AN ASSOCIATION BETWEEN CARDIO-ANKLE VASCULAR INDEX (CAVI) AND VENTRICULAR-ARTERIAL COUPLING IN THAI CHRONIC KIDNEY DISEASE PATIENTS

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Abstract

Background: Cardiovascular remodeling is a recognized chronic kidney disease (CKD) complication. The clinical implication of heart failure with mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) in CKD, including their underlying pathogenic mechanisms, remains incompletely understood.

Objectives: This study aimed to determine the association between arterial stiffness, as measured by the cardio-ankle vascular index (CAVI), and impaired interaction between the left ventricle and the arterial system by ventricular-arterial coupling (VAC) determined by echocardiography with heart failure with HFmrEF or HFpEF in non-dialysis CKD. Secondly, to evaluate the prognostic impact of baseline HFmrEF/HFpEF, abnormal CAVI, and VAC on long-term outcomes.

Methods: A cross-sectional and prospective analysis was conducted in the CORE-CKD cohort of 66 non-dialysis CKD patients, stages 3-5. The relationship between CAVI or VAC and HFmrEF/HFpEF at baseline was assessed using multivariate logistic regression. Subsequently, the association between HFmrEF/HFpEF, high CAVI, and high VAC with a composite outcome of all-cause mortality and cardiovascular hospitalization was evaluated using the multivariate Cox proportional hazards model.

Results: At baseline, those with HFmrEF/HFpEF (n=18) had significantly higher CAVI (9.4 vs. 8.4, p=0.001) and VAC values (1.02 vs. 0.88, p=0.033) than those without HFmrEF/HFpEF. High CAVI was significantly associated with HFmrEF/HFpEF by multivariate analysis (OR 5.11, 95% CI: 1.27-20.42). This prospective study showed that the median follow-up time was six years. The risk for primary composite outcome was substantially higher in patients with HFmrEF/HFpEF than those without (HR 43.8, 95%CI: 5.89-304.8).

Conclusion: HFmrEF/HFpEF was associated with increased arterial stiffness, impaired left ventricular-arterial coupling, and a significantly elevated risk of mortality or cardiovascular hospitalization among CKD patients.

Keywords: Chronic kidney disease, heart failure with mildly reduced ejection fraction, heart failure with preserved ejection fraction, cardio-ankle vascular index, ventricular-arterial coupling, mortality.

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Introduction

Chronic kidney disease (CKD) is a significant public health problem, affecting approximately 10-15% of the global adult population.[1] Patients with CKD are at an increased risk of developing cardiovascular complications, including heart failure, which is the leading cause of morbidity and mortality in this population.[2,3] The pathophysiology of cardiovascular disease in CKD is multifactorial, resulting in structural and functional changes in the heart and vasculature, including arterial stiffness, vascular calcification, and endothelial dysfunction.[4,5] Arterial stiffness refers to the loss of elasticity and compliance of the arterial walls, leading to increased pulse wave velocity and elevated pulse pressure.[6] The cardio-ankle vascular index (CAVI) is a non-invasive measure of arterial stiffness proposed as a helpful tool for cardiovascular risk assessment.[7,8] A recent meta-analysis of different populations, including CKD, showed that high CAVI increased the risk of cardiovascular events and kidney function decline.[8] High CAVI increased all-cause mortality in Japanese hemodialysis patients,[9] and major adverse cardiovascular events (MACE) in predialysis CKD patients.[10] In addition, high CAVI is associated with renal progression in high cardiovascular-risk Thai subjects.[11]

Another essential concept in assessing cardiovascular function is ventricular-arterial coupling (VAC), which describes the interaction between the left ventricle and the arterial system.[12] Specifically, it refers to the dynamic relationship between the heart-pumping action and the loading conditions imposed by the vascular system.[13] VAC is indexed by the ratio of effective arterial elastance (Ea) to end-systolic elastance (Ees).[14,15] Ea measures the net arterial load imposed on the left ventricle. It encompasses the effects of both resistive and pulsatile afterload components.[16] Ea can be calculated as the ratio of end-systolic pressure (ESP) to stroke volume (SV). Ees measures the contractile properties of the left ventricle, reflecting its systolic stiffness or elastance. VA coupling (Ea/Ees) is close to 1.0 in healthy individuals, which means optimal coupling between the heart and arterial system. When VA coupling is <1.0, the heart pumping remains close to optimal values. Still, when VA coupling is >1.0, it suggests that the arterial load is too high relative to ventricular contractility. This may lead to reduced cardiovascular efficiency and impaired left ventricular performance, including increased risk of heart failure. VAC is a predictor for clinical outcomes in many different settings, including aortic valve replacement, myocardial infarction, hemodialysis, and chemotherapy-related cardiac impairment.[17-20] Patients with early-stage CKD (stages 2-3) may have reduced aortic distensibility, increased arterial elastance (Ea), and increased end-systolic and end-diastolic ventricular elastances (Ees) consistent with increased arterial and ventricular stiffness compared to controls.[21] However, limited data on VAC in non-dialysis CKD remains.

Heart failure with mildly reduced ejection

fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) are growing public health problems, particularly in the elderly population and those with CKD.[22] HFmrEF or HFpEF (HFmrEF/HFpEF) is associated with an increased risk of adverse cardiovascular outcomes and mortality. [23,24] HFpEF is characterized by impaired diastolic function, increased left ventricular stiffness, and abnormal vascular arterial coupling despite preserved left ventricular ejection fraction. [25] A relationship between arterial stiffness and left ventricular diastolic function has been shown in patients with IgA nephropathy. [26] Still, limited studies evaluate the associations of CAVI with VAC and heart failure with mildly reduced ejection fraction or preserved ejection fraction in CKD.

