BMC Cardiovascular Disorders

RESEARCH

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Carotid intima thickness and elasticity combined with MHR predicting the severity of coronary artery stenosis in patients with premature coronary artery disease

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Abstract

Background Carotid intima thickness (CIT) and hardness coefficient (HC) are sensitive indicators of structural and functional changes in the carotid arteries in the subclinical stage of atherosclerosis. The monocyte to high-density lipoprotein cholesterol ratio (MHR), which is a biomarker of inflammation, has been shown to correlate with cardiovascular disease. The aim of this study was to assess the predictive value of CIT and HC with MHR in determining the severity of coronary artery stenosis in patients with premature coronary artery disease (PCAD).

Methods This prospective study included 85 PCAD patients who underwent coronary angiography. Patients were categorized into high-score (42 cases) and low-score (43 cases) groups based on the median Gensini score. Additionally, 41 volunteers matched by body mass index (BMI), age, and gender served as a control group. CIT, carotid media thickness (CMT) and carotid intima-media thickness (CIMT) were measured using a 24 MHz ultra-high frequency ultrasound probe. Diameter (Diam), distance (Dist), pulse wave velocity (PWV), and HC were evaluated through RF-data based quantitative analysis on vessel stiffness. Binary logistic regression identified risk factors influencing the severity of coronary artery stenosis. Receiver operating characteristic curves were plotted to evaluate the diagnostic performance of CIT, HC, and MHR, both individually and in combination, for predicting coronary artery stenosis severity in PCAD patients.

Results CIT, HC and MHR were significantly higher in the high group than in the low and control groups. CIT (AUC = 0.731, 95%CI: 0.624–0.838, $P < 0.001$) and HC (AUC = 0.783, 95%CI: 0.683–0.882, $P < 0.001$) individually demonstrated good diagnostic performance in assessing the severity of coronary artery stenosis, with the combined use of carotid parameters and MHR achieving the highest diagnostic efficacy (AUC = 0.849, 95%CI: 0.770–0.929, $P < 0.001$).

Conclusion Patients in the high group had elevated CIT, CIT/CMT, and HC compared to those in the low group. Combining CIT and HC with MHR demonstrated high efficacy in predicting coronary artery stenosis severity in PCAD patients.

Keywords Ultra-high frequency ultrasound, Premature coronary artery disease, Carotid intima thickness, Carotid artery elasticity, Monocyte to high-density lipoprotein cholesterol ratio, Severity of coronary artery stenosis

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Introduction

Coronary artery disease (CAD) is a leading cause of mortality worldwide. Statistics indicate that the global prevalence of CAD reached 197.2 million, with an increasing impact on younger populations [1]. The American National Cholesterol Education Program—Adult Treatment Panel III defines CAD occurring in males ≤ 55 years and females ≤ 65 years as premature coronary artery disease (PCAD) [2]. The primary pathology of PCAD is atherosclerosis (AS), which begins early and may remain latent before AS plaques form [3]. Thus, identifying a simple and accessible imaging method for early detection of high-risk individuals and timely PCAD management is critical.

As a window to AS, the carotid artery is easily accessible for scanning. Structural and functional changes in the carotid artery have been a focal point of recent research, as they are considered cardiovascular risk factors [4]. Non-invasive ultrasound enables early detection of changes in vascular wall structure and function. Measuring carotid intima-media thickness (CIMT) is a common method for assessing subclinical AS [5]. However, intimal thickening, an early AS morphological change, excludes media thickness [6]. Previous studies have demonstrated the utility of carotid ultrasound parameters in predicting cardiovascular risk, yet traditional CIMT measurements often fail to distinguish between intimal and medial layers, limiting their sensitivity to early structural alterations [7]. The 2019 European Society of Cardiology guidelines indicated that CIMT-based screening for cardiovascular risk assessment is no longer recommended for asymptomatic individuals, highlighting limitations in evaluating early carotid structural changes in AS [8]. With advancements in ultra-high frequency technology, a 24 MHz ultrasound probe can distinguish between the carotid intima and media, allowing precise measurement of intima thickness (IT). In addition to carotid intima thickness (CIT), carotid artery elasticity is valuable for detecting mechanical changes in the arterial wall during AS progression, potentially revealing alterations before structural changes occur [9]. RF-data based quantitative analysis on vessel stiffness (R-VQS) enables precise assessment of local carotid wall characteristics through an automatic hardness coefficient (HC).

Simultaneously, we sought an accessible laboratory marker to aid in evaluating ultrasound parameters for PCAD patients in early-stage AS assessment. The monocyte to high-density lipoprotein cholesterol ratio (MHR), an inflammatory marker that reflects the interplay between inflammation and lipid metabolism abnormalities, has been identified in multiple studies as a predictor of cardiovascular adverse events [10, 11]. Few studies have explored the combined use of CIT, HC, and MHR in predicting coronary artery stenosis severity in PCAD patients. Based on previous findings, we hypothesized that: 1) Would CIT, HC, and MHR levels be higher in PCAD patients compared to healthy controls, with significant differences between PCAD subgroups? 2) Would CIT, HC, and MHR serve as strong predictors for assessing coronary artery stenosis severity in PCAD patients?

