ORIGINAL ARTICLE

# Predictive value of cardio-ankle vascular index for the risk of end-stage renal disease

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## ABSTRACT

**Background.** Arterial stiffness is associated with increased cardiovascular morbidity and mortality. However, the predictive value of the cardio-ankle vascular index (CAVI), one of the indicators for arterial stiffness, for the risk of end-stage renal disease (ESRD) remains unknown.

**Methods.** A total of 8701 patients with documented CAVI measurements by pulse wave velocity (PWV) were included in the study. Patients were divided according to the quartiles of CAVI. The hazard ratio (HR) of ESRD was calculated using the Cox model, after adjustment for multiple variables or death.

**Results.** During the median follow-up period of 7 years (maximum 12 years), ESRD and mortality occurred in 203 and 1071 patients, respectively. The median value of CAVI was 8.5 (interquartile range 7.7–9.3). The risk of ESRD was higher in the fourth-quartile group than the first-quartile group [adjusted HR 2.46 (IQR 1.62–3.71), $P < 0.001$]. When a death-adjusted risk analysis was performed, the fourth quartile of CAVI had a higher risk of ESRD than the first quartile [adjusted HR 2.35 (IQR 1.58–3.49), $P < 0.001$].

**Conclusions.** The measurement of CAVI by PWV may be needed to predict the risk of ESRD.

**Keywords:** arterial stiffness, cardio-ankle vascular index, end-stage renal disease, mortality, pulse wave velocity

## INTRODUCTION

Arterial stiffness is associated with increased cardiovascular morbidity and mortality in several pathologic conditions [1–3]. When arterial stiffness increases, left ventricular afterload and myocardial oxygen demand also increase. Subsequently, hypertrophy of the left ventricle occurs via arterial stiffness, which may cause a cardiac event [4]. Based on this pathophysiology, there may be a direct link between arterial stiffness and the real risk of cardiovascular disease. The precise estimation and monitoring of arterial stiffness are therefore critical to the prevention and management of cardiovascular disease [5].

Arterial stiffness is determined via the propagation velocity of the pressure wave in the arterial segments by pulse wave velocity (PWV). There are several mechanical indicators for PWV [6, 7]; however, the cardio-ankle vascular index (CAVI) reflects systemic arterial stiffness from the aorta to the ankle arteries. One important feature of CAVI is its independence from blood pressure during measurement [6, 8]. CAVI has successfully predicted cardiovascular morbidity and mortality [9]. However, the ability of CAVI to predict the risk of end-stage renal disease (ESRD) as a hard outcome of renal progression has not been determined. The cardiovascular risk in patients with ESRD is up to 20-fold greater than that of the general population, and half of these deaths are caused by cardiovascular disease [10–12]. Given that arterial stiffness may drive the pathophysiology of ESRD [13–15], it is important to determine whether ESRD is predicted by the measurement of arterial stiffness. Herein we address whether CAVI can be used to predict ESRD in an outpatient cohort where both CAVI and subsequent kidney function have been measured. Furthermore, the death-adjusted risk of ESRD was evaluated, as the risks of ESRD and death might be competing [16].

## MATERIALS AND METHODS

### Study subjects and variables

The study protocol was approved by the institutional review board at the Seoul National University Hospital (H-1809-005-968) and was conducted in accordance with the principles of the Declaration of Helsinki. A total of 9194 patients ≥18 years of age with CAVI measurements from Seoul National University Hospital (January 2006–December 2016) were reviewed. Patients with underlying ESRD (*n* = 56), kidney transplantation (*n* = 3), no baseline renal function (*n* = 26), no blood pressure or ankle–brachial index measurements (*n* = 80) or those with data derived from only one side of the limb (*n* = 24) were excluded. Patients with aortic insufficiency (*n* = 9), <0.9 bilateral ankle–brachial index (*n* = 153) and atrial fibrillation (*n* = 142) were also excluded from the analysis. Consequently, 8701 patients were analyzed in this study.