Our study's primary objective was to investigate the association between CAVI or VAC and HFmrEF/HFpEF. The secondary aim was to examine the association between HFmrEF/HFpEF and long-term outcomes, including death and cardiovascular hospitalization, as well as the rate of progression to end-stage renal disease requiring renal replacement therapy.

Methods

Study design and population

A prospective and cross-sectional analysis was conducted; this study was part of a planned prospective substudy of the "Cohort of CKD Patients with High Risk for Cardiovascular Events or Renal Disease Progression Multicenter Study" (CORE-CKD Thailand). CORE-CKD Thailand study (TCTR20211209001) (www.thaiclinicaltrials.org) is a multicenter prospective cohort study of CKD and its complications and outcomes. In this substudy, CKD patients aged over 18 years enrolled from 2 sites (Ramathibodi Hospital and Ratchaburi Hospital) from November 2015 to December 2018, with echocardiogram and CAVI performed at the time of enrollment were included. CKD was defined as an estimated glomerular filtration rate lower than 60ml/min/1.73m^2, calculated by the CKD epidemiology formula for >3 months. Exclusion criteria included previous kidney transplantation, end-stage kidney disease requiring dialysis, advanced cirrhosis or malignancy, known peripheral arterial disease or Ankle-Brachial Index(ABI) <0.9 or limb amputations, prior cardiac surgery, mechanically assisted or biventricular pacemaker implantation or those with left ventricular ejection fraction less than 40%, at baseline, and patients with unsuitable echocardiographic images.

This study was approved by the Ethics Research Ethics Board at Ramathibodi and the Central Research Ethics Committee (ID: COA-CREC 005/57 and MURA2024/371) and conducted according to the Declarations of Helsinki. All participants gave written informed consent.

Study protocol

The study collected demographic, clinical, laboratory, and medication data on CKD patients at baseline by direct interview and review of medical charts by trained nurses under a standardized protocol. Blood was obtained after an overnight fast. Serum creatinine was measured by enzymatic method, and estimated GFR was calculated using the CKD Epidemiology formula for non-Blacks [27] as the Nephrology Society of Thailand recommended. CKD stages were assigned according to KDIGO 2012. [28] The patients were followed up every six months for up to eight years to determine outcomes. Medical therapy was administered by physicians based on standard guidelines without knowledge of CAVI or echocardiography results. [27]

Definitions

HFmrEF and HFpEF were diagnosed according to current international guidelines[29-31] as patients with LVEF ≥40% and LVEF ≥50%, respectively, with a clinical syndrome of characteristic clinical signs and symptoms of pulmonary congestion confirmed by chest radiography. All of the patients in our study were treated with intravenous diuretics, confirming the clinical congestion.

Hypertension was defined using office-based blood pressure as systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg.[32] Diabetes mellitus (DM) was defined as fasting plasma glucose ≥126 mg/dl or HbA1C ≥6.5%.[33]

Measurement of Ventricular-arterial coupling

Ventricular-arterial coupling (VAC) was measured non-invasively by transthoracic echocardiography. Echocardiography parameters were measured by trained sonographers unaware of patient clinical details using an ultrasound machine (Phillip IE33, The Netherlands) and following the standard imaging protocols recommended by the American Society of Echocardiography.[34]

Left ventricular end-systolic elastance was derived from arm-cuff blood pressure measurement. Effective arterial elastance was calculated using echo-Doppler derived stroke volume, the time intervals from onset to end-ejection, and ejection fraction (EF). Stroke volume (SV) was determined from the aortic outflow velocity-time integral multiplied by the cross-sectional area.

Ea can be calculated as the ratio of end-systolic pressure (ESP) to stroke volume (SV). Ees measures the contractile properties of the left ventricle, reflecting its systolic stiffness or elastance. It is the slope of the end-systolic pressure-volume relationship (ESPVR).[35] The ESPVR is a linear relationship between ESP, end-systolic volume (ESV), and its slope. Ees can be calculated as Ees = ESP/(ESV-V0), where V0 represents the left ventricular volume at zero pressure. [36] VAC can be calculated by the formula. [37]

$$VAC = Ea/Ees = (ESP/SV)/[ESP/(ESV-V0)]$$

Measurement of Cardio-ankle Vascular Index

Cardio-ankle Vascular Index (CAVI) was measured with a VaSera CAVI instrument (Fukuda Denshi Co. Ltd, Tokyo, Japan) using the methods described in the literature. [7] Patients rested supine for 10-15 minutes before the measurement, with the ECG and PCG monitored. Blood pressure cuffs were placed on the upper arms and ankles of the four limbs. The CAVI was derived from the pulse wave velocity (PWV) and blood pressure using the equation calculation.

$$CAVI = \{(2p \div \Delta P) \times \ln (Ps \div Pd) \times PWV^2\}$$

Ps is systolic blood pressure, Pd is diastolic blood pressure, ΔP is Ps-Pd, p is the blood density, and PWV denotes the cardio-ankle pulse wave velocity.

Outcomes

The outcomes evaluated consisted of a cross-sectional outcome and prospective outcomes. The cross-sectional outcome was the presence of heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF).

The long-term outcomes consisted of primary and secondary outcomes: The primary long-term outcome was a composite endpoint of all-cause mortality or hospitalization due to cardiovascular events with ICD10 codes [nonfatal myocardial infarction (I21), nonfatal stroke (I64), or heart failure hospitalization (I50)].

