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The relationship of endothelial function and arterial stiffness with subclinical target organ damage in essential hypertension

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Abstract

This study aimed to explore whether brachial-ankle pulse wave velocity (baPWV) and brachial artery flow-mediated dilation (FMD) or the interaction of both parameters are associated with subclinical target organ damage (STOD) indices in patients with essential hypertension. A total of 4618 patients registered from January 2015 to October 2020 were included. baPWV and FMD were measured to evaluate arterial stiffness and endothelial dysfunction. Whereas left ventricular hypertrophy (LVH), urine albumin-creatinine ratio (UACR), and carotid intima-media thickness (CIMT) were obtained as STOD indicators. On multivariable logistic regression analysis with potential confounders, higher quartiles of baPWV and FMD were significantly associated with an increased risk of STOD. In patients <65 years of age, the odds ratio (OR) of LVH, UACR, and CIMT ≥.9 mm for the fourth versus the first quartile of baPWV were 1.765 (1.390–2.240), 2.832 (2.014–3.813), and 3.075 (2.315–4.084), respectively. In interaction analysis, an increase in baPWV shows a progressively higher risk of STOD across the quartiles of FMD. Also, the estimated absolute risks of LVH, UACR, and CIMT ≥.9 mm for the first to fourth quartile of baPWV increased from 1.88 to 2.75, 2.35 to 4.44, and 3.10 to 6.10, respectively, in patients grouped by FMD quartiles. The addition of baPWV to FMD slightly improved risk prediction for STOD. BaPWV and FMD were independently associated with an increased risk of STOD in patients with essential hypertension especially among patients <65 years of age. Patients with elevated baPWV and decreased FMD parameters are at increased risk of STOD.

KEYWORDS
arterial stiffness, brachial artery flow-mediated dilation, brachial-ankle pulse wave velocity, endothelial function, subclinical target organ damage

1 | INTRODUCTION

Hypertension-induced subclinical target organ damage (STOD) is the primary risk factor for cardiovascular diseases (CVDs) and mortality.[1–3] Endothelial dysfunction and arterial stiffness, the independent predictors of hypertension, are increasing with age-related physiological alterations.[4–7] At the same time, the prevalence of STOD dramatically increases with uncontrolled blood pressure (BP) levels.[8,9] Although endothelial dysfunction and arterial stiffness increase with hypertension synchronously, the correlation between endothelial dysfunction and arterial stiffness with STOD was controversial in previous studies.[10] It remains unknown whether endothelial dysfunction

and arterial stiffness amplify the risk of STOD in the hypertension population.

Some studies suggested that chronic elevation in BP resulted in arterial stiffness through its unfavorable effects on structural and functional alterations in the walls of central elastic arteries.[11–13] In contrast, other studies showed that arterial stiffness led to higher BP because of the changes in the buffering function of conduit arteries.[14] Scientifically, both theories may justify an increase in BP contributes to arterial stiffness but whether an increase in arterial stiffness predicts the preceding STOD remains unknown. From a hemodynamic perspective, the body maintains normal BP by adjusting peripheral resistance and cardiac output.[15] Also, other studies have suggested that target organ damage characterized by left ventricular hypertrophy (LVH), high levels of albuminuria (UACR), and carotid intima-media thickness (CIMT) significantly predicts future cardiovascular and renal events in hypertensive patients.[4,5] In this context, we hypothesize that vascular resistance resulting from endothelial dysfunction and arterial stiffness may positively associate with STOD indicators.

Both endothelial dysfunction and arterial stiffness contribute to physiological hardening of the arterial system and are surrogate markers for impaired vascular function and structure. One method to assess systemic arterial stiffness is brachial-ankle pulse wave velocity (baPWV).[16] Whereas, endothelial dysfunction that associate with a decrease in bioavailability of vasodilator factors has been reported to associate with atherogenesis, atherothrombotic complications, and subclinical organ damage[8,9] and can be determined using brachial artery flow-mediated dilation (FMD).[10,11] Recent evidence illustrated the relationships among endothelial dysfunction, arterial stiffness, and STOD, based on animal studies[17] and small clinical studies.[10] However, this hypothesis has not been tested in large-scale epidemiological studies. Elucidating the association between endothelial dysfunction, arterial stiffness and STOD is significant because hypertension-induced STOD will lead to an increased clinical burden of CVDs and mortality. Thus, we investigated the association between endothelial dysfunction, arterial stiffness, and STOD in a large hospital-based cohort including 4618 adults.

2 | METHODS

2.1 | Study participants

We examined patients with hypertension who were hospitalized between January 2015 and October 2020 at the First Affiliated Hospital of Dalian Medical University. Those with diagnosis of secondary hypertension defined based on 2018 ESC/ESH guidelines[18]) ($n = 106$), malignancy ($n = 21$), severe arrhythmia ($n = 102$), moderate and severe kidney dysfunction (estimated glomerular filtration rate [eGFR] ≤60 ml/min/1.73 m^2), proteinuria (>300 mg/24 h) ($n = 122$), left ventricular systolic dysfunction (LVEF <50%) ($n = 58$), severe valvular heart disease ($n = 26$), peripheral vascular diseases (PAD) ($n = 62$), and myocardial infarction or unstable angina pectoris ($n = 117$).

Also, electronic health records data comprises substantial missing information that if left unaddressed could decrease the validity of conclusions drawn.[19] Therefore, missing data of the key variables that rule out the aforementioned disease conditions were also excluded to control selection bias and avoid interpretation of our results ($n = 2774$). Finally, the present study included a total of 4618 patients. Figure 1 describes a brief overview of the selection of study participants. The research was conducted in accordance with the Helsinki declaration guidelines and was approved by the institutional review board of the First Affiliated Hospital of Dalian Medical University. The informed consent provision was waived and all procedures listed here were carried out in compliance with the approved guidelines.