Baseline variables such as age, sex, body mass index (BMI), ankle–brachial index, mean arterial pressure and comorbidities including diabetes mellitus, hypertension, chronic kidney disease (CKD), ischemic heart disease, cerebrovascular disease and peripheral vascular disease were recorded. Details of patient medications, including angiotensin-converting enzyme inhibitors (ACEis)/angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers, diuretics and statins, were obtained from electronic medical records. Hemoglobin, albumin, blood urea nitrogen and creatinine were also measured. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [17]. Proteinuria and hematuria were defined when a dipstick test indicated ≥1+. These variables were obtained when the patients was in stable condition without evidence of acute kidney injury.

The CAVI was measured by three experts using VaSera VS-1000 equipment (Fukuda Denshi, Tokyo, Japan) in patients who had remained in the supine position for 10 min. Electrocardiogram electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum and cuffs were wrapped around both arms and ankles. Blood pressure and pulse rate were measured by pressurizing four points at the same time. A phonocardiogram was measured at the same time on two left sternal borders. The time from the two sounds (close to the aortic valve) to attainment of the pulse wave was estimated. The average of the right and left CAVI values was used for the analysis.

### Outcome variables

ESRD, defined as receiving dialysis or kidney transplantation, was determined by supplementary information on the Korean Society of Nephrology database. Additionally, renal progression as a composite outcome was defined as a doubling of creatinine levels, a ≥50% decrease of the eGFR or development of ESRD during the follow-up period. Data on all-cause death were obtained from the Korean national database of statistics. The patients were followed until May 2019, except for the death-censored cases.

### Statistical analysis

Statistical analyses were performed using SPSS (version 23.0; IBM, Armonk, NY, USA) and R software (version 3.3.3; R Foundation, Vienna, Austria; http://cran.r-project.org). Categorical and continuous variables are expressed as proportions and the mean ± standard deviation (SD) for normally distributed variables and as the median with interquartile range (IQR) for non-normally distributed variables. The normality of the distribution was analyzed by the Kolmogorov–Smirnov test. The chi-square test was used to compare categorical variables (Fisher's exact test if not applicable). The Student's *t*-test or the Mann–Whitney U test was used to compare continuous variables with or without normal distributions, respectively. For the main analyses, the patients were divided into four groups according to the quartiles of CAVI value. Kaplan–Meier curves, stratified by quartiles of CAVI, were used to graphically summarize the crude relationship between CAVI and the rate of ESRD. A stepwise Cox proportional hazards regression model was applied to calculate hazard ratios (HRs) of the outcome risks. Age, sex, eGFR, ACEi/ARB and other variables with a P-value <0.1 in the univariate model were applied to multivariate analysis. A subdistribution hazard model was applied with two competing risks of ESRD and all-cause death to evaluate the death-adjusted effects of CAVI [18]. Statistical significance was defined as P < 0.05.

## RESULTS

### Baseline characteristics

Table baseline characteristics of the study patients are shown in Table 1. The mean age of the patients was 60 ± 11 years and 50.3% were male. The mean BMI was 24.6 ± 3.4 kg/m$^2$ and the mean eGFR was 78.7 ± 19.3 mL/min/1.73 m$^2$ at baseline. The proportion of patients with eGFR <60 mL/min/1.73 m$^2$ was 15.3%. The mean and median values of CAVI were 8.5 ± 1.2 and 8.5 (IQR 7.7–9.3), respectively. When the CAVI quartile groups were compared, the high-quartile groups were older and had lower BMI and higher mean arterial pressure than the low-quartile groups. The proportions of hypertension and other comorbidities were greater in the high-quartile groups than in the low-quartile groups, except for diabetes mellitus.