Study population

This prospective study enrolled eighty-five PCAD patients at Henan Provincial People's Hospital from October 2023 to May 2024. All PCAD patients were recruited from the Department of Cardiology and underwent initial coronary arteriography (CAG) at the hospital. Two experienced interventional cardiologists assessed the severity of coronary artery stenosis using the Gensini scoring method [12]. Based on the median Gensini score, patients were divided into high-score (≥ 38 scores) and low-score (< 38 scores) groups. Additionally, 41 healthy volunteers, matched by gender, age, and body mass index (BMI) and without hypertension or diabetes mellitus (DM), served as a control group.

Inclusion criteria for the case group were: (1) CAG showing ≥ 50% stenosis in at least one major coronary artery [8], and patients aged ≤ 55 years (males) or ≤ 65 years (females); (2) all subjects were undergoing CAG for the first time; (3) ultrasound examination indicating no AS plaques in bilateral carotid arteries; (4) absence of lipid-regulating medication; (5) long-term, well-managed antihypertensive or antidiabetic therapy, with hospital admission measurements showing systolic blood pressure (SBP) ≤ 145 mmHg, diastolic blood pressure (DBP) ≤ 90 mmHg, and fasting blood glucose (FBG) < 6.5 mmol/L.

Exclusion criteria included: (1) prior carotid artery stenting or endarterectomy; (2) severe arrhythmias, congenital heart disease, valvular disease, or peripheral vascular disease; (3) history of stroke or cerebrovascular surgery; (4) myocardial bridging; (5) familial hypercholesterolemia; (6) systemic or autoimmune diseases; (7) BMI ≤ 18.5 kg/m^2 or ≥ 24 kg/m^2; (8) alcohol abuse; (9) malignancy; (10) pregnancy or lactation; (11) liver or renal dysfunction; and (12) poor ultrasound imaging quality for carotid arteries. All patients underwent carotid ultrasound and blood tests prior to CAG. Ultrasound physicians, laboratory physicians, and patients were all blinded to CAG results during data collection. The study received approval from the Ethics Committee of Henan Provincial People's Hospital (No.63/2021), and written informed consent was obtained from all participants prior to conducting the study.

Data collected included gender, age, number of postmenopausal females, BMI, hypertension, DM, and

smoking status. Baseline levels of FBG, blood pressure, monocyte count, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and MHR were recorded. MHR was calculated as monocyte count / HDL-C. Record the medication information of patients with hypertension (such as calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, etc.) and patients with DM (such as oral medications: biguanides, sulfonylurea secretagogues, etc., and injectable medications: insulin, etc.).

Quantification of Gensini Score in PCAD patients

The Gensini scoring method was used to assess coronary artery stenosis severity [12]. Each blood vessel's lesion score was determined by multiplying its base score by a weight coefficient. Each patient's total score was calculated by summing the scores of all affected vessels.

Carotid intima thickness ultrasonography and image analysis

All participants underwent carotid artery examination in the supine position with the neck adequately exposed. A 24 MHz transducer (PLI-2004BX) on an ultrasound system (Aplio i900, Canon-Toshiba Ultrasound, Tochigi-ken, Japan) was used to scan both carotids. Cine loops of at least three consecutive beats and frozen images were digitally stored, and an electrocardiogram was simultaneously recorded. Long-axis views visualized the carotid bifurcation and the region 3 cm below, enabling measurement of CIT, carotid media thickness (CMT), and CIMT on the posterior wall. Measurements were taken at the thickest intima point within the carotid arteries, aligned with the R wave peak on the electrocardiogram, using consistent magnification and gain. The average of bilateral measurements was calculated. Two experienced ultrasound technicians specializing in vascular imaging conducted these procedures (Fig. 1).

Carotid artery elasticity ultrasonography and image analysis

Carotid artery elasticity examinations were conducted using an ultrasound system (Resona8, Mindray, China) equipped with an 11-MHz vascular probe (L11-3U). The built-in R-VQS software assessed carotid artery stiffness. The R-VQS technology achieves fully automatic real-time measurement of carotid artery diameter changes through radiofrequency data and precise vessel wall tracing. It automatically calculates carotid artery pulse wave velocity (PWV) and HC by incorporating SBP and DBP values. After a 15-min rest, blood pressure was measured in the right upper arm with an electronic sphygmomanometer (Omron-HEM-7200), and these values were entered into the ultrasound system. Participants were positioned supine with fully exposed necks to ensure clear visualization of the common carotid artery (CCA) posterior walls. The region of interest was set 1.5 cm proximal to the bifurcation, with measurements taken over at least six cardiac cycles. Images were frozen when the standard deviation dropped below 0.05. The software then calculated diameter (Diam), distance (Dist), PWV, and HC, recording the results. These parameters were obtained for the left CCA of each subject (Fig. 2).