2.2 | Clinical measurements and definition of explanatory variables

Demographic and clinical data including age, gender, current smoking, diabetes mellitus, cardiovascular disease, use of antihypertensive drugs, hypoglycemic drugs and statin were retrieved from the electronic data record of the First Affiliated Hospital of Dalian Medical University. Participants were deemed current smokers if reported they are currently smoking or registered smoking at least 100 cigarettes during their lifetime.[20,21] Body mass index (BMI) was calculated as weight in kg per squared height measured in meters. Data on biochemical parameters including total cholesterol (TC), triglycerides (TG), High-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol (LDL-C), hypersensitivity C-reactive protein (hs-CRP) were also retrieved from the First Affiliated Hospital of Dalian Medical University and all these biochemical parameters were performed using the standard protocols. eGFR was calculated according to the equation suggested by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration.[22] Diabetes mellitus (DM) was defined as fasting plasma glucose ≥7.0 mmo/L or 2 h plasma glucose ≥11.1 mmo/L or a self-reported history of diabetes mellitus or currently receiving antidiabetic treatments. Peripheral artery disease (PAD) was defined as ABI <.9, stent implantation, or according to the past medical records. LVH was defined according to 2018 ESC/ESH guidelines and we strictly adhered in the criteria of echocardiography LVH (LV mass index: men >50 g/m$^{2.7}$; women >47 g/m$^{2.7}$ [height in m$^{2.7}$]; indexation for body surface area [BSA] may be used in normal-weight patients; LV mass/BSA g/m^2 >115 [men] and >95 [women]). Also, data on urinary albumin-to-creatinine ratio was produced from the first urine in the morning. Elevate UACR was defined as 30–300 mg/g.

2.3 | Echocardiography

All subjects received echocardiography examinations at rest in the left lateral decubitus position using the Vivid E95 ultrasound system. The left ventricular end-diastolic diameter, left ventricular posterior wall thickness, interventricular septal thickness, and left ventricular
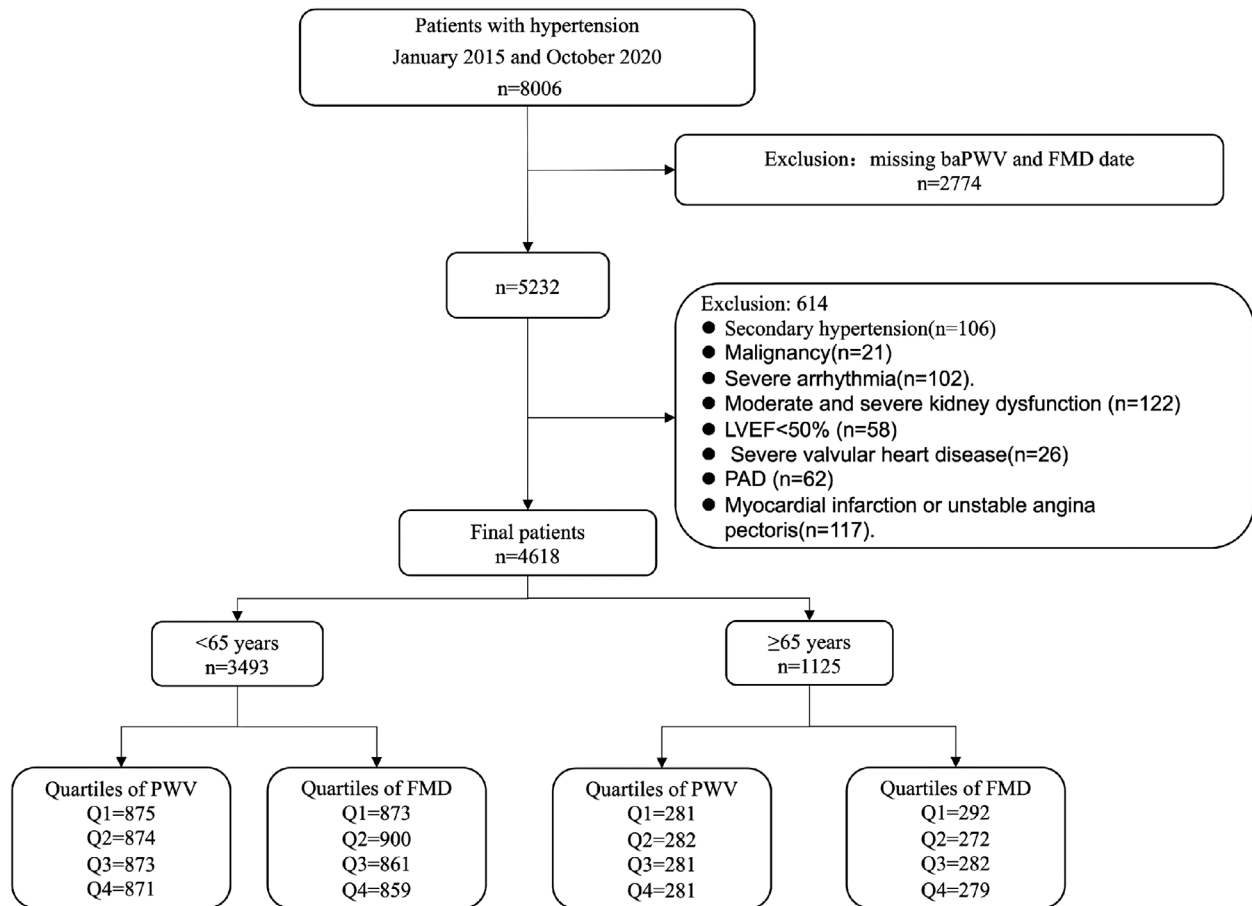
FIGURE 1 A brief overview of the selection of study participants.

ejection fraction were measured. LVMI was calculated by using the Devereux formula[23] via these measurements.

2.4 | Ultrasonographic examination of the carotid arteries

All subjects received Bilateral duplex US (Philips iU-22 Ultrasound System, Philips Medical Systems, Bothell, Washington, USA) examinations in the supine position. Longitudinal images of the common carotid artery, 1 cm proximal to the bifurcation in which the far wall intima-media interface (M-line) was clearly defined, were magnified and recorded on videotape for later analysis. The distance between the leading edge of the intima and the media-adventitia interface was measured with ultrasonic calipers. Three measurements were taken in both the right and left common carotid arteries, and a mean IMT was calculated as previously described.[24] CIMT ≥.9 mm was defined as positive.

2.5 | Measurement of FMD

Patients were examined in the supine position after 15 min rest and after at least a 6-h fasting. An automated sphygmomanometer

(Dinamap device) was used to monitor blood pressure and pulse in the left arm at 5-min intervals throughout the exam. A standard blood pressure cuff was positioned around the right arm, two inches below the antecubital fossa, and the artery was imaged 5–9 cm above the antecubital fossa. A linear-array multifrequency transducer operating at 9 MHz (GE Logiq 700 Device) was used to acquire images of the right brachial artery. After obtaining baseline images, the cuff was inflated to 50 mm Hg above the participant's systolic blood pressure for 5 min. Images of the right brachial artery were captured continuously for 30 sec before cuff inflation, and for 2 min beginning immediately before cuff deflation to document the vasodilator response. Images of the brachial artery diameters were captured in diastole (gated with electrocardiograph R-wave). The semi-automated readings of these digitized images generated the baseline and maximum diameters of the brachial artery from which the rate FMD was computed.