### Risk of ESRD as predicted by CAVI values

During the median follow-up period of 7 years (IQR 5–10; maximum 12 years), ESRD was diagnosed in 203 patients (2.3%). The prevalence of ESRD was 1.4% (incidence 19.7/10 000 person-years), 2.0% (27.4/10 000 person-years), 2.1% (27.4/10 000 person-

**Table 1. Baseline characteristics of the study patients**

| Variables | Total (n = 8701) | First quartile (n = 2147) | Second quartile (n = 2181) | Third quartile (n = 2200) | Fourth quartile (n = 2173) | P-value |
|---|---|---|---|---|---|---|
| CAVI, mean ± SD | 8.47 ± 1.21 | 6.95 ± 0.59 | 8.05 ± 0.24‡ | 8.88 ± 0.23‡ | 9.97 ± 0.72‡ | <0.001 |
| Age (years), mean ± SD | 60.4 ± 11.4 | 50.1 ± 11.1 | 59.2 ± 8.9‡ | 63.7 ± 8.3‡ | 68.2 ± 8.2‡ | <0.001 |
| Male (%) | 50.3 | 51.8 | 47.8† | 48.3* | 53.3 | 0.312 |
| BMI (kg/m²), mean ± SD | 24.6 ± 3.4 | 25.5 ± 4.0 | 24.6 ± 3.5‡ | 24.3 ± 3.1‡ | 23.8 ± 2.9‡ | <0.001 |
| Right ABI, mean ± SD | 1.119 ± 0.083 | 1.109 ± 0.081 | 1.124 ± 0.081‡ | 1.123 ± 0.081‡ | 1.121 ± 0.088‡ | <0.001 |
| Left ABI, mean ± SD | 1.116 ± 0.086 | 1.108 ± 0.082 | 1.120 ± 0.083‡ | 1.120 ± 0.086‡ | 1.116 ± 0.093‡ | <0.001 |
| Mean arterial pressure (mmHg), mean ± SD | | | | | | |
|   Right brachial | 98.6 ± 10.8 | 95.5 ± 10.1 | 97.1 ± 10.3‡ | 99.8 ± 10.4‡ | 102.2 ± 11.0‡ | <0.001 |
|   Right ankle | 100.6 ± 11.7 | 96.9 ± 11.0 | 99.2 ± 11.0‡ | 101.8 ± 11.1‡ | 104.6 ± 12.2‡ | <0.001 |
|   Left brachial | 97.9 ± 10.7 | 94.4 ± 9.9 | 96.2 ± 10.2‡ | 98.9 ± 10.2‡ | 101.9 ± 11.0‡ | <0.001 |
|   Left ankle | 100.6 ± 11.6 | 97.0 ± 11.0 | 99.1 ± 11.0‡ | 101.8 ± 11.0‡ | 104.3 ± 12.1‡ | <0.001 |
| CKD (%) | 1.0 | 0.4 | 0.7 | 1.0† | 1.7‡ | <0.001 |
| Diabetes mellitus (%) | 88.1 | 88.9 | 88.0 | 87.5 | 87.9 | 0.233 |
| Hypertension (%) | 18.3 | 12.1 | 17.6‡ | 21.2‡ | 22.1‡ | <0.001 |
| Ischemic heart disease (%) | 7.2 | 4.1 | 6.6‡ | 8.0‡ | 10.1‡ | <0.001 |
| Cerebrovascular disease (%) | 6.7 | 3.5 | 4.9* | 8.1‡ | 10.2‡ | <0.001 |
| Peripheral vascular disease (%) | 0.7 | 0.5 | 0.5 | 0.5 | 1.1* | 0.016 |
| Medications (%) | | | | | | |
|   ACEi/ARB | 38.0 | 25.9 | 34.0‡ | 42.6‡ | 49.2‡ | <0.001 |
|   β-blocker | 17.0 | 11.6 | 15.6‡ | 18.9‡ | 21.7‡ | <0.001 |
|   Calcium channel blocker | 25.5 | 15.7 | 22.5‡ | 27.8‡ | 35.8‡ | <0.001 |
|   Diuretics | 19.4 | 12.9 | 18.0‡ | 21.3‡ | 25.1‡ | <0.001 |
|   Oral antidiabetic drugs | 64.0 | 59.1 | 62.8* | 66.1‡ | 67.8‡ | <0.001 |
|   Insulin | 28.2 | 25.4 | 23.8 | 28.4* | 35.3‡ | <0.001 |
|   Antiplatelet agents | 35.2 | 21.3 | 31.5‡ | 40.0‡ | 47.7‡ | <0.001 |
|   Statin | 39.4 | 32.3 | 39.2‡ | 42.6‡ | 43.3‡ | <0.001 |
| Laboratory findings | | | | | | |
|   Hemoglobin (g/dL), mean ± SD | 13.8 ± 1.7 | 14.1 ± 1.7 | 13.8 ± 1.6‡ | 13.7 ± 1.6‡ | 13.4 ± 1.7‡ | <0.001 |
|   Albumin (g/dL), mean ± SD | 4.3 ± 0.4 | 4.4 ± 0.4 | 4.4 ± 0.4‡ | 4.3 ± 0.4‡ | 4.3 ± 0.4‡ | <0.001 |
|   Blood urea nitrogen (mg/dL), mean ± SD | 16.5 ± 6.6 | 15.0 ± 5.4 | 16.3 ± 6.9‡ | 16.7 ± 6.1‡ | 18.1 ± 7.3‡ | <0.001 |
|   Serum creatinine (mg/dL), mean ± SD | 0.97 ± 0.43 | 0.91 ± 0.29 | 0.94 ± 0.42* | 0.98 ± 0.45‡ | 1.07 ± 0.49‡ | <0.001 |
|   eGFR (mL/min/1.73 m²), mean ± SD | 78.7 ± 19.3 | 89.1 ± 18.5 | 81.3 ± 17.5‡ | 75.5 ± 17.3‡ | 68.8 ± 17.8‡ | <0.001 |
|   Proteinuria (%) | 18.5 | 13.2 | 16.1† | 19.3‡ | 25.2‡ | <0.001 |
|   Hematuria (%) | 7.0 | 6.9 | 6.7 | 6.2 | 8.3 | 0.045 |

