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Noninvasive markers of arterial stiffness and renal outcomes in patients with chronic kidney disease

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Abstract

Our study aimed to explore the intercorrelations of brachial-ankle pulse wave velocity (baPWV), ankle-brachial index (ABI), ambulatory arterial stiffness index (AASI), 24-hour mean pulse pressure (24-h PP), and augmentation index (AIx, AIx@75, the AIx standardized to a heart rate of 75) and compare the effectiveness of these markers for predicting renal outcomes. A total of 117 patients with chronic kidney disease (CKD) who received noninvasive arterial stiffness examinations were enrolled. We used correlation analysis and linear regression to explore the correlations between these five arterial stiffness markers and the Cox proportional hazards model and receiver operator characteristic (ROC) curve to assess the associations of markers with kidney disease outcomes. The median (interquartile range) of age and eGFR were 61 (49-65) years and 50.5 (35.5-84.1) ml/min/1.73 m^2, respectively. In Pearson correlation analysis, baPWV was significantly associated with 24-h PP (r = .531, p < .001), AIx@75 (r = .306, p < .001). Additionally, 24-h PP was associated with AASI (r = .507, p < .001) and AIx@75 (r = .217, p = .019). During follow-up for a median of 25 months, 26.5% (n = 31) of patients had a composite outcome; of these, 10 initiated dialysis, 17 had 40% eGFR loss, and 4 died. Increased AASI, 24-h PP, and baPWV were associated with poor renal outcomes in a univariate Cox analysis. After adjusting for age, sex, MAP, eGFR, and 24 hours proteinuria, 1-SD increase in AASI and 24-h PP was associated with renal outcomes. The ROC analysis yielded the largest area under the curve (AUC) of 0.727 (95% CI: 0.624 to 0.831; p < .001) for 24-h PP. When the Youden's index was at its maximum, the 24-h PP value was 52 mmHg. In conclusion, 24-h PP, baPWV, and AIx@75 were linked well to one another. Arterial stiffness is a target for delaying the decline in kidney function. The use of 24-h PP as an arterial stiffness marker should be valued in CKD clinical practice.

1 | INTRODUCTION

Arterial stiffness (AS) is characterized by the long-term process of structural alterations in the viscoelastic properties of biomaterials constituting the media of the arterial wall. To assess arterial stiffness, noninvasive arterial stiffness measurements were developed, and markers such as the brachial-ankle pulse wave velocity (baPWV), ankle-brachial index (ABI), ambulatory arterial stiffness index (AASI), 24-hour mean pulse pressure (24-h PP), and augmentation index (AIx, AIx@75, the AIx standardized to a heart rate of 75) have emerged. These are all peripheral artery stiffness markers and indirectly indicate the status of general arterial stiffness. However, not all the markers are closely linked to one another based on previous studies, which indicates that arterial stiffness markers are not always interchangeable and may provide different physiological information.[1-3]

Arterial stiffness is increased in patients with chronic kidney disease (CKD), and contributes to the increased medical financial burden. Although the relationship between CKD and arterial stiffness has been investigated widely, that arterial stiffness is currently a prognostic factor for poor prognosis in CKD is controversial.[4-8] Studies that simultaneously explore the relationships of these mainstream markers in CKD patients are rare. For the above reasons, our study aimed to explore the intercorrelations of ABI, baPWV, AIx@75, AASI, and 24-h PP and to compare the effectiveness of these markers for predicting renal outcomes.

2 | METHODS

2.1 | Study participants

In this cohort study, 120 patients with CKD (with evidence of kidney damage lasting >3 months) who volunteered to undergo noninvasive arterial stiffness examinations at the First Medical Center of the Chinese PLA General Hospital between December 2017 and December 2018 were enrolled. Patients who were missing ABPM data on nighttime blood pressure (n = 2) or had unilateral recordings of baPWV (n = 1) were excluded. Finally, 117 patients were studied. The study was approved by the ethics review board of the Chinese PLA General Hospital (No. S2017-038-01). All participants provided written informed consent for this study.