2.6 | Measurement of baPWV

BbaPWV measurements were obtained using a volume-plethysmography device (VP-1000, OMRON, Dalian, China), which measures both brachial and posterior tibial artery pressure waveforms using an oscillometric method with cuffs placed around both arms

and ankles of the patients. baPWV was calculated automatically by time-phased analysis, and the distance between the upper arm and ankle was estimated based on height. The baPWV values were obtained from the right and left measurements, and the higher reading of the two measurements was used for analysis.[25]

2.7 | Outcome definition

Hypertension-related STOD is characterized by significant changes in LVH, CIMT, and UACR.[18] Therefore, we used LVH, CIMT, and UACR as the indices of STOD. We defined STOD if any one of the following exists (i) echocardiographic LVH; (ii) CIMT ≥.9 mm; or (iii) UACR between 30 and 300 mg/g.

2.8 | Statistical analysis

All statistical analyses were conducted using SPSS version 26.0. Participants were categorized based on age into two groups, including <65 years of age and ≥65 years of age, and were stratified into quartiles based on the baPWV and FMD values. Kolmogorov–Smirnov test was used to test the normality of distribution. Quantitative variables with a normal distribution were specified as the mean ± standard deviation. Whereas the non-normal distributed data was present as median (percentile 25, percentile 75). Analysis of variance (ANOVA) was used to compare whether the differences between three or more groups were statistically significant in variables comprising numerical data. Chi-squared test was computed to analyze categorical data and results were expressed as counts and percentiles. The likelihood of STOD associated with baPWV or FMD was calculated using a logistic regression model. While running logistic regression analysis, the baPWV or FMD quartiles were entered in the models with the first baPWV or FMD-specific quartile as a reference to assess the odds ratio (OR) and 95% Confidence Interval (95% CI). The logistic regression analysis was carried out in three models. Model 1 was unadjusted, model 2 was adjusted for age and sex, and model 3 was adjusted for age, sex, BMI, eGFR, smoking, SBP, DBP, use of calcium channel blocker, angiotensin-converting enzyme receptor blocker, β-Blocker, diuretic, α-Blocker, use of statins, diabetes, and stable angina. To compute whether elevated baPWV combined with reduced FMD or vice versa influences the risk of STOD, we estimated the OR and 95% CI of STOD using multivariate regression analysis among those participants grouped in different quartiles of baPWV/FMD along with their corresponding FMD/baPWV quartiles. Receiver operator characteristics (ROC) curve analysis was used to evaluate the productive power of baPWV, FMD, and baPWV+FMD for STOD. Also, Youden's index statistics were calculated to capture the performance of the parameters.[26] We further run a sub-analysis to calculate the OR for STOD associated with quartiles of baPWV grouped by FMD or vice versa to establish the effect of the interaction of the two parameters (baPWV and FMD). All statistical analyses were two-sided, and a p-value of less than .05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of the participants

Among the 8006 subjects during the study period, 4618 participants had sufficient data on baPWV and FMD. The prevalence of LVH, UACR, and CIMT were 49.7%, 20.7%, and 84.8%, respectively. The characteristics for patients with age <65 and ≥65 years based on baPWV and FMD quartiles are presented in Tables 1 and 2. Also, characteristics including heart rate, Hs-CRP and drugs using have been shown in Supplementary Tables S1 and S2, respectively for patients with age <65 and ≥65 years based on baPWV and FMD quartiles. Table 1 showed patients in higher quartiles of baPWV and FMD had higher mean values of SBP, UACR, and LVMI. Also, patients in higher quartiles of baPWV and FMD were more likely to have CIMT ≥.9 mm, LVH, DM, and stable angina. Likewise, they had a higher proportion of older age and decreased rate of LVEF. However, unlike the patients in higher quartiles of baPWV, those patients with higher quartiles of FMD were more likely to be males and smokers. In the group of ≥65 years of age, the proportion of patients with LVH, UACR, and CIMT ≥.9 mm was increasing across the quartiles of baPWV. Conversely, there were no significant differences in age, smoking status, and mean TC and HDL-C levels across the baPWV and FMD quartiles (Table 2).

3.2 | Relationship between baPWV/FMD and STOD indices in patients <65 years of age

Table 3 presents the ORs of STOD indices among patients <65 years of age (Table 3). The patients in the highest baPWV/FMD quartile had a significantly increased risk of STOD. This association persisted even after adjusting for potential confounding factors, including age, sex, BMI, eGFR, smoking, SBP, DBP, antihypertensive use including calcium channel blocker, angiotensin-converting enzyme receptor blocker, β-Blocker, Diuretic, α-Blocker, use of statins, diabetes, and stable angina. The OR (95% CI) of LVH and UACR for the fourth versus the first quartile of baPWV were 1.765 (1.390–2.240) and 2.832 (2.014–3.813) and, whereas for the fourth versus the first quartile of CIMT ≥.9 mm was 3.075 (2.315–4.084).

The ORs and 95% CI for STOD were further evaluated using the quartile of FMD. Importantly, the patients in the highest FMD quartile had a significantly increased risk of STOD. The OR (95% CI) of LVH, UACR, and CIMT ≥.9 mm for the fourth versus first quartile of FMD were 1.428 (1.151–1.772), 1.503 (1.148–1.968), and 2.323 (1.796–3.005), respectively.

3.3 | Relationship between baPWV/FMD and STOD indices in patients ≥65 years of age

The association between the baPWV/FMD and the risk of STOD among patients ≥65 years of age is presented in Table 4. The patients in the highest baPWV quartiles had a significantly increased risk of

TABLE 1 Characteristics of participants <65 years of age grouped by Quartile of brachial-ankle pulse wave velocity and flow-mediated dilation