The secondary long-term outcomes were individual components of 1) hospitalization due to cardiovascular events, 2) all-cause mortality, and 3) initiation of renal replacement therapy (RRT).

Cardiovascular events and mortality, hospital admission, and initiation of RRT were obtained from medical records and National statistics, chart review, and telephone interviews with patients or relatives.

Statistical Analysis

Data was presented as mean and standard deviation, with a median and interquartile range for continuous variables. Categorical variables data were shown as a percentage. Comparisons were made between HFmrEF/HFpEF and non-HFmrEF/HFpEF groups using an independent T-test for normally distributed parameters and a Mann-Whitley test for non-normally distributed data. The correlation between various clinical parameters and VAC and CAVI was analyzed using a chi-square test. Multivariate analysis was performed using logistic regression analysis to identify the independent risk factor of HFmrEF/HFpEF groups. The sensitivity and specificity of CAVI and VA coupling to detect HFmrEF/HFpEF or other outcomes in CKD will be analyzed using a receiver-operating-characteristic (ROC) curve. The association between HFmrEF/HFpEF, high CAVI, high VAC, and other factors

with a primary composite outcome of all-cause mortality and cardiovascular hospitalization was evaluated using the multivariate Cox proportional hazards model. Kaplan-Meier curves assessed the cumulative *incidence* of all-cause mortality and cardiovascular hospitalization. For all tests, a $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 28.0 (IBM, Armonk, NY).

Results

Baseline characteristics

Data are shown in mean ± SD and median with interquartile range (IQR). Baseline characteristics are shown in **Table 1**. Sixty-six CKD patients were enrolled; 43 (65.2%) were male, and 23 (34.8%) were female. The median age of patients was 67.5(15) years, the mean BMI was 25.1 ± 4.1, and the mean eGFR was 31.9±13.3 mL/min. CKD stages were: stage 3A (n=12), stage 3B (n=21), stage 4 (n=27) and stage 5 (n=6). Forty-three patients had DM, and 55 patients had hypertension. The mean LVEF was 65 ± 8%. The median CAVI was 8.7 (1.58), and the mean VAC was 0.91 ± 0.24.

Table1. Baseline characteristics of the enrolled patients

	Overall	**no HFmrEF/HFpEF**	**HFmrEF/HFpEF**	*p* -value
	(n=66)	(n=48)	(n=18)	
Age (years)	67.5 (15)	64.5 (14)	71 (14)	**0.011**
Male (N,%)	43 (65.2)	34 (70.8)	9 (50)	0.114
BMI (kg/m²)	25.1±4.1	25.4±4.2	24.2±4.0	0.306
eGFR(ml/min)	31.9 ±13.3	32.0 ±11.8	31.5 ±17.0	0.883
CAVI	8.7 (1.58)	8.4 (1.25)	9.4 (1.80)	**0.001**
VAC	0.91±0.24	0.88 ±0.21	1.02 ±0.28	**0.033**
LVEF (%)	65±8	66 ±8	63±7	0.112
Stroke volume (mL)	63.5 ±20.4	63.1±21.2	64.4 ±18.8	0.823
SBP (mmHg)	143±21	143±21	143±20	0.863
DBP (mmHg)	80 ±14	81 ±13	79 ±15	0.512
Diabetes mellitus (N, %)	43 (65.2)	29 (60.4)	14 (77.8)	0.187
Hypertension (N, %)	55 (83.3)	39 (81.1)	16 (88.9)	0.713
Dyslipedemia (N, %)	43 (65.2)	33 (68.6)	10 (55.6)	0.316
CAD (N,%)	12 (18.2)	7 (14.6)	5 (27.8)	0.284
Medications				
ACEI/ARB (N, %)	24 (36.4)	19 (39.6)	5 (27.8)	0.566
CCB (N, %)	37 (56.0)	25 (52.1)	12 (66.7)	0.288
Beta-blocker (N, %)	35 (53.0)	23 (47.9)	12 (66.7)	0.174
Outcomes				
Primary composite-Outcome (N, %)	21 (31.8)	11 (22.9)	10 (55.5)	**0.017**
Secondary outcomes (N, %)				
CV hospitalization	10 (15)	1 (2)	9 (50)	**0.001**
All-cause mortality	13 (19.7)	10 (20.8)	3 (16.7)	1.000
RRT	17 (25.8)	13 (27.0)	4 (22.2)	0.763

Data are mean ± SD, median (IQR), or n (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI/ARB; angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; CAD, coronary artery disease; RRT, renal replacement therapy

The relationship between parameters at baseline was evaluated. In addition, we assessed the associations of baseline heart failure, high VAC, or high CAVI with long-term outcomes.

Cross-sectional analysis of baseline parameters

The associations between CAVI and VAC (r = -0.035, p = 0.780) or between eGFR and VAC. (r = 0.011, p = 0.931) or eGFR with CAVI (r = -0.011, p = 0.931) at baseline was not observed.