Statistical analysis

Statistical analyses were performed using SPSS 26.0. The Shapiro–Wilk test checked normality, and the Levene test assessed variance homogeneity for quantitative data. Normally distributed data are expressed as mean ± standard deviation ($\bar{x} \pm s$). Comparisons among the three groups were conducted with one-way ANOVA (for homogeneous variances) or Welch ANOVA (for heterogeneous variances). For significant differences,

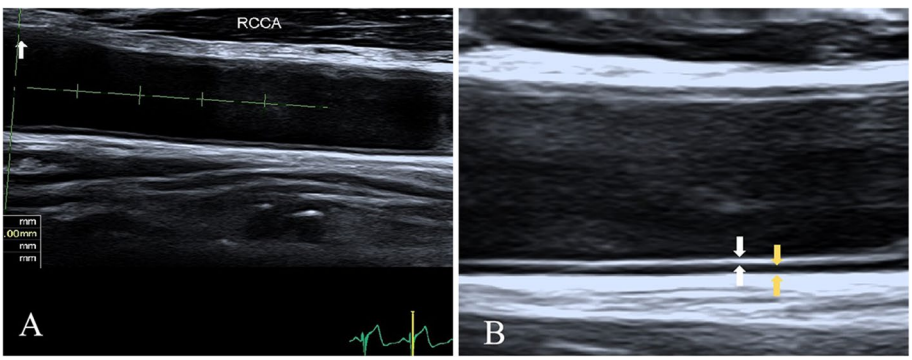

Fig. 1 **A** Ultrasound examination of the right carotid artery by 24 MHz probe. **B** The carotid intima thickness (white arrow), the carotid media thickness (yellow arrow)

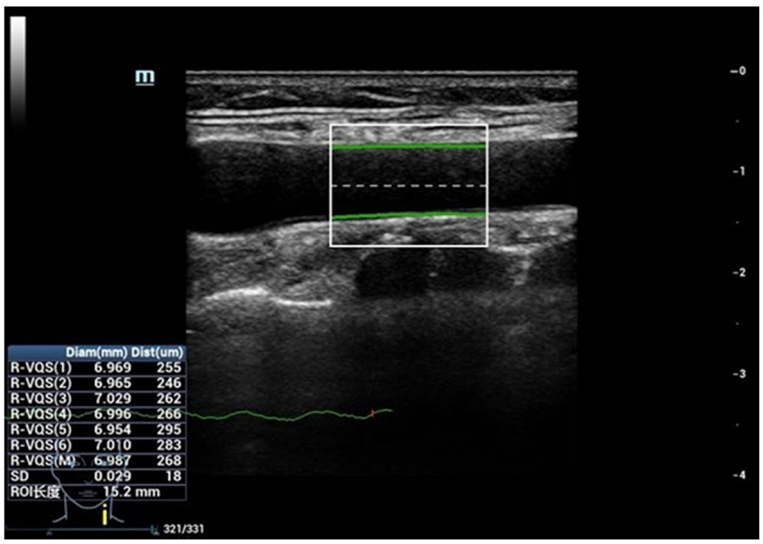

Fig. 2 R-VQS data of the left carotid artery in patients with PCAD

pairwise comparisons were performed using the LSD-t test (homogeneous variances) or Tamhane's T2 test (heterogeneous variances). Non-normally distributed data are presented as median (IQR), with group comparisons conducted using the Kruskal–Wallis H test and pairwise comparisons with the Bonferroni method. Two-way ANOVA assessed the impact of two factors on the dependent variable, analyzing each factor's individual effect. Categorical data are shown as counts. Binary logistic regression assessed the risk factors for severity of coronary artery stenosis. Receiver operating characteristic (ROC) curves were plotted to calculate the area under the curve (AUC), evaluating MHR and ultrasound parameters' diagnostic value for determining coronary artery stenosis severity in PCAD patients. Intraclass correlation coefficients (ICC) assessed intra- and inter-observer reproducibility, with ICC > 0.75 indicating good reproducibility and ICC < 0.4 indicating poor reproducibility. A *P*-value < 0.05 was considered statistically significant.

Results

Demographic data

The demographic and biochemical data of the participants are presented in Table 1. No significant differences were found among the three groups in terms of age, gender, postmenopausal female count, BMI, or TC (all $P > 0.05$). However, significant differences in SBP, DBP, MHR, monocyte count, HDL-C, and TG were observed between PCAD patients and healthy controls (all $P < 0.05$). LDL-C was higher in the high group than in the control group, while the difference in LDL-C was not statistically significant when comparing the low group with the control group.

In our study, more than the average number of people with PCAD had hypertension, and one in four had DM. The high group showed elevated levels of MHR, monocyte count, and HDL-C compared to the low group (all $P < 0.05$). However, no statistically significant differences in SBP, DBP, or TG were observed between the two groups (all $P > 0.05$).