	Quartile of baPWV, cm/s in patients <65 years of age					Quartile of FMD, % in patients <65 years of age				
	Q1 (792.5–1351.5)	Q2 (1352–1503.5)	Q3 (1504–1682.5)	Q4 (1683–3474)	p-value	Q1 (6.8–19.4)	Q2 (4.8–6.7)	Q3 (2.9–4.7)	Q4 (0–2.8)	p-value
Number of subjects	875	874	873	871		859	861	900	873	
Age, years	45.5 ± 11.1	47.4 ± 10.8	49.3 ± 10.6	52.6 ± 10.1	<.001	45.8 ± 11.7	47.8 ± 11.1	49.5 ± 10.6	51.5 ± 9.8	<.001
Female, N (%)	331 (37.8)	346 (39.6)	360 (41.2)	399 (45.8)	.005	444 (51.7)	347 (40.3)	334 (37.1)	311 (35.6)	<.001
BMI, kg/m²	27.2 ± 4.1	27.2 ± 3.9	27.0 ± 3.9	27.0 ± 3.9	<.001	26.6 ± 4.1	27.0 ± 4.1	27.3 ± 3.8	27.1 ± 3.7	.003
Current smoking, N (%)	223 (25.5)	236 (27.0)	232 (26.6)	203 (23.3)	.11	165 (19.2)	224 (26.0)	239 (26.6)	266 (30.5)	<.001
SBP, mm Hg	160.2 ± 18.2	166.9 ± 19.0	172.6 ± 21.7	179.0 ± 21.8	<.001	165.3 ± 19.7	169.0 ± 20.7	171.2 ± 21.8	173.1 ± 22.4	<.001
DBP, mm Hg	105.7 ± 15.1	110.0 ± 14.9	111.9 ± 16.5	113.5 ± 16.9	<.001	108.2 ± 15.9	110.0 ± 15.9	111.4 ± 16.3	111.5 ± 16.1	<.001
eGFR, ml/min/1.73 m²	110.7 ± 21.4	110.6 ± 21.6	110.7 ± 23.4	108.7 ± 23.9	.192	112.7 ± 22.4	111.1 ± 22.9	109.4 ± 21.6	107.6 ± 23.3	<.001
TC, mmol/L	4.8 ± 1.1	4.8 ± 1.2	4.9 ± 1.0	5.0 ± 1.0	.041	4.9 ± 1.0	4.8 ± 1.0	4.9 ± 1.0	4.9 ± 1.4	.673
TG, mmol/L	1.5 (1.0–2.1)	1.5 (1.0–2.2)	1.5 (1.1–2.2)	1.6 (1.1–2.2)	.404	1.4 (1.0–2.0)	1.5 (1.1–2.2)	1.6 (1.1–2.2)	1.6 (1.1–2.3)	.003
HDL-C, mmol/L	1.2 ± .3	1.2 ± .3	1.2 ± .3	1.2 ± .3	.097	1.2 ± .3	1.2 ± .3	1.2 ± .3	1.2 ± .3	.024
LDL-C, mmol/L	2.7 ± .6	2.7 ± .7	2.7 ± .7	2.8 ± .7	.051	2.7 ± .7	2.7 ± .7	2.7 ± .7	2.7 ± .7	.772
UACR, N (%)	97 (11.1)	139 (15.9)	218 (25.0)	266 (30.5)	<.001	134 (15.6)	181 (21.0)	181 (20.1)	224 (25.7)	<.001
CIMT ≥.9 mm, N (%)	633 (72.3)	698 (79.9)	726 (83.2)	774 (88.9)	<.001	639 (74.4)	663 (77.0)	763 (84.8)	766 (87.7)	<.001
LVEF, %	59.0 ± 1.6	59.1 ± 1.2	59.0 ± 1.5	58.9 ± 1.5	.009	59.2 ± 1.3	59.0 ± 1.3	58.9 ± 1.6	58.9 ± 1.4	<.001
LVH, N (%)	293 (33.5)	389 (44.5)	412 (47.2)	501 (57.5)	<.001	366 (42.6)	372 (43.2)	403 (44.8)	454 (52.0)	.008
Diabetes mellitus, N (%)	100 (11.4)	125 (14.3)	174 (19.9)	227 (26.1)	<.001	119 (13.9)	146 (17.0)	157 (17.4)	204 (23.4)	<.001
Stable angina, N (%)	94 (10.7)	92 (10.5)	96 (11.0)	131 (15.0)	.009	69 (8.0)	98 (11.4)	103 (11.4)	143 (16.4)	<.001

Abbreviations: BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UACR, urine albumin–creatinine ratio.

TABLE 2 Characteristics of participants ≥65 years of age grouped by quartile of brachial-ankle pulse wave velocity and flow-mediated dilation

	Quartile of baPWV, cm/s in patients ≥65 years of age					Quartile of FMD, % in patients ≥65 Years of age				
	Q1 (874–1562)	Q2 (1562.5–1770)	Q3 (1770.5–2016)	Q4 (2016.5–3539)	p-value	Q1 (5.5–16.8)	Q2 (3.6–5.4)	Q3 (2.2–3.5)	Q4 (0–2.1)	p-value
Number of subjects	281	282	281	281		279	282	272	292	
Age, years	69.8 ± 4.8	70.7 ± 4.7	72.2 ± 5.7	74.3 ± 6.1	<.001	71.7 ± 5.7	71.4 ± 5.3	72.2 ± 5.8	71.6 ± 5.7	.323
Female, N (%)	163 (58.0)	166 (58.9)	183 (65.1)	189 (67.3)	.057	174 (62.4)	190 (67.4)	168 (61.8)	169 (57.9)	.135
BMI, kg/m²	26.0 ± 3.2	26.0 ± 3.3	25.2 ± 3.4	25.1 ± 3.5	<.001	25.2 ± 3.4	25.80 ± 3.2	25.7 ± 3.5	25.5 ± 3.5	.169
Current smoking, N (%)	37 (13.2)	35 (12.4)	28 (10.0)	25 (8.9)	.477	30 (10.8)	36 (12.8)	23 (8.5)	36 (12.3)	.534
SBP, mm Hg	160.3 ± 18.0	166.8 ± 18.3	167.9 ± 17.7	174.1 ± 19.7	<.001	164.9 ± 18.4	167.4 ± 18.3	167.6 ± 18.5	169.0 ± 20.6	.077
DBP, mm Hg	94.1 ± 13.1	97.3 ± 13.7	97.6 ± 14.0	97.7 ± 13.2	.004	96.6 ± 13.0	97.6 ± 13.7	95.1 ± 13.4	97.3 ± 14.1	.129
eGFR, ml/min/1.73 m²	99.7 ± 20.4	99.5 ± 21.1	102.2 ± 21.9	96.7 ± 18.6	.018	99.2 ± 19.4	100.5 ± 21.6	99.1 ± 21.3	99.3 ± 20.1	.825
TC, mmol/L	4.8 ± 1.0	4.9 ± 1.1	4.9 ± 1.1	5.0 ± 1.0	.261	4.9 ± 1.1	4.9 ± 1.1	4.9 ± 1.0	4.8 ± 1.0	.839
TG, mmol/L	1.2 (.9–1.7)	1.3 (1.0–1.9)	1.3 (.9–1.8)	1.3 (1.0–1.7)	.637	1.2 (.9–1.7)	1.3 (1.0–1.9)	1.3 (1.0–1.8)	1.2 (.9–1.7)	.958
HDL-C, mmol/L	1.2 ± .3	1.2 ± .3	1.3 ± .3	1.2 ± .3	.117	1.2 ± .3	1.2 ± .3	1.2 ± .3	1.2 ± .3	.978
LDL-C, mmol/L	2.6 ± .7	2.7 ± .8	2.7 ± .7	2.7 ± .7	.520	2.7 ± .7	2.7 ± .8	2.7 ± .7	2.7 ± .7	.767
UACR, N (%)	37 (13.2)	46 (16.3)	57 (20.3)	98 (34.9)	<.001	60 (21.5)	58 (20.6)	53 (19.5)	67 (22.9)	.778
CIMT ≥.9 mm, N (%)	261 (92.9)	274 (97.2)	273 (97.2)	276 (98.2)	.004	266 (95.3)	272 (96.5)	261 (96.0)	285 (97.6)	.523
LVEF, %	58.6 ± 1.1	58.7 ± 1.4	58.6 ± 1.3	58.4 ± 2.0	.083	58.6 ± 1.3	58.6 ± 1.7	58.4 ± 1.7	58.6 ± 1.2	.409
LVH, N (%)	150 (53.4)	184 (65.2)	182 (64.8)	184 (65.5)	.006	174 (62.4)	181 (64.2)	165 (60.7)	180 (61.6)	.852
Diabetes mellitus, N (%)	68 (24.2)	79 (28.0)	86 (30.6)	109 (38.8)	.002	74 (26.5)	82 (29.1)	92 (33.8)	94 (32.2)	.244
Stable angina, N (%)	68 (24.2)	83 (29.4)	73 (26.0)	79 (28.1)	.514	70 (25.1)	66 (23.4)	72 (26.5)	95 (32.5)	.073