Comparison between groups with or without HFmrEF/HFpEF at baseline

Of the 66 patients, 18 (27%) had HFmrEF/HFpEF [HFmrEF (n= 1), HFpEF (n=17)], and 48 (73%) had no HFmrEF/HFpEF at baseline. **(Table 1).** Patients with HFmrEF/HFpEF were older than those without HFmrEF/HFpEF (p = 0.011). The mean LVEF were similar (p = 0.112). Systolic and diastolic blood pressure and the prevalence of DM or hypertension or use of ACEI or ARB, CCB, and beta-blockers were not significantly different in those without HFmrEF/HFpEF compared to those with HFmrEF/HFpEF. Median CAVI was significantly higher in HFmrEF/HFpEF compared to the patients without HFmrEF/HFpEF [9.4 (1.80) vs. 8.4 (1.25), p=0.001] (**Figure 1A**). VAC was significantly higher in HFmrEF/ HFpEF than patients without HFmrEF/HFpEF (1.02 ± 0.28 vs. 0.88 ± 0.21, p = 0.033). **(Figure 1B)**

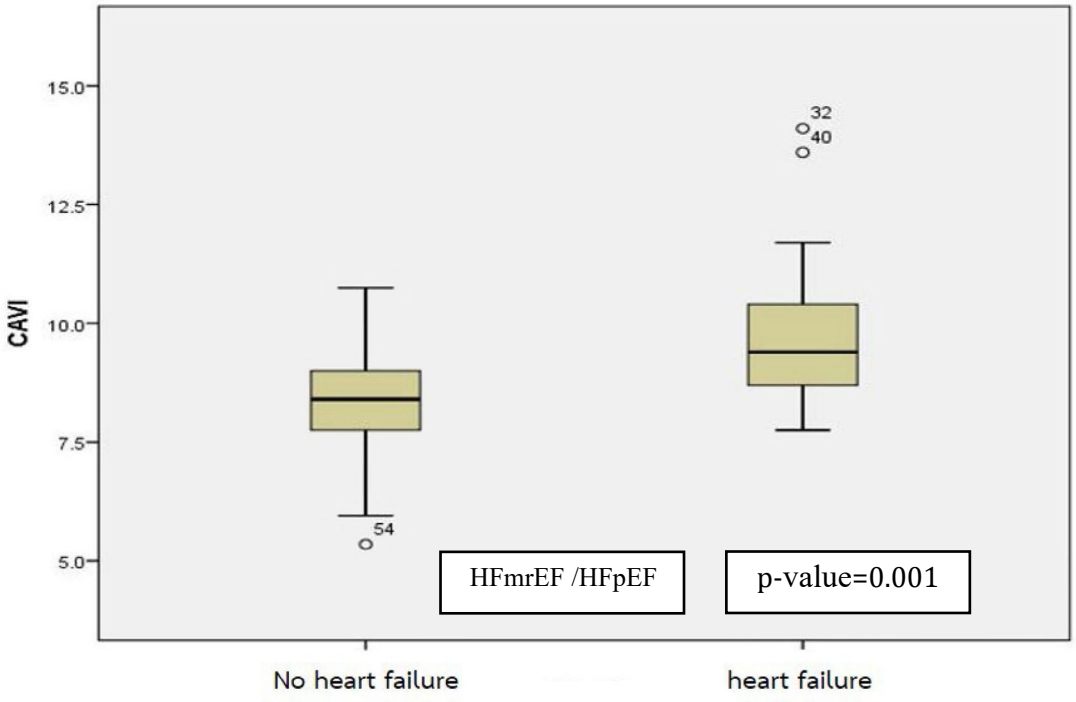

Figure 1A. Box and plot show CAVI in CKD with versus without HFmrEF/HFpEF

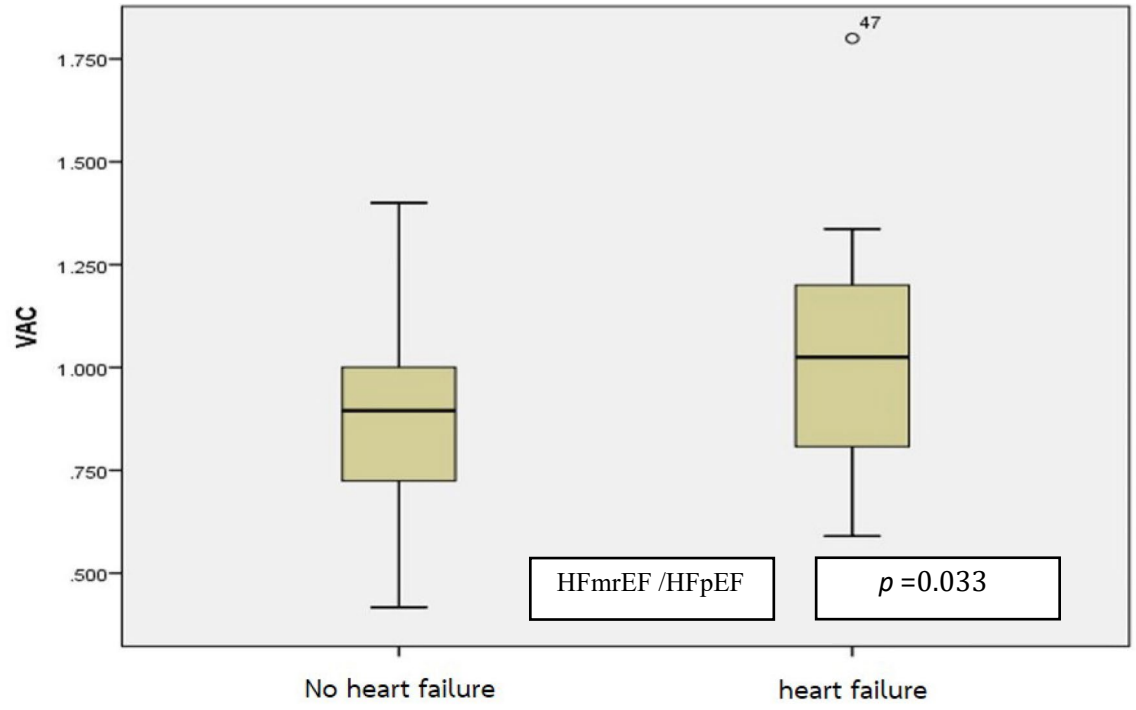

Figure 1B. Box and plot show VAC in CKD with versus without HFmrEF/HFpEF

Analysis of discrimination of HFmrEF/HFpEF at baseline

Using an ROC curve analysis, we determined the optimal cut-off for CAVI predicting HFmrEF/HFpEF. The ROC curve for the presence of HFmrEF/HFpEF revealed that a high CAVI (≥ 8.8) had a sensitivity of 72% and specificity of 63% (**Figure 2A**). In comparison, a high VAC (≥ 0.91) yielded a sensitivity of 67% and a specificity of 48% (**Figure 2B**). Applying these cut-offs, we found that high CAVI was significantly associated with a 4.7-fold increased risk of baseline HFmrEF/HFpEF (p = 0.010), whereas high VAC was not significant (**Table2**). Multivariate analysis using a forced entry regression model including CAVI, VAC, age, hypertension, diabetes mellitus, and coronary artery disease identified high CAVI as an independent risk factor for HFmrEF/HFpEF (OR 5.11, 95% CI: 1.27-20.42) (**Table2**).

Effects of HFmrEF and HFpEF, high CAVI or high VAC on long-term outcomes

Primary long-term outcome

After a median follow-up time of 6 (4,7.5) years, 21 patients (33%) experienced the primary composite outcome of CV hospitalization or all-cause mortality (10 CV hospitalization and 13 all-cause mortality) **(Table 1).** The most common causes of death were malignancy (4/13, 30.9%), infection (3/13, 23%), cardiovascular (1/13, 7.7%), and unknown causes (2/13, 15.4%). Other causes accounted for three deaths (23%). Cardiovascular events included nonfatal myocardial infarction, nonfatal stroke, and heart failure. The Kaplan-Meier survival curve for the primary composite outcome of CV hospitalization and all-cause mortality of HFmrEf/HFpEF or non-HFmrEF/HFpEF patients is shown in **Figure 3**.

The long-term primary composite endpoint risk was significantly higher in HFmrEF/HFpEF (p = 0.034). By contrast, high CAVI (p = 0.754) and high VAC (p = 0.633) were not associated with primary long-term outcomes. Multivariate analysis using forced entry regression model using HFmrEf/HFpEF, CAVI, VAC, age, hypertension, diabetes mellitus, and coronary artery disease, HFmrEF/HFpEF was an independent risk of the long-term primary composite endpoint (HR 43.8, 95% CI: 5.89-304.8) (**Table3**).

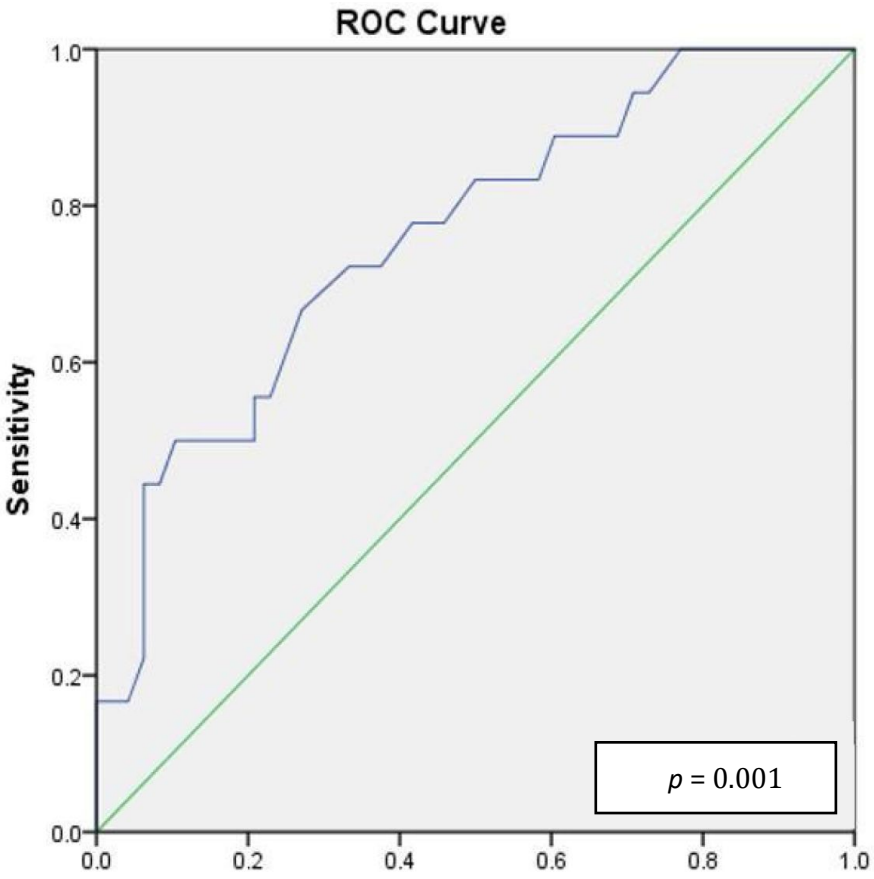

Figure 2A. ROC of CAVI in CKD with HFmrEF/HFpEF.

