shown in the present study may represent the influence of common risk factors. In addition, inflammation may be involved as an underlying pathophysiological mechanism, given its potential association with elevated PWV.[45] There have been several reports that CAVI predicts cardiovascular events: CAD patients with CAVI >8.325 and diabetic patients with CAVI >9.0 had a higher incidence of cardiovascular events.[46,47] A recent review of vascular function has proposed CAVI ≥9.0 as a marker of vascular dysfunction.[48]

The top 4 cancer types in the present study (gastric, prostate, lung and colorectal) are the same as the top 4 types in the general male population in Japan.[49] In the analysis of individual cancer types, CAVI appeared to have a significant predictive value for lung cancer, although a limited sample size may have precluded statistical significance for other cancer types. Dzaye et al. revealed the coronary artery calcification score calculated from non-contrast cardiac-gated computed tomography scanning predicts the risks of colon and lung cancers.[37] Lung and colorectal cancers are strongly linked to modifiable risk factors that have a relevant overlap with the risk factor profile of CVD and also account for a substantial proportion of cancer deaths.[50] Although a cancer screening system has been well established in Japan, the cancer screening uptake rate has remained flat, and the mortality rate for the 5 cancers regulated under the national cancer screening guidelines has barely improved.[51] Therefore, it is important to promote rational health behaviors to improve people's cancer screening uptake rate. According to the results in the present study, CAVI might contribute to the identification of patients at high risk of future cancer and encourage cancer screening for these patients.

Study Limitations

The present study has several limitations. First, since the study was performed in a single center with a relatively small number of patients, analysis for high CAVI and individual cancer types may not be sufficient. Second, the incidence of new cancer diagnoses may have been underestimated compared with the actual incidence, given that these diagnoses partially depended on reports from attending physicians at referral hospitals after discharge. Third, there were unmeasured confounding factors such as exercise habits and dietary pattern, which might have influenced the results of the multivariate analysis. Last, the present study lacked data to analyze the stage of cancer diagnosed.

Conclusions

High CAVI was associated with the risk of future cancer in patients with CAD. CAVI may contribute to the identification of patients at high risk and enable early detection of cancer.

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Disclosures

The authors declare that there are no conflicts of interest.

IRB Information

The study protocol was approved by the Ethics Committee of Fukushima Medical University (Reference no. 823).

Data Availability

The deidentified participant data will not be shared.

References

1. Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, Gupta R, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): A prospective cohort study. *Lancet* 2020; **395:** 785–794, doi:10.1016/S0140-6736(19)32007-0.
2. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37:** 2768–2801, doi:10.1093/eurheartj/ehw211.
3. Barrett-Lee PJ, Dixon JM, Farrell C, Jones A, Leonard R, Murray N, et al. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. *Ann Oncol* 2009; **20:** 816–827, doi:10.1093/annonc/mdn728.
4. Hasin T, Gerber Y, Weston SA, Jiang R, Killian JM, Manemann SM, et al. Heart failure after myocardial infarction is associated with increased risk of cancer. *J Am Coll Cardiol* 2016; **68:** 265–271, doi:10.1016/j.jacc.2016.04.053.
5. Banke A, Schou M, Videbaek L, Møller JE, Torp-Pedersen C, Gustafsson F, et al. Incidence of cancer in patients with chronic heart failure: A long-term follow-up study. *Eur J Heart Fail* 2016; **18:** 260–266, doi:10.1002/ejhf.472.
6. Yoshihisa A, Ichijo Y, Watanabe K, Sato Y, Kanno Y, Takiguchi M, et al. Prior history and incidence of cancer impacts on cardiac prognosis in hospitalized patients with heart failure. *Circ J* 2019; **83:** 1709–1717, doi:10.1253/circj.CJ-19-0279.
7. Lau ES, Paniagua SM, Liu E, Jovani M, Li SX, Takvorian K, et al. Cardiovascular risk factors are associated with future cancer. *JACC CardioOncol* 2021; **3:** 48–58, doi:10.1016/j.jaccao.2020.12.003.
8. Leiva O, AbdelHameid D, Connors JM, Cannon CP, Bhatt DL.