Abbreviations: BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVH, left ventricular ejection fraction; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UACR, urine albumin–creatinine ratio.

TABLE 3 ORs (95% CIs) for subclinical target organ damage associated with quartile of brachial-ankle pulse wave velocity and flow-mediated dilation in participants <65 years of age

		Quartile of baPWV <65 years of age					Quartile of FMD <65 years of age				
		Q1	Q2	Q3	Q4	P-for trends	Q1	Q2	Q3	Q4	P-for trends
LVH	Model 1	1(Ref)	1.593 (1.313–1.934)	1.775 (1.463–2.154)	2.690 (2.215–3.267)	<.001	1(Ref)	1.025 (.847–1.240)	1.092 (.905–1.319)	1.460 (1.208–1.764)	<.001
	Model 2	1(Ref)	1.609 (1.312–1.972)	1.749 (1.425–2.145)	2.542 (2.063–3.132)	<.001	1(Ref)	1.186 (.967–1.454)	1.312 (1.070–1.607)	1.814 (1.474–2.233)	<.001
	Model 3	1(Ref)	1.490 (1.204–1.845)	1.392 (1.116–1.736)	1.765 (1.390–2.240)	<.001	1(Ref)	1.055 (.854–1.304)	1.109 (.898–1.371)	1.428 (1.151–1.772)	.005
UACR	Model 1	1(Ref)	1.517 (1.148–2.003)	2.669 (2.057–3.465)	3.526 (2.731–4.553)	<.001	1(Ref)	1.440 (1.125–1.843)	1.362 (1.065–1.742)	1.867 (1.471–2.371)	<.001
	Model 2	1(Ref)	1.679 (1.265–2.229)	3.300 (2.522–4.319)	5.169 (3.939–6.782)	<.001	1(Ref)	1.568 (1.220–2.014)	1.577 (1.226–2.028)	2.350 (1.834–3.012)	<.001
	Model 3	1(Ref)	1.385 (1.031–1.859)	2.261 (1.700–3.007)	2.832 (2.014–3.813)	<.001	1(Ref)	1.293 (.990–1.688)	1.133 (.865–1.484)	1.503 (1.148–1.968)	.016
CIMT≥.9 mm	Model 1	1(Ref)	1.516 (1.214–1.893)	1.888 (1.499–2.379)	3.051 (2.357–3.948)	<.001	1(Ref)	1.153 (.925–1.437)	1.917 (1.512–2.432)	2.465 (1.912–3.177)	<.001
	Model 2	1(Ref)	1.519 (1.217–1.897)	1.896 (1.504–2.389)	3.079 (2.378–3.987)	<.001	1(Ref)	1.153 (.925–1.437)	1.917 (1.512–2.432)	2.465 (1.912–3.177)	<.001
	Model 3	1(Ref)	1.650 (1.306–2.084)	1.987 (1.551–2.547)	3.075 (2.315–4.084)	<.001	1(Ref)	1.146 (.916–1.433)	1.858 (1.460–2.364)	2.323 (1.796–3.005)	<.001

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CI, Confidence Interval; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation; LVH, left ventricular hypertrophy; OR, odds ratio; UACR, urine albumin–creatinine ratio.

TABLE 4 ORs (95% CIs) for subclinical target organ damage associated with quartile of brachial-ankle pulse wave velocity and flow-mediated dilation in participants ≥65 years of age

		Quartile of baPWV, cm/s					Quartile of FMD, %				
		Q1	Q2	Q3	Q4	P-for trends	Q1	Q2	Q3	Q4	P-for trends
LVH	Model 1	1(Ref)	1.640 (1.168–2.302)	1.606 (1.144–2.253)	1.657 (1.179–2.327)	0.006	1(Ref)	1.081 (.767–1.525)	.931 (.660–1.312)	.970 (.692–1.360)	.853
	Model 2	1(Ref)	1.681 (1.171–2.413)	1.421 (.987–2.046)	1.336 (.917–1.946)	.04	1(Ref)	1.017 (.705–1.465)	.912 (.632–1.314)	1.038 (.724–1.489)	.903
	Model 3	1(Ref)	1.451 (.999–2.107)	1.315 (.901–1.919)	1.125 (.751–1.685)	.208	1(Ref)	.948 (.655–1.372)	.839 (.579–1.216)	.922 (.639–1.332)	.824
UACR	Model 1	1(Ref)	1.285 (.805–2.053)	1.678 (1.068–2.636)	3.532 (2.3131–5.396)	<.001	1(Ref)	.945 (.630–1.419)	.883 (.584–1.337)	1.087 (.732–1.613)	.779
	Model 2	1(Ref)	1.285 (.805–2.053)	1.678 (1.068–2.636)	3.532 (2.311–5.396)	<.001	1(Ref)	.960 (.638–1.445)	.860 (.567–1.305)	1.090 (.733–1.622)	.722
	Model 3	1(Ref)	1.022 (.628–1.665)	1.337 (.833–2.146)	2.393 (1.527–3.750)	<.001	1(Ref)	.883 (.583–1.336)	.793 (.520–1.210)	.962 (.642–1.442)	.71
CIMT≥.9 mm	Model 1	1(Ref)	2.625 (1.136–6.063)	2.615 (1.132–6.041)	4.230 (1.565–11.435)	.007	1(Ref)	1.990 (.782–5.063)	1.160 (.510–2.635)	1.329 (.573–3.084)	.534
	Model 2	1(Ref)	2.632 (1.133–6.071)	2.493 (1.076–5.776)	3.972 (1.465–10.770)	.01	1(Ref)	2.073 (.812–5.289)	1.167 (.512–2.659)	1.276 (.548–2.970)	.493
	Model 3	1(Ref)	2.647 (1.141–6.141)	2.789 (1.192–6.526)	4.374 (1.596–11.986)	.006	1(Ref)	2.016 (.789–5.151)	1.139 (.499–2.602)	1.224 (.524–2.861)	.524