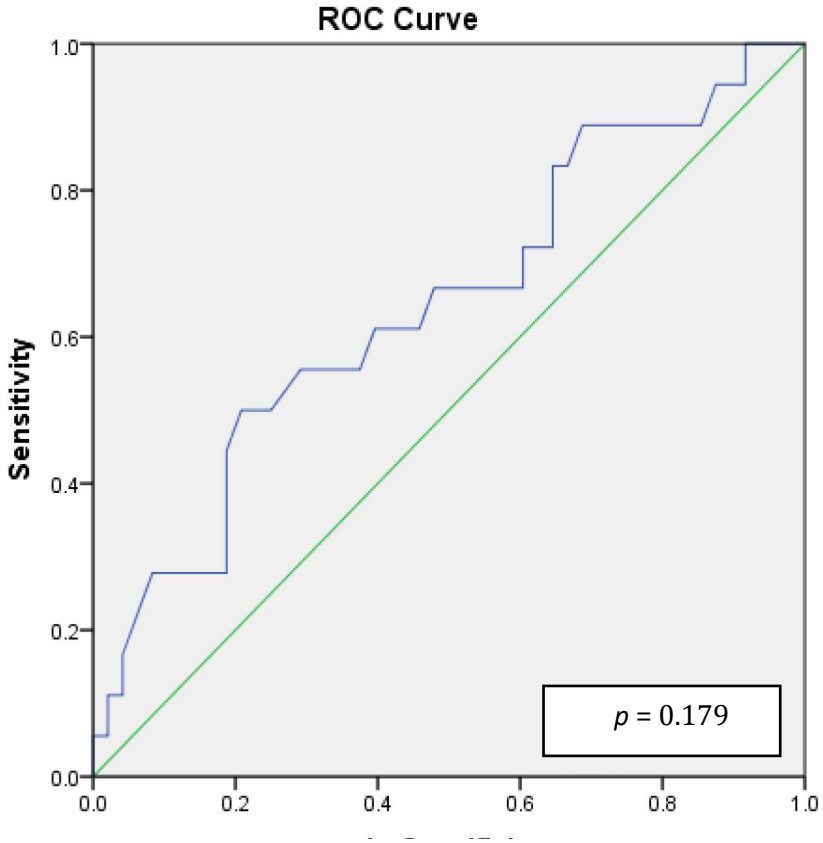

Figure 2B. ROC of VAC in CKD with HFmrEF/HFpEF.

Table 2. Factors associated with heart failure with mildly reduced or preserved ejection fraction at baseline

Factors	Total	No-HFmrEF/HFpEF	HFmrEF/HFpEF	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value
		n	n				
High CAVI							
<8.8	36	31	5	Ref.		Ref.	
≥8.8	30	17	13	4.74 (1.44-15.57)	0.01	5.11 (1.27-20.42)	0.021
High VAC							
<0.91	31	25	6	Ref.		Ref.	
≥0.91	35	23	12	2.17 (0.70-6.74)	0.179	2.55 (0.64-10.09)	0.181
Age(years)							
<65	29	24	5	Ref.		Ref.	
≥65	37	24	13	2.60 (0.80-8.43)	0.11	3.92 (0.90-17.08)	0.069
Hypertension							
Yes	55	39	16	2.25 (0.45-11.34)	0.314	2.28 (0.34-15.20)	0.392
No	13	11	2	Ref.		Ref.	
Diabetes mellitus							
Yes	43	29	14	2.29 (0.65-8.03)	0.194	1.98 (0.45-8.68)	0.382
No	23	19	4	Ref.		Ref.	
CAD							
Yes	12	7	5	2.25 (0.61-8.31)	0.223	1.45 (0.31-6.66)	0.631
No	54	41	13	Ref.		Ref.	

* CAVI,cardio-ankle vascular index; VAC,ventricular-arterial coupling; CAD , Coronary artery disease

Secondary long-term outcomes

All-cause mortality

Table 1 shows the rates of each secondary outcome. Death occurred in 13 (19.7%). The presence of HFmrEF/HFpEF, high CAVI, or high VAC was not associated with increased risk.

Cardiovascular hospitalization

CV hospitalization occurred in 10 (15%) patients. The CV hospitalization rate was significantly higher in the HFmrEF/HFpEF group (p = 0.001) (9 out of 18 patients vs. 1 out of 48 patients). By contrast, there were no differences in CV admission rate between high CAVI (p = 0.684) or high VAC (p = 0.713) or combined high CAVI and high VAC (p = 0.308).

Renal replacement therapy

Seventeen patients (25.8%) developed end-stage kidney disease. The proportion of patients who initiated renal replacement therapy (RRT) did not differ significantly between the HFmrEF/HFpEF and no HFmrEF/HFpEF groups, with four patients (22.2%) in the HFmr/HFpEF group and 13 patients (27%) in the no HFmrEF/HFpEF group (p =0.763). Similarly, the percentage that reached RRT did not differ in the group with combined high CAVI and high VAC (p = 0.977).