Common pathophysiology in cancer, atrial fibrillation, atherosclerosis, and thrombosis: *JACC: CardioOncology* State-of-the-Art Review. *JACC CardioOncol* 2021; **3:** 619–634, doi:10.1016/j.jaccao.2021.08.011.
9. Sueta D, Hokimoto S, Utsunomiya D, Tabata N, Akasaka T, Sakamoto K, et al. New aspects of onco-cardiology. *Int J Cardiol* 2016; **206:** 68–70, doi:10.1016/j.ijcard.2016.01.051.
10. Tabata N, Sueta D, Yamamoto E, Takashio S, Arima Y, Araki S, et al. A retrospective study of arterial stiffness and subsequent clinical outcomes in cancer patients undergoing percutaneous coronary intervention. *J Hypertens* 2019; **37:** 754–764, doi:10.1097/HJH.0000000000001949.
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *BMJ* 2007; **335:** 806–808, doi:10.1136/bmj.39335.541782.AD.
12. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, et al. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. *Circulation* 2018; **138:** 2741–2750, doi:10.1161/CIRCULATIONAHA.118.037152.
13. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145:** 247–254, doi:10.7326/0003-4819-145-4-200608150-00004.
14. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham study. *N Engl J Med* 1971; **285:** 1441–1446, doi:10.1056/NEJM197112232852601.
15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18:** 891–975, doi:10.1002/ejhf.592.
16. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44:** 2064–2089, doi:10.1161/STR.0b013e318296aeca.
17. Sato Y, Yoshihisa A, Ichijo Y, Watanabe K, Hotsuki Y, Kimishima Y, et al. Cardio-ankle vascular index predicts post-discharge stroke in patients with heart failure. *J Atheroscler Thromb* 2021; **28:** 766–775, doi:10.5551/jat.58727.
18. Sakuma Y, Shimizu T, Kurosawa Y, Ohara H, Muto Y, Sato Y, et al. Impact of bleeding event for new cancer diagnosis in patients with antiplatelet therapy after percutaneous coronary intervention. *J Cardiol* 2023; **82:** 460–466, doi:10.1016/j.jjcc.2023.04.012.
19. Hu Y, Zhang X, Ma Y, Yuan C, Wang M, Wu K, et al. Incident type 2 diabetes duration and cancer risk: A prospective study in two US cohorts. *J Natl Cancer Inst* 2021; **113:** 381–389, doi:10.1093/jnci/djaa141.
20. Gallagher EJ, LeRoith D. Obesity and diabetes: The increased risk of cancer and cancer-related mortality. *Physiol Rev* 2015; **95:** 727–748, doi:10.1152/physrev.00030.2014.
21. Hay N. Reprogramming glucose metabolism in cancer: Can it be exploited for cancer therapy? *Nat Rev Cancer* 2016; **16:** 635–649, doi:10.1038/nrc.2016.77.
22. Patra KC, Hay N. The pentose phosphate pathway and cancer. *Trends Biochem Sci* 2014; **39:** 347–354, doi:10.1016/j.tibs.2014.06.005.
23. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; **364:** 829–841, doi:10.1056/NEJMoa1008862.
24. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: A systematic review and meta-analysis. *JAMA* 2008; **300:** 2754–2764, doi:10.1001/jama.2008.824.
25. Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: A pooled analysis of three large-scale cohort studies. *J Epidemiol* 2008; **18:** 251–264, doi:10.2188/jea.je200742.
26. Tsugane S, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer* 2004; **90:** 128–134, doi:10.1038/sj.bjc.6601511.
27. Banda KJ, Chiu HY, Hu SH, Yeh HC, Huang HC. Associations of dietary carbohydrate and salt consumption with esophageal cancer risk: A systematic review and meta-analysis of observational studies. *Nutr Rev* 2020; **78:** 688–698, doi:10.1093/nutrit/nuz097.
28. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, et al. Untreated hypertension and subsequent incidence of colorectal cancer: Analysis of a nationwide epidemiological database. *J Am Heart Assoc* 2021; **10:** e022479, doi:10.1161/JAHA.121.022479.
29. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377:** 1119–1131, doi:10.1056/NEJMoa1707914.
30. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: Exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **390:** 1833–1842, doi:10.1016/S0140-6736(17)32247-X.
31. Rinde LB, Småbrekke B, Hald EM, Brodin EE, Njølstad I, Mathiesen EB, et al. Myocardial infarction and future risk of cancer in the general population-the Tromsø Study. *Eur J Epidemiol* 2017; **32:** 193–201, doi:10.1007/s10654-017-0231-5.
32. Suzuki M, Tomoike H, Sumiyoshi T, Nagatomo Y, Hosoda T, Nagayama M, et al. Incidence of cancers in patients with atherosclerotic cardiovascular diseases. *Int J Cardiol Heart Vasc* 2017; **17:** 11–16, doi:10.1016/j.ijcha.2017.08.004.
33. Kwak S, Choi YJ, Kwon S, Lee SY, Yang S, Moon I, et al. De novo malignancy risk in patients undergoing the first percutaneous coronary intervention: A nationwide population-based cohort study. *Int J Cardiol* 2020; **313:** 25–31, doi:10.1016/j.ijcard.2020.04.085.
34. Suzuki M, Tomoike H, Dai Z, Hosoda T, Sumiyoshi T, Hosoda S, et al. Polyvascular disease and the incidence of cancer in patients with coronary artery disease. *JMA J* 2022; **5:** 498–509, doi:10.31662/jmaj.2022-0098.
35. Diao Y, Liu Z, Chen L, Zhang W, Sun D. The relationship between cancer and functional and structural markers of subclinical atherosclerosis: A systematic review and meta-analysis. *Front Cardiovasc Med* 2022; **9:** 849538, doi:10.3389/fcvm.2022.849538.
36. Henson KE, Reulen RC, Winter DL, Bright CJ, Fidler MM, Frobisher C, et al. Cardiac mortality among 200 000 five-year survivors of cancer diagnosed at 15 to 39 years of age: The Teenage and Young Adult Cancer Survivor Study. *Circulation* 2016; **134:** 1519–1531, doi:10.1161/CIRCULATIONAHA.116.022514.
37. Dzaye O, Berning P, Dardari ZA, Mortensen MB, Marshall CH, Nasir K, et al. Coronary artery calcium is associated with increased risk for lung and colorectal cancer in men and women: The Multi-Ethnic Study of Atherosclerosis (MESA). *Eur Heart J Cardiovasc Imaging* 2022; **23:** 708–716, doi:10.1093/ehjci/jeab099.
38. Namekata T, Suzuki K, Ishizuka N, Shirai K. Establishing baseline criteria of cardio-ankle vascular index as a new indicator of arteriosclerosis: A cross-sectional study. *BMC Cardiovasc Disord* 2011; **11:** 51, doi:10.1186/1471-2261-11-51.
39. Okura T, Watanabe S, Kurata M, Manabe S, Koresawa M, Irita J, et al. Relationship between cardio-ankle vascular index (CAVI) and carotid atherosclerosis in patients with essential hypertension. *Hypertens Res* 2007; **30:** 335–340, doi:10.1291/hypres.30.335.
40. Ohira M, Endo K, Oyama T, Yamaguchi T, Ban N, Kawana H, et al. Improvement of postprandial hyperglycemia and arterial stiffness upon switching from premixed human insulin 30/70 to biphasic insulin aspart 30/70. *Metabolism* 2011; **60:** 78–85, doi:10.1016/j.metabol.2010.06.001.
41. Kubozono T, Miyata M, Ueyama K, Hamasaki S, Kusano K, Kubozono O, et al. Acute and chronic effects of smoking on arterial stiffness. *Circ J* 2011; **75:** 698–702, doi:10.1253/circj.CJ-10-0552.
42. Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, et al. Clinical significance and reproducibility of new arterial distensibility index. *Circ J* 2007; **71:** 89–94, doi:10.1253/circj.71.89.
43. Satoh N, Shimatsu A, Kato Y, Araki R, Koyama K, Okajima T, et al. Evaluation of the cardio-ankle vascular index, a new indicator of arterial stiffness independent of blood pressure, in obesity and metabolic syndrome. *Hypertens Res* 2008; **31:** 1921–1930, doi:10.1291/hypres.31.1921.