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CI, Confidence Interval; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation; LVH, left ventricular hypertrophy; OR, odds ratio; UACR, urine albumin–creatinine ratio.
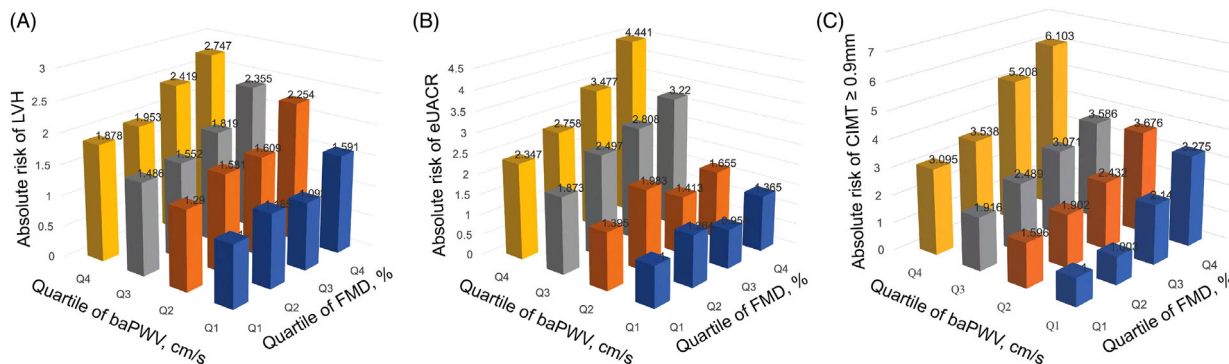
FIGURE 2 The risk of STOD based on baPWV quartiles in patients grouped by FMD quartiles. (A). The risk of LVH based on baPWV quartiles in patients grouped by FMD quartiles. (B). The risk of UACR based on baPWV quartiles in patients grouped by FMD quartiles. (C). The risk of CIMT ≥.9 mm based on baPWV quartiles in patients grouped by FMD quartiles. STOD, subclinical target organ damage; baPWV, brachial-ankle pulse wave velocity; FMD, flow-mediated dilation; LVH, left ventricular hypertrophy; UACR, urine albumin–creatinine ratio; CIMT, carotid intima-media thickness

STOD. Compared with patients in the first quartile of baPWV, the OR (95%CIs) of UACR for the subjects in quartile four was 2.39 (1.53–3.75), *P* for trends <.001. Likewise, compared with patients of the first quartile of baPWV, the multivariate-adjusted ORs and 95% CIs of CIMT ≥.9 mm were 2.647 (1.141–6.141), 2.789 (1.192–6.526), 4.374 (1.596–11.986) for the second, third, and fourth quartiles, respectively. However, the risk of STOD, assessed by LVH, was weakly associated with baPWV in patients ≥65 years of age. Also, we observed no significant association between the highest FMD quartiles and STOD indicators.

3.4 | Interaction effect of baPWV and FMD in STOD in patients <65 years of age

To compute the interaction effect of elevated baPWV and reduced FMD among participants <65 years of age, we evaluated the risk of STOD and estimated the OR and 95% CI of STOD among those participants grouped in different quartiles of baPWV along with their corresponding FMD quartiles. An increase in baPWV shows a progressively higher risk of STOD across the quartiles of FMD (Figure 2). Those patients at higher quartiles of baPWV grouped by FMD had a higher risk of LVH, with patients in quartile four accounting for the highest risk of LVH (OR = 2.75). Also, the estimated risks of UACR for the first and fourth quartile of PWV increased from 2.35 to 4.44 in patients grouped by FMD quartiles. Similarly, the estimated risk of CIMT ≥.9 mm surged from 3.10 in quartile 1 to 6.10 in quartile four of baPWV in patients grouped by FMD quartiles.

3.5 | Receiver operating characteristics (ROC) analysis in patients <65 years of age

ROC analysis was used to evaluate the capacity of baPWV and FMD models to predict STOD in patients <65 years of age (Figure 3A). The AUC of baPWV and FMD models to predict LVH were .700 and .683,

respectively. The sensitivity and specificity of baPWV were 47.2% and 68.2%, respectively. And Youden's index was .154 with the highest J value of 1576.25 cm/s. Similarly, the sensitivity and specificity of FMD were 74.2% and 32.9%, respectively with a Youden's index of .071. The highest J value was 3.15%. Then we further combined baPWV and FMD in a single model with the aim to evaluate whether the predictive power of the model can increase, and the AUC of the combined model reached .706.

We also performed ROC analysis to determine the diagnostic utility of the baPWV, FMD, and the combined model to identify patients with STOD assessed by UACR. The AUC for baPWV and FMD models were .641 and .563, respectively. The sensitivity and specificity of baPWV were 61.8% and 61.3%, respectively. Youden's index was .231 and the highest J value was 1543.75 cm/s. Likewise, the sensitivity and specificity of FMD were 68.2% and 41.2%, and Youden's index was .094 and the highest J value was 3.45%. We tested then models to improve the identification of STOD by combining both baPWV and FMD parameters. The combination of the baPWV and FMD model reached the highest AUC of .642. The AUC results for the baPWV and FMD models and the combined model are shown in Figure 3B.

Briefly, the AUC of the baPWV, FMD, and the combined models for the risk of STOD assessed by CIMT ≥.9 mm were .619, .602, and .642 (Figure 3C). The sensitivity and specificity of baPWV were 41.2% and 75.2%, respectively, and Youden's index was .173 and the highest J value was 1576.75 cm/s. Whereas the sensitivity and specificity of FMD were 60.9% and 56.8%, respectively, and Youden's index was .177 and the highest J value was 4.95%.