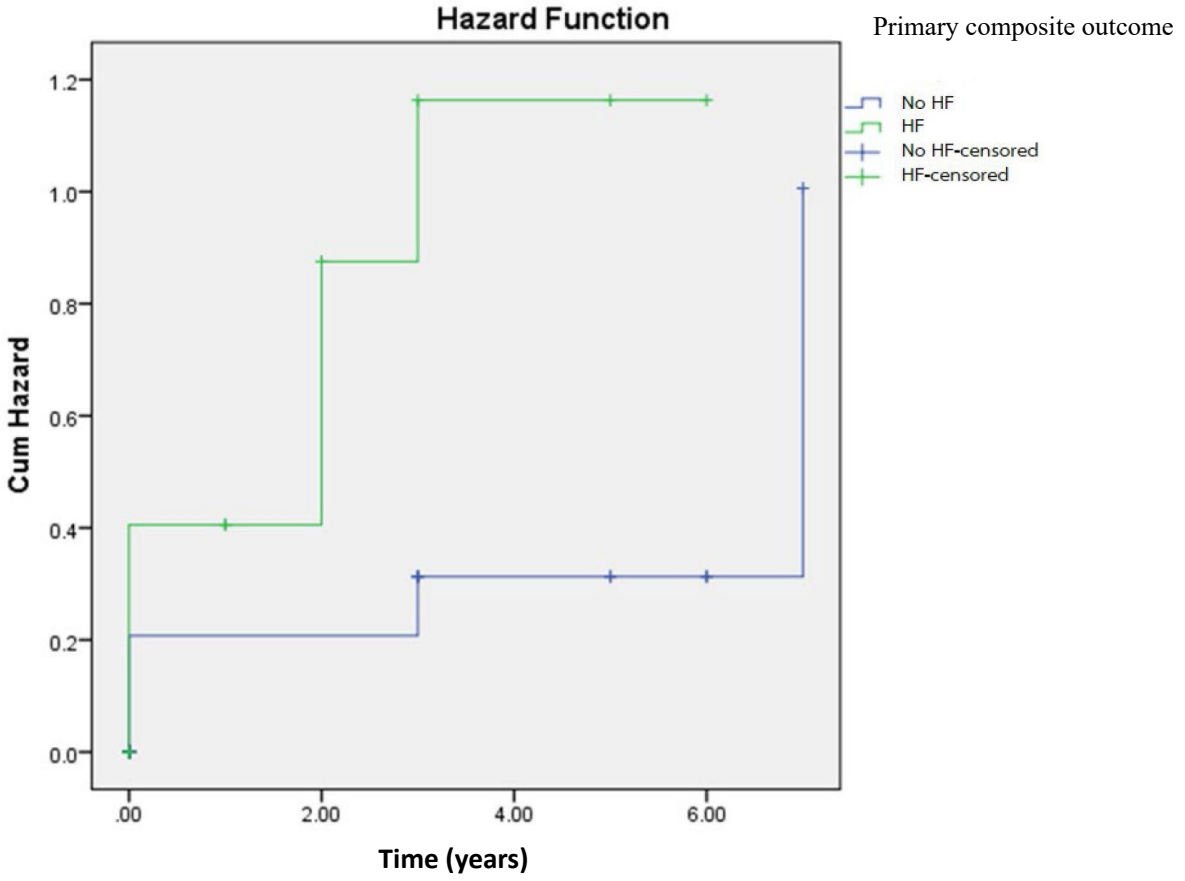

Figure 3. The Kaplan-Meier survival curve for the primary composite outcome of CV hospitalization and all-cause mortality of HFmrEf/HFpEF or non-HFmrEF/HFpEF patients.

Table 3. Risk of parameters at baseline for long-term primary outcome

Factors	Total	No-Primary outcome	Primary outcome	Crude HR (95%CI)	*p*-value	Adjusted HR (95%CI)	*p*-value
		n	n				
HFpEF							
Yes	**18**	8	10	47.1 (5.28-411.8)	0.034	43.8 (5.89-304.8)	0.002
No	**48**	37	11	Ref.		Ref.	
High CAVI							
<8.8	**30**	20	10	Ref.		Ref.	
≥8.8	**36**	25	11	**1.24 (0.32-4.76)**	0.754	0.11 (0.01-1.76)	0.118
High VAC							
<0.91	**35**	22	13	Ref.		Ref.	
≥0.91	**31**	23	8	1.40 (0.36-5.49)	0.633	0.38 (0.03-3.95)	0.418
Age(years)							
<65	**37**	24	13	Ref.		Ref.	
≥65	**29**	21	8	1.21 (0.31-4.76)	0.785	0.18 (0.01-2.54)	0.206
Hypertension							
Yes	**55**	41	14	1.39 (0.21-9.23)	0.727	0.83 (0.03-19.92)	0.908
No	**11**	4	7	Ref.		Ref.	
Diabetes mellitus							
Yes	**43**	28	15	1.30 (0.30-5.58)	0.727	0.92 (0.08-9.94)	0.948
No	**23**	17	6	Ref.		Ref.	
CAD							
Yes	**11**	6	5	1.15 (0.21-6.26)	0.872	0.61 (0.06-6.52)	0.686
No	**55**	39	16	Ref.		Ref.	

* CAVI, cardio-ankle vascular index; VAC, ventricular-arterial coupling; DM, Diabetes mellitus**;** CAD, Coronary artery disease

Discussion

This study investigated the association between CAVI and VAC with heart failure in CKD patients with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF). Patients with HFmrEF/HFpEF had higher CAVI and VAC values than those without HFmrEF/HFpEF. ROC curve analysis demonstrated that a CAVI value > 8.8 had a sensitivity of 72% and specificity of 65% for predicting HFmrEF/HFpEF, while VAC values > 0.91 had a sensitivity of 67% and specificity of 48%. Patients with HFmrEF/HFpEF had a substantially higher primary composite outcome of all-cause mortality and cardiovascular hospitalization compared to those without HFmrEF/HFpEF. However, the rates of primary outcomes were not significantly different between high CAVI or high VAC groups at the end of the median of 6 years follow-up.