2.2 | Measures of arterial stiffness

2.2.1 | Ankle-brachial index and brachial-ankle pulse wave velocity measurement (ABI and baPWV)

The ABI and baPWV were measured using a validated automatic device (OMRON, BP-203RPEIII, Japan), which simultaneously measured pulse waves in the brachial and ankle arteries using the oscillometric method with bilateral arm and ankle blood pressure. The ABI was defined as the ratio of ankle SBP to brachial SBP. All the participants were measured after at least 5 minutes of rest in the supine position. The lower of the ABI and higher baPWV values between the right and left extremities were used for analysis.

2.2.2 | Augmentation index (AIx@75) measurement

Peripheral AIx was assessed using the EndoPAT-2000 device (Itamar, Medical Ltd.). The PAT device comprises a pneumatic plethysmograph that applies uniform pressure to the surface of the distal finger, allowing the measurement of pulse volume changes that are sensed by pressure transducers in the finger cuff and transmitted to the EndoPAT-2000 device. AIx is calculated using a formula based on the forward wave measured pulse and the augmented (reflected wave) pulse.[9] The patients were tested in the supine position in a temperature-controlled room kept at 21 to 24°C with dimmed light and a quiet environment and were given a 30-min resting period before analysis. During measurement, patients were asked to neither speak nor sleep.

2.2.3 | Ambulatory arterial stiffness index and 24-hour pulse pressure (AASI and 24-h PP)

ABPM was carried out using a validated device (ABPM-05, Meditech, Hungary). A reading was taken every 15 minutes throughout the day and every 30 minutes at night. Patients with monitors were advised to maintain their usual activities. Valid measurements were those with ≥90% continuous recordings. Day and night durations were defined by wide fixed-clock intervals (6:00 AM to 10:00 PM for the day and 10:00 PM to 6:00 AM for the night) or according to the self-reports of patients. The parameters evaluated were 24-hour diurnal and nocturnal systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), and heart rate (HR). From individual 24-h recordings, we computed the regression slope of diastolic BP over systolic BP and calculated the AASI (1-the coefficient of the regression slope).

All the measurements were taken by skilled physicians in accordance with the instructions and were performed once in each individual. For each individual, measurements were sequentially performed in random order.

2.3 | Demographic, medical, and laboratory data

We collected demographic and medical data, including age; sex; smoking history (current smoker versus noncurrent smoker); and history of hypertension, diabetes, and cardiovascular disease (myocardial infarction, angina pectoris, congestion heart failure, cerebrovascular disorder). Hypertension was defined as office blood pressure (BP) ≥140/90 mmHg, self-reported history of hypertension, or current treatment with antihypertension drugs. Diabetes mellitus was defined as a fasting glucose level ≥ 7.0 mmol/L, glycated hemoglobin ≥ 6.5%,

self-reported history of diabetes, or current treatment with antidiabetic drugs. Body mass index (BMI) was calculated as the ratio of weight in kilograms divided by the square of height in meters. The CKD Epidemiology Collaboration (CKD-EPI) creatinine equation was adopted to calculate the estimated glomerular filtration rate (eGFR).[10] Specific causes of CKD were mainly dependent on pathologic diagnoses when the biopsy results were available, otherwise, it depended on the clinical diagnoses made by nephrologists. All enrolled patients were categorized as the following subgroups: CKD with uncertain reason, membranous nephropathy, IgA nephropathy, diabetic nephropathy, hypertensive nephropathy, and others. We also collected blood and urine samples and performed laboratory examinations, including serum intact parathyroid hormone (PTH), serum calcium concentration (Ca), serum phosphorus concentration (P), hemoglobin (Hb), serum creatinine (Scr), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and uric acid (Ua). All blood and urine samples were collected during hospitalization.

2.4 | Definition of endpoints

The study endpoints were defined as 40% eGFR decline over the follow-up period, commencement of dialysis or death. Patients who did not present to the hospital as scheduled were followed up with telephone calls or online contact every 6 months until June 2020. More than 95% of the patients maintained contact during this period.

2.5 | Statistical analysis

Analyses were performed with IBM SPSS 25.0 software (SPSS Institute; IBM). Correlations between pairs of arterial stiffness factors were analyzed individually (Pearson's coefficient of correlation, described by scatter plots), and those with significant correlations ($p < .1$) were included in the multiple linear regression analysis to allow adjustment for potential confounders (age, sex, presence of diabetes, 24-hour SBP, 24-hour DBP, eGFR and 24 hours proteinuria). Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the associations between arterial stiffness and renal outcomes with adjustment for traditional risk factors such as age, gender, MAP, eGFR, and 24 hours proteinuria. The arterial stiffness markers with the discriminatory values for predicting renal outcomes were obtained and analysed using ROC curves.