3.6 | Sensitivity analysis

We run the sensitivity analysis with the aim to estimate the magnitude of the risk of bias attributed to the missing data. Interestingly. we find that there was no statistically significant difference in the group of patients with missing data and the group of patients without missing data (Supplementary Table S3).
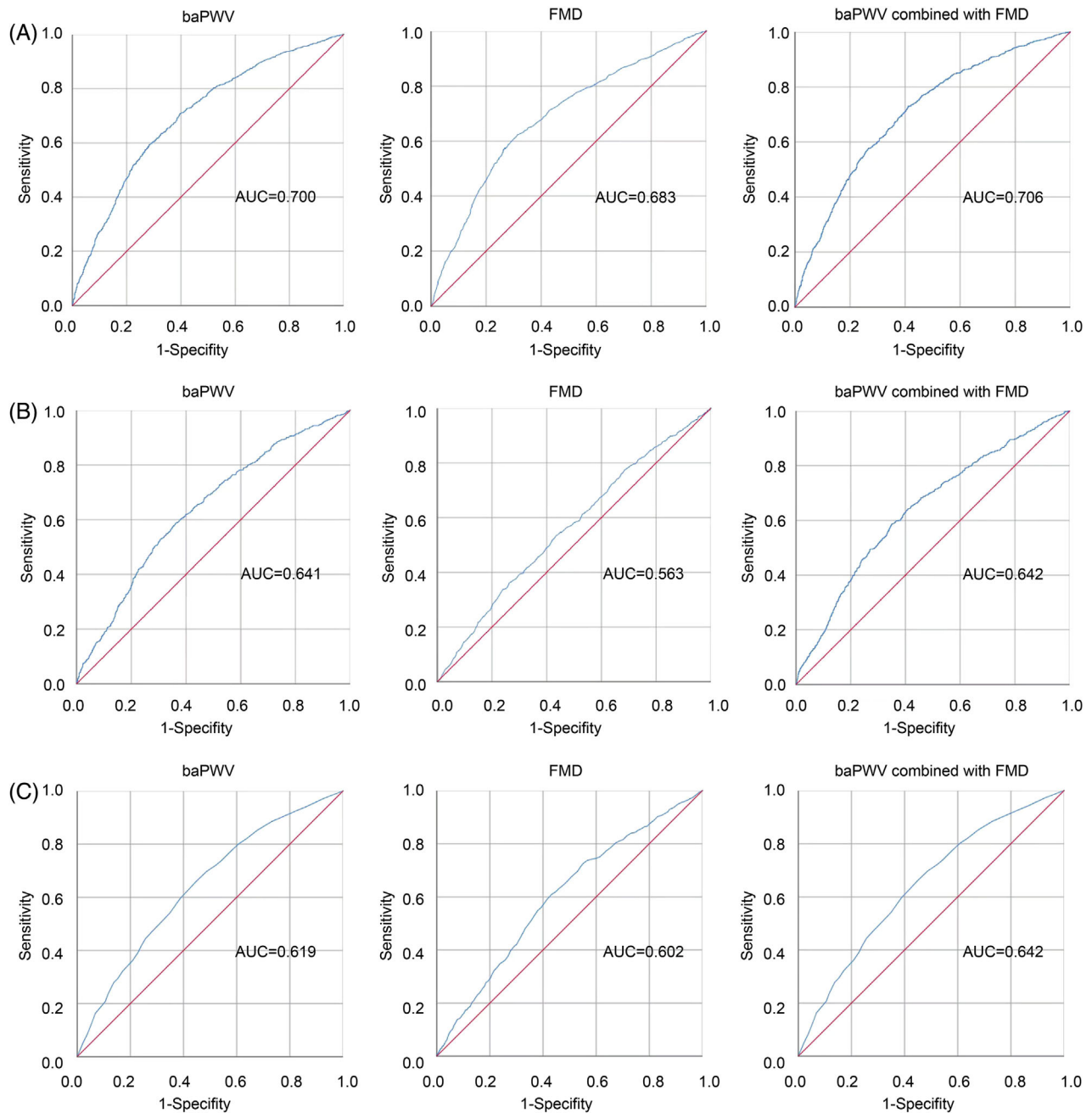
FIGURE 3 Receiver-operating characteristics (ROC) curves for prediction of STOD with baPWV, FMD, and combined with baPWV and FMD. (A) ROC curve for prediction of LVH with baPWV, FMD, and combined with baPWV and FMD, respectively. (B) ROC curve for prediction of eUACR with baPWV, FMD, and combined with baPWV and FMD, respectively. (C) ROC curve for prediction of CIMT ≥.9 mm with baPWV, FMD, and combined with baPWV and FMD, respectively. STOD, subclinical target organ damage; baPWV, brachial-ankle pulse wave velocity; FMD, flow-mediated dilation; LVH, left ventricular hypertrophy; UACR, urine albumin–creatinine ratio; CIMT, carotid intima-media thickness

4 | DISCUSSION

In this retrospective cross-sectional study, baPWV and FMD parameters were positively associated with STOD indicators in patients with essential hypertension. This association of the baPWV and FMD with STOD indicators remain consistent even after adjusting for potential confounders. Participants with the highest quartile of baPWV and FMD (baPWV ≥1683 cm/s, FMD ≤2.8% in <65 years of age, respec-

tively) had the highest risk of STOD compared with patients in the lowest quartiles of baPWV and FMD. However, there was no significant relationship between baPWV and FMD measurements and the risk of STOD in patients ≥65 years of age.

In the past, various studies reported that baPWV is associated with cardiovascular morbidity and mortality, as well as with several cardiovascular risk factors.[27–30] The PWV has also been thoroughly examined, and an elevated baPWV has been identified as a marker of

vascular function.[16] Furthermore, arterial stiffness might be involved in a vicious cycle with the development/progression of hypertension, chronic kidney disease, and diabetes mellitus,[31] suggesting high baPWV and low FMD are not only considered as risk factors for hypertension but also consequences of the damage that hypertension causes on the vessels and heart. In this study, the risk of STOD increases across baPWV and FMD quartiles. The findings regarding baPWV and FMD associations with STOD indicators remain consistent after multivariate adjustment for the potential confounding factors, suggesting that a vascular status evaluation is not inferior to the control strategy of hypertension-related complications. Thus, our results provide insights into the significance of strict measurement of baPWV and FMD parameters to predict STOD as endothelial dysfunction and arterial stiffness processes may lead to an increased socioeconomic burden of hypertension-associated CVDs and mortality.

baPWV is a marker of arterial stiffness and has been used for the assessment of vascular function. Moreover, baPWV and STOD are known to be independent predictors of future cardiovascular events.[32] According to our study, baPWV was independently associated with an increased risk of LVH, which was consistent with Tomiyama's demonstration.[10] Mechanically, PWV reflects segmental arterial elasticity, and contraction of the left ventricle generates a pulse wave that is propagated throughout the arterial tree. Evidently, an increase in arterial stiffness/baPWV is reported to associate with an increase in the propagation speed of this pulse wave, which could contribute to a greater magnitude of blood flow back from the peripheral artery to the aortic artery during late systole.[33] These changes in the blood circulation could again aggravate the left ventricular afterload and eventually may lead to LVH.