*$P < 0.05$.
†$P < 0.01$
‡$P < 0.001$ (compared with the lowest quartile).
ABI, ankle–brachial index.

years) and 3.8% (47.5/10 000 person-years) from the first- to the fourth-quartile group, respectively. Figure 1 shows a Kaplan–Meier plot of the crude risk of ESRD stratified according to CAVI quartiles. The high-quartile groups were at greater risk of ESRD than the low-quartile groups. HRs of the ESRD risk, where the first-quartile group served as a reference group, are shown in Table 2. In univariate analysis (Model 1), the fourth-quartile group had a higher risk of ESRD than the first-quartile group, with an HR of 2.46 (IQR 1.62–3.71). When age, sex, eGFR, ACEi/ARB (Model 2) and other confounding variables (Model 3) were adjusted, the high-quartile groups had greater HRs of ESRD than the first-quartile group. When the composite outcome (i.e. a doubling of creatinine levels, a ≥50% decrease of the eGFR or development of ESRD) was evaluated, the high-quartile groups had more renal progression than the first-quartile group (Figure 2). The relationship between high CAVI and renal progression was independent on other clinical and laboratory parameters (Table 3).

During the follow-up period, 1071 patients (12.3%) died. A competing risk analysis was performed because the prediction of CAVI for ESRD could have been affected by the high death rate
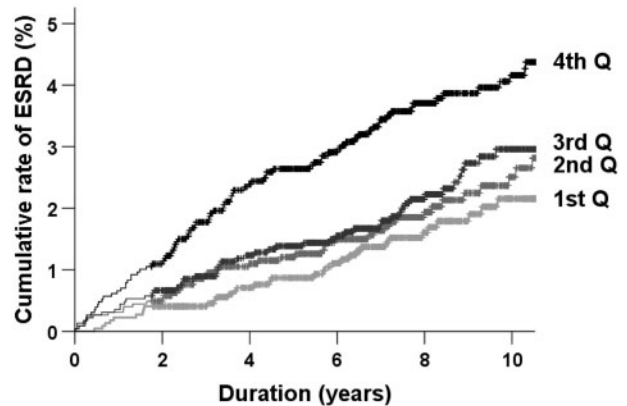