3 | RESULTS

3.1 | Characteristics of the patients

The clinical characteristics of the study patients are shown in Table 1. All the patients completed all the measures at a median interval of 3 (2-7) days. The sample included 80 men (68.4%). The values (Interquartile Range, IQR) of age and eGFR were 61 (49-65) years and 50.5 (35.5-84.1) ml/min/1.73 m^2, respectively. The means (Standard Deviation, SD) of AASI, 24-h PP, ABI, baPWV, and AIx@75 were 0.459 (0.142), 53.1 (10.8), 1.15 (0.10), 1697.9 (386.1), and 10.6 (15.1), respectively, in the CKD patients.

3.2 | Correlations between arterial stiffness markers

In Pearson correlation analysis, baPWV was significantly associated with 24-h PP ($r = .531$, $p < .001$), AIx@75 ($r = .306$, $p < .001$), and ABI ($r = .220$, $p = .017$) in Figure 1. There were significant associations between 24-h PP and AASI ($r = .507$, $p < .001$) and AIx@75 ($r = .217$, $p = .019$). Table 2 showed that in multivariable linear regression analysis, higher 24-h PP was associated with higher AASI ($\beta = .507$), baPWV ($\beta = .352$), and AIx@75 ($\beta = .149$). Higher baPWV was associated with higher AIx@75 ($\beta = .324$). In general, 24-h PP, baPWV, and AIx@75 were linked most closely to one another. AASI did not have an association with baPWV ($p = .116$) in our study.

3.3 | Cox analysis testing associations between per 1-SD difference in arterial stiffness measures and incident renal outcomes

During follow-up for a median of 25 months, 26.5% ($n = 31$) of patients developed a composite outcome; of these, 10 initiated dialysis, 17 had 40% eGFR loss, and 4 died. Table 3 showed that in the univariate Cox analysis, increased AASI, 24-h PP, and baPWV were associated with poor renal outcomes. In the multivariate Cox analysis, after adjusting for age, sex, MAP, eGFR, and 24 hours proteinuria, a 1-SD increase in AASI and 24-h PP was associated with renal outcomes.

3.4 | Receiver operator characteristic curve analysis of AASI, 24-h PP, baPWV, ABI, and AIx@75

Figure 2 showed the ROC curves of AASI, 24-h PP, baPWV, ABI, and AIx@75 as classifiers of CKD progression (eGFR decline ≥ 40% and dialysis) and all-cause mortality. The area under the curve (AUC) for 24-h PP was 0.727 (95% CI 0.624-0.831 $p < .001$). When Youden's index was at its maximum, the value was 52 mmHg, and the sensitivity and specificity were 81% and 61%, respectively.

4 | DISCUSSION

We collected mainstream arterial stiffness markers and explored their effectiveness for predicting outcomes in CKD patients for the first time. Our study illustrates at least three important findings.