44. Kato M, Kumagai T, Naito R, Maeno K, Kasagi S, Kawana F, et al. Change in cardio-ankle vascular index by long-term continuous positive airway pressure therapy for obstructive sleep apnea. *J Cardiol* 2011; **58:** 74–82, doi:10.1016/j.jjcc.2011.03.005.
45. Aminuddin A, Lazim MRMLM, Hamid AA, Hui CK, Mohd Yunus MH, Kumar J, et al. The association between inflammation and pulse wave velocity in dyslipidemia: An evidence-based review. *Mediators Inflamm* 2020; **2020:** 4732987, doi:10.1155/2020/4732987.
46. Gohbara M, Iwahashi N, Sano Y, Akiyama E, Maejima N, Tsukahara K, et al. Clinical impact of the cardio-ankle vascular index for predicting cardiovascular events after acute coronary syndrome. *Circ J* 2016; **80:** 1420–1426, doi:10.1253/circj.CJ-15-1257.
47. Chung SL, Yang CC, Chen CC, Hsu YC, Lei MH. Coronary artery calcium score compared with cardio-ankle vascular index in the prediction of cardiovascular events in asymptomatic patients with type 2 diabetes. *J Atheroscler Thromb* 2015; **22:** 1255–1265, doi:10.5551/jat.29926.
48. Tanaka A, Tomiyama H, Maruhashi T, Matsuzawa Y, Miyoshi T, Kabutoya T, et al. Physiological diagnostic criteria for vascular failure. *Hypertension* 2018; **72:** 1060–1071, doi:10.1161/HYPERTENSIONAHA.118.11554.
49. Katanoda K, Hori M, Saito E, Shibata A, Ito Y, Minami T, et al. Updated trends in cancer in Japan: Incidence in 1985–2015 and mortality in 1958–2018: A sign of decrease in cancer incidence. *J Epidemiol* 2021; **31:** 426–450, doi:10.2188/jea.JE20200416.
50. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin* 2018; **68:** 31–54, doi:10.3322/caac.21440.
51. Katanoda K, Ito Y, Sobue T. International comparison of trends in cancer mortality: Japan has fallen behind in screening-related cancers. *Jpn J Clin Oncol* 2021; **51:** 1680–1686, doi:10.1093/jjco/hyab139.

Supplementary Files

Please find supplementary file(s);
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