**FIGURE 1:** Kaplan–Meier curves of the cumulative rate of ESRD according to the quartiles of CAVI.

[19]. Although the risk of death was also adjusted, a high CAVI value remained a risk factor for ESRD (Table 4). The risk curves of ESRD and death also supported these results (Figure 3).

**Table 2. Risk of ESRD according to the CAVI level**

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| CAVI group | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| First quartile | 1 (Reference) | | Reference | | Reference | |
| Second quartile | 1.40 (0.88–2.21) | 0.155 | 2.70 (1.63–4.47) | <0.001 | 2.30 (1.38–3.84) | 0.001 |
| Third quartile | 1.40 (0.89–2.21) | 0.145 | 2.90 (1.68–5.01) | <0.001 | 2.70 (1.56–4.63) | <0.001 |
| Fourth quartile | 2.46 (1.62–3.71) | <0.001 | 3.53 (2.07–6.02) | <0.001 | 2.99 (1.72–5.19) | <0.001 |

Model 1: unadjusted.
Model 2: adjusted for age, sex, eGFR and ACEis/ARBs.
Model 3: adjusted for variables with P < 0.1 in univariate model plus Model 1.
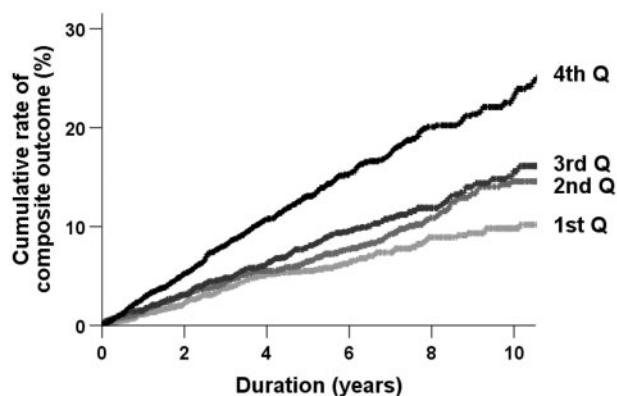CI, confidence interval.



**FIGURE 2:** Kaplan–Meier curves of the cumulative rate of composite outcome according to the quartiles of CAVI.
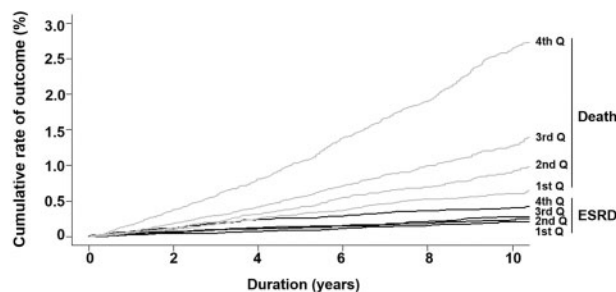


**FIGURE 3:** Death-adjusted risk of ESRD, according to the quartiles of CAVI.

**Table 3. Risk of composite renal outcome according to the CAVI level**

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| CAVI group | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| First quartile | 1 (Reference) | | 1 (Reference) | | 1 (Reference) | |
| Second quartile | 1.36 (1.06–1.74) | 0.150 | 1.58 (1.22–2.04) | 0.001 | 1.37 (1.06–1.78) | 0.016 |
| Third quartile | 1.53 (1.20–1.94) | <0.001 | 1.74 (1.34–2.27) | <0.001 | 1.40 (1.07–1.84) | 0.014 |
| Fourth quartile | 2.53 (2.03–3.15) | <0.001 | 2.49 (1.91–3.25) | <0.001 | 1.75 (1.32–2.31) | <0.001 |

Model 1: unadjusted.
Model 2: adjusted for age, sex, eGFR and ACEis/ARBs.
Model 3: adjusted for variables with P < 0.1 in univariate model plus Model 1.
CI, confidence interval.