TABLE 1 Characteristics of the study patients

Characteristics	All patients (*n* = 117)
Age (years)	61 (49-65)
Male gender (%)	68.4
Current smoker (%)	22.2
Diabetes mellitus (%)	38.5
Hypertension (%)	77.8
History of cardiovascular diseases (%)	23.9
24-h mean systolic BP (mmHg)	128.2 ± 15.6
24-h mean diastolic BP (mmHg)	74.4 ± 9.7
24-h MAP (mmHg)	92.1± 10.1
24-h heart rate (heats/min)	72 ± 8
Body mass index (kg/m^2)	25.7 ± 3.4
Stage of CKD	
Stage 1 (%)	22.2
Stage 2 (%)	19.7
Stage 3 (%)	38.4
Stage 4 (%)	17.1
Stage 5 (%)	2.6
Etiology of CKD	
CKD with uncertain reason, *n* (%)	19.7
Membranous nephropathy *n* (%)	38.5
IgA nephropathy, *n* (%)	14.5
Diabetic nephropathy, *n* (%)	11.1
Hypertensive nephropathy, *n* (%)	3.4
Others, *n* (%)	12.8
Arterial stiffness markers	
AASI	0.459 ± 0.142
24-h PP (mmHg)	53.1± 10.8
ABI	1.15 ± 0.10
baPWV (cm/s)	1697.9 ± 386.1
AIx@75	10.6 ± 15.1
Laboratory parameters	
Albumin (g/L)	35.1 (26.8-39.6)
Fasting glucose (mmol/L)	4.68 (4.21-5.50)
Triglyceride (mmol/L)	1.72 (1.25-2.48)
Total cholesterol (mmol/L)	4.76 (3.72-5.66)
HDL-cholesterol (mmol/L)	1.11 (0.88-1.39)
LDL-cholesterol (mmol/L)	2.79 (2.13-3.65)
Hemoglobin (g/L)	121.2 ± 22.0
Baseline eGFR (ml/min per 1.73 m^2)	50.5 (35.5-84.1)
Serum calcium (mmol/L)	2.10 (1.99-2.23)
Serum phosphate (mmol/L)	1.23 ± 0.24
Uric acid (μmol/L)	371.7 ± 94.8
PTH (pg/ml)	33.2 (21.8-59.2)
24 hours proteinuria (g/d)	1.85 (0.68-4.13)
Medications	
ACEI and/or ARB use (%)	61.5
β-blocker use (%)	29.9
Calcium channel blocker use (%)	47.9
Diuretic use (%)	6.0
Statin use (%)	53.8
Aspirin use (%)	25.6

Note: Categorical characteristics are presented number (percentage) and continuous characteristics are presented mean ± standard deviation or median (25th-75th percentile).

Abbreviations: 24 -h PP, 24 -h pulse pressure; AASI, ambulatory arterial stiffness index; ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; AIx@75, augmentation index standardized to a heart rate of 75; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; PTH, parathyroid hormone.

First, arterial stiffness markers are not always interchangeable. Twenty-four hour PP, baPWV, and AIx@75 were closely linked. Second, our data demonstrated an association of arterial stiffness with poor CKD prognosis, which added evidence to the role of arterial stiffness in raising the risk of CKD progression and mortality. Third, we found that 24-h PP was the best marker for predicting renal outcomes, followed by baPWV, AASI, AIx@75, and ABI. The use of 24-h PP as an arterial stiffness marker should be valued in clinical practice related to CKD.

Noninvasive arterial stiffness markers were not perfectly linked in previous studies.[2,11-15] In the population with stage 2-5 CKD,[2] linear relationships between 24-h PP and PWV, 24-h PP and AASI, and AIx@75 and PWV were observed, with correlation coefficients of 0.65, 0.56, and 0.34, respectively. By comparison, we found similar relationships between these three pairs, and the coefficients were 0.53, 0.51, and 0.31, respectively. In contrast to this previous study, we did not find a relationship between AASI and baPWV. The relationship between AASI and baPWV is controversial and worthy of further investigation. Elizabeth S et al[16] suggested that there was a modest association between AASI and PWV, with a coefficient of 0.12. Khaleghi M and Kullo IJ suggested that a higher AIx was independently associated with a lower ABI.[17] However, our study did not find above relationships.

Our results demonstrated that 24-h PP, baPWV, and AASI were inversely correlated with CKD prognosis, whereas AIx@75 and ABI were not. This piece of evidence is consistent with that of a cross-sectional study that showed that higher AASI, PWV, and 24-h PP increased the likelihood of lower eGFR, whereas higher AIx did not.[2] Sanaz Sedaghat et al[18] observed the same result and confirmed the association between pulse pressure and kidney function decline using genetic variants as less-biased proxies for the arterial stiffness parameters. Furthermore, Geng TT et al[19] conducted a longitudinal study of 30 636 participants and found that PP remained