Heart failure with preserved ejection fraction (HFpEF) and CKD share common risk factors, including obesity, diabetes, and metabolic syndrome, as well as similar pathophysiology, including systemic inflammation, oxidative stress, elevated neurohormones, mineralocorticoid-receptor activation, and venous congestion.[38] Previous studies in non-CKD patients have reported a higher incidence of cardiovascular events, including myocardial infarction and stroke, in patients with heart failure with preserved and reduced ejection fraction.[39] There are few extensive epidemiologic studies on the prevalence and severity of HFmrEF/HFpEF in CKD. In the US Chronic Renal Insufficiency Cohort (CRIC), when CKD patients without prior HF were followed for hospitalization for HF over ten years, more patients developed HFpEF-related events than HFrEF-related events.[40] Additionally, HFmrEF is independently associated with an increased risk of 30-months all-cause mortality or rehospitalization in CKD stage 3-4 patients in the UK. [41] Our findings of increased rehospitalization risk in Thai CKD patients with HFmrEF/ HFpEF are consistent with these findings.

Several mechanisms contribute to the pathogenesis of arterial stiffening in CKD patients. [5] The increase in aortic stiffness leads to higher cardiac workload and decreased perfusion of the coronary arteries, which, in turn, may lead to microvascular cardiac ischemia, myocardial fibrosis, heart failure, and fatal arrhythmias. [42] The higher CAVI values in HFmrEF/HFpEF patients in our study align with the notion that arterial stiffness is a critical factor in the development of HFmrEF/HFpEF. A recent meta-analysis highlighted the prognostic value of CAVI for cardiovascular and kidney outcomes, with high CAVI increasing the risk of cardiovascular events and GFR decline.[8] These studies generally encompassed high cardiovascular risk and dialysis patients, but there have been fewer studies in predialysis CKD. Murakami et al. (2021) demonstrated that high CAVI predicted mortality in hemodialysis patients.[9] In 460 Japanese patients with predialysis CKD, the risk for major cardiovascular events was significantly higher in those with high CAVI after six years of follow-up.[10] Aiumtrakul et al. (2022) conducted a prospective cohort study in Thailand, which showed that high CAVI was associated with mortality in high cardiovascular-risk subjects, including those with chronic kidney disease. [11] Together, these findings emphasize the importance of arterial stiffness as a prognostic marker of cardiovascular risk in CKD patients.

The lack of association between CAVI and cardiovascular and all-cause mortality in this study contrasts with previous findings that have shown increased arterial stiffness was associated with worse outcomes in patients with CKD. [8] This discrepancy may be attributed to the relatively small sample size, resulting in limited power to detect significant differences in outcomes between the groups and the potential for unmeasured confounders to influence the results. Many of our patients died of cancers or infectious complications, which may be unrelated to arterial stiffness. In the high cardiovascular-risk Thai subjects described above, [11] high CAVI was also a risk factor for GFR decline. Our study differed from the previous study by focusing exclusively on CKD patients and using the timing of dialysis initiation as the outcome rather than GFR decline. While dialysis initiation is a chal-

lenging clinical outcome, it may also be affected by several factors, including death, which may have occurred before the need for dialysis.

Fewer studies have examined the prognostic value of VAC in CKD. In Japanese hemodialysis patients, VAC was an independent predictor for the primary composite endpoint: all-cause death, nonfatal myocardial infarction, and hospitalization due to worsening heart failure over two years. [19] A recent study evaluating echocardiograms before and after dialysis in hemodialysis patients has shown that VAC did not markedly alter due to the HD session. VA uncoupling was found to be related to abnormal cardiac structure and worse systolic function; this suggests that VAC obtained from echocardiography is likely volume-independent and valuable as a reliable index for stratifying the risk of cardiovascular diseases in hemodialysis.[43] Studies in predialysis CKD are limited. So far, data on associations of VAC with long-term data in predialysis CKD is lacking. The relationship between arterial stiffness, diastolic dysfunction, and renal function was evaluated in 79 patients with IgA nephropathy. Although this study showed correlations between arterial stiffness and diastolic dysfunction, the study did not assess the association of VAC with heart failure or long-term outcomes. [26]

The findings of this study have important clinical implications. So far, limited studies have explored the relationship of mildly reduced or preserved ejection fraction with CAVI and VAC in non-dialysis patients. The association of high CAVI and VAC values with HFmrEF/HFpEF observed in our study suggests a complex interplay between kidney dysfunction, vascular aging, and cardiac remodeling. In CKD, HFmrEF/HFpEF may further exacerbate the already increased arterial stiffness and impaired VAC, leading to a vicious cycle of cardiovascular dysfunction. The identification of increased CAVI and VAC in patients with CKD and HFmrEF/HFpEF highlights the need for close monitoring and management of cardiovascular risk factors in this population. The potential utility of combining CAVI and VAC as a screening tool for HFmrEF/HFpEF and long-term outcome predictions in patients with CKD warrants further investigation in larger, prospective studies.

This study encountered some limitations. First, the small sample size and low event numbers might result in large confidence intervals and hazard ratios that have reduced statistical power to detect significant outcome differences between groups. Second, due to the complex nature of our CKD population, our results could be affected by residual confounding factors even after multiple adjustments for several covariates. Third, the study was conducted at only two hospital centers, which limits the generalizability to other populations. Our study mainly included patients with preserved ejection fraction; therefore, results likely pertain to this group rather than patients with mildly reduced ejection fraction. Finally, the study did not assess the potential impact of intervention to reduce arterial stiffness or improve VAC on outcomes.

Conclusion

In non-dialysis CKD, the presence of heart failure with mildly reduced or preserved ejection fraction is associated with vascular stiffness and abnormal vascular arterial coupling. Patients with HFmrEF/HFpEF had an increased risk of mortality or cardiovascular hospitalization and should be monitored closely. Future prospective studies are needed to understand better the complex relationship between arterial stiffness, ventricular function, and outcomes in patients with CKD and heart failure to identify potential therapeutic targets for improving patient care.

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