Ultrasound measurement of carotid artery structures

No statistically significant differences in CMT were found among the three groups (all $P > 0.05$). Both CIT and CIMT were significantly thicker in PCAD patients than in the control group (both $P < 0.05$), with significant differences between the high and low groups as well (both $P < 0.05$). The CIT/CMT values showed a gradual decrease across the three groups (0.86 ± 0.10 vs 0.79 ± 0.07 vs 0.72 ± 0.08) (Table 2). The comparison of CIT, CMT, and CIMT between the right and left sides of the carotid arteries did not show any statistically significant differences (Table 5).

A two-way ANOVA was conducted to examine the effects of hypertension, DM, smoking, and menopause status on IT, with Gensini grouping as a factor. When CIT or HC was used as the dependent variable, no statistically significant differences were observed in relation to hypertension, DM, smoking or menopausal status were observed (all $P > 0.05$) (Table 3).

Table 1 Demographic and biochemical data in patients with premature coronary artery disease and healthy controls

	High group ($n=42$)	Low group ($n=43$)	Control group ($n=41$)	$F/X^2/H$-value	P-value
Age(years, $\bar{x} \pm s$)	49.55 ± 6.43	49.70 ± 5.81	47.41 ± 5.81	1.867	0.159
Male, n (%)	24 (57.14%)	24 (55.81%)	19 (46.34%)	1.155	0.561
postmenopausal woman, n (%)	10 (23.81%)	9 (20.93%)	8 (19.51%)	0.237	0.888
BMI [kg/m^2, *M*(IQR)]	23.16 (1.80)	23.13 (2.43)	22.77 (1.74)	4.801	0.091
Smoking, n (%)	13 (30.95%)	13 (30.23%)	5 (12.20%)	5.050	0.080
Hypertension, n (%)	22 (52.38%)[b]	22 (51.16%)[b]	0 (0%)	32.626	< 0.001
SBP (mmHg, $\bar{x} \pm s$)	131.10 ± 9.17[b]	127.84 ± 8.12[b]	120.73 ± 9.96	14.055	< 0.001
DBP (mmHg, $\bar{x} \pm s$)	82.62 ± 6.40[b]	81.67 ± 5.58[b]	78.02 ± 6.46	6.376	0.002
DM, n (%)	12 (28.57%)[b]	11 (25.58%)[b]	0(0%)	13.699	< 0.001
FBG [mmol/L, $\bar{x} \pm s$]	5.53 ± 0.62[b]	5.33 ± 0.61	5.12 ± 0.53	4.991	0.008
Monocyte count [$\times 10^{10}$/L, *M*(IQR)]	4.65 (1.67)[ab]	3.20 (1.20)[b]	2.90 (0.64)	42.965	< 0.001
HDL-C (mmol/L, $\bar{x} \pm s$)	1.01 ± 0.16[ab]	1.09 ± 0.19[b]	1.29 ± 0.15	31.420	< 0.001
LDL-C (mmol/L, $\bar{x} \pm s$)	2.47 ± 0.62[b]	2.29 ± 0.68	2.13 ± 0.39	3.562	0.031
TC (mmol/L, $\bar{x} \pm s$)	4.50 ± 0.71	4.27 ± 0.86	4.24 ± 0.49	1.987	0.144
TG (mmol/L, *M*(IQR)	1.52 (1.13)[b]	1.47 (0.77)[b]	1.18 (0.62)	15.091	0.001
MHR [*M*(IQR)]	4.53(1.87)[ab]	3.24(1.41)[b]	2.20(0.56)	68.575	< 0.001

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *FBG* fasting blood glucose, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *TC*, total cholesterol, *TG* triglyceride, *MHR* monocyte to high-density lipoprotein cholesterol ratio. Comparison with low group

[a] $P < 0.05$; Comparison with control group

[b] $P < 0.05$

Table 2 Ultrasound measurement of carotid artery structures in patients with premature coronary artery disease and healthy controls

	CIT [$\times 10^{-2}$ mm $\bar{x} \pm s$]	CMT [$\times 10^{-2}$ mm, *M*(IQR)]	CIMT [$\times 10^{-2}$ mm, $\bar{x} \pm s$]	CIT/CMT [$\bar{x} \pm s$]
High group ($n=42$)	33.33 ± 4.20[ab]	38.50(4.00)	72.17 ± 6.44[ab]	0.86 ± 0.10[ab]
Low group ($n=43$)	30.09 ± 2.64[b]	38.00(3.00)	68.09 ± 4.84[b]	0.79 ± 0.07[b]
Control group ($n=41$)	26.71 ± 3.09	38.00(4.00)	64.12 ± 4.44	0.72 ± 0.08
F/H-value	34.979	3.534	22.883	28.380
P-value	< 0.001	0.171	< 0.001	< 0.001

CIT carotid intima thickness, *CMT* carotid media thickness, *CIMT* carotid intima-media thickness. Comparison with low group

[a] $P < 0.05$; Comparison with control group

[b] $P < 0.05$

Ultrasound measurement of carotid artery elasticity

No statistically significant differences in Diam were found among the three groups (all $P > 0.05$). Compared to the control group, the high and low groups showed increased PWV and HC values and decreased Dist values (all $P < 0.05$). Within the PCAD patients, the high group exhibited higher PWV and HC and lower Dist than the low group (all $P < 0.05$) (Table 4). The comparison of Diam, Dist, PWV and HC between the right and left sides of the carotid arteries did not show any statistically significant differences (Table 5).