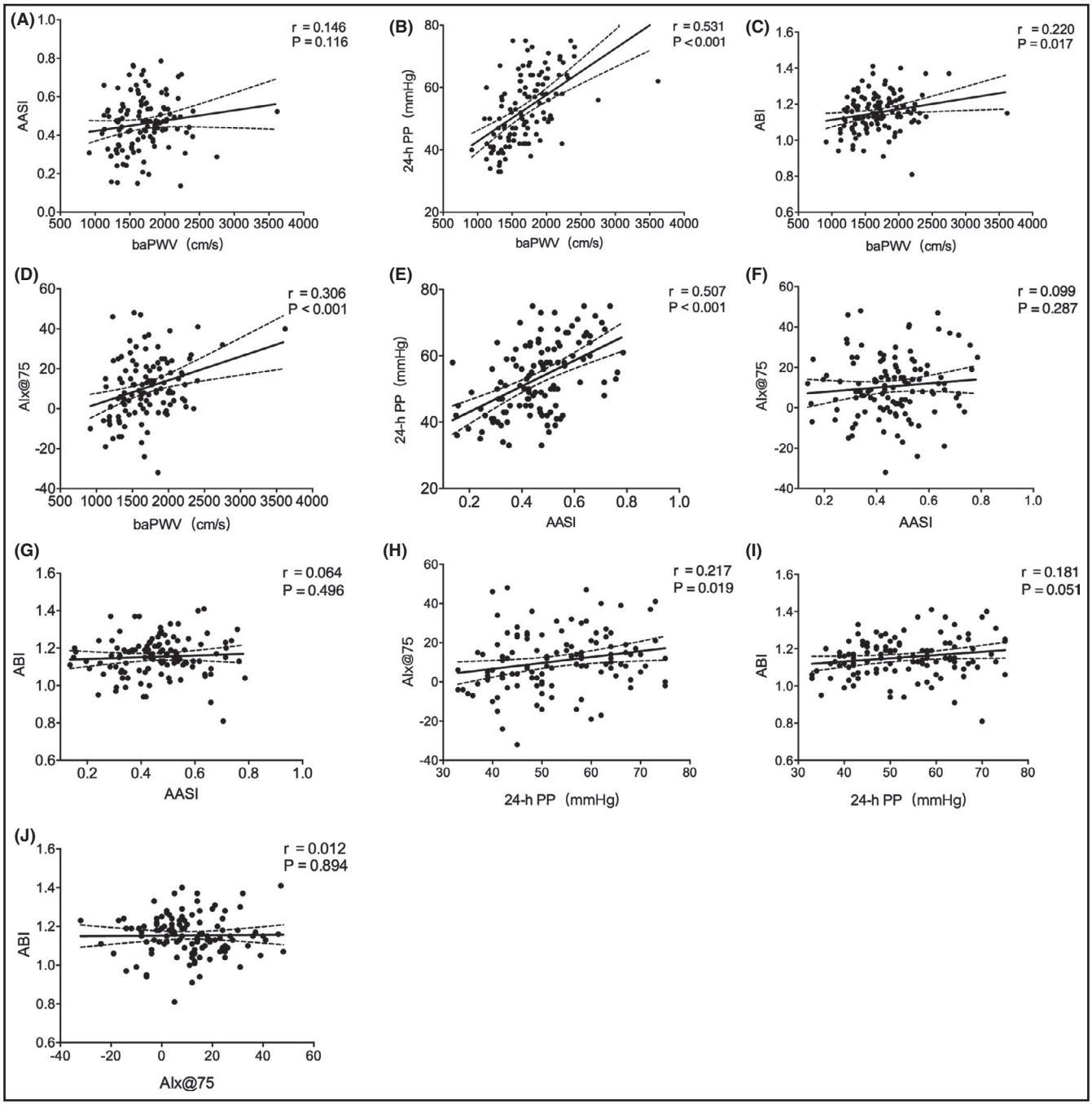

FIGURE 1 Correlations between markers of arterial stiffness. A for baPWV versus AASI; B for baPWV versus 24-h PP; C for baPWV versus ABI; D for baPWV versus AIx@75; E for AASI versus 24-h PP; F for AASI versus AIx@75; G for AASI versus ABI; H for 24-h PP versus AIx@75; I for 24-h PP versus ABI; J for AIx@75 versus ABI. AASI, ambulatory arterial stiffness index; AIx@75, augmentation index standardized to a heart rate of 75; 24-h PP, 24-hour mean pulse pressure; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index

significantly associated with ESRD risk in a dose-dependent manner after adjusting for systolic and diastolic BP. For ABI, Hiroshi Sonoda et al[20] demonstrated that low ABI independently predicted the development of CKD in the Asian population. Unfortunately, we did not find this relationship in our study.