## DISCUSSION

The prediction of ESRD is an important issue because of its high morbidity and mortality. Several factors have been suggested to determine the risk of ESRD, although precise prediction is still a question. This study determined whether high CAVI values, as a representative marker of arterial stiffness, could predict ESRD or renal progression. The predictive value of CAVI remained consistent even when other confounding variables, including death, were taken into account.

Previous studies have evaluated the relationship between arterial stiffness and renal dysfunction in various clinical conditions [20–24]. In the Chronic Renal Insufficiency Cohort, patients with the third tertile of carotid–femoral PWV were at higher risk of ESRD, a 50% decline in eGFR and death than those in the first tertile [20]. The Atherosclerosis Risk in Communities study also used the cardio-femoral PWV values, and the high-quartile groups had lower eGFR and a higher random urine albumin:creatinine ratio than the low-quartile groups [21]. This study utilized CAVI, one of the measurement tools for arterial stiffness and identified that high CAVI values predicted renal progression to ESRD, which supports earlier results. However, another study with 135 patients with Stages 2–4 CKD found that an aortic PWV value predicted death but not renal progression, although the sample size was small [22]. Although several parameters can be obtained from PWV, these may give different predictions for renal outcome. The CAVI value was a relevant predictive parameter for renal progression. CAVI is a strong objective measure, given that it is independent of blood pressure, highly reproducible and sensitive [6, 25–27].

Table 4. Competing risk regression analysis for ESRD

| CAVI group | HR (95% CI) | P-value |
|---|---|---|
| First quartile | 1 (Reference) | |
| Second quartile | 1.38 (0.90–2.11) | 0.140 |
| Third quartile | 1.25 (0.80–1.93) | 0.330 |
| Fourth quartile | 2.35 (1.58–3.49) | < 0.001 |

CI, confidence interval.

The pathophysiologic mechanisms underlying the role of arterial stiffness in the deterioration of kidney function are still under investigation, but certain mechanisms might explain this. Arterial stiffness represents elevated pulse pressure [28], wherein both an increase in systolic blood pressure and a decrease in diastolic blood pressure occur [29, 30]. High pulse pressure mediated by arterial stiffness contributes to a highly pulsatile flow in several segments of organ-supplying arteries, including the renal vasculature. This can potentially result in glomerular damage and loss of renal function because of low resistance in the kidney [31]. The kidneys are exposed to a large volume of blood flow and are thus vulnerable to hemodynamic change. Therefore, arterial stiffness may further influence renal perfusion and function [32]. Arterial stiffness is attributable to excessive activation of the renin–angiotensin–aldosterone system (RAAS) [33] and thus arterial stiffness may be a mediator between the activation of this system and renal progression [34]. Because angiotensin II is involved in the process of arterial calcification, blocking the RAAS improves arterial stiffness by ameliorating the degradation of elastin and reducing the collagen content of the aortic wall in preclinical models [35, 36]. Others have shown that pharmacological inhibition with ACEi reduces carotid–femoral PWV in middle-aged hypertensive patients [37].

Although our results are informative, there are some limitations to be considered. This study was retrospective, which did not allow the determination of a causal relationship between CAVI and the risk of ESRD or its underlying mechanisms. Subsequent monitoring of CAVI values was not possible, which would have been more predictive of outcomes than a single measurement. Other unidentified factors such as lifestyle, diet, smoking, cholesterol and genetic factors may have confounded the association between CAVI and ESRD.

This study demonstrates the predictive value of CAVI for ESRD, which is independent of death risk and clinical and laboratory variables. Future studies should aim to confirm an appropriate strategy for monitoring and reducing CAVI to reduce the risk of ESRD.

## FUNDING

## CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract form.

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