Diagnostic value of carotid ultrasonic parameters and MHR for PCAD

Combining the clinical data, laboratory results, and ultrasound parameters of patients with PCAD, we sequentially included gender, age, BMI, FBG, SBP, DBP, MHR, monocyte count, HDL-C, LDL-C, TC, TG, CIT, and HC in univariate logistic regression analyses. After collinearity diagnostics, MHR (OR: 1.727, 95%CI: 1.046–2.850), CIT (OR: 1.251, 95%CI: 1.053–1.487), and HC (OR: 2.554, 95%CI: 1.123–5.805) were

Table 3 Result of two-way ANOVA in patients with premature coronary artery disease and healthy controls

	CIT			HC		
	***F*-value**	***P*-value**	**η^2**	***F*-value**	***P*-value**	**η^2**
Hypertension	1.877	0.173	0.015	0.185	0.668	0.002
Gensini groups[1]	25.547	< 0.001	0.297	76.736	< 0.001	0.559
DM	2.778	0.098	0.022	1.182	0.279	0.010
Gensini groups[2]	31.719	< 0.001	0.344	89.298	< 0.001	0.596
Smoking	1.987	0.161	0.016	0.513	0.475	0.004
Gensini groups[3]	18.501	< 0.001	0.236	58.868	< 0.001	0.495
postmenopause	0.121	0.728	0.001	0.824	0.366	0.007
Gensini groups[4]	22.765	< 0.001	0.275	69.581	< 0.001	0.537

CIT carotid intima thickness, *HC* hardness coefficient, *DM* diabetes mellitus

Gensini groups[1] and hypertension as independent variables, Gensini groups[2] and DM as independent variables, Gensini groups[3] and smoking as independent variables, Gensini groups[4] and postmenopause status as independent variables

Table 4 Ultrasound measurement of carotid artery elasticity in patients with premature coronary artery disease and healthy controls

	Diam [mm, *M*(IQR)]	**Dist [mm, $\bar{x} \pm s$]**	**PWV [m/s, *M*(IQR)]**	**HC [*M*(IQR)]**
High group($n=42$)	7.57(0.75)	314 ± 53^{ab}	7.98(1.04)[ab]	5.22(0.91)[ab]
Low group($n=43$)	7.20(0.95)	350 ± 60^{b}	7.44(1.06)[b]	4.31(1.10)[b]
Control group($n=41$)	6.94(1.08)	440 ± 55	6.08(0.79)	3.14(0.42)
H/F-value	5.676	55.439	75.953	83.330
P-value	0.059	< 0.001	< 0.001	< 0.001

Diam diameter, *Dist* distance, *PWV* pulse wave velocity, *HC* hardness coefficient. Comparison with low group

[a] $P < 0.05$; Comparison with control group

[b] $P < 0.05$

Table 5 Ultrasound measurement of bilateral carotid parameters

	CIT [$\times 10^{-2}$ mm, $\bar{x} \pm s$]	**CMT [$\times 10^{-2}$ mm, *M*(IQR)]**	**CIMT [$\times 10^{-2}$ mm, *M*(IQR)]**	**Diam [mm, $\bar{x} \pm s$]**	**Dist [mm, $\bar{x} \pm s$]**	**PWV [m/s, *M*(IQR)]**	**HC [*M*(IQR)]**
right side ($n=126$)	30.07 ± 4.30	38.00(3.00)	67.00(8.00)	7.28 ± 0.73	367 ± 77	7.27(1.50)	4.27(1.84)
left side ($n=126$)	31.07 ± 4.55	37.00(4.00)	69.00(7.00)	7.42 ± 0.72	385 ± 79	7.00(1.51)	4.59(2.05)
Z/t-value	-1.794	-1.670	-1.931	-1.611	-1.859	-1.709	-1.811
P-value	0.074	0.095	0.053	0.108	0.064	0.088	0.070

CIT carotid intima thickness, *CMT* carotid media thickness, *CIMT* carotid intima-media thickness. *Diam* diameter, *Dist* distance, *PWV* pulse wave velocity, *HC* hardness coefficient

Table 6 Result of binary logistic regression in patients with premature coronary artery disease and healthy controls

Factors	***β***	**Wald X^2-value**	***P*-value**	**OR**	**95%CI**
MHR	0.546	4.560	0.033	1.727	1.046–2.850
CIT	0.224	6.456	0.011	1.251	1.053–1.487
HC	0.938	5.007	0.025	2.554	1.123–5.805

OR odds ratio, *CI* confidence interval, *MHR* monocyte to high-density lipoprotein cholesterol ratio, *CIT* carotid intima thickness, *HC* hardness coefficient

identified as potential risk factors influencing the severity of coronary artery stenosis in PCAD patients (Table 6).