Arterial stiffness is a key driver of the enhanced chronic kidney disease burden in the elderly. Atherosclerosis is a systemic disease that can affect all arteries, ranging from the aorta to small arteries in organs. The associations between renal outcomes and arterial stiffness are not yet clear. However, there are some potential explanations. First, intrarenal arteries are associated with generalized atherosclerosis when different measurements are used.[21] Second, arterial stiffness and CKD share similar risk factor profiles, such as age, gender, blood pressure, proteinuria, and so on. However, we found that the association between arterial stiffness and CKD outcomes remained significant after those risk factors were taken

TABLE 2 Correlation coefficients (β) between markers of arterial stiffness in multiple linear regression analysis

	24 -h PP (mmHg)	baPWV (cm/s)
AASI	0.507**	—
baPWV (cm/s)	0.352**	—
ABI	−0.040	0.015
AIx@75	0.149*	0.324**

Note: Significant correlations of arterial stiffness factors in unadjusted Pearson's coefficient were put in multivariate linear regression. Adjusted for age, sex, diabetes, 24 h SBP, 24 h DBP, eGFR and 24 h proteinuria. Significance of the correlation coefficients: *$p < .05$, **$p < .01$.

Abbreviations: 24 h PP, 24-h pulse pressure; AASI, ambulatory arterial stiffness index; ABI, ankle-brachial index; AIx@75, augmentation index standardized to a heart rate of 75 ; baPWV, brachial-ankle pulse wave velocity. Correlation coefficients (β) were standardized beta coefficients derived from linear regression analysis with 24-h PP and baPWV as dependent variables.

TABLE 3 Cox proportional hazards model analysis testing associations between per 1-SD difference in arterial stiffness markers and incident renal outcomes

Markers	HR (95%CI)	*p* Value
AASI		
Univariable	1.657 (1.162-2.363)	.005
Multivariable[a]	1.519 (1.062-2.171)	.022
24-h PP (mmHg)		
Univariable	2.089 (1.440-3.030)	<.001
Multivariable[a]	1.672 (1.159-2.412)	.006
baPWV (cm/s)		
Univariable	1.441 (1.150-1.864)	.005
Multivariable[a]	1.061 (0.760-1.048)	.728
ABI		
Univariable	1.135 (0.809-1.592)	.464
Multivariable[a]	0.890 (0.615-1.287)	.535
AIx@75		
Univariable	1.390 (0.987-1.957)	.059
Multivariable[a]	1.031 (0.676-1.573)	.888

Abbreviations: 24-h PP, 24-hour mean pulse pressure; AASI, ambulatory arterial stiffness index; ABI, ankle-brachial index; AIx@75, augmentation index adjusted by a heart rate of 75; baPWV, brachial-ankle pulse wave velocity; CI, confidence intervals; HR, hazard ratios.

[a]Multivariable models include age, sex, MAP, eGFR, 24 hours proteinuria.

into consideration in analyses, which means that there are potential risks underlying these two pathophysiological processes. Third, arterial stiffness can result in or result from CKD. On the one hand, arterial stiffening, especially in the aortic vasculature, facilitates the transmission of excessive pressure and flow pulsatility into the microvascular beds of the kidneys, which are low-resistance, high-flow end organs. Hemodynamic stress on the kidney vasculature may result in endothelial dysfunction and microvascular ischemia, leading to kidney damage. On the other hand, it is probable that common pathophysiological processes caused by CKD, such as inflammation,[22] oxidant stress, endothelial dysfunction,[23,24] and calcium and phosphorus metabolism disorder, contribute to arterial stiffness.