Recently, several studies recommended UACR[18,34] as predictors of STOD in patients with hypertension. However, there was a lack of robust knowledge on whether the combination of the endothelial dysfunction and arterial stiffness indicators is sufficient to predict the STOD assessed by the UACR. To the extent of our knowledge, this was the first study to evaluate the association between baPWV and FMD and STOD, and we found that elevated baPWV and FMD were independently linked with STOD indicators including UACR in middle-aged hypertension patients. Also, the interaction analyses between baPWV and FMD parameters show that patients in higher baPWV quartiles grouped by the FMD quartiles reflect prominent UACR, indicating that high/low values baPWV/FMD are associated with an increased risk of STOD.

Earlier evidence established that elevated arterial stiffness linked with early stages of chronic kidney disease,[35] and vascular calcification related to advanced chronic kidney disease may amplify this increase in arterial stiffness.[36] Various reasons could explain the observed relationship between endothelial dysfunction and arterial stiffness indicators and UACR. Hypertension is a component of metabolic syndrome, and endothelial dysfunction has been reported as an early pathogenic event in metabolic syndrome.[37] What's more, Tomiyama and colleagues[38] found that persistent metabolic syndrome status aggravates the progression of arterial stiffness. The other possible linkage is through the renal resistive index. Previous studies have reported

that microalbuminuria and arterial stiffness are related to resistive index.[39] Also, chronic inflammation-induced endothelial dysfunction increases the progression to atherosclerosis and aggravates permeability of the capillary basement membrane of the glomerulus, which could further lead to albumin leak from the basement membrane and may cause the appearance of UACR.[40,41]

Arterial stiffness and atherosclerosis often coexist in the same vascular territories and share similar risk factors. And the presence of atherosclerosis decreases the compliance of blood vessels, leading to stiffening of the arteries.[28] In addition, atherosclerosis may also increase arteriosclerosis in its advanced stage.[29] In the present study, we found that baPWV and FMD were positively associated with CIMT $\geq$.9 mm. This could be explained by the fact that arterial stiffness could be related to atherosclerosis through endothelial dysfunction, mechanical force on the inner wall of blood vessels, extracellular matrix disorder, elevated endothelial permeability, and vascular aging.[26,27]

The high values of baPWV were significantly associated with the risk of STOD in participants younger than 65 years of age, whereas this association was weakened to a nonsignificant level when we analyzed data in the age group $\geq$65 years. PWV is known to be positively associated with age.[42] Of the many risk factors associated with endothelial dysfunction and arterial stiffness, age and hypertension are by far the most important factors influencing vascular function.[43,44] Aging per se is a promoter of arterial stiffness, especially in the older population.[45] Consequently, this may mask the associations between baPWV for STOD in the age category $\geq$65, but not in patients <65 years of age. Therefore, further longitudinal studies are needed to validate the potential benefit of implementing baPWV and FMD screening in order to detect STOD in the middle-aged population.

The present study demonstrated that baPWV and FMD biomarkers own a good prognostic performance for STOD independently. Compared with the baPWV model alone, the unified model that combined the baPWV and FMD offered a slight increase in the AUC in STOD detection. Therefore, simultaneous application of both baPWV and FMD parameters facilitates the prediction of the risk of STOD more accurately among patients with essential hypertension.

5 | LIMITATIONS

The current study has certain advantages and disadvantages. To the best of our knowledge, no study has looked into the interaction between baPWV and FMD to predict STOD in hypertension. patients using hospital data. This study, however, should be interpreted with some limitations. First, the single-centered retrospective design has limited the cause-and-effect relationship between baPWV/FMD and the risk of STOD in hypertension. Also, our data cannot provide data on the long-term visit-to-visit variabilities of baPWV and FMD and their association with STOD prognosis. Third, the prevalence of STOD increases dramatically in cases of uncontrolled blood pressure, and in many cases, BP was not controlled. Consequently, it is unclear whether the STOD risk is related to the presence of essential hypertension or to the effectiveness or otherwise of therapy as every medication

is known to have a positive or negative effect on cardiovascular risk. Thus, our study would have benefited from dividing patients according to blood pressure values at the time of evaluation of baPWV and FMD parameters. However, we considered the adjustment of the individual antihypertensive drugs including calcium channel blocker, angiotensin-converting enzyme receptor blocker, β-Blocker, Diuretic, and α-Blocker in the regression model to minimize the risk of bias inherited to the possible positive and negative effects of the different types of antihypertensive use.

6 | CONCLUSION

We found strong independent associations between baPWV and FMD parameters and the risk of STOD, assessed by LVH, UACR, CIMT $\geq$.9 mm, in hypertension patients. Also, our study identified that elevated baPWV and decreased FMD were independent prognostic markers for STOD in middle-aged hypertension patients. The combination of baPWV and FMD significantly improved the prediction of STOD in hypertension patients, indicating that the simultaneous application of this unified model can slightly improve discrimination for STOD in hypertension patients.

CONFLICTS OF INTEREST
The authors declare that there is no conflict of interest.

PATIENT CONSENT STATEMENT
Informed consent was obtained from all individual participants involved in the study.

AUTHOR CONTRIBUTIONS
Yancui Sun contributed to study concept and design, acquisition of data, and interpretation of data. Fei Liu contributed to acquisition of data and interpretation of data. Ying Zhang, Yan Lu, Zhuolin Su and Haizhe Ji contributed to study design and statistical analysis. Yunpeng Cheng, Wei Song and Tesfaldet H. Hidru contributed to acquisition of data. Xiaolei Yang contributed to study concept and design, interpretation of data and study supervision. Yinong Jiang contributed to study concept and design, interpretation of data and critical revision of manuscript for intellectual content.

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SUPPORTING INFORMATION