To further investigate the diagnostic efficacy of CIT, HC and MHR on the severity of coronary artery stenosis in patients. Based on these results, several diagnostic models were developed. Model 1 included MHR and CIT; Model 2 comprised MHR and HC; Model 3 incorporated MHR, CIT, and HC. The AUC values for MHR, CIT, HC, Model 1, Model 2 were 0.786 (95%CI: 0.688–0.884, $P < 0.001$), 0.731 (95%CI: 0.624–0.838, $P < 0.001$),

0.783 (95%CI: 0.683–0.882, $P<0.001$), 0.816 (95%CI: 0.728–0.905, $P<0.001$), 0.813 (95%CI: 0.723–0.904, $P<0.001$), respectively. Multi-parameter diagnostics, particularly Model 3, demonstrated higher diagnostic power (AUC = 0.849, 95%CI: 0.770–0.929, $P<0.001$) for differentiating the severity of coronary stenosis in PCAD patients, with a sensitivity and specificity of 81% and 72.1%, respectively (Table 7, Fig. 3). The positive predictive value (PPV), negative predictive value (NPV), and relative risk (RR) of MHR were 0.750, 0.780, and 1.068 (95% CI: 0.962–1.185), respectively. For CIT, the PPV was 0.711, the NPV was 0.681, and the RR was 1.050 (95% CI: 0.998–1.106). For HC, the PPV was 0.706, the NPV was 0.824, and the RR was 1.556 (95% CI: 1.145–2.114).

Reproducibility of ultrasound measurements

To assess inter-observer reproducibility, 15 subjects were randomly selected from each group, and another vascular sonographer repeated the ultrasound measurements. All ultrasound parameters in Table 8 demonstrated good consistency.

Discussion

This study revealed that CIT, HC and MHR were significantly higher in the high group than in the low and control groups. Our study appears to be novel in that the combination of CIT, HC, and MHR showed a good ability to predict the severity of coronary stenosis in patients with PCAD.

As a distinct category of CAD, PCAD poses a serious threat to public health due to its rapid progression, high mortality rate, and poor long-term prognosis. The

Table 7 Result of receiver operating characteristic curves in patients with premature coronary artery disease

Factors	Cut off value	AUC (95%*CI*)	sensitivity	specificity	*P*-value
MHR	3.785	0.786 (0.688–0.884)	78.6%	74.4%	< 0.001
CIT	31.5	0.731 (0.624–0.838)	64.3%	74.4%	< 0.001
HC	4.605	0.783 (0.683–0.882)	85.7%	65.1%	< 0.001
Model 1	-	0.816 (0.728–0.905)	73.8%	76.7%	< 0.001
Model 2	-	0.813 (0.723–0.904)	90.5%	62.8%	< 0.001
Model 3	-	0.849 (0.770–0.929)	81%	72.1%	< 0.001

MHR monocyte to high-density lipoprotein cholesterol ratio, *CIT* carotid intima thickness, *HC* hardness coefficient. Model 1 contained CIT and MHR; Model 2 contained HC and MHR; Model 3 contained CIT, HC and MHR

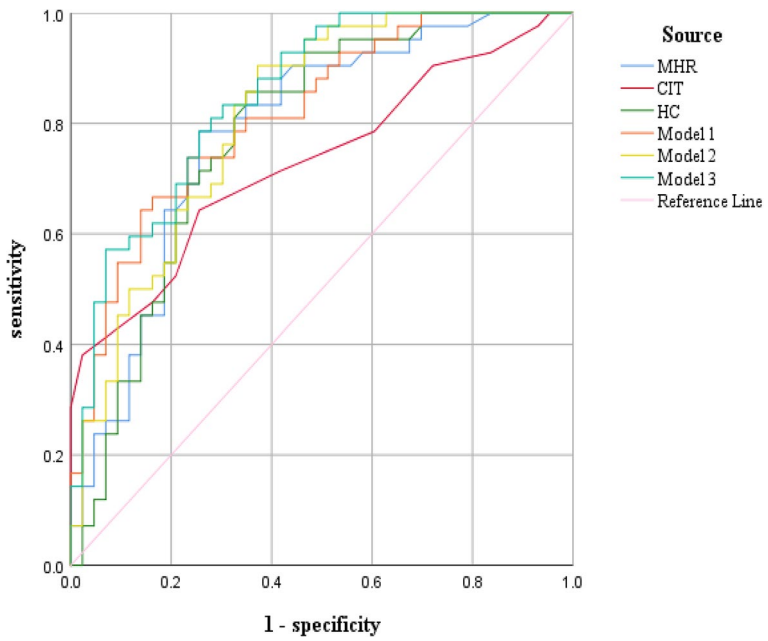

Fig. 3 ROC curves generated by different variables and combination models for differentiating the severity of coronary stenosis in patients with PCAD. Model 1 contained CIT and MHR; Model 2 contained HC and MHR; Model 3 contained CIT, HC and MHR