There are several limitations that need to be considered. We performed these analyses in a small population, which limited us from controlling for more potential confounders and determining the prognostic effect of arterial stiffness on kidney function decline or death. However, we adjusted for the most important risk factors, such as age, blood pressure, eGFR, and proteinuria. The results of this study might not be generalizable due to the imbalance in CKD diagnoses, of which membranous nephropathy was the most common. Arterial stiffness might differ according to the cause of CKD. All the noninvasive arterial stiffness markers were measured only once, which cannot reflect ambulatory changes in arterial stiffness. All the markers were measures of peripheral arterial stiffness rather than central measurements which may more precisely reflect the status of arterial stiffness. In the ABPM measurement, day and night durations were defined by wide fixed-clock intervals (6:00 AM to 10:00 PM for the day and 10:00 PM to 6:00 AM for the night). The fact that some patients may be asleep and others may be awake during these periods represents a source of data inaccuracy. AIx@75 was an index obtained by measuring the reflected wave of the fingertip artery. However, other arterial stiffness indicators obtained through brachial or ankle artery. This may result in heterogeneity of arterial stiffness and lead to bias. In conclusion, among the popular arterial stiffness markers, 24-h PP, baPWV, and AIx@75 were linked to each other well. Arterial stiffness could be considered a target for delaying the decline in kidney function. The use of 24-h PP as an arterial stiffness marker should be valued in clinical practice related to CKD.

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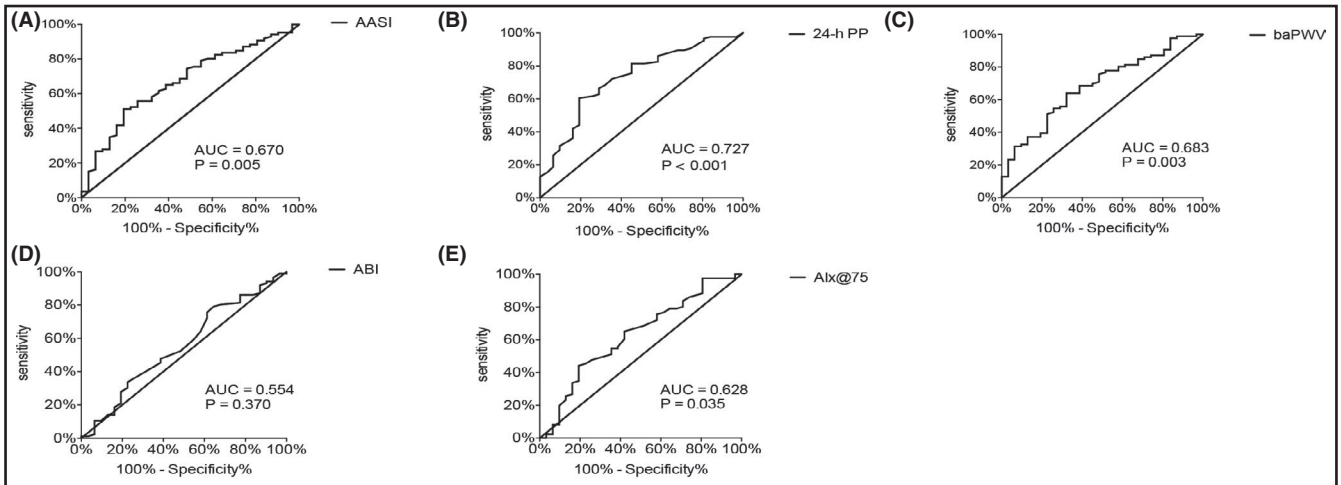
CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Xinru Guo: Substantial contributions to the conception, design, analysis, drafting of the work, and revising it critically for important intellectual content. Yisha Li: Contributions to collecting data for the work and revising it critically for important intellectual content. Ying Yang: Contributions to collecting data and analysis for the work. Wenling Wang: Contributions to collecting data and analysis for the work. Shuang Liang: Contributions to collecting data and analysis for the work. Ying Zheng: Contributions to analysis for the work. Xiangmei Chen: Contributions to revising it critically for important intellectual content. Guangyan Cai: Substantial contributions to the conception, design, revising it critically for



	AUC	95% CI	P value	Cut-off	Sensitivity (%)	Specificity (%)
AASI	0.670	0.563-0.778	0.005	0.433	81	51
24-h PP (mmHg)	0.727	0.624-0.831	<0.001	52	81	61
baPWV (cm/s)	0.683	0.578-0.788	0.003	1717	68	64
ABI	0.554	0.434-0.675	0.370	1.21	36	79
AIx@75	0.628	0.511-0.745	0.035	5.5	81	44

FIGURE 2 Areas under the ROC curve describing the ability of arterial stiffness markers to predict renal outcomes. Letter a for AASI; b for 24-h PP; c for baPWV; d for ABI; e for AIx@75

important intellectual content and final approval of the version to be published.

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