Table 8 Result of reproducibility test in patients with premature coronary artery disease and healthy controls

Factors	Inter-observer		Intra-observer	
	ICC-value	95%*CI*	*ICC*-value	95%*CI*
CIT	0.902	0.828 ~ 0.945	0.914	0.849 ~ 0.952
CMT	0.881	0.790 ~ 0.934	0.907	0.832 ~ 0.948
CIMT	0.959	0.926 ~ 0.977	0.965	0.938 ~ 0.981
Diam	0.902	0.828 ~ 0.945	0.912	0.844 ~ 0.951
Dist	0.896	0.781 ~ 0.948	0.906	0.811 ~ 0.951
PWV	0.904	0.808 ~ 0.950	0.875	0.776 ~ 0.931
HC	0.915	0.843 ~ 0.954	0.879	0.781 ~ 0.933

CIT carotid intima thickness, *CMT* carotid media thickness, *CIMT* carotid intima-media thickness, *Diam* diameter, *Dist* distance, *PWV* pulse wave velocity, *HC* hardness coefficient

prevalence of PCAD has been substantially underestimated, leading most patients to miss the opportunity for early intervention [13]. Therefore, there is an urgent need for a non-invasive, simple, and rapid screening method for high-risk populations. In our study, our findings suggest that CIT, HC, and MHR may serve as potential risk factors influencing the severity of coronary stenosis in patients with PCAD. ROC revealed that CIT and HC demonstrated relatively good and similar diagnostic efficacy, whether used independently or in combination with MHR. Further, a prediction model combining all three parameters yielded a significant increase in the AUC to 0.849, with high sensitivity and specificity (81% and 72.1%, respectively). These results suggest that CIT, HC and MHR have a strong combined predictive value for the severity of coronary stenosis in patients with PCAD.

Based on our analysis, we attempted to explain the reasons why these parameters may serve as predictors of the severity of coronary stenosis. CIMT is often regarded as a non-invasive measure of subclinical AS and is widely used to assess cardiovascular disease risk. However, CIMT thickening involves not only the intima but also the media, which primarily comprises vascular smooth muscle cells and elastic tissue. Increasing evidence suggests that endothelial dysfunction and vascular smooth muscle cell proliferation and migration are key features in the early stages of AS lesions. Therefore, intimal thickening may represent the earliest marker of AS [14]. Previous studies have demonstrated CIT thickening occurring before CIMT thickening and plaque formation, CIT may serve as a more valuable parameter than CIMT for assessing early-stage AS [15]. In our study, CIT was thicker in PCAD patients compared to controls, with a statistically significant difference between the two PCAD subgroups. Considerable research also indicates that diabetes, hypertension, smoking and estrogen are independent risk factors in AS development [16, 17]. To minimize the influence of these factors, we controlled for them sequentially and reanalyzed the data. Despite these adjustments, CIT remained statistically different among the three groups. Notably, the CIT/CMT ratio differed significantly between the PCAD and control groups, with a higher ratio in the high group than in the low group. This finding aligns with our hypothesis that intima thickening may represent the earliest morphological change in AS, consistent with the findings of Jin et al. [6].

Furthermore, arterial stiffness has been identified as a detectable and predictable marker of AS severity [18]. The R-VQS technique has been employed in several studies to assess alterations in carotid artery elasticity among high-risk populations [19, 20]. In our study, PWV and HC were significantly higher in PCAD patients than in healthy controls, with significant differences between the high and low groups. We hypothesize that HC may act as a sensitive indicator of changes in carotid artery elasticity at the early stages of AS, supporting our initial hypothesis.

AS, a primary pathological basis of CAD, involves inflammatory responses and lipid metabolism abnormalities throughout its development. When vascular endothelial cells are damaged, monocytes are activated by inflammatory factors, differentiate into macrophages, and transform into foam cells through phagocytosis of lipid components, forming lipid streaks [21]. Monocytes contribute to inflammation in this process. HDL-C can inhibit monocyte activity, curbing their proliferation and differentiation, thereby mitigating AS progression through various mechanisms [22]. plaque vulnerability plays a pivotal role in the clinical management of PCAD. Vulnerable plaque features (e.g., thin fibrous cap, large lipid core, and macrophage infiltration) are closely associated with acute cardiovascular events [23]. Thus, MHR, as an inflammatory marker that integrates these interactions, provides a more comprehensive reflection of AS progression than inflammatory or lipid markers alone. Our study found statistically significant differences in MHR among the three groups, with the high group displaying an elevated MHR compared to the low group, consistent with findings reported by Guo et al. [24]. Combined with the thickening of CIT, this suggests that an elevated MHR may accelerate intimal damage, indicating a potential role of chronic inflammation in this process.

Although CAG is the gold standard for diagnosing PCAD, it is invasive, costly, and involves radiation exposure, which some patients may not be able to risk. Additionally, CAG is not suitable for patients with lower degrees of coronary artery stenosis in widespread clinical practice. Previously, due to limitations in ultrasound

resolution, it was challenging to distinguish between intima and media thickness. The 24 MHz ultrasound probe used in this study has an ultra-high resolution of approximately 60 μm with substantial tissue penetration, allowing for accurate measurement of carotid intima thickness. Some researchers have compared IT measurements obtained from a 24 MHz ultrasound probe with histologic findings and found a high degree of consistency between them [15]. Although traditional noninvasive indicators such as the ankle-brachial index and PWV are widely used in cardiovascular risk assessment, their measurement methods are limited by the long time required and high operational demands [25]. In contrast, HC utilizing R-VQS technology overcomes the limitations of traditional holistic measurements. It can precisely locate segments with abnormal vascular elasticity and demonstrates significant advantages in repeatability and stability. The R-VQS software automatically calculates PWV and HC to assess vascular elasticity by integrating the average of Diam and Dist over six cardiac cycles with brachial blood pressure. This software provides real-time data to the operator, allowing for more accurate and repeatable results. This result is promising, as the three parameters (CIT, HC, MHR) are easily obtained at low cost, potentially facilitating widespread use in PCAD prevention and early detection in large populations.

The combined model of CIT, HC, and MHR (AUC = 0.849) provides a novel non-invasive tool for risk stratification in PCAD patients. Based on ROC analysis, we propose the following cut-off values to optimize clinical decisions: CIT: 31.5×10^{-2} mm (AUC = 0.731, 95%CI: 0.624–0.838); HC: 4.605 (AUC: 0.783, 95%CI: 0.683–0.882); MHR: 3.785 (AUC = 0.786, 95%CI: 0.688–0.884). When all three parameters are significantly elevated, CAG should be strongly recommended to confirm stenosis severity, even in patients with atypical symptoms. For low-risk management, if only a single parameter is positive, CAG may be selectively performed based on clinical risk scores and other relevant examinations results. Notably, in resource-limited settings, these cut-off values could serve as a primary screening tool to prioritize high-risk patients for referral to cardiac centers that are able to perform CAG screening. It is critical to emphasize that the generalizability of these thresholds requires further validation through multi-center studies. Future research should explore machine learning models to enhance personalized predictive capabilities.

Our study had several limitations. First, our study is still in its preliminary stage, and the lack of long-term follow-up of the study subjects. Future research will involve multi-center studies and long-term follow-up to further validate our findings. Second, we did not categorize the groupings by clinical presentation. Third, the control group included individuals without CAD-related clinical symptoms, no electrocardiographic signs of myocardial ischemia, and negative CT angiograms or CAG; however, some volunteers did not undergo CAG examination (7 cases in total).

Conclusions

In summary, patients in the high group had elevated CIT, CIT/CMT, and HC compared to those in the low group, suggesting that clinical assessment of the early stage of AS in PCAD patients should emphasize IT and vascular elasticity. CIT and HC measured by noninvasive ultrasound, combined with MHR, presented high diagnostic value in predicting coronary stenosis severity. This approach could serve as a simple, effective imaging tool for assessing coronary stenosis in PCAD patients, providing a valuable reference for early clinical intervention and timely treatment.

Abbreviations

CAD	Coronary artery disease
PCAD	Premature coronary artery disease
AS	Atherosclerosis
MHR	Monocyte to high-density lipoprotein cholesterol ratio
CAG	Coronary arteriography
BMI	Body mass index
DM	Diabetes mellitus
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglycerides
IT	Intima thickness
CIT	Carotid intima thickness
CMT	Carotid media thickness
CIMT	Carotid intima-media thickness
R-VQS	RF-data based quantitative analysis on vessel stiffness
Diam	Diameter
Dist	Distance
PWV	Pulse wave velocity
HC	Hardness coefficient
CCA	Common carotid artery
ROC	Receiver operating characteristic
AUC	Area under curve
ICC	Intraclass correlation coefficients

Acknowledgements

Not applicable.

Authors' contributions

CJX: Conceptualization, methodology, formal analysis, writing-original draft, writing-reviewing and editing; MW: Investigation, writing-reviewing and editing; XJZ: Conceptualization, methodology; KKS: Methodology; YYG: Formal analysis; JJY: writing-reviewing and editing, funding acquisition; HHZ: Conceptualization, methodology, writing-reviewing and editing, funding acquisition; Both the authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (82171963, 82371980), Medical Scientific and Technological Research

Project of Henan Provincial Science and Technology Department, China (222102310053).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study protocol was reviewed and approved by the Ethics Committee of Henan Provincial People's Hospital (No.63/2021) in accordance with regulatory and ethical guidelines and performed in accordance with the ethical standards set forth in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to conducting the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 18 October 2024 Accepted: 20 March 2025
Published online: 01 April